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Maleic Anhydride (CAS: 108-31-6): A Valuable Tool for both Industry and Scientific Research

Anidrido Maleico (CAS: 108-31-6): Uma Ferramenta Valiosa Tanto para a Indústria quanto para a Pesquisa Científica

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Maleic anhydride (CAS: 108-31-6) is a very interesting molecule since it has both a C=C bond and an anhydride carboxyl in its structure, forming a strained and very reactive five-membered cycle. This reactivity allows it to be used as a raw material both in the laboratory and industry. Important industrial substances such as tetrahydrofuran, butyrolactone, 1,4-butanediol and succinic acid are produced from maleic anhydride. It is also a monomer used in condensation polymerization, generating polyester resins that are very important in the automotive components industry and in other material molding sectors, as well as in electronics, varnishes and anti-corrosive coatings, among other applications. Maleic anhydride also copolymerizes by addition with different alkenes, generating materials used, for example, in the construction industry. It is an excellent raw material for organic synthesis, providing the basis for producing maleamic acids, maleimides and esters with different applications, such as generating conjugates with biomolecules from biomass or proteins. It can be acylated, undergo conjugated addition, Diels-Alder cycloaddition and Alder-ene reaction, among other interesting reactions for the synthesis of new materials. Maleic anhydride is obtained by two main industrial processes: oxidation of benzene or butane. Studies have also been conducted to produce it from biomass, but it has not yet been obtained industrially from that source.

Keywords: Maleic acid; maleimides; polyesters; cross-couplings; biomass; polymers.

1. Introduction

Maleic anhydride (**MA**) (**1**) is a cyclic organic anhydride (OO=C-C=C-C=O) with an α, β double bond (Figure 1) and the molecular formula $C_4H_2O_3$. It is also considered a member of the furan family. It is a white or even colorless crystalline solid that is commercially available with various morphologies, including needle-like forms, pellets, flakes, rods, or even as a molten mass (Figure 2).[1] Its IUPAC name is furan-2,5-dione, but other names can also be found: *cis*-butenedioic anhydride; *Z*-butenedioic anhydride; 2,5-furandione; 2,5-dioxofuran; maleic acid anhydride; and toxilic anhydride.[1]

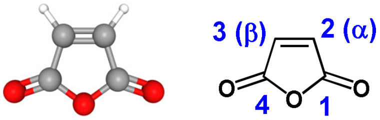


Figure 1. Chemical structure of maleic anhydride

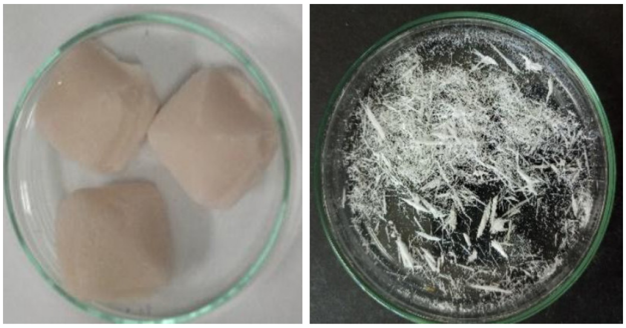


Figure 2. MA briquettes provided by the company Elekeiroz and MA obtained after crystallization in $CHCl_3$

MA is a multifunctional compound containing a double bond and an anhydride carboxyl group, rendering high reactivity to its structure. Although it was first prepared in 1830,[1-3] it only became commercially available in 1933. Here we focus on a method developed by the National Aniline & Chemical Co., Inc. employing vanadium pentoxide (V_2O_5) as catalyst to oxidize benzene to **MA**.[1]

MA is hygroscopic and can be hydrolyzed to maleic acid (*Z*-butenedioic acid, **2**) at room temperature (Scheme 1). Maleic acid **2**, in turn, can be dehydrated to **MA** either by removing water from aqueous solutions of maleic acid or by azeotropic distillation. Maleic acid can be isomerized to fumaric acid (*E*-butenedioic acid, **3**) at temperatures between 130 and 230 °C. Some catalysts, such as thiourea, molecular bromine, ammonium bromide, silica and zeolites can promote this isomerization. Above 230 °C, fumaric acid **3** can be dehydrated to **MA** (Scheme 1).[4]

Based on its structure and properties, it has a wide range of commercial and industrial applications. These include the preparation of agrochemicals and food additives, surfactants, polyester resins and even resin modifiers, among others.[5] Considering not only the breadth of the readership, but also their different areas of interest and potential convergences in relation to the use of the compound under study, this text presents the applications and potentials of maleic anhydride. To this end, the text was divided considering the following themes: properties, toxicity and handling, reactions, applications and preparation methods. In the sections where the properties and aspects related to handling are presented, we sought to provide a chemical basis by making a relationship with the structure, so that the text can also serve as material for chemical education, showing the differences in properties of cyclic compounds such as anhydride maleic with its acyclic "relatives" and the impacts of geometric isomerism to differentiate the properties of maleic and fumaric acids. In all of them, we sought to present precursor and classic reports, as well as bring forward the advances achieved through the most recent publications (until 2024). This text seeks to awaken readers from different areas by showing the resources that this simple raw material, produced by Brazilian industries, can offer. Not all possible reactions and applications for this compound are addressed and there is no intention to do so. Important reactions were highlighted both in the context of organic synthesis and the production of materials and biomaterials likely to impact health, construction, the naval and oil industries, analytical methods such as solid phase extraction, electrochemistry, among other areas. In the same sense, the classic preparation methods are presented, but the horizon is also opened so that new processes based on biomass can be developed, showing the current obstacles and what needs to be overcome.

2. Properties, Toxicity and Handling

MA features a double bond with poor electron density coupled with a cyclic anhydride. **MA**'s double bond length (C-H = 1.1 Å, C=C = 1.3 Å) falls within the typical alkene double bond length range, such as ethylene (C-H = 1.08 Å, C=C = 1.33 Å).[5]

In Figure 3, the bond lengths and angles of maleic anhydride are highlighted, revealing that the angles deviate significantly from 120°. This reflects the ring strain of the five-membered cyclic structure. All internal angles are 104° except for the angle between the C-O-C bonds, which is 102°. Additionally, all atoms of **MA** lie in the same plane. Therefore, it has a completely planar and very compact structure. Consequently, **MA**'s density is high (1.48 g/cm^3), reflecting its compact organization in the solid state.[5]

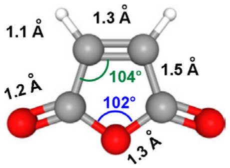
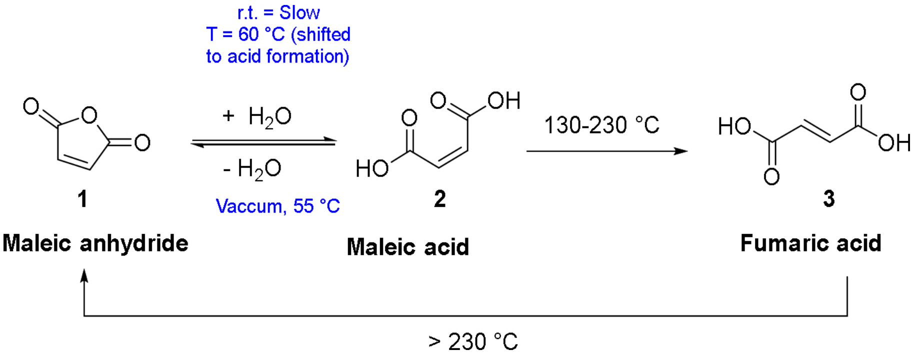


Figure 3. MA's bond lengths and angles[5]

Maleic anhydride possesses a high dipole moment (3.96 Debye) and strong Coulombic attraction between its molecules. Hence, the melting (51-56 °C) and boiling (200 °C) points (Table 1) are high due to its very small neutral molecules. This can be understood by observing the electronic density map of the molecule (Figure 4a), where an electropositive region (blue) is observed for the double bond and an electronegative region (red) for the anhydride function.[5]



Scheme 1. MA hydrolysis, dehydration, isomerization[5]

It is also possible to observe through resonance structures (Scheme 2) the electron-poor double bond profile of **MA** and the different regions (electron-rich and electron-poor) that this molecule possesses. Through the electron density surface (Figure 4b), hydrogens can be observed as points of low electron density and oxygens as points of high electron density. This is perfectly consistent with the organization of **MA** in the solid state, forming orthorhombic crystals whose unit cell contains 4 molecules of **MA**. In these crystals, the double bond (electron-poor region) of one **MA** unit aligns with the electron-rich region (anhydride) of the other unit. Orthorhombic **MA** needles can be obtained from recrystallization with chloroform. The first researchers to deduce its crystal structure were Marsh and co-workers.[6] Structurally similar substances, such as maleic acid and fumaric acid, form monoclinic crystals, unlike maleic anhydride.[5] The main properties of **MA** are presented in Table 1.

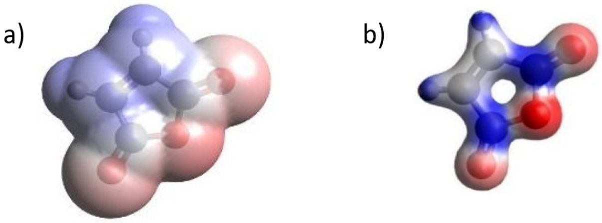
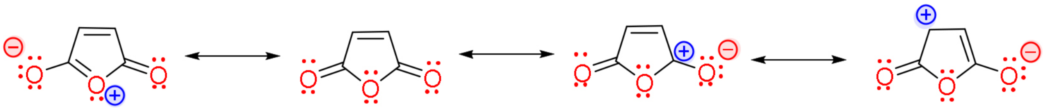


Figure 4. a) Electron density map (van der Walls surface) colored by electrostatic potential b) Electron density surface colored by electrostatic potential[5]

Although solid at room temperature (m.p. = 51-56 °C, b.p. = 202 °C)[7], **MA** can be transported either in solid or molten state. When sold commercially, it typically is molten or in the form of solid briquettes (Figure 2). **MA** sublimes slowly (50-60 °C)[8] and has a pungent odor (penetrating, sharp, and intense), partly due to its high vapor pressure.[1,7]

Since **MA** is prone to hydrolysis during storage, obtaining pure maleic anhydride requires purification before usage. Commercially, purification is achieved through



Scheme 2. MA's resonance contributors[5]

Table 1. Maleic anhydride properties

Properties	Value	Properties	Value
M.W. (g/mol)[7]	98.06	**Viscosity (cP)[1]**	0.61 (60 °C) 1.07 (90 °C) 0.6 (150 °C)
Density[1]	0.934 (4 °C) 1.5 g/cm^3 (20 °C)	**Corrosivity[1]**	Corrosive
M. P. (°C)[7]	51-56	**Sublimation temperature [8]**	50-60 °C
B.P. (°C)[7]	200	**Heat of combustion[1]**	- 1389, 5 KJ mol^{-1}
Flash point (°C)[7]	103	**Ionization energy[1]**	9.90 eV
Auto-ignition temperature (°C)[7]	477	**pH aqueous solution[1]**	2.42 (1 x 10^{-2} M) 2.62 (5 x 10^{-3} M) 3.10 (1 x 10^{-4} M)
Odor[1]	pungent	**Ultraviolet spectrum (isooctane)[9]**	$\lambda_{máx}$: 208 nm (log ε = 3.90) and 290 nm (log ε = 1.11)
H bond donors[1]	0	**Infrared spectrum (KBr, cm^{-1})[10]**	3185; 3130; 1932; 1856 (ν_s C=O); 1774 (ν_{ass} C=O); 1630; 1289; 1268; 1243; 1051 (C-O)
H bond acceptors[1]	3	**^{1}H-RMN ($CDCl_3$, δ ppm)[11]**	7.048 ($\underline{H}$C=CH)
logP[1]	1.62	**^{13}C-RMN ($CHCl_3$, δ ppm)[12]**	164.6 (C=O); 136.8 (C=C)
Dipole moment (Debye)[1]	3.96	**Mass spectrum (180°C, 75 eV)[13]**	Molecular ion: 98 *m/z*
Solubility (g/100 g)[8]	Acetone: 227; ethyl acetate = 112, chloroform = 52.5; benzene = 50; toluene = 23.4; *o*-xylene = 19.4, carbon tetrachloride = 0.6	**Refraction index[1]**	1.55
Solubility[1,8]			T > 150 °C with acid smoke and irritating fumes. Decomposes exothermically (T > 150 °C) in presence of $NHMe_2$, NEt_3, pyridine, quinoline or inorganic bases.

distillation. On a small scale, in the laboratory, the anhydride can be purified by sublimation or recrystallization. Chloroform or aromatic solvents such as toluene, xylene and benzene function well for recrystallization.[14] **MA** is soluble in water via formation of maleic acid (Scheme 1), and it is hygroscopic. It also dissolves in alcohols through reaction, albeit with the formation of esters. Therefore, when the logP is measured in octanol, it is important to note that this value can have a certain error, since octanol is capable of reacting with **MA**.[8]

The solubility of **MA** is higher in aprotic polar solvents, such as dioxane and methyl ethyl ketone (MEK), and is moderate in nonpolar solvents, such as benzene and toluene (Table 1).[8] **MA** decomposes at 120 °C through decarboxylation, with the elimination of carbon dioxide. However, if decarboxylation occurs too quickly, the formation of significant amounts of CO_2 increases the explosion risk.[8]

Absorption bands related to the conjugated double bond and the carbonyl group are observed in regions between 220-250 nm of the spectrum in the ultraviolet/visible region (Figure 5).[9] In the infrared (IR) region, characteristic bands are observed at 3130 cm^{-1} (Csp^2-H stretching), 1856 cm^{-1} (asymmetric stretching of anhydride C=O), 1774 cm^{-1} (symmetric stretching of anhydride C=O), 1630 cm^{-1} (C=C stretching), 1030 cm^{-1} and 700 cm^{-1} (out-of-plane C-H stretching of *Z*-alkene).[10]

In the ^{1}H-NMR spectrum (proton nuclear magnetic resonance), due to the molecule's symmetry, there is only one signal: a singlet, at 7.05 ppm ($CDCl_3$). If part of the anhydride is hydrolyzed, a signal between 10-12 ppm is characteristic of the acid's presence. As for the ^{13}C-NMR in $CDCl_3$ (carbon-13 nuclear magnetic resonance), also due to the molecule's symmetry plane, only two signals appear: 136 ppm (olefinic carbon) and 165 ppm (OC=O carbon of the anhydride).[5, 12]

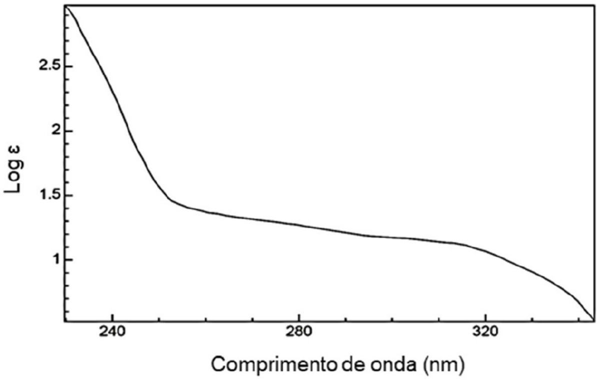


Figure 5. UV/Vis spectrum of MA[9]. (Adapted from the National Institute of Standards and Technology - NIST)

Maleic anhydride is employed as a reagent or synthetic intermediate in many industrial processes, which leads to its presence in various waste streams and thus in the environment. As it rapidly hydrolyzes to maleic acid, it is found in this form in moist soils and water bodies. For this reason, its bioconcentration in aquatic organisms is unlikely. The hydrolyzes half-life of maleic anhydride to maleic acid in water at 25 °C is approximately 22 seconds. Hence, it is important to evaluate the toxicity and environmental pollution of both. Once in the environment, maleic acid goes to hydroxylated to malic acid (2-hydroxybutanedioic acid, $HO_2CCH_2CH(OH)CO_2H$), which can participate in the Krebs cycle in organisms, be excreted unchanged, or be bioconjugated. Maleic acid is biodegradable under aerobic conditions. [3]

Due to its low vapor pressure (0.25 mmHg), it is also unlikely that **MA** volatilizes from dry soil surfaces.[3] There are some studies in the literature on the remediation of soils contaminated with maleic anhydride from petrochemical plants. Alternatives for remediation include the addition of lime or sawdust to the soil followed by the addition of nutrients, with or without soil aeration. The studies show good results, with high degradation rates for maleic anhydride in a brief period.[3]

Maleic anhydride can be found in effluents and atmospheric samples close to industrial plants, especially those of phthalic anhydride.[3] Among the precautions that an industrial plant must take to contain this atmospheric release are the use of air scrubbers and filters to control the emission of maleic anhydride particles and its periodic cleaning, achieving better efficiency when coupled with a combustion-type device.[3]

Intoxication by **MA** in most cases occurs through occupational exposure, for example, of workers in industries where **MA** is produced or used as a raw material or synthetic intermediate. Most of these occupational exposure cases are through dermal contact or inhalation.[3]

There are reports of asthmatic responses and dyspnea developed by individuals exposed to **MA**, which can be attributed to intoxication by this compound. People who have worked with polyester resin lacquers in which **MA** is present without the use of personal protective equipment (PPE) have reported acute symptoms of nervous, cardiovascular and/or respiratory disorders. However, people who do not work directly with **MA** are not at risk of intoxication with the anhydride, even if it is present in vapor form in dry air, because it is hydrolyzed very rapidly.[3]

Although alterations in hamster chromosomes have been observed, these changes were unable to produce mutations. Additionally, no effect of **MA** on cholinesterase activity has been reported. However, exposure to the anhydride can sensitize the skin and respiratory system. In humans, there are reports of its association with nasal irritation after just one minute of exposure to 1.5-2 ppm, followed by eye irritation if exposure is prolonged for 15 minutes.[3]

Contact with maleic anhydride in the form of powder or vapor can cause conjunctivitis, inflammation and swelling of the eyelids, excessive tearing, and even photophobia. Dermal exposure can lead to itching and first or second-degree burns, which can be aggravated when in contact with

Table 2. Sensory response of volunteers exposed to MA in different concentrations[15]

Concentration (mg/m³)	Sensory response
270	Nasal and eye irritation, smell impairment, mild to severe pulmonary discomfort of 3 of the 5 subjects
179	Eye irritation, mild pulmonary discomfort of 1 of the 5 subjects
54	Rare pulmonary discomfort and smell impairment
45	Rare pulmonary discomfort and smell impairment
22	Response not described in the study

water. To evaluate the effects of human exposure to maleic anhydride, a study was conducted in an exposure chamber, where men aged 22-27 were exposed to **MA** for different periods at different concentrations. Table 2 presents the sensory responses obtained.[15]

In animals such as rats and rabbits, symptoms of oral and dermal exposure were similar: reduced appetite and/or activity, increasing weakness, collapse, and death. Dermal exposure caused irritation and redness. Inhalation, on the other hand, resulted in coughing, sneezing and throat irritation. Maleic anhydride vapors can cause severe eye irritation.[15]

The dose capable of killing 50% of laboratory animals (LD_{50}) was determined by different contact methods. The oral LD_{50} of **MA** had similar values for mice (465 mg/kg), rats (400 mg/kg), and guinea pigs (390 mg/kg). However, for rabbits, this dose was much higher: around 875 mg/kg. The dermal LD_{50} was determined for guinea pigs and the rabbits. In both cases, a much higher dose was needed to cause the death of 50% of the animals just by skin contact, compared to the oral LD_{50}. The LD_{50} for intraperitoneal injection in rats was 97 mg/kg (Table 3).[3] There is no antidote for poisoning. Treatment depends on the symptoms presented by the patient.[15]

The Hommel diagram (NFPA 704) for maleic anhydride can be found in Figure 6.

According to the U.S. National Fire Protection Association (NFPA), this compound has a health hazard rating of 3 (blue), indicating it can cause severe or permanent damage. It has a flammability hazard rating of 1 (red), meaning it must be preheated for ignition to occur. Finally, it has a reactivity hazard rating of 1 (yellow), indicating it is normally stable but can become unstable at high temperatures and pressures.[16]

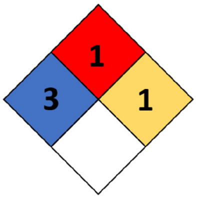


Figure 6. MA's Hommel diagram

In Brazil, Regulatory Standard 26 (NR-26) establishes criteria for classifying chemical products, ensuring their correct identification in a universal language. One of the items of this NR establishes rules for labeling and safety information. According to this standard, chemical products must be classified according to the guidelines of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS). Some of the guidelines for maleic anhydride are provided below.[17]

The labels of maleic anhydride must include pictograms for corrosion, indicating that the material is corrosive; designation of health hazard, indicating the material can be carcinogenic, a respiratory sensitizer, toxic to reproduction, or mutagenic; and contain an exclamation mark, indicating possible irritation to the skin and eyes, acute toxicity, toxicity to a specific organ, or harmful to the ozone layer (Figure 7). The hazard class codes associated with these pictograms are CP5, CP7, and CP9, respectively.[17]

The signal word that should appear on the label of **MA** is DANGER. Signal words are used to indicate the severity of the hazard and alert users to potential harm from exposure. The word "danger" is associated with higher levels of severity, while "caution" is associated with less severe levels.[17]

Table 4 reports the hazard statements that describe the

Table 3. Lethal doses for intraperitoneal injection in rats

TYPE SPECIES OF CONTACT	MICE	RATS	GUINEA PIGS	RABBITS
				
ORAL LD_{50}	465 mg/kg	400 mg/kg	390 mg/kg	875 mg/kg
DERMAL LD_{50}	-	-	20000 mg/kg	2620 mg/kg
INTRAPERITONEAL LD_{50}	-	97 mg/kg	-	-

LD_{50} - Median lethal dose, dose of the substance required to kill 50% of the test population.

Figure 7. Hazard pictograms of MA

nature of the danger associated with **MA**. These statements are represented by codes starting with the letter "H" for "Hazard," followed by three digits specifying the type of hazard. The numerical sequence starting with the digit 2 (H2XX) denotes physical risks such as explosion, corrosion, etc., while those starting with the digit 3 (H3XX) designate health hazards. Maleic anhydride presents only health hazard risk statements. The precautionary statements are initiated by the letter "P" for "Precautionary" and describe the prevention and response measures of contact with **MA**. Prevention measures indicate the equipment that should be used to achieve the necessary precautions. For example, these include the use of gloves or goggles and/or the need to wash hands, among others. On the other hand, emergency response measures describe what to do after an accident. This information should be included in the SDS (Safety Data Sheet).[18]

3. Reactions

Maleic anhydride (**MA**) is a highly versatile chemical compound in terms of its reactions, since it can react both through the double bond and the anhydride group. The double bond of **MA** is highly reactive due to the electron deficiency generated by the carboxyl group present in the molecule, which is strong electron-withdrawing. The reactivity of the double bond results in **MA**'s participation in alkylation reactions, Diels-Alder reactions, addition reactions, reduction reactions, etc.

3.1. Acidity and decomposition

As shown in the previous section (Scheme 1), the hydrolysis of maleic anhydride is slow in water at room temperature. This is attributed to the strong attractive forces that bind the molecules of the anhydride, making dissolution and hydrolysis difficult. However, due to the proximity of the two carboxyl groups derived from the *cis* configuration of maleic acid **2** resulting from the hydrolysis of **MA**, dehydration easily occurs to regenerate the anhydride (55 °C under vacuum). Conditions must be more severe (e.g., T > 230 °C) to transform fumaric acid **3**, where the carboxyl groups are on opposite sides (*trans* configuration), into maleic anhydride. The *cis* configuration of maleic acid also affects the first ionization of this acid ($pKa_1 = 1.5$) (Scheme 3). This high acidity is not observed for the first ionization of its *trans* analogue, fumaric acid **3** ($pKa_1 = 3.0$). The resulting monoanion from the first ionization of maleic acid is stabilized by the *cis* configuration, allowing the proton to be exchanged between the two carboxyl groups. This stabilization is not possible for fumaric acid, where the two carboxyl groups are on opposite sides ($pKa_1 = 3.0$). However, fumaric acid has a lower pKa for the second ionization ($pKa_2 = 4.5$), since in this case, the separation

Table 4. MA danger and precautionary statements that appear in SDS[18]

HAZARD STATEMENTS	
H302	Harmful if swallowed
H314	Causes severe skin burns and eye damage
H317	May cause an allergic skin reaction
H334	If inhaled, may cause allergy or asthma symptoms or breathing difficulties
PRECAUTIONARY STATEMENTS	
Prevention	
P260	Do not inhale dust, fumes, smoke, fogs or aerosols.
P264	After handling, wash hands carefully.
P280	Wear protective gloves, clothing, eye protection and face protection.
P284	Use pulmonary protection devices.
Emergency response	
P301 + P330 + P331	IF INGESTED, wash mouth. DO NOT provoke vomiting.
P303 + P352	IF ON SKIN (or hair), immediately remove all contaminated clothing. Rinse skin abundantly with water.
P304 + P341	IF INHALED, remove person to fresh air and keep comfortable for breathing. Immediately call a poison center/doctor.
P305 + P351 + P338	IF IN EYES, rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

between the carboxylate groups minimizes the repulsion in the conjugate base of the second ionization, making it more stable than the conjugate base resulting from the second ionization of maleic acid **2** (pKa_2 = 6.5). The *cis* configuration results in significant repulsion due to the proximity of the carboxylate groups.[19]

Both **MA** and maleic acid can decarboxylate when heated to high temperatures (Scheme 4). When **MA** absorbs moisture, it can form maleic acid **2**, which ionizes easily due to its low pKa. This provides the necessary acidic catalysis for decomposition. Due to the higher pKa of fumaric acid **3**, a higher temperature is required to induce decarboxylation (T > 240 °C). The decomposition temperature decreases in the presence of weak bases such as amines or pyridine. In this case, decomposition occurs with polymerization, forming a resinous mass.[5]

3.2. Reactions of anhydride

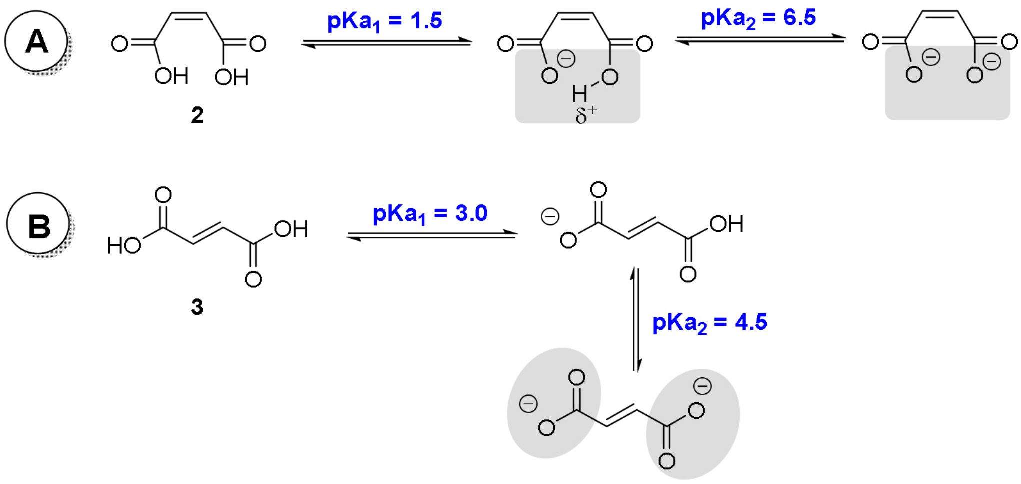
3.2.1. Friedel-Crafts acylation

The first acylation of an aromatic compound catalyzed by a Lewis acid using maleic anhydride is credited to Von Pechmann.[20] This reaction produces a β-aryl-acrylic acid (Scheme 5, example: (*E*)-4-oxo-4-phenylbut-2-enoic acid **6**). In this case, the preferential product is the *trans* isomer, and in the case of substituted aromatics, the *para* product is formed with yields between 70 and 90%. The major *trans* product is usually yellowish, while the *cis* product is white. An excess of the aromatic compound can be used as the solvent for the reaction. However, the best yields are obtained with chlorinated solvents (e.g., 1,2-dichloroethane).[5,21-23]

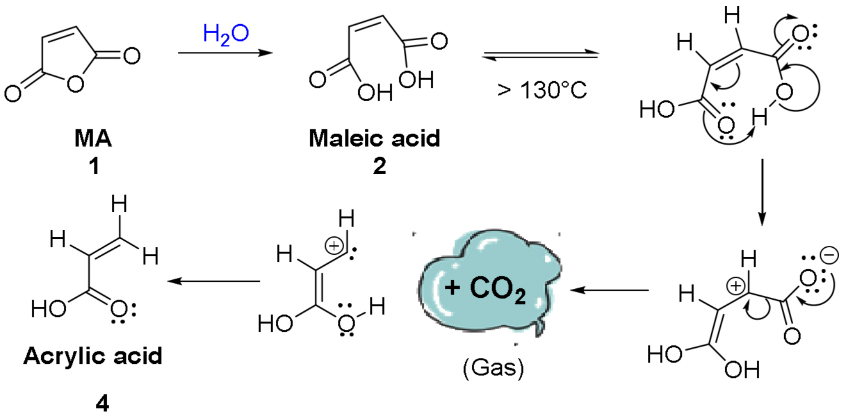
The β-aryl-acrylic acids obtained by acylation with maleic anhydride can serve as useful intermediates for obtaining bioactive compounds.[24-26]

Friedel-Crafts reactions with maleic anhydride can be utilized when involving polymers. For instance, the obtained aryl-acrylic acids **6** can undergo photopolymerization (Scheme 6a, polymer **7**). Another possibility is modification of polymers containing aromatic units **8** that can be acylated with maleic anhydride **1** (Scheme 6b).[5] Other catalysts besides $AlCl_3$ can be employed.[27-31] Coustet and Cortizo employed zinc oxide under microwave irradiation (Scheme 7) to acylated polystyrene (PS) **9**.[32]

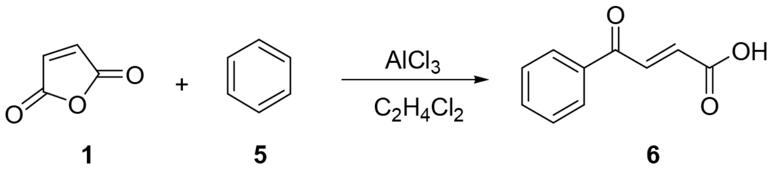
Heteroaromatics such as thiophene can also be acylated by maleic anhydride.[33] The aroylacrylic acids derived from thiophene can be important intermediates in the synthesis of dyes.[34]



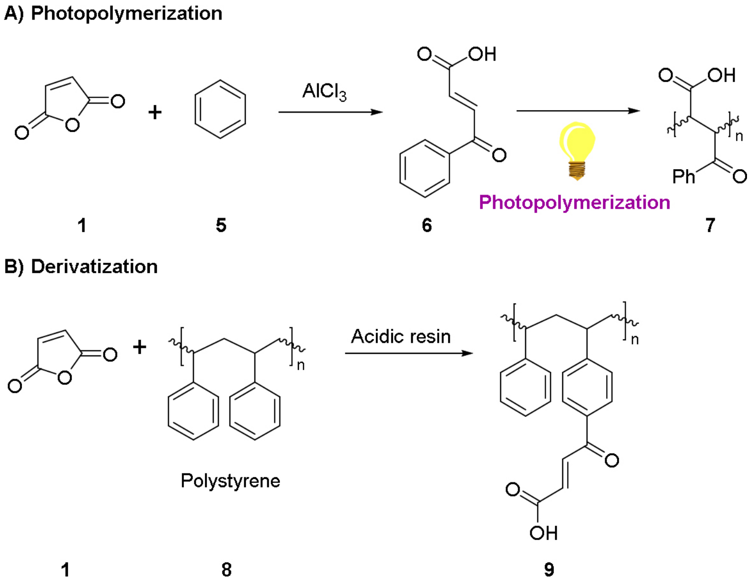
Scheme 3. Acidity of maleic and fumaric acid[19]



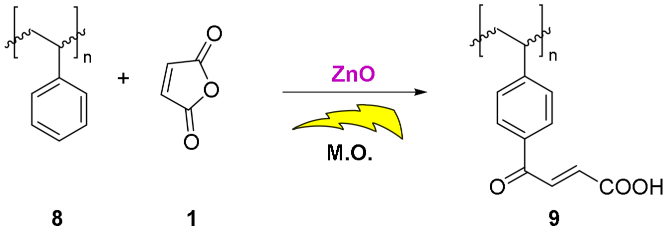
Scheme 4. MA decomposition[5]



Scheme 5. Friedel-Crafts reaction with MA[5]

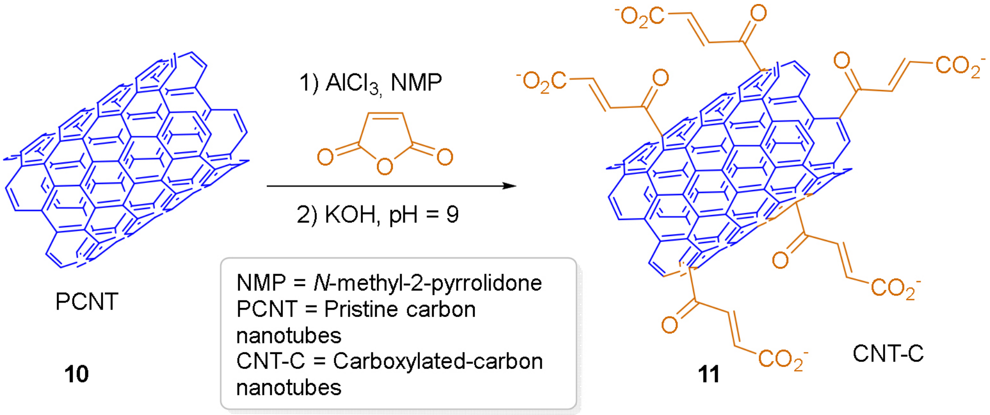


Scheme 6. Acylation in polymer production[5]



Scheme 7. Polystyrene acylation with MA[32]

An interesting application of Friedel-Crafts acylation with maleic anhydride is the modification of carbon nanotubes **10**.[35] Wu *et al.* [36] reported this was an interesting strategy to obtain carboxylated carbon nanotubes **11** (Scheme 8), which were not only more hydrophilic but also enabled the anchoring and stabilization of metal nanoparticles (Pt/Ru). Nano-hybrids were evaluated as electrocatalysts for methanol oxidation.[36] Other materials such as graphene can also be functionalized.[37,38]



NMP = *N*-methyl-2-pyrrolidone
PCNT = Pristine carbon nanotubes
CNT-C = Carboxylated-carbon nanotubes

Scheme 8. Carbon nanotube modification through acylation iwith MA[36]

3.2.2. Preparation of acid chlorides

The production of acid chlorides from both maleic anhydride **1** and maleic acid **2** using acyl chloride-forming agents such as thionyl chloride ($SOCl_2$), phthaloyl chloride or phosphorus pentachloride (PCl_5) is not straightforward. The reason is that once the acyl chloride **12** is formed, maleic anhydride **1** is regenerated (Scheme 9). This difficulty does not occur with fumaric acid, which can be converted to acyl chloride or dichloride due to the separation of the carboxylic groups, which does not allow easy cyclization.[5]

3.2.3. Esterifications

The monoesterification of maleic anhydride **1** with alkyl alcohols **13** (Scheme 10) can be carried out at temperatures between 80 and 90 °C. These monoesters **14** have much lower acidity than maleic acid. Primary alcohols are more reactive than secondary alcohols, which in turn are more reactive than tertiary alcohols. This reactivity depends on steric factors. Esterifications are equilibrium reactions. Although primary alcohols react more rapidly at low temperatures, they are less stable, so their esters are more easily hydrolyzed than esters of secondary or tertiary alcohols. Esterifications with tertiary alcohols require a large excess of alcohol and higher temperatures (100-120 °C) to occur. Esterifications can be catalyzed by acids such as trifluoroacetic acid, methanesulfonic acid or *p*-toluenesulfonic acid, for example. Copper catalysts or inorganic acids can also be used, in addition to BF_3, zinc salts and aluminum halides. Additionally, ion exchange resins containing sulfonic acid groups are widely used in continuous bed reactors.[5, 39-42]

Esters of maleic anhydride are used as plasticizers, for the production of γ-butyrolactone and solvents such as tetrahydrofuran (THF), and as dienophiles in organic synthesis, among other examples.[42-46] Dimethyl maleate **15** (R = Me, Scheme 10) is used in the synthesis of the pesticide malathion (Figure 8).[47]

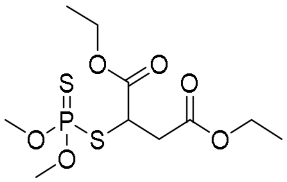
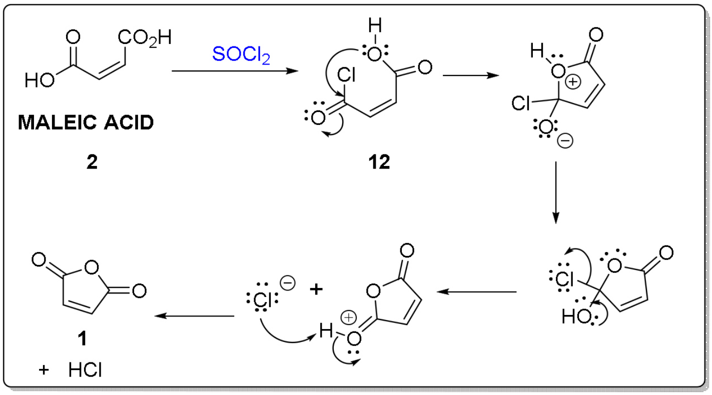


Figure 8. Structure of the pesticide malathion

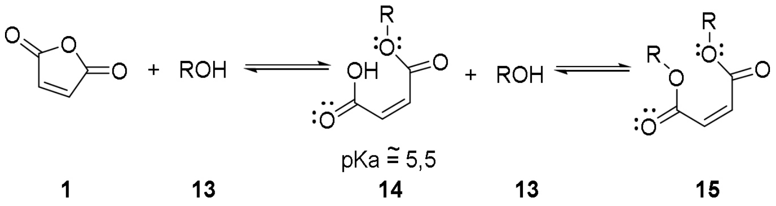
The Fischer esterification of **MA** with methanol and sulfuric acid as catalysts can be utilized to produce dimethyl maleates, for example (Scheme 10, R = Me).[48] Monoesters can also be esterified to generate dimaleates **15**, but the reaction should be carried out above 100 °C, since monoesters **14** can be converted back to maleic anhydride **1**.[5]

Maleic anhydride esterifications are tools for the modification of polymers, such as natural polymers (cellulose, starch, etc.) (Figure 9). These polymers typically have hydroxyl groups that can be esterified by maleic anhydride, such as those present in carbohydrates.[49] The esterification of these materials serves to improve their properties. Treatment of wood, for example, can enhance hardness, dimensional stability, and durability against degradation caused by environmental factors such as wind, rain and UV radiation, etc.[50]

The replacement of petroleum-derived polymers with more environmentally friendly and biodegradable polymers is a growing concern, especially in the food packaging industry. Starch, for example, is used in the preparation of biodegradable packaging. It is cheap, readily available and fully biodegradable. However, its hydrophilicity,



Scheme 9. Acyl chloride **12** formation and MA regeneration[5]



Scheme 10. MA esterification

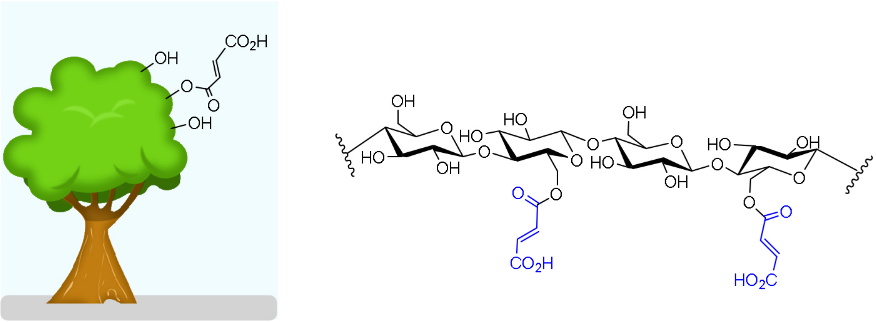


Figure 9. Esterification of biomass materials with maleic anhydride[49]

low dimensional stability and unsatisfactory mechanical properties limit its applicability. Esterification of starch with maleic anhydride can improve its thermoplastic properties as well as its hydrophobicity.[51,52] Maleated starch salts are used as inhibitors of starch gelation and as bread softeners.[53,54]

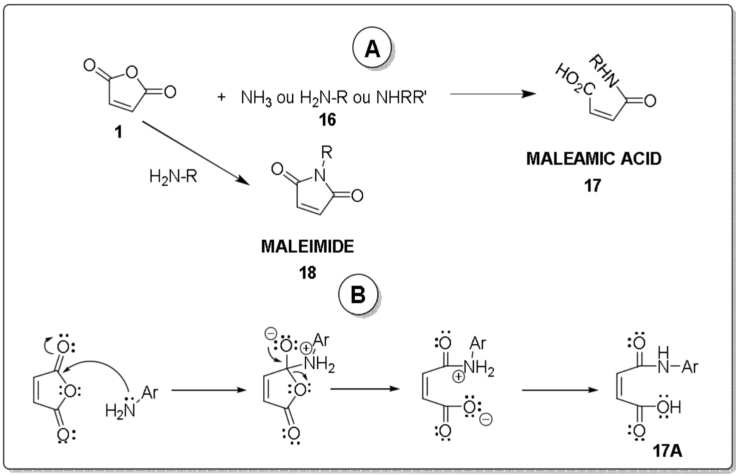
Cellulose nanocrystals modified with maleic anhydride were prepared from stems of the weed *Eichhornia crassipes* by Kara *et al*. These researchers studied the absorption of Cd^{2+} by this nanomaterial from wastewater and found a much higher absorption capacity compared to unmodified cellulose nanocrystals.[55,56]

3.2.4. Amidations

The reaction of maleic anhydride **1** with ammonia or primary and secondary amines **16** can produce maleamic acids **17**, which are acyclic molecules containing both a carboxylic acid and an amide group. They are also known as amic acids or half-amides of maleic acid **2**. Maleic anhydride can also react with amines to produce maleimides **18**, which are cyclic molecules where the oxygen of the original maleic anhydride **1** is replaced by N-R groups (Scheme 11). Maleamic acids **17** are typically formed under mild reaction conditions, such as at room temperature. Maleamic acid (*Z*)-4-amino-4-oxobut-2-enoic acid (CAS: 557-24-4, Scheme 11, **17** with R = H) is a natural product found in *Trypanosoma brucei*.[57,58]

It can be obtained by reacting maleic anhydride with anhydrous ammonia in benzene at room temperature (yield = 70%) or at 50 °C for 5 hours (yield = 95%).[14]

The reaction of **MA** with primary amines produces *N*-alkylmaleamic acids with good yields. Excellent yields of maleanilinic acids **17A** are also achieved by the reaction with aromatic amines (**ArNH$_2$**). Isomerization of the double bond and Michael addition of amines to the double bond result in reduced yields of maleamic acids, generating byproducts.[14] When the product of Michael addition is desired, esters of maleic acid are used instead of **MA**.[5] Different solvents can be used in the preparation of amic acids, such as dichloromethane (room temperature, 2 hours, 96-99%),[59] acetic acid,[60,61] tetrahidrofurane,[62,63] ethyl ether,[64] dioxane,[65] and toluene, or solvent-free reactions can be achieved by mechanochemical processes.[66,67] Maleamic acids are used as bidentate ligands for lanthanides ($La^{3+,}$ Eu^{3+}, Tb^{3+}, and Yb^{3+}) and transition metals (Cu^{2+}, for example).[67-70] Maleamic acids are used in smart systems to deliver nucleic acids, proteins and drugs.[71-77] This is possible due to the high pH sensitivity of maleamic acids and their derivatives, since their amide bonds can be hydrolyzed even in the weakly acidic environments present in physiological conditions.[78] Maleamic acids can also be used to produce materials capable of regenerating their properties, such as self-healing materials. For example, they can regenerate mechanically damaged properties.[79] Maleamic acid derivatives can modify materials, such as nanoparticles,



Scheme 11. Maleic anhydride reaction with amines[57,58]

to absorb drugs.[80] There are also reports of applications in polymer modification.

Li *et al.*[81] synthesized a series of quinolinone derivatives **20** containing a butenediamide fragment from **MA**. These researchers obtained maleamic acids **17A** with different anilines and then coupled another amine containing the quinolinone unit **19** to the carboxyl group of the acid.[81] The series of 3-amino-3,4-dihydroquinolin-2(1*H*)-one **20** had various *in vitro* inhibition percentages (IPs) (e.g., concentration of 300 μg/mL, IP of the polioxin control = 87.5%). Three molecules exhibited IPs greater than 70%, and the derivative of *m*-toluidine (R = 3-Me) showed an IP comparable to that of the control (82.3% versus 87.5%).

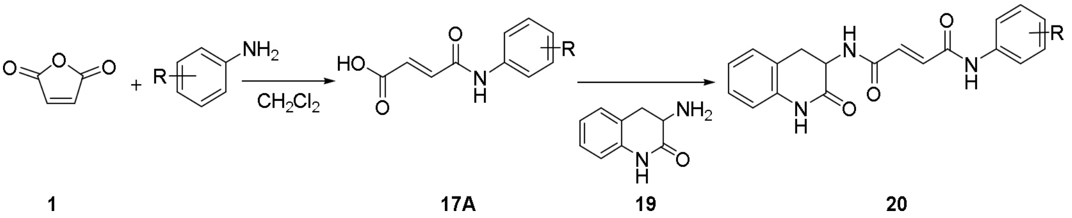
Maleamic acids **17** can also be employed to prepare heterocycles. Badru and Singh[82] prepared 2-thioxo-1,3-oxazepine-4,7-diones **21** (R = 88-96%) through the condensation of maleamic acids (Y = 56-74%) with thiophosgene catalyzed by triethylamine under anhydrous conditions (Scheme 13).

Sun and Zhang[62] prepared fluoroalkylacrylamides **24** with high selectivity for the *E* diastereoisomer through a photoinduced multicomponent reaction where maleamic acids, generated from the reaction of maleic anhydride **1A** with different amines **16**, underwent decarboxylation and were then reacted with fluorinated alkyl iodides **22** (Scheme 14). Through this reaction, maleic anhydride **1A** was doubly functionalized in a photoinduced process. Alkylamines, anilines, heteroaromatic amines, secondary and primary amines, as well as monoprotected amino acids, were successfully employed. However, thiols, phenylhydrazines and hydroxylated nucleophiles failed to be produced in this reaction. Sun and Zhang[62] emphasized that the reaction could not proceed without the presence of three components: photosensitizer **23**, light source and base. Otherwise, it did not occur.

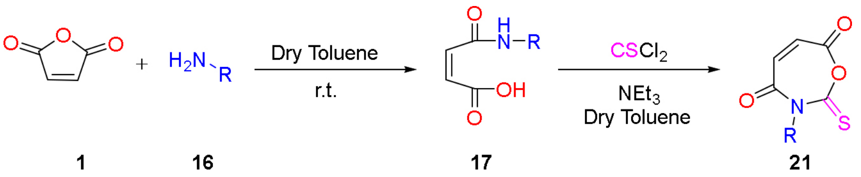
Suárez-Moreno, González-Zamora and colleagues prepared several maleamic acids **25A-H** (Figure 10, 16 to 99%) with the aim of subsequently using them in the construction of metal-organic frameworks (MOFs). These authors also synthesized a maleamic acid **25A** as a polydentate ligand by the basic hydrolysis of a bismaleimide **26** (Scheme 15).[61]

The reaction of **MA 1** with hydroxylamine **27** affords the corresponding hydroxamic acid **28** (Scheme 16a). This compound displays bactericidal and fungicidal properties. Maleuric acids **30**, on the other hand, can be produced by the reaction with ureas **29** (Scheme 16b)[5,83-85] while the reaction of **MA** with hydrazines **31** can form more than one type of product depending on the reaction conditions (Scheme 16c).

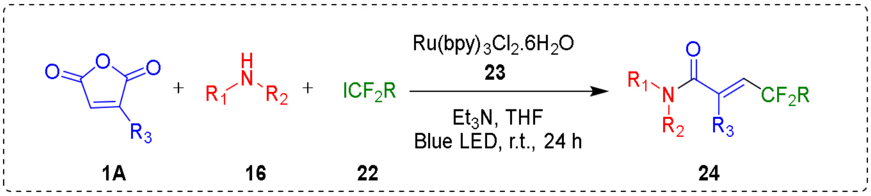
Maleuric acid (CAS: 105-61-3, *N*-Carbamoylmaleamic acid) (Scheme 16b, R = H, **30A**) can be employed in the synthesis of orotic acid (CAS: 65-86-1).[86] Maleic acid hydrazide **34** (CAS: 123-33-1) is used in agriculture as a plant growth regulator in crops such as tomato, onion and tobacco, among others, as well as in ornamental plants. [87] Maleic acid hydrazide residues should be monitored, since they may have carcinogenic and genotoxic effects.[88] Maleic acid hydrazide **34** is also employed in organic synthesis to prepare pyridazines and pyridazinones. [89] This hydrazide exhibits three tautomeric forms (Scheme 16c, **34**, **35**, **36**), two of which have hydroxyl groups that can be functionalized.[89,90]



Scheme 12. Synthetic pathway of 3-amino-3,4-dihydroquinolin-2(1H)-one derivatives **20**[81]



Scheme 13. Synthesis of 2-thioxo-1,3-oxazepine-4,7-dione derived from amic acids[82]



Scheme 14. MA photoinduced amino-fluoroalkylation[62]

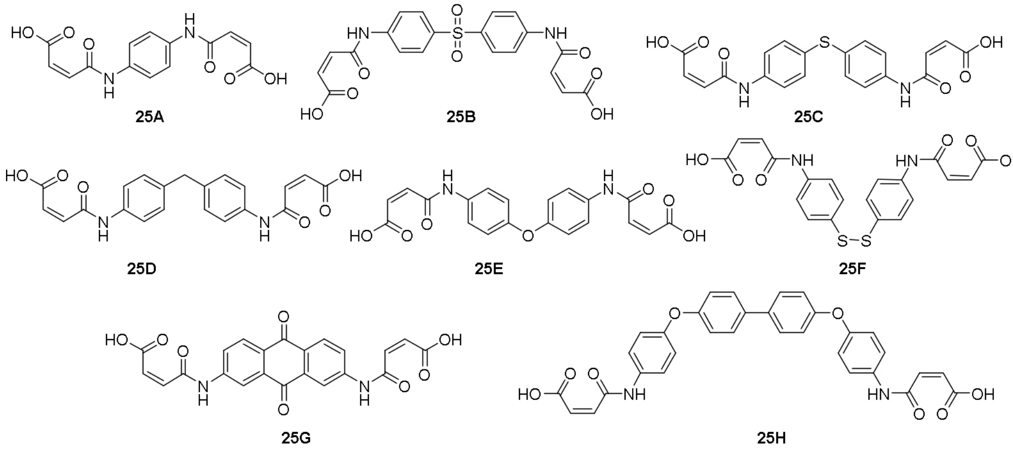
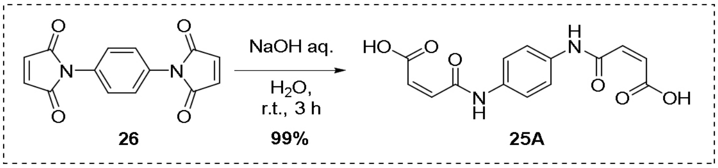
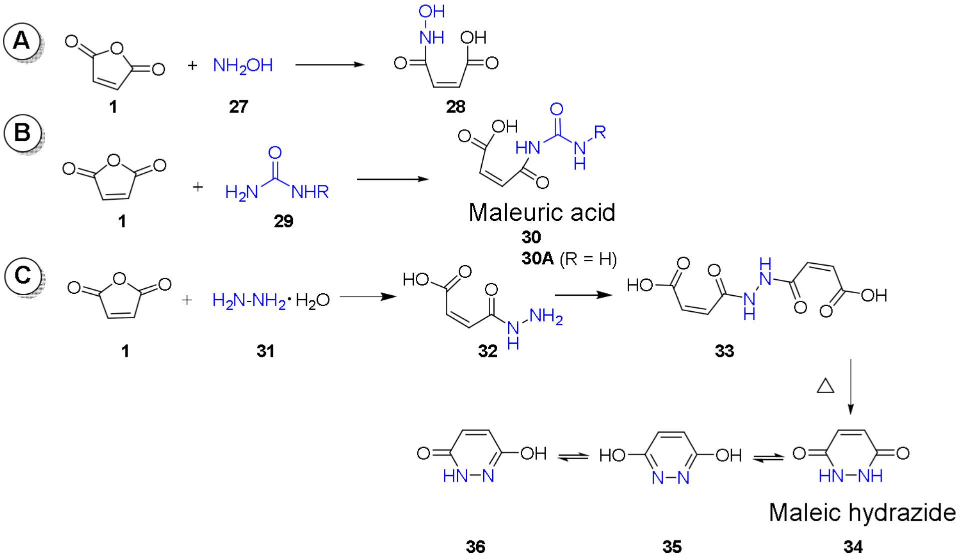


Figure 10. Examples of maleamic acids used as ligands for MOFs (**25A-H**)



Scheme 15. Amic acid through basic hydrolysis of maleimide **26**



Scheme 16. MA reactions with hydroxylamine, hydrazide and ureas

Many natural products have maleic anhydride as part of their chemical structure (Figure 11).[91] Natural products containing **MA** units are secondary metabolites, many of which belong to the family of polyketides derived from fungi, with great potential for biological applications. Cornexistin and scytalidin, for example, have herbicidal activity, and zopfielin has antifungal action. Heveadride acts as an antifungal against some yeasts that are pathological to humans (e.g. Trichosporon sp.), as well as filamentous fungi. In human chronic myeloid leukemia cells, it has been reported that heveadride is capable of producing a TNFa-induced downregulation of NF-kb, which is dose dependent and whose IC$_{50}$ is reported to be of 82 ± 11 µM (Figure 11). Rubratoxins have anti-tumor potential and strongly and specifically inhibits protein phosphatase 2A (PP2A). VrTrb2.1.1.1 and AnspCr1.1.1 were isolated from potato dextrose broth medium. AnspCr 1.1.1 showed moderate antifungal activity (MIC = 62.6 µg mL^{-1}) as well VrTrb2.1.1.1, showing that the substances obtained from Amazon rainforest have immense potential to yield novel natural products with bioactivity.

There are also natural products that are formed by derivatives of maleic anhydride. It is the case of maleimides, which are synthetic targets of great relevance, since they are part of the structure of many bioactive natural products or synthetic compounds with interesting biological activities (Figure 11).[91-94] Polycitina A, for example, is an inhibitor of DNA polymerases and reverse transcriptase.[95-97]

Maleimides **18** are prepared by dehydration/cyclization of maleamic acids **17** (Scheme 17). This can be achieved simply by heating the maleamic acid **17** with concurrent removal of water. In the absence of an acidic catalyst, temperatures of 130 °C or higher may be required. In order to reduce the processing temperature, water should be simultaneously removed by distillation. It is also possible to employ esters of maleamic acids to prepare maleimides, using an acidic catalyst. The use of strongly acidic cation-exchange resins is also common, due to the ease of their removal at the end of the process.[5] The method of mixed anhydride **38** involves using acetic anhydride **37** with triethylamine (Scheme 18).[98] In Scheme 19, some examples of conditions found in the literature for the preparation of maleimides are shown.

The *N*-carbamoylmaleamic acid **30** produced by the reaction of **MA** with urea or alkylurea **29** can be converted into *N*-carbamoyl-maleimide **40** (CAS: 3345-50-4) at temperatures of 100 or 140 °C (Scheme 20a). After thermolysis in DMF, ammonia and isocyanate **41** are formed as byproducts. The reaction of **MA** with protected hydrazides yields maleimido-hydrazides **45**. In this case, carbon dioxide and isobutylene **46** are formed as byproducts (Scheme 20b).[5]

In single-photon emission computed tomography (SPECT) imaging, technetium-99m is one of the most commonly used isotopes, since it emits gamma rays with photon energy of 141 eV. Ono and co-workers used five synthetic steps to prepare bidentate ligands of the Ham-Cys **50** and Ham-RGD **52** types based on maleimide derivatives of anilines to coordinate with technetium-99m

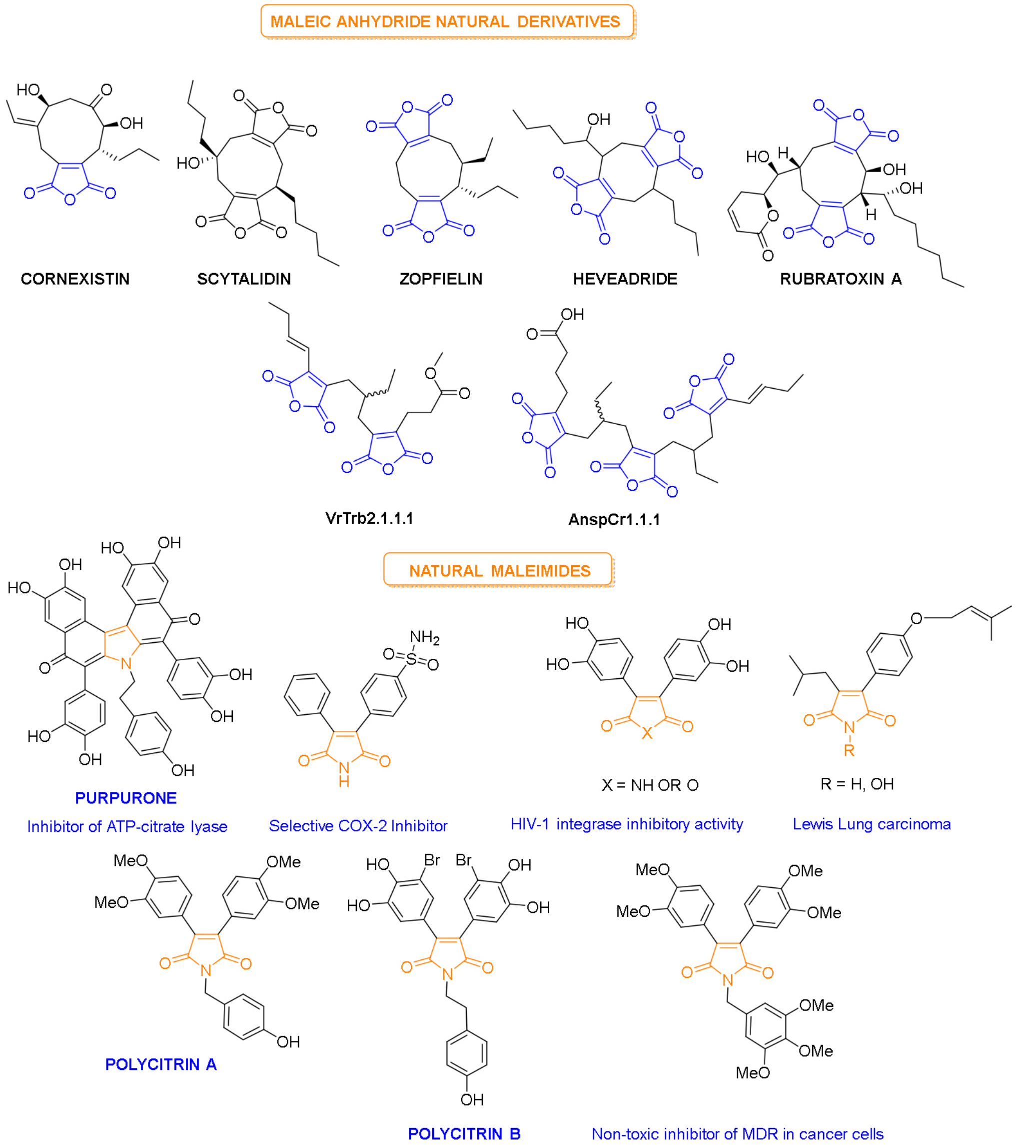
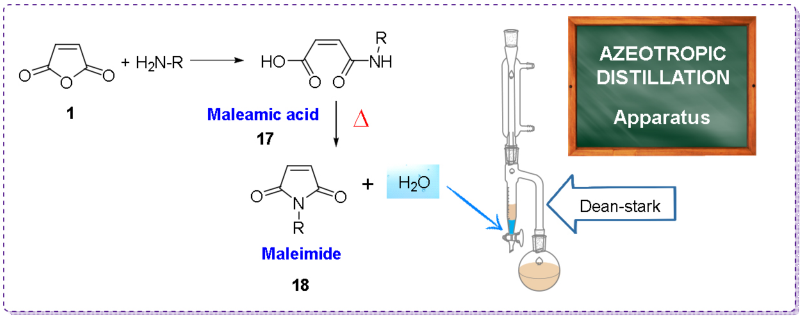
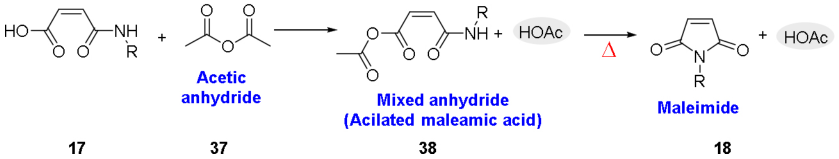


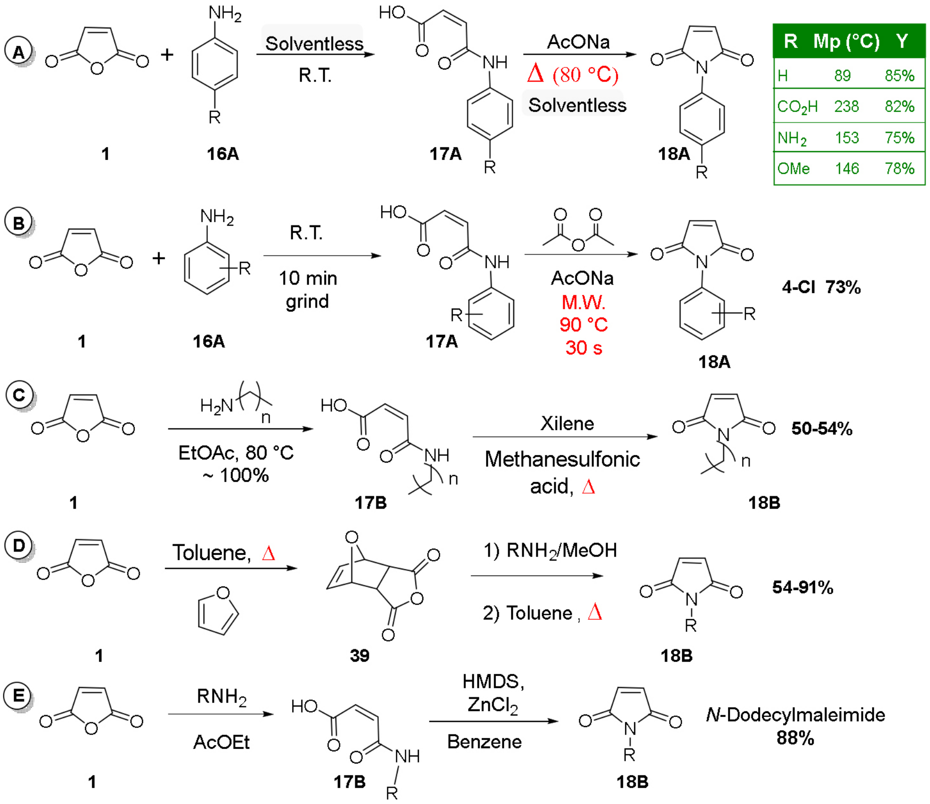
Figure 11. Natural maleic anhydrides and maleimides



Scheme 17. Preparation of maleimides by heating



Scheme 18. Preparation of maleimides by the method of mixed anhydride[98]

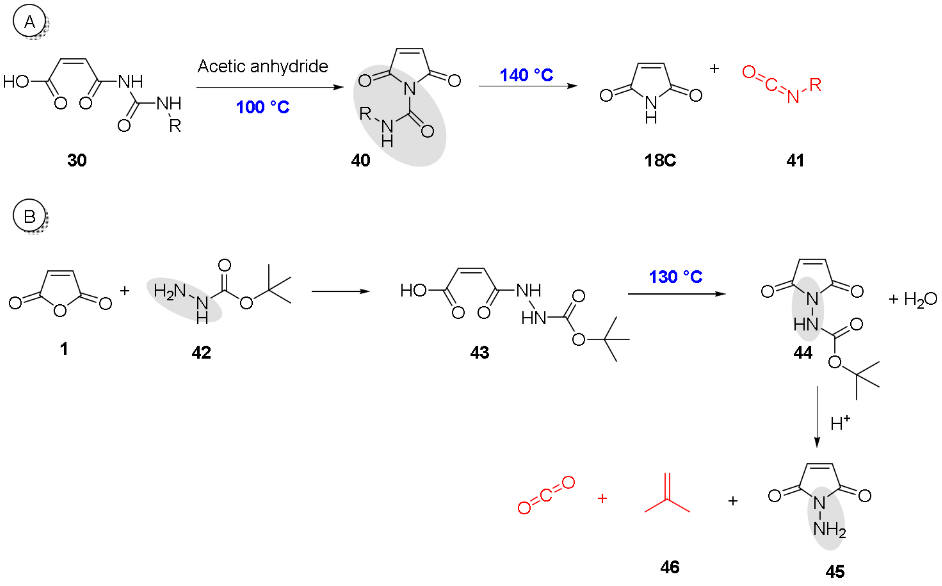


R	Mp (°C)	Y
H	89	85%
CO_2H	238	82%
NH_2	153	75%
OMe	146	78%

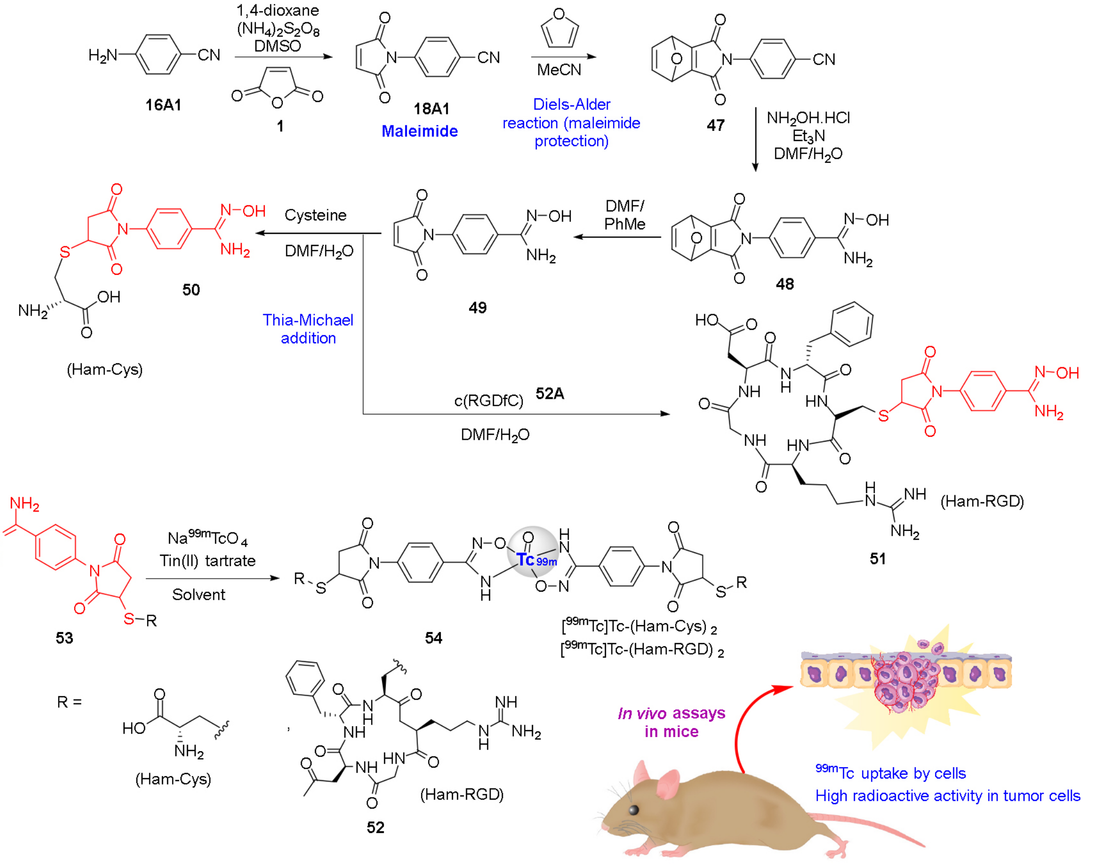
Scheme 19. Examples of maleimide synthesis in the literature[66, 99-102]

(99mTc). There was significant uptake of technetium by U87MG cells (cells with high expression of $\alpha_v\beta_3$). *In vivo* assays indicated high radioactivity in tumor cells of mice. This synthetic route (Scheme 21) also shows that maleimides are useful dienophiles in cycloadditions, since in the second step, the maleimide **18A1** reacts with furan via a Diels-Alder reaction. Additionally, maleimides are excellent Michael acceptors, and in this ligand synthesis, a thia-Michael reaction with cysteine on a maleimide is employed (product **50**).[103]

Schmidt and Eschig[100] developed a new two-step method for the synthesis of *N*-alkylated maleimides (**18B**). In the first step, maleic anhydride reacted with fatty amines to form maleamic acids, which were then converted into maleimides via intramolecular condensation under acidic conditions. At the end of the condensation/cyclization step, maleamic acids **17B** remained in the medium. These species were recovered and subjected to additional successive cyclization steps, achieving nearly 99% conversion to maleimides. The synthetic route followed by the authors has several benefits,



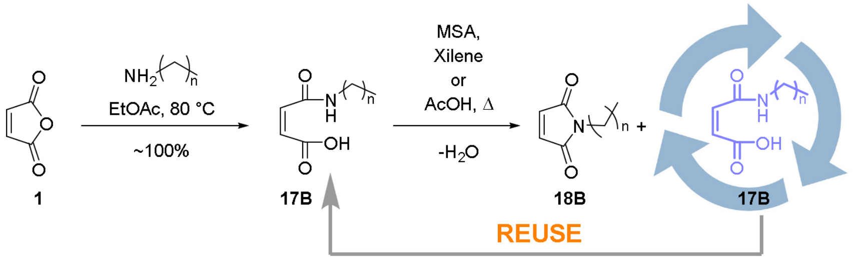
Scheme 20. Reaction of MA with ureas and hydrazides[5]



Scheme 21. Preparation of bidentate ligands and complexation with technetium (^{99m}Tc)[103]

including atom economy, easy identification, selectivity, excellent yields, and sustainability, since it repurposes an unwanted product to obtain the desired product. These characteristics enhance the value of the method compared to others cited by the researchers themselves. According to these authors, the presence of the *N*-alkylated maleimide group can confer various properties to the material, such as hydrophobicity, thermal stability and antibacterial activity, to name a few.

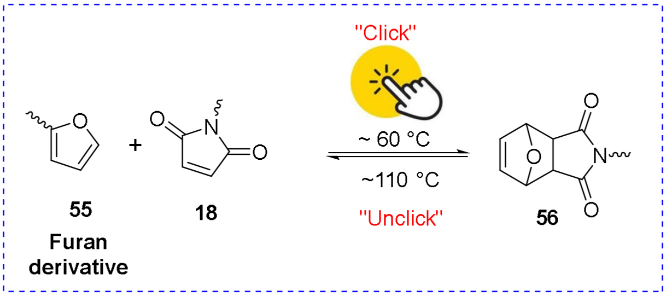
Various innovative materials can be prepared based on the thermal reversibility of Diels-Alder (**DA**) cycloadditions between furans **55** and maleimides **18** (Scheme 23).[104-106] The reversibility of these cycloadditions can be promoted by other stimuli, such as light, mechanical or magnetic force.



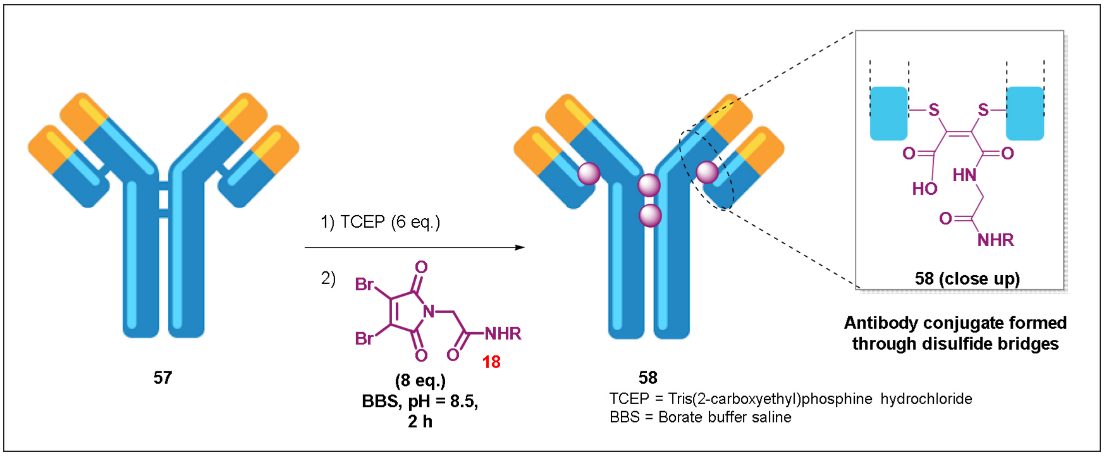
Scheme 22. Obtaining *N*-alkylated maleimides by reusing amic acids[100]

Additionally, various furans can be obtained from biomass, which is highly desirable from a sustainability vantage point.[107] The **DA** reactions are widely used in the design of self-healing polymers, since curing takes place at lower temperatures and reversion at relatively mild temperatures (100-140 °C). These reactions are called carbon-economy click reactions and are considered key reactions in the sense of carrying out chemical transformations towards a carbon-neutral society. Through these reactions, click networks are produced where polymers form crosslinks that can be remade "indefinitely". This type of dynamic or functional material has applications in soft robotics, recyclable adhesives and biomedical materials, for example. In addition, they can replace rubber made from conventional crosslinks, in which thermosetting ends up making them non-recyclable.[108-110]

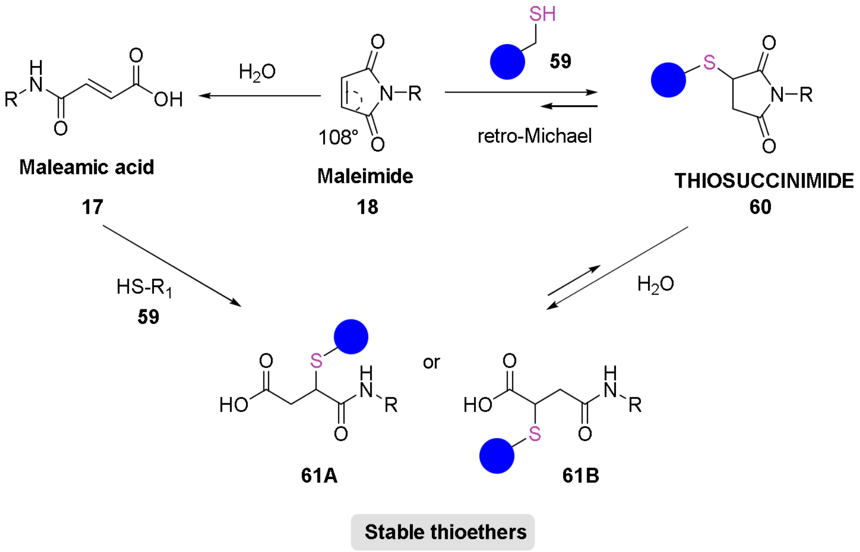
The generation of stable antibody conjugates **58** for *in vitro* and *in vivo* processes is of great interest for various biological applications. Maleimides offer many opportunities for generating these conjugates **58**,[111-113] for example through the formation of disulfide bridges[114] generated at specific sites on the antibody **57** that can be regenerated after being reduced in the process (Scheme 24).[115-117] Michael additions to maleimides **18** are the platform used to synthesize various bioconjugates for different purposes (Scheme 25). The reactivity of maleimides for Michael additions is superior compared to other electrophiles such as vinylsulfones, acrylates and vinylpyridines. The LUMO energy of maleimides is reduced by the imide system and undergoes the effect of ring tension, which gives the alkene even more reactivity. Michael additions to maleimides are also influenced by the type of thiol **59** and the solvent, for instance. Maleimides can be hydrolyzed to maleamic acids, and these do not undergo Michael addition under physiological conditions. The hydrolysis of thiosuccinimides **60** provides stable thioether-type bioconjugates **61** derived from succinamic acid.[118]



Scheme 23. Thermoreversible cycloaddition between furans and maleimides[104-106]



Scheme 24. Maleimide-based antibody conjugates[115-117]



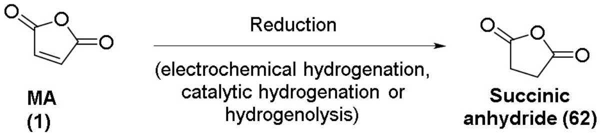
Scheme 25. Hydrolysis processes and Michael addition in the chemistry of maleimide-derived bioconjugates[118]

3.3. Reactions involving the double bond

3.3.1. MA reduction

The double bond of **MA** can undergo various reactions, such as hydrogenation, oxidation, addition, etc. Conjugation with the carboxyl of the anhydride makes the **MA**'s double bond electron deficient, activating it for nucleophilic additions. Reactions of maleic anhydride at the double bond lead to a diversity of industrial processes to make products used in agriculture, paints, varnishes, surfactants and lubricants, among others.[5,14]

The hydrogenation of **MA** and its derivatives can produce succinic anhydride **62** (Scheme 26) using hydrogen based on the catalysis of transition metals such as Ni, Pd, and Pt, as well as electrochemical methods. Since the products of this type of reaction are of great industrial importance, this point will be further expanded in the section on industrial applications.[5,14,119-123]



Scheme 26. MA reduction to succinic anhydride

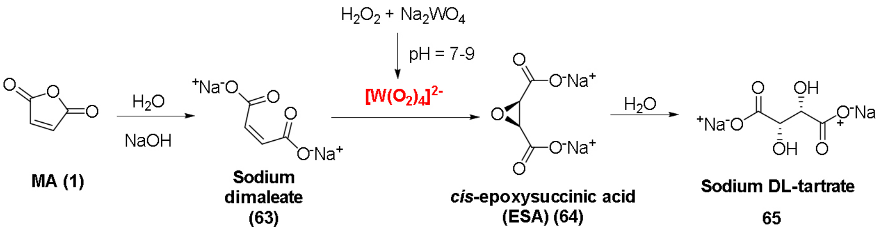
3.3.2. Oxidation

MA derivatives can undergo epoxidation, generating derivatives of *cis*-epoxysuccinic acid (ESA) **64** (CAS: 16533-72-5), a very important synthetic intermediate also used as a plasticizer and surfactant, which has interesting biological properties.[124-127] (Scheme 27). ESA is an intermediate in the preparation of DL-tartaric acid **65** and its derivatives.[128-131]

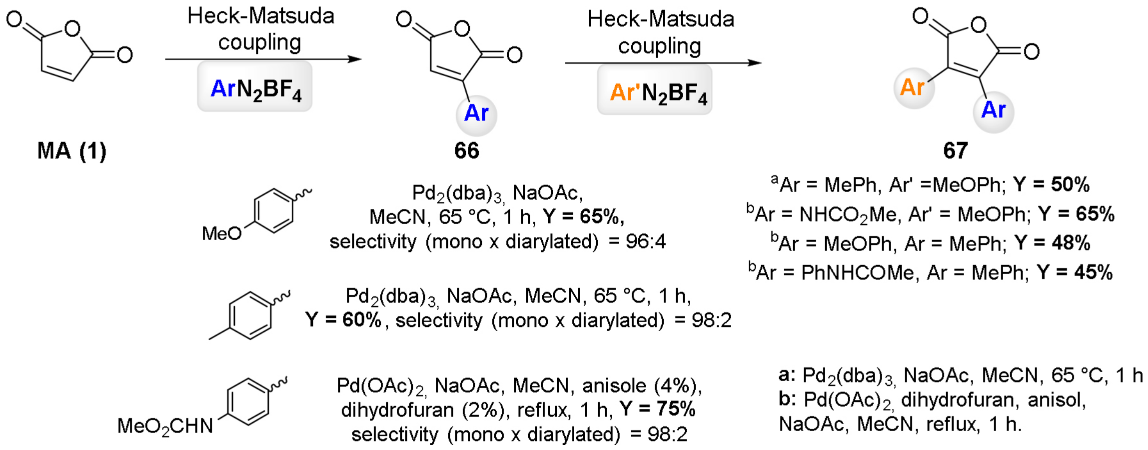
3.3.3. Halogenation/C-C coupling

The double bond of **MA** is reactive for palladium-catalyzed couplings, such as the Heck-Matsuda arylation reaction (Scheme 28). Through palladium-catalyzed Heck coupling, monoaryl **66** as well as symmetrical and asymmetrical diarylated anhydrides **67** can be obtained.[132] This approach provides alternative routes for the synthesis of important diarylmaleimides, such as polycitrins A and B. This class of bioactive compounds is found in natural products and is highly relevant in medicinal chemistry. Some examples of molecules containing a diarylmaleimide core with biological activity are the selective COX-2 inhibitor,[133] a nontoxic inhibitor of multidrug-resistant cancer cells, and HIV integrase inhibitors (Figure 11).[135]

Beccalli and co-workers[136] reported the first synthesis of the diaryl substituted maleimide polycitrin B in eight steps. Taking advantage of the possibility of C-C coupling, in 2013 Canto *et al.*[91] proposed a new and more concise synthetic route (Scheme 29).[91] In this route, the researchers were able to arylate **MA** through the Heck-Matsuda reaction



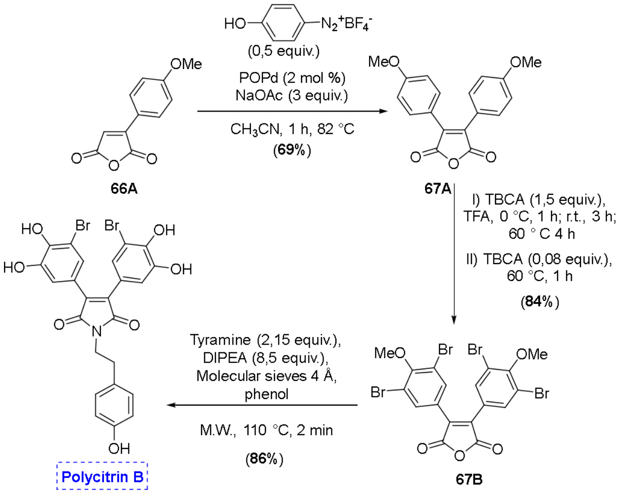
Scheme 27. Route for obtaining tartaric acid derivatives from MA[124-127]



Scheme 28. Heck-Matsuda coupling with MA[132]

using arenediazonium tetrafluoroborates, thus obtaining symmetrical and asymmetrical diarylmaleic anhydrides. The final step of the synthesis, in this case, involved converting the **MA** core into maleimide through the reaction of diarylated maleic anhydride with tyramine under microwave irradiation. Therefore, more complex diaryl maleimides could be synthesized in just thre steps. However, this method could not be extended to the synthesis of maleic anhydrides or heteroarylated maleimides due to the difficulty in synthesizing heteroarenediazonium tetrafluoroborates.

Another way to functionalize maleimides is through the Suzuki-Miyaura C-C coupling reaction. In this reaction, maleic anhydride or halogenated maleimide (I or Br) **68** can react with aryl or heteroaryl boronic acids **69** in the presence of palladium and a base. In the case of some heteroarylboronic acids, it was reportedly necessary to perform prior esterification in order to obtain satisfactory yields (Scheme 30).[137] Regarding the halogenated species, Viaud-Mossuard and colleagues observed an increase of about 15% in yield when iodinated maleimides were used rather than brominated species.[138]

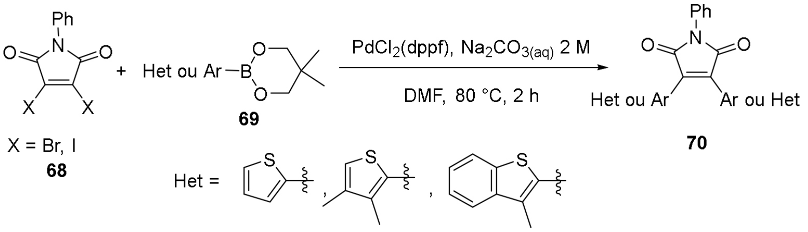


Scheme 29. Synthesis of polycitrin B by Heck-Matsuda couplings[91]

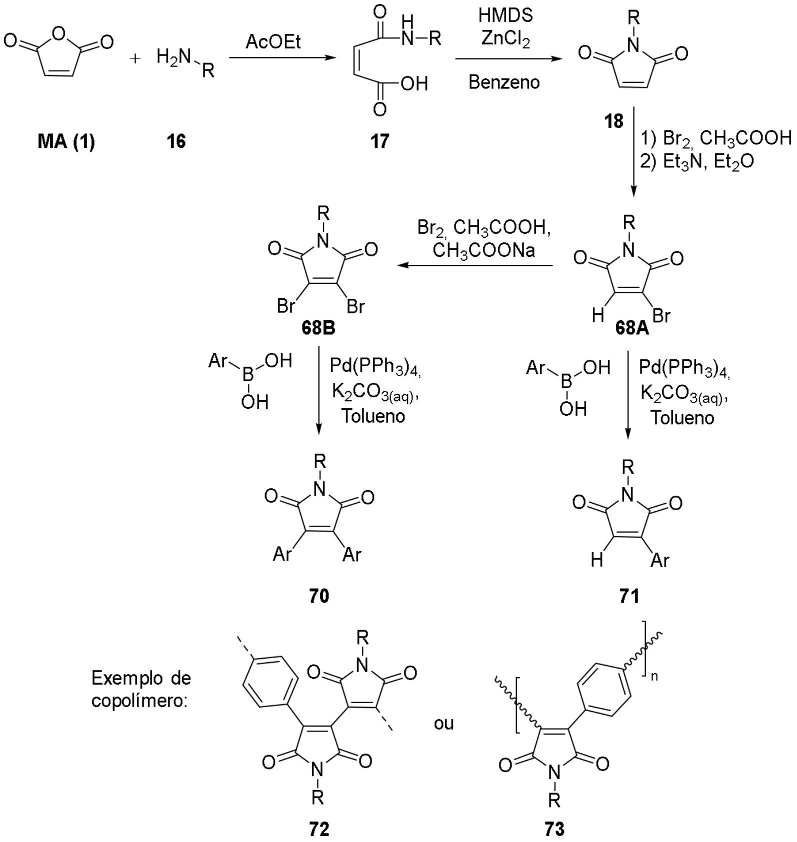
Oishi and colleagues achieved the transformation of maleic anhydride into *N*-substituted maleimides, either mono- or di-brominated, which then underwent a Suzuki-Miyaura coupling reaction, obtaining mono- **71** and di-aryl maleimides **70** (Scheme 31). The *N*-substituted di-brominated maleimides were obtained in two steps. The first step involved bromination in acetic acid of the double bond, followed by dehydrobromination in the presence of a base, forming the 2-bromo-*N*-substituted maleimide. Subsequently, the monobrominated maleimide **68A** was treated with bromine in the presence of sodium acetate to obtain the 2,3-dibromo-*N*-substituted maleimide **68B**. Both were subjected to the Suzuki-Miyaura coupling reaction with arylboronic acids, using Pd(PPh$_3$)$_4$ as a catalyst and K$_2$CO$_3$ as a base. These structures were used in the synthesis of copolymers with fluorescent properties (**72** and **73**).[139] It was observed that the photoluminescence and the electronic state of the maleimide derivatives depended on the Ar group used, the nitrogen substituent, and the copolymer sequence.

3.3.4. Hidratation at the double bond

In water, maleic anhydride undergoes hydrolysis to form maleic acid, which can be further hydrated at high



Scheme 30. Synthesis of heteroarylated maleimides from boronic acid esters



Scheme 31. Suzuki reaction with dibrominated maleimides

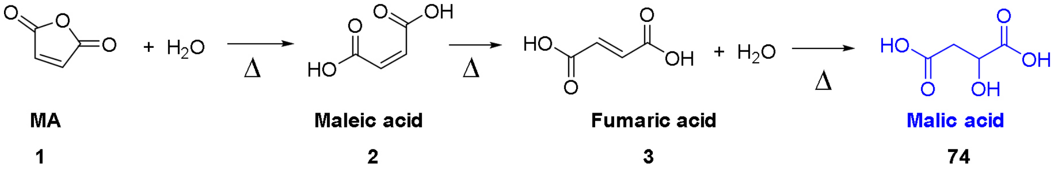
temperatures (160-220 °C) under pressure in a corrosion-resistant reactor, yielding a racemic mixture of malic acid (Scheme 32, **74**).[140] The latter acid is commonly found in fruits such as apples, grapes, cherries and apricots. The racemic mixture of malic acid can be resolved through the crystallization of diastereoisomeric salts of malic acid with cinchonine.[5,14] In cases where enantiomerically pure or enriched malic acid is required, biocatalysis is employed using either immobilized fumarate hydratase or microorganisms that possess this enzyme (such as *Brevibacterium ammoniagenes* or *Saccharomyces cerevisiae*). L-malic acid is the natural enantiomer present in organisms (from bacteria to humans), while D-malic acid is physiologically less assimilable. For this reason, racemic mixtures of malic acid cannot be used as food additives in products sold for consumption by children.[141] Maleic acid was first obtained from the decomposition of malic acid.[5,14]

Alcohols react with **MA,** mainly producing esters, which in the presence of strong bases such as alkoxides, can add to the double bond.[5,14] Amines also primarily react with the anhydride portion of **MA**, rather than adding to the double bond.[142] Maleimides, on the other hand, are more reactive towards aza-Michael type reactions.[143-145]

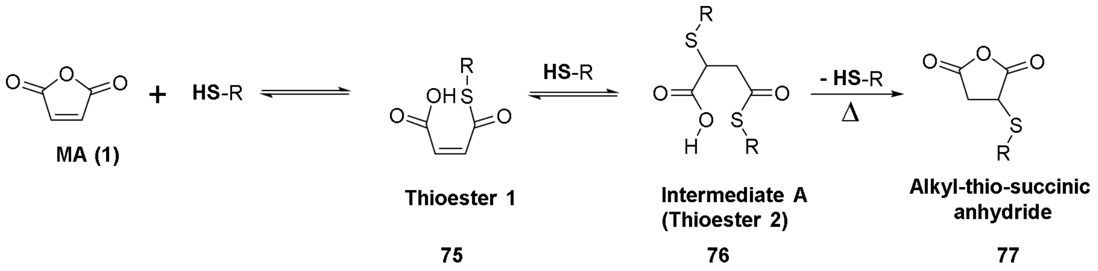
3.3.5. Addition of sulfur nucleophiles

Thioesters of maleic anhydride can be obtained through reactions with thiols. However, reactions of maleic anhydride with thiols can generate mixtures of products, since the double bond of maleic anhydride is highly reactive to sulfur nucleophiles. The thioester intermediates **75** (intermediate A) are quite labile, and the reaction can be thermodynamically directed towards the formation of the *S*-alkylation product **77** (Scheme 33). Base-catalyzed sulfur nucleophile additions are very useful synthetically and are known as thiol-ene reactions (Scheme 34).[5,146,147]

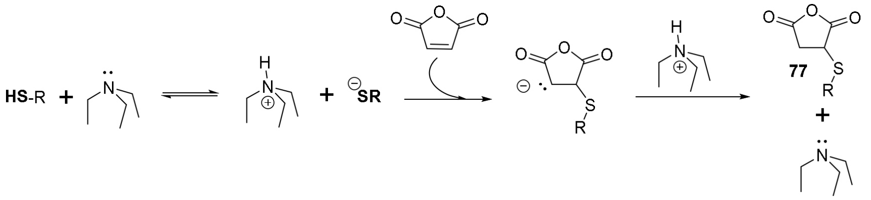
Maleic anhydride and its derivatives, such as maleimides, are widely used in proteomics. The amino-terminal unit of proteins (from lysine residues, for example) can interact with the anhydride, generating maleamic acids or maleimides. The conjugated double bonds of maleic anhydride and its derivatives can interact with thiol units of proteins.[148] Some examples of this type have already been mentioned



Scheme 32. MA hydrolysis to malic acid



Scheme 33. MA reaction with thiols[5]

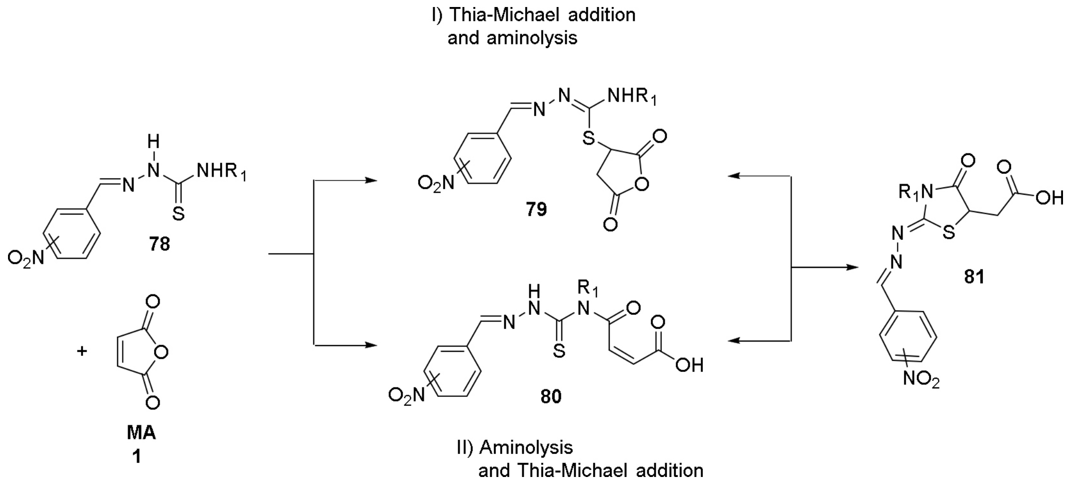


Scheme 34. S-alquilation of MA in basic medium[5]

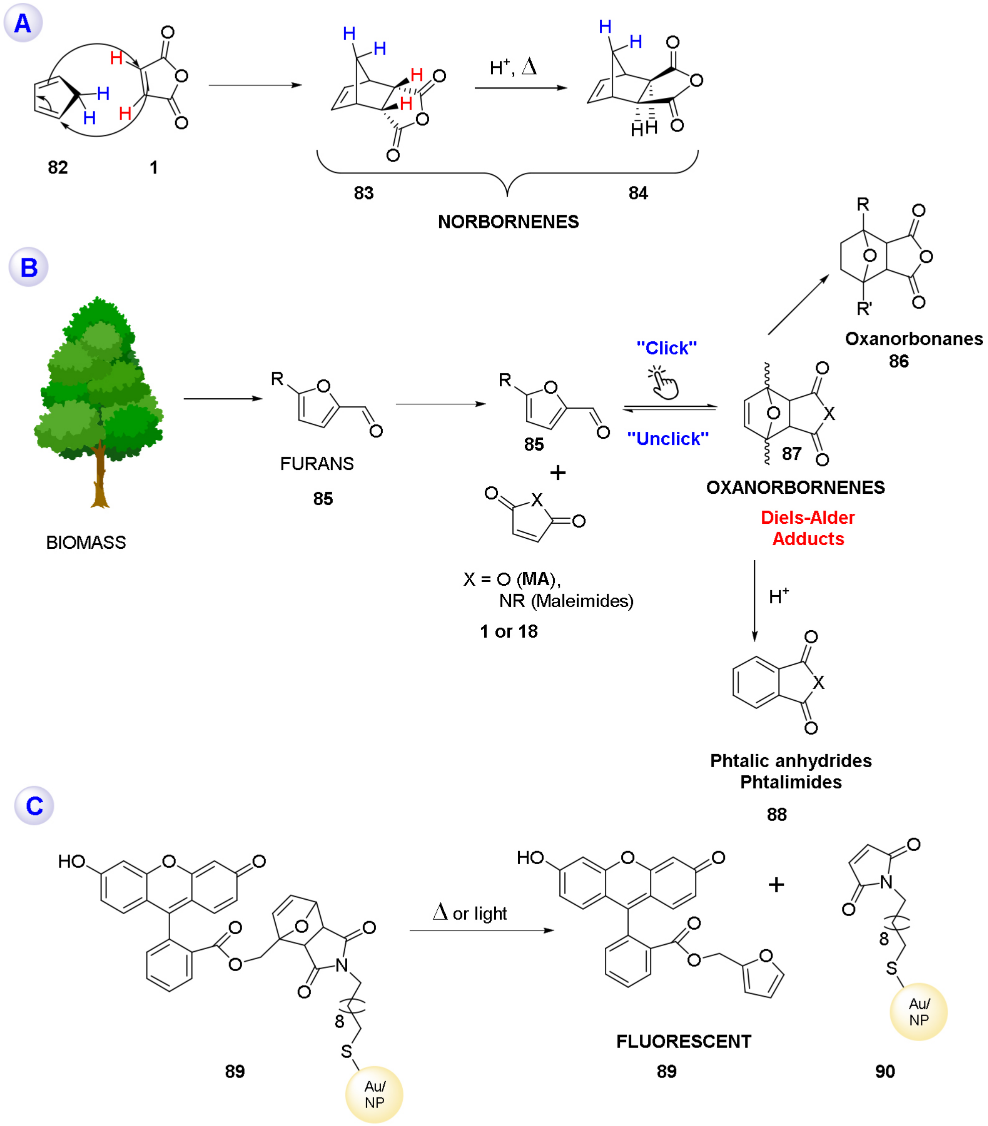
in the section on reaction with amines (amidations). An interesting application of 1,4 addition of sulfur nucleophiles is the preparation of heterocycles such as thiazolidin-4-ones **81**. Thiosemicarbazides are in equilibrium between two tautomeric forms (thiol/thione). Thiols can add to the double bond of maleic anhydride (Scheme 35).[149] Many of these heterocycles prepared from maleic anhydride have shown interesting biological activities, such as against *Toxoplasma gondii*, a protozoan parasite that causes toxoplasmosis.[150-154]

3.3.6. Diels-Alder and Alder-ene reactions

Diels-Alder (**DA**) reactions, also known as [2 + 4] cycloaddition reactions, occur between a diene (a 4-electron π-system) and an alkene or alkyne (a 2-electron π-system, dienophile), resulting in a cyclic product. Examples of dienophiles that can be used in **DA** reactions include alkenes, alkynes, allenes, and benzynes. If one of the components, either in the diene or in the dienophile, is different from carbon, the reaction is termed hetero-Diels-Alder.[155] In 1950, this discovery earned a Nobel Prize for the researchers O. Diels and K. Alder, who correctly identified the structure of the cycloadduct formed in the reaction between *p*-benzoquinone and cyclopentadiene.[156] It is among the most widely employed reactions in organic synthesis due to its peculiar characteristics: 1) simultaneous generation of two C-C bonds; 2) regioselectivity; 3) stereospecificity; 4) possibility of simultaneously forming 4 stereogenic centers; and 5) possible enantioselectivity with the appropriate chiral catalyst. **MA** is considered an excellent dienophile in **DA** reactions because the electron-withdrawing effect of the carboxyl group in the anhydride makes it more reactive to the diene. In general, the kinetic product is the *endo* cycloadduct, while the *exo* product is thermodynamically favored, for cyclopentadiene as well as furans, thiophenes and pyrroles.[5] The product of the reaction with cyclopentadiene is a norbornene (Scheme 23A), while with furan it is an oxanorbornene (Scheme 36A). The latter compound is very useful for generating a series of important industrial products such as phthalic anhydride and phthalic acid. Additionally, these products are structural analogs of bioactive terpenes like cantharidins. Maleimide derivatives of **MA** can also provide the cycloadducts, which



Scheme 35. Thiazolidin-4-one synthesis through MA reaction with thiosemicarbazones[149]

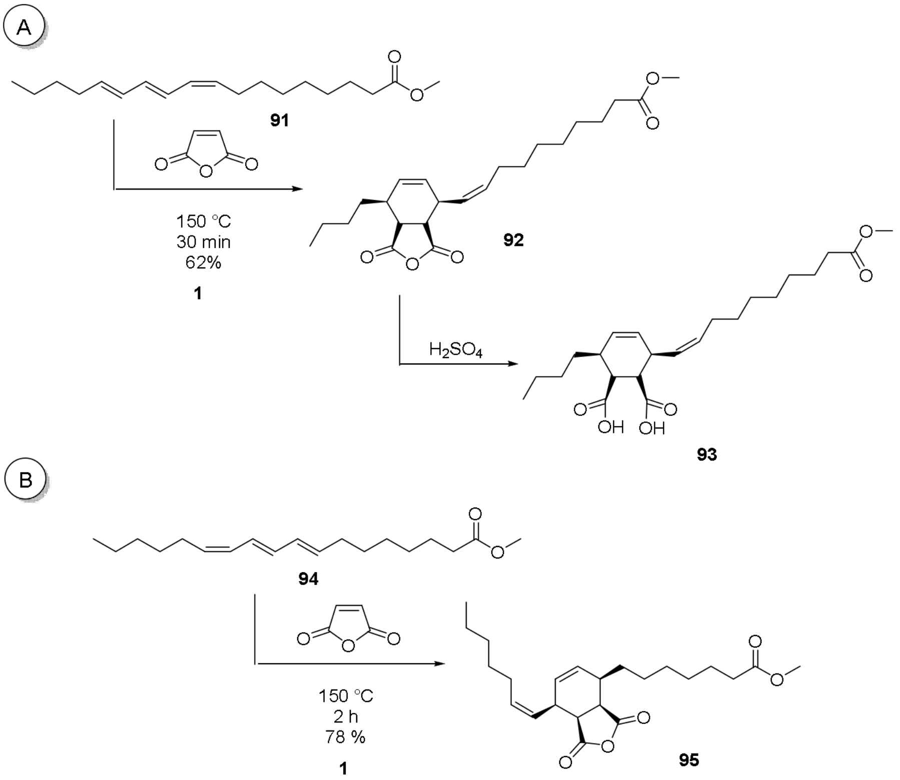


Scheme 36. Diels-Alder reactions with MA[5,157]

can be transformed into phthalimides. These **DA** reactions between **MA** or maleimides and furans are very useful in various fields, mainly because furans are an important platform for obtaining compounds of interest from biomass. Furthermore, these **DA** reactions are reversible, a feature that is important in the construction of dynamic molecular architectures capable of responding to stimuli such as light, heat, etc. Furans from biomass can undergo **DA** reactions with **MA** or maleimides, producing interesting materials for the pharmaceutical, polymer and bioconjugate fields, to name a few examples.[157-162] Some examples of applications are shown in Scheme 36.

The fatty acids present in biomass have conjugated double bonds that can react via Diels-Alder cycloaddition with maleic anhydride.[163] Metzger and colleagues studied the regio- and stereo-selectivity of Diels-Alder reactions between maleic anhydride **1** and conjugated trienes present in the seed oil of *Calendula officinalis* L., methyl calendulate **94**, and methyl α-eleostearate **91**, an oil abundant in the nuts of the Tung tree (Scheme 37).[164] The Diels-Alder reaction with calendulate **94** forms the *endo* adduct **95** through carbons C8 and C11, retaining the *Z* configuration of the double bond (C12). Methyl α-eleostearate **91** also reacts with maleic anhydride **1**, yielding the *endo* product **92** by reacting with the conjugated *E* double bonds while retaining the *Z* double bond at C9. The *endo* product **92** was hydrolyzed to **93**. Both reactions occurred with high regio- and stereo-selectivity.

Another example of the application of the Diels-Alder reaction with **MA** is the modification of activated carbon **96** (Scheme 38). This material is composed of polycyclic aromatics that can act as dienes in the Diels-Alder reaction. Porous carbon materials are very useful in gas storage and catalysis, among other applications. When carboxylic groups are present, functionalizing these materials, they become very interesting in catalysis, being used in the oxidation of methanol and the hydrolysis of cellulose, among others. The reaction of polyaromatics with **MA** **1** as a dienophile,

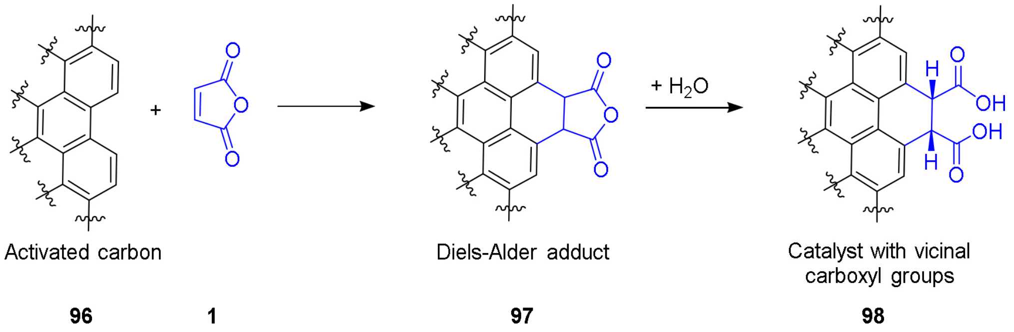


Scheme 37. Diels- Alder reaction with vegetable oil trienes[164]

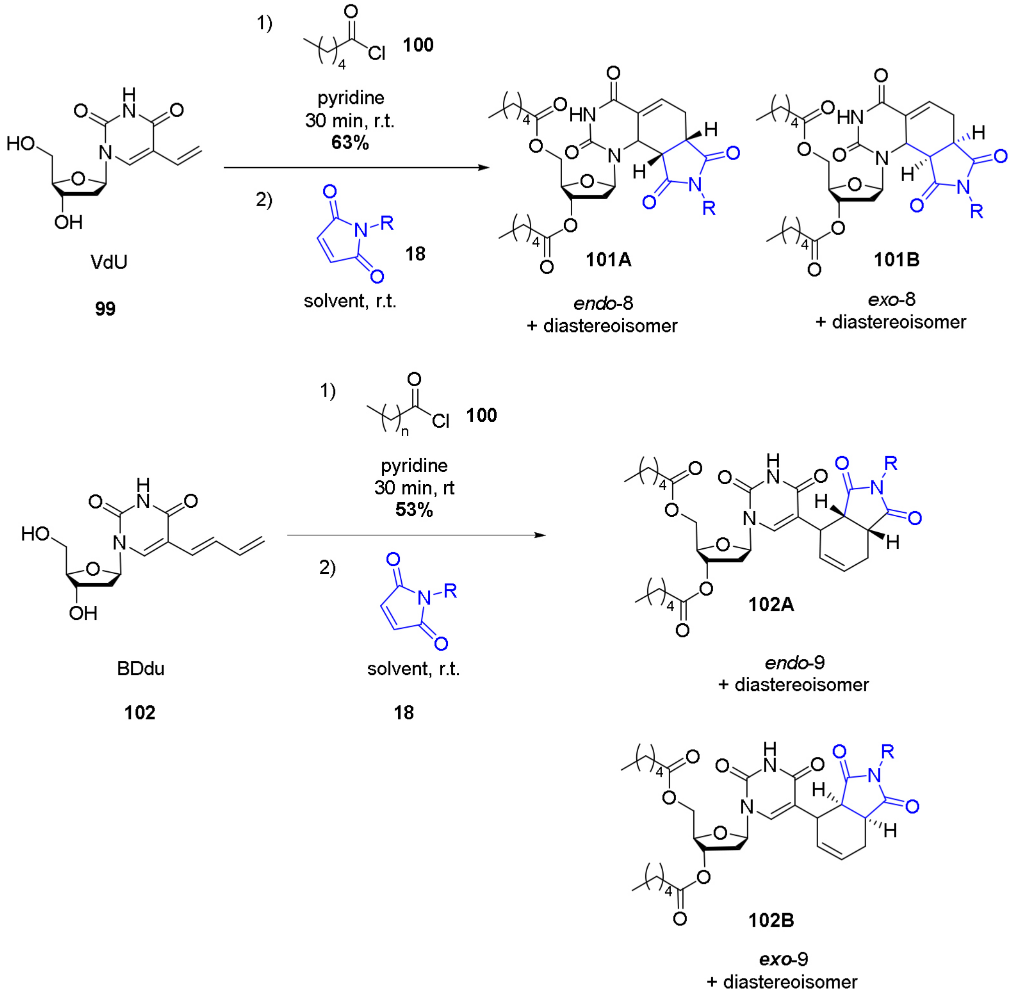
followed by the hydrolysis of the succinic anhydride unit of the cycloadduct **97**, can generate carbon materials containing carboxyl units as useful catalysts **98** (Scheme 38).[165]

Maleimides are widely employed in cycloadditions. Basran and co-workers[166] studied bioconjugation reactions involving maleimides **18** and modified nucleosides of the uracil base (5-(vinyl)-2'-deoxyuridine (VdU, **99**) and 5-(1,3-butadienyl)-2'-deoxyuridine (BDdU, **102**)) (Scheme 39). The resulting DNA double strands acquired fluorescence, allowing the labeling of cells to visualize biological processes at the molecular level. The authors suggested that the reaction proceeds through a highly polarized transition state and/or a zwitterionic intermediate, since the reactions were accelerated in the presence of polar solvents. Regarding the stereochemistry of the bioconjugation products, reactions with VdU resulted predominantly in *exo*-type products **101B**, while reactions with BDdU predominantly yielded *endo*-type products **102A**. Metabolic labeling studies in HeLa cells were efficient because when the bioconjugation product was incorporated into DNA, fluorescence occurred.

Platts *et al.*[167] explored Diels-Alder reactions between maleimide **104** and pentafulvene **103** in buffer systems at different pHs (Scheme 40), aiming to understand the stability of the reagents, especially maleimide, which is susceptible to hydrolysis, along with the efficiency, reaction rate of cycloaddition and product stability. According to the authors, this knowledge is crucial for the development of application strategies in biological systems. Among the potential applications of these products in biological systems are bioconjugation, protein labeling and preparation of therapeutic conjugates, among others. Pentafulvene showed great stability, even at more acidic pH values (3.5) after 1 hour in contact. Maleimide was stable only in acidic buffers. In neutral and basic buffers, the maleimide group began to hydrolyze, which was not the objective of the study. The



Scheme 38. MA cycloadditions for porous carbon material modification

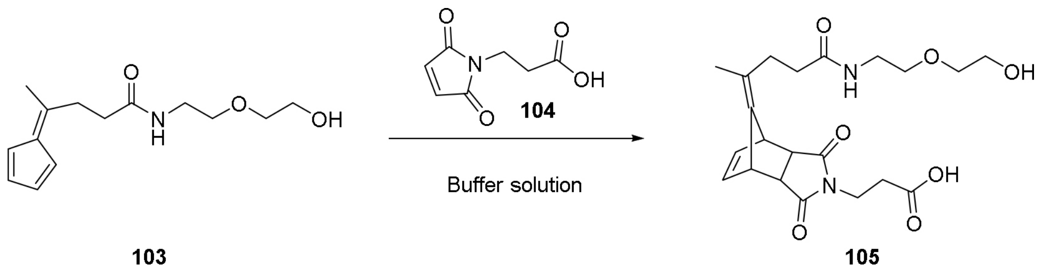


Scheme 39. Diels-Alder reactions between MA and modified nucleosides of the uracil base

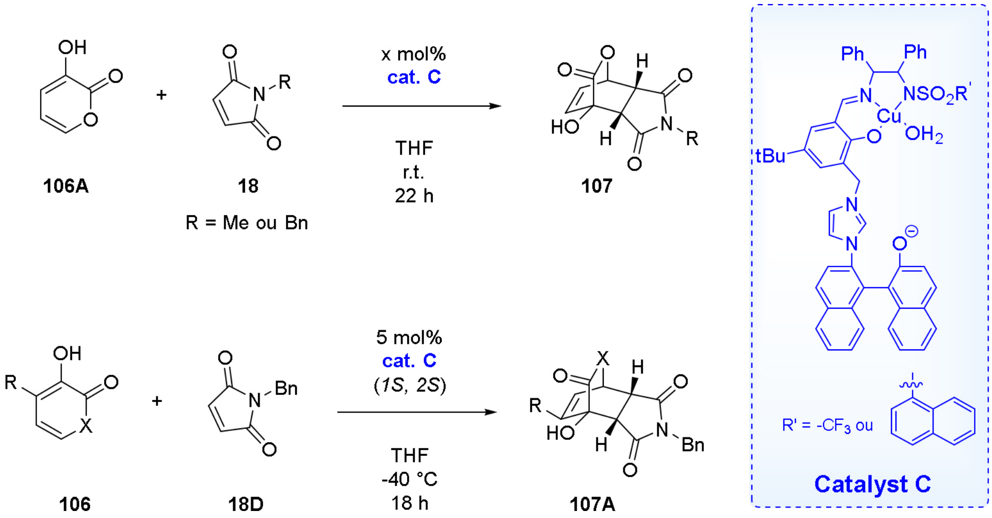
acidic range of the pH scale was found to be the best for the reaction to proceed. The *exo* products **105** were predominant and showed stability in acidic aqueous solutions, with no evidence of hydrolysis or retro-Diels-Alder reactions for at least 24 hours. These results indicated that the products are stable under conditions similar to those of biological systems.

Vukoslava *et al.*[168] explored maleimide as a dienophile in an innovative synthetic route for the preparation of six-membered cycles with high enantioselectivity and stereospecificity, using zwitterionic Lewis acid catalysts (Scheme 41). The reaction yields were above 90%, resulting in diastereopure cycloadducts **107** with high enantiomeric selectivity.

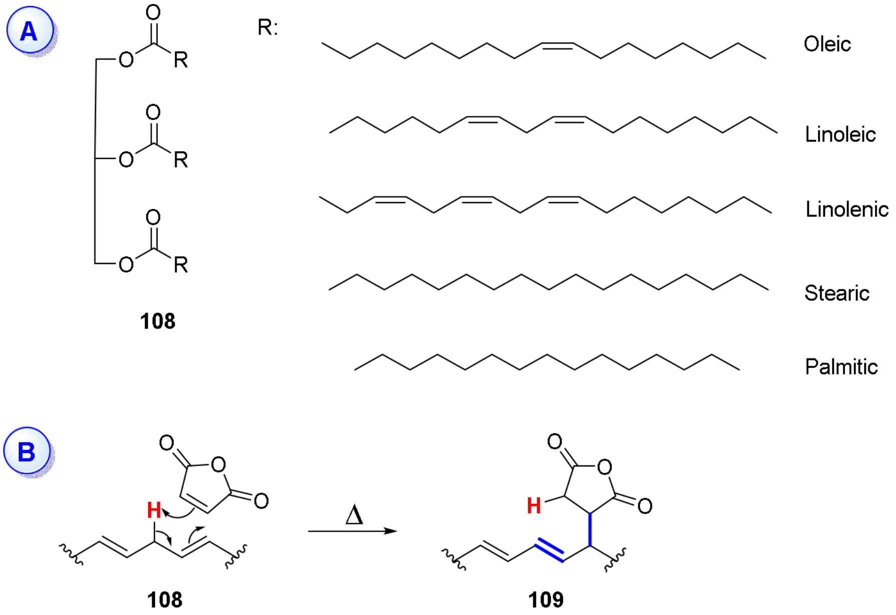
The Alder-ene reaction is a type of pericyclic reaction involving four electrons, occurring between an alkene and a C-H bond of an allylic system, with the displacement of the C=C bond. The allylic system is termed the enophile, analogous to the dienophile in the **DA** reaction. Typically, these reactions require high temperatures to promote the cleavage of the allylic C-H bond and fulfill the stereochemical requirements for the reaction. Maleic anhydride **1** can also participate in Alder-ene reactions, interacting with allylic systems **108** (Scheme 42). Like Diels-Alder additions, Alder-ene reactions with **MA** are employed for the valorization of vegetable oils. Indeed, this is considered a sustainable route for obtaining alkene-



Scheme 40. Diels-Alder reaction between MA and pentafulvene



Scheme 41. Diels-Alder reaction of 3-hydroxy-2-pyrones and maleimides



Scheme 42. Alder-ene reaction with MA and common fatty acids in oils

substituted succinic anhydrides **109**. Highly functionalized maleated oils have various industrial applications, serving as crosslinking agents or monomers for the synthesis of novel polyesters, food additives and adhesives, among others.[169,170]

3.3.7. Polymerization

Maleic anhydride can polymerize both through reactions at the double bond and at the anhydride unit. Since the polymers produced are of significant industrial interest, polymerization reactions will be discussed in the **MA** applications section.

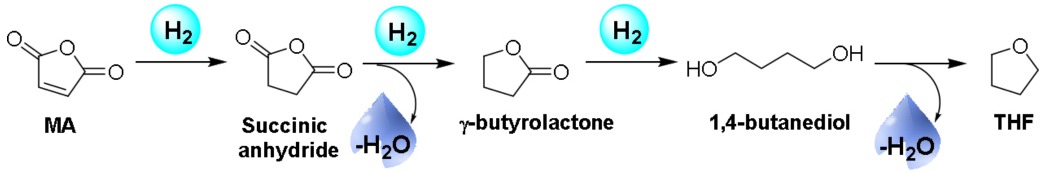
4. Applications

Due to the reactivity of maleic anhydride, it can be transformed into various other interesting substances, serving as a raw material in the synthesis of several compounds of interest in areas such as food, agriculture, pharmaceuticals and polymers, among others.[5]

4.1. Production of industrially important products

Hydrogenation and hydrogenolysis of maleic anhydride **1** can be used to obtain succinic anhydride **62**, g-butyrolactone **110**, tetrahydrofuran **112** (THF), and 1,4-butanediol **111** (Scheme 43). These products are important from an industrial point of view.

Maleic anhydride has various industrial applications, such as in the production of alkyd resins,[171,172] paints and coatings,[173,174] plasticizers,[175,176] and unsaturated polyesters,[177,178] among others. g-Butyrolactone **110** also has various applications. It is an important intermediate in the production of other chemicals, such as g-hydroxybutyric



1 **62** **110** **111** **112**

Scheme 43. MA hydrogenation/hydrogenolysis products

acid (GHB), which is used as an anesthetic and as a medication to treat narcolepsy and insomnia. It can also be used in the production of 1,4-butanediol **111** and tetrahydrofuran **112** (THF).[179] Additionally, g-butyrolactone **110** is also used in the production of polymers, such as poly(4-hydroxybutyric acid), which is a bioplastic with properties similar to polyethylene. This bioplastic can be used in various applications, such as in general packaging,[180] food packaging, toys and automotive parts.[181,182]

THF **112** is an important solvent in organic synthesis, widely used for the production of pharmaceutical intermediates,[183,184] surface treatment agents, adhesives and sealants.[185-187] Several substances are miscible in THF,[188,189] enabling performance of chromatographic analyses of rubber using THF as the sample solvent.[190,191]

1,4-Butanediol **111** is an organic compound that is industrially used as a solvent and the manufacture of certain types of plastics and elastic fibers.[192,193] It can also be used for the synthesis of g-butyrolactone **110** (GBL).[193] 1,4-Butanediol is a chemical intermediate used in the production of thermoplastic polyurethane (TPU), which is also utilized in the manufacture of synthetic leather shoe soles.[194,195]

4.2. Polymer preparation

Maleic anhydride can also be polymerized, both through addition and condensation reactions (Scheme 44). In addition polymerization (Scheme 44A), alkenes are employed as monomers, where the double bonds serve as reactive sites for chain growth. On the other hand, in condensation polymerization (Scheme 44B), the monomers have other functional groups that, upon interaction, eliminate a small molecule such as water, alcohol, ammonia, etc.[14]

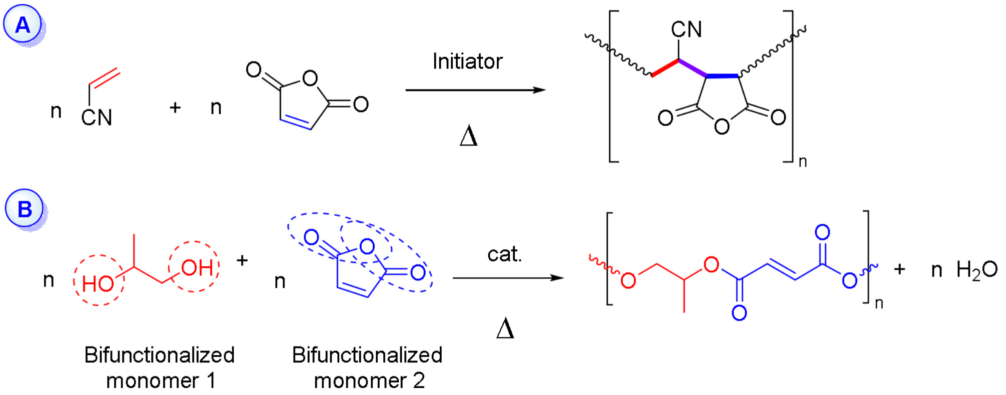
Until the 1960s, it was believed that **MA** did not form addition homopolymers due to the steric hindrance and polar effects present in the molecule. The presence of **MA** was still an indicator that these factors delayed or prevented the homopolymerization of 1,2-disubstituted olefins. However, in the late 1960s, appropriate conditions for the production of poly(maleic anhydride) **113** (CAS: 24937-72-2) (Scheme 45) began to be reported.[196-198] Examples were the use of irradiation with energy in the gamma ray and ultraviolet (UV) regions, employing pyridines under high pressure or even radical reaction initiators.[14,199]

With the advancement of polymer science, other polymerization methods have been developed for the production of poly(maleic anhydride), such as the use of bases, transition metals[200] and radical initiators in the presence of photosensitizers.[201-209]

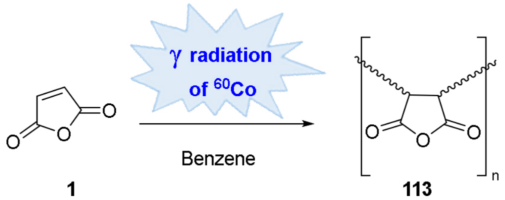
The functionalization of the anhydride group in the homopolymer chain through hydrolysis **116**, esterification **117**, amination **115** and imidation, for example, allows the preparation of a series of derivatives with different properties and potentials for various applications (Scheme 46).[210-112]

There is a wide range of applications for poly(maleic anhydride) and its derivatives, which can be used in coatings to counteract formation of scale and rust, to name a few applications.[213,214] Poly(maleic anhydride) **113** and its derivatives also have applications in fiber adhesives, additives for mechanical cleaning, detergent builders, and pigment dispersion agents.[5,215] These derivatives also have potential uses as bactericides and virucides.[5,215]

Unlike homopolymerization of **MA**, which requires more stringent conditions, copolymerization of this anhydride can occur with a variety of monomers.[216] Copolymers of **MA**

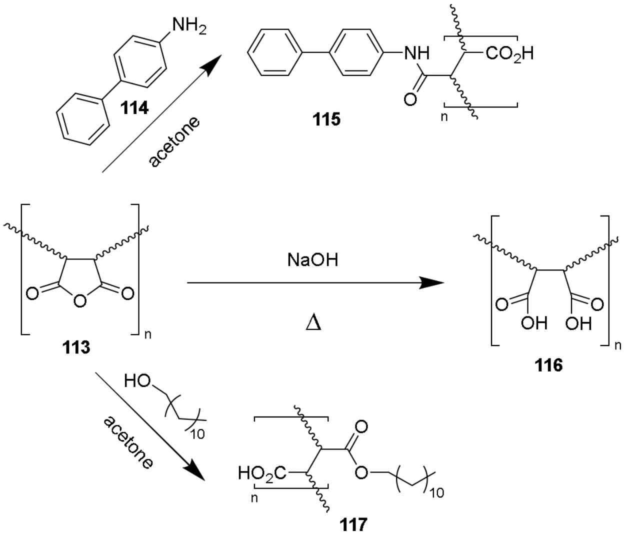


Scheme 44. Addition and condensation polymerizations of MA. In (A), addition polymerization between acrylonitrile and MA, and in (B), polymerization between propylene glycol and MA.



1 **113**

Scheme 45. Preparation of the homopolymer poly(maleic anhydride) using gamma ray energy.



Scheme 46. Obtaining new polymeric derivatives through functionalization of poly(maleic anhydride)

with olefins such as styrene, ethylene, acrylates, vinyl esters, and other types of monomers are well known and widely explored in the literature (Figure 12).[217-223]

The presence of **MA** in the polymer chain of these copolymers allows a series of functionalizations, providing great versatility to the resulting polymers.[224-227]

Poly(ethylene maleic anhydride) and its derivatives are excellent dispersants. They also have applications in the petroleum industry and as additives in fuels and lubricating oils. When applied as additives of oil well drilling fluids, they help reduce water loss in the filtration process and act as viscosity controllers.[228,229]

They can also be used as enteric coatings for medications (delayed release) or as drug delivery systems, proving useful in combating viral infections in animals and even inhibiting tumors and infections when present in vaccines.[5,230-233]

Isobutylene and **MA** copolymers have uses in adhesives, paints, and bonding agents, where they are effective dispersants. They can also be employed as stabilizers in emulsion polymerization reactions, water-based binders for ceramic powders, binders for fiberglass, lubricants for forging and casting, and hardening agents. In agriculture, these copolymers are highly effective to prevent soil aggregation.[5,233,234]

Poly(butadiene-maleic anhydride) and its derivatives can be used in surface coatings, acting as corrosion inhibitors, adhesives, and binders.[14,235-237]

Copolymers of acrylic acid with maleic anhydride along with their derivatives have applications in textiles, as chelating dispersants, in dental materials and cosmetics, as viscosity regulators, in surface protection and adhesive formulations, among others.[14,238-240]

These polymers also are useful in the composition of electrolytes for batteries and as stabilizers, antistatic agents and drug carriers.[14,241-243]

Poly(acrylonitrile-maleic anhydride) polymers are useful as polyelectrolytes, soil conditioners, resin additives, antistatic additives, ion exchange resins, and sizing agents in the textile industry.[14,244-246]

Among the monomers copolymerized with **MA**, styrene stands out due to the wide range of applications of the resulting copolymer, which is called poly(styrene-co-maleic anhydride) or SMA (Figure 13). Copolymerization reactions of styrene with **MA** typically occur at temperatures between 40-100 °C, in the presence of radical initiators such as organic peroxides or azobisisobutyronitrile (AIBN) in aromatic hydrocarbons.[14,247,248]

One of the major applications of SMA is in the coating sector. Materials coated with SMA resins exhibit corrosion resistance, [249,250] and these resins can also be used as substitutes in bonding processes, as binders for paints, and as resins for papermaking. SMA and its derivatives also are utilized in leather tanning processes and the production of packaging that comes into direct contact with food.

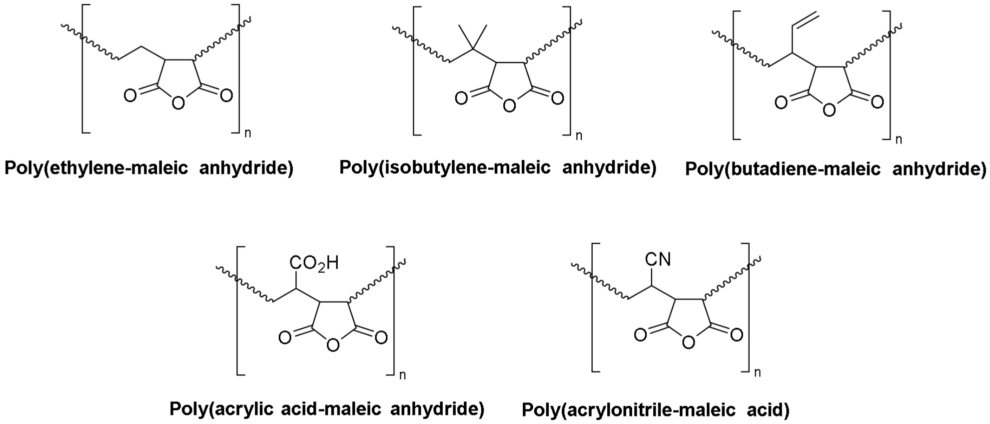


Figure 12. Structures of some copolymers of MA with olefins

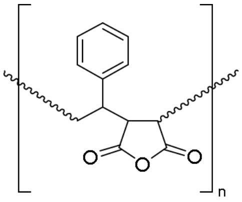


Figure 13. Structure of poly(styrene-co-maleic anhydride) (SMA)

Finally, electrolytes prepared with SMA can be used in the purification of wastewater (by isolating viruses and heavy metal ions) and as agents for coagulating petroleum emulsions.[14,251,252]

Medical and pharmaceutical applications for SMA copolymers have also been reported,[253-257] for example in controlled drug release systems or serving as a male contraceptive.[258,259] Furthermore, anti-HIV-1 activity has been reported.[260,261] To control the effects of diabetes mellitus, oral administration of insulin is highly desirable. However, to make this feasible, it is necessary to overcome the possibility of rapid degradation of insulin in the stomach, as well as improve its intestinal absorption so that it effectively reaches portal circulation. Oral administration of insulin is a convenient and safe physiological route for controlling diabetes mellitus. Bahman and colleagues studied a SMA micelle system for insulin administration in an animal model. They observed that this system was able to promote hypoglycemic effects 3 hours after administering a single dose. They concluded that SMA micelles can enhance the effectiveness of oral drug delivery systems.[262] SMA polymers can also be used in the enteric coating of medications.[14,263,264]

In the case of condensation polymers, **MA** can form unsaturated polyesters. These polyesters **119** result from the combination of acids, acid chlorides, or organic anhydrides such as **MA**, with a glycol **118** (Scheme 47).[14,215,263]

Among the commonly used glycols in the preparation of these polymers are ethylene glycol **118**, propylene glycol, dipropylene glycol, 2,2,4-trimethyl-1,3-pentanediol glycol and bisphenol A.[14,215,265]

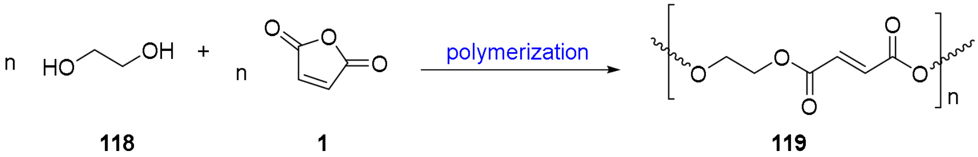
Some catalysts have been described in the literature to produce unsaturated polyesters from **MA** with faster processing. These catalysts are chosen not only for their shorter reaction time, but also for their ability to produce substances with high molecular weight. Recommended catalysts include tetrabutyl titanate, tetrabutyl zirconate, mixtures of stannous oxalate, tributyltin hydroxide, sodium acetate, and tin compounds such as stannous chloride, stannic chloride, and dibutyltin oxide.[14,265]

It's also possible to obtain unsaturated polyesters **121** using the reaction of cyclic ethers **120** with **MA** (Scheme 48). The replacement of glycol with cyclic ethers results in faster reactions. Additionally, the starting cyclic ethers **120** used in the polymerization, such as ethylene oxide and propylene oxide, are cheaper than their corresponding glycol.[14] A wide variety of catalysts have been studied, such as $LiCl_2$, $ZnCl_2$, $Mg(OEt)_2$, and a large number of zinc, magnesium, chromium, cobalt, manganese, iron, aluminum, and nickel coordination compounds.[14,266-268]

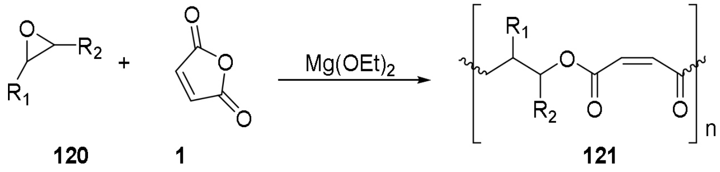
It is also interesting to have fumarate residues in the polymer structure **122** or the isomer of maleate **121**, because this contributes to increase the hardness, distortion temperature, viscosity and lifespan of uncured resins. Several studies have focused on the development of conditions for isomerization, and examples of catalysts used in this process include piperidine and diethylamine ($HNEt_2$) (Scheme 49), among others.[14,266-268]

Unsaturated polyesters can be employed in the production of molded parts, such as knife and umbrella handles, in the encapsulation of decorative articles, and in the assembly of electronic devices.[14,269] They can be used for anticorrosive coatings of naval materials [268] and industrial equipment such as ducts, pipes, and conduits, as well as for coating floors and materials made of concrete or steel, in order to provide resistance to mineral acids.[269] They can be used in the automotive sector for manufacturing car bodies as well as truck cabins and trailers.[14,270]

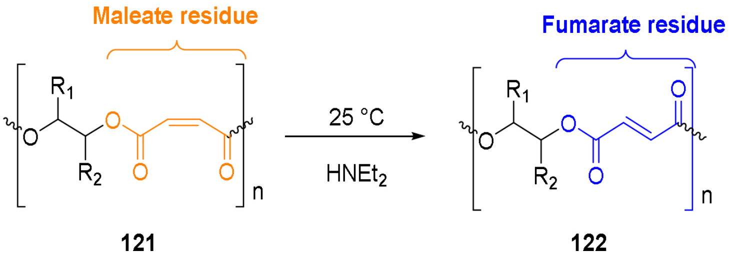
In the construction sector, these polyesters can be used to produce flat and corrugated sheets, which can be used as partitions, roofs, hoardings and awnings.[14,269,271,272] Unsaturated polyesters can be added to the composition of paving asphalt to improve its mechanical properties and provide better resistance to chemical agents.[14,269,273,274] These polyesters can also be added to concrete formulations, resulting in a material with high surface hardness and scratch resistance, etc.[14,275,276]



Scheme 47. Polymerization reaction of MA with ethylene glycol



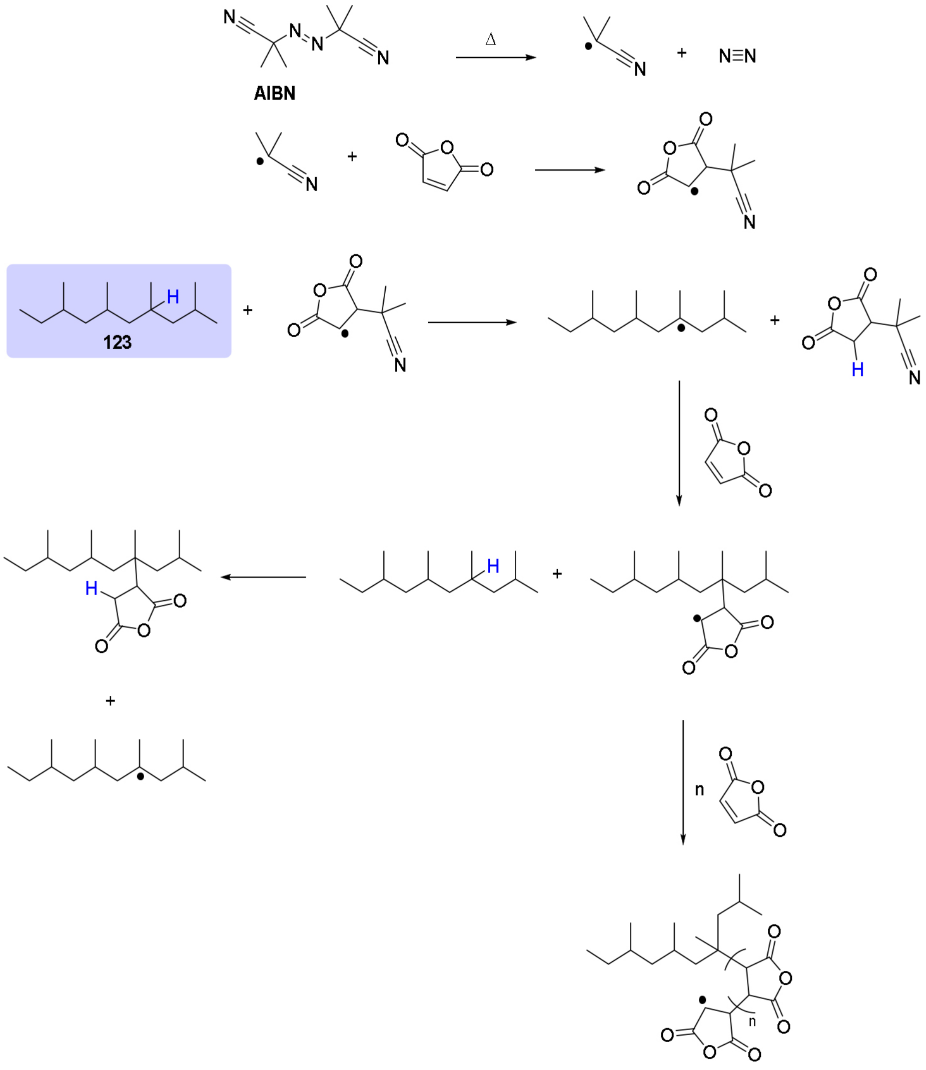
Scheme 48. Polymerization reaction between a cyclic ether and MA



Scheme 49. Isomerization reaction of an unsaturated polyester catalyzed by diethylamine

Polymers can also be modified with **MA** after their synthesis. Generally, the modifications occur with **MA** and the material to be modified in the molten state in the presence of initiators (e.g. organic peroxides, AIBN), resulting in branched or crosslinked polymer chains. This modification directly impacts the properties of the polymeric material, such as molecular weight, mechanical performance, and compatibility with other materials (Scheme 50).[277-279]

One of the best-known examples of polymers modified with **MA** is polypropylene (PP) **123**. It is a high-volume product used for packaging, automotive parts, construction materials and household goods, among others. PP **123** itself is nonpolar and does not have reactive sites, which makes its interaction with a wide range of materials challenging. The solution commonly employed to overcome these drawbacks is the incorporation of **MA** in the polymer structure. **MA**-modified PP exhibits higher polarity, improved mechanical performance, and depending on the synthetic route, higher or lower molecular weight.[5] **MA**-modified PP is primarily used in the formulation of polymer composites,[280,281] which are

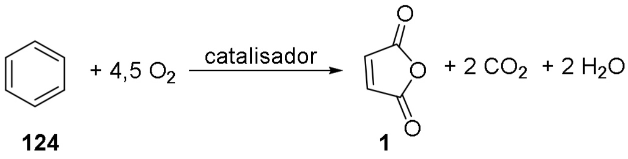


Scheme 50. Modification of PP with maleic anhydride.

multiphase materials, such as materials with complementary properties or blends.[282,283]

5. Preparation Methods

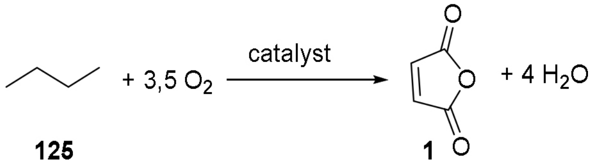
Maleic anhydride is industrially produced through the catalytic oxidation of hydrocarbons in the gas phase. The first and oldest production method is the vapor-phase oxidation of benzene **124** (Scheme 51). The development of this method allowed National Aniline & Chemical Company to start producing **MA** around 1930. In this industrial process, benzene is catalytically oxidized by oxygen from the air in a fixed-bed reactor containing a catalyst of vanadium-molybdenum pentoxide.[5,14,284]



Scheme 51. Selective oxidation of benzene to maleic anhydride

More recently, the use of C4 hydrocarbons, such as *n*-butane **125**, as raw materials has gained greater industrial interest (Scheme 52). In 2015, it was estimated that the **MA** production capacity was approximately 2.3 million tons, a figure expected to grow to 3.4 million tons by 2029 (Figure 14).[285]

Of this total **MA** output, 80% is produced using *n*-butane **125** and 20% employing benzene **124**. At present, the benzene oxidation method is practically nonexistent worldwide due to safety and economic reasons. Nonetheless, benzene **124**, a byproduct of manufacturing of coke, continues to be a major source of **MA** in China.[286]



Scheme 52. Catalytic oxidation of n-butane to MA

The production of **MA** from benzene begins with the addition of the hydrocarbon in a preheated air stream, forming a homogeneous mixture of air/benzene. This mixture flows through a multitubular fixed-bed reactor, where the reaction takes place within a temperature range of 400-450 °C and with controlled pressure between 0.15-0.25 MPa. This process is highly exothermic, with approximately $\Delta H = -1875$ kJ/mol released. In addition to the desired reaction, secondary combustion reactions also occur, which are also highly exothermic. For this reason, "hot spots" (340-500 °C) are observed on the catalyst surface. Effective dissipation of this heat is crucial for process efficiency, since the presence of hot spots can increase the formation of unwanted byproducts, as well as catalyst deactivation. To achieve this, a eutectic mixture of molten salts circulates around the reactor tubes to promote heat exchange. The hot eutectic mixture is then cooled in a second heat exchanger.[287]

Upon exiting the reactor, the gas mixture is cooled to 150-160 °C. Therefore, neither water nor **MA** condenses. Subsequently, the gas is further cooled (to 55 °C) in a partial condenser, where 40-60% of the **MA** is obtained in liquid form. Product removal must be rapid, because prolonged contact between **MA** and the water formed in the reaction can lead to maleic acid formation. The remaining maleic anhydride not recovered in the partial condenser is obtained after washing with water and subsequent dehydration. During washing, the remaining **MA** is converted into maleic acid, requiring a dehydration step. Industrially, temperatures above 130 °C are used for this process. However, at this temperature some of the maleic acid is isomerized to fumaric acid. In order to reduce isomerization, the mixture is subjected to high temperatures for the shortest residence time possible.[287] Pure maleic anhydride is obtained after the material passes through a batch-type azeotropic dehydration/distillation column.[286] Some byproducts of the benzene oxidation reaction are benzoquinone, formaldehyde and formic acid.

The catalyst for this process typically consists of a mixture of vanadium pentoxide and molybdenum

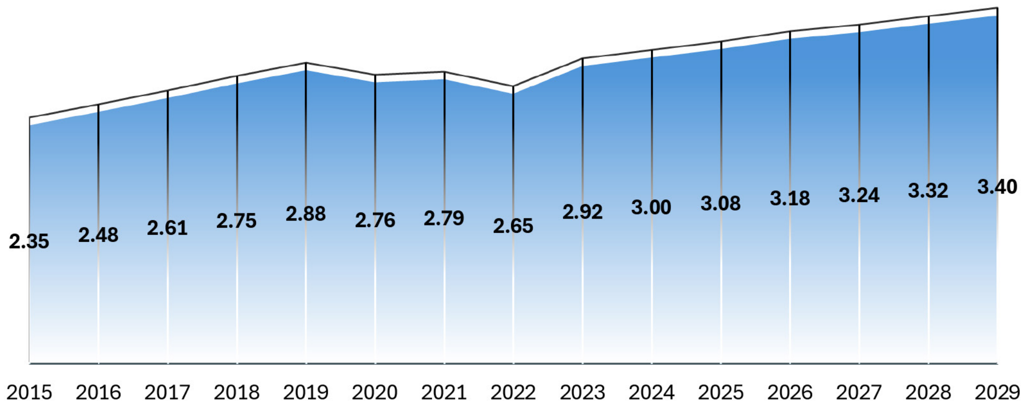


Figure 14. Market volume of MA worldwide from 2015 to 2021 (in million metric tons). Adapted from reference 285

trioxide (V_2O_5 + MoO_3)[288] supported on an inert and highly conductive material, such as alumina (Al_2O_3) or silica (SiO_2).[289] In most cases, this catalyst is modified with phosphorus,[290] titanium[291] or boron oxide to enhance catalytic activity and selectivity.[292,293] The benzo oxidation process has the advantages of high conversion rate (96%) and high selectivity (73%). In a typical reaction of 100 moles of benzene, 73 moles is oxidized to maleic anhydride, 23 moles is "burned," and 4 moles of benzene is recovered.[287] On the other hand, the environmental impact of benzene due to its toxicity and the increasing market value of benzene have driven the expansion of industrial plants based on *n*-butane. Only in China does the use of benzene still make financial sense, but this route has been decreasing over time, and more plants using *n*-butane have been built in the country.[294,295]

Since the 1980s, practically all maleic anhydride (**MA**) in the USA has been produced through the oxidation of butane in fixed bed, fluidized bed or other types of reactors. This has prevented any significant technological advancement in industrial processes related to benzene oxidation. Nevertheless, some more recent articles can be found aiming to improve the catalyst or optimize the design of the industrial plant to make this process more economically and environmentally attractive.[293,296]

Mangili and Prata conducted a preliminary analysis based on the principles of eco-efficiency and found that even with some optimizations, the process using *n*-butane was only 34% more eco-efficient than the process using benzene.[297]

In the 1970s, Monsanto[298] and Chevron[299] filed patents for the production of vanadium-phosphorus oxide (VPO) catalysts and their use in fixed-bed reactors.[300] These inventions revolutionized the industry and enabled the oxidation of alkanes, specifically *n*-butane, to **MA**. Since then, *n*-butane has gradually replaced benzene as a raw material in the production of **MA**. In the 1980s, some companies, such as Mitsubishi,[301] SOHIO,[302] Du Pont[303] and Alusuisse.[304] introduced the *n*-butane vapor-phase oxidation technology in a fluidized bed reactor, using VPO as a catalyst. However, due to complications of this process, the use of fixed-bed reactors is still predominant.

- Costs: *n-Butane is cheaper than benzene* (*n*-butane: 595 USD/ton,[305] benzene: 1268 USD/ton in 2024)[306]

- Toxicity: *n*-Butane has low toxicity.[307] On the other hand, benzene has proven carcinogenicity.[308]

- Atomic economy (ratio of the number of carbon atoms in the product to that in the reactant). For *n*-butane, the ratio is 1 (C4/C4), whereas for benzene, it is 0.67 (C4/C6, 2 carbons are lost to produce CO_2). This higher atomic efficiency of *n*-butane results in a higher mass yield (Table 5), less waste, and lower CO_2 generation.[286] According to the calculations by Mangili and colleagues, the benzene oxidation process (0.283 tCO_2/kmol) produces nearly twice the amount of CO_2 compared to *n*-butane (0.1615 tCO_2/kmol).[297]

- Catalyst: Reaction catalyst lifetime (*n*-butane > 5 versus benzene = 3-4 years) (Table 5).[286]

Table 5. Typical industrial data for oxidation processes using fixed-bed technology[286]

Data	*n*-BUTANE	BENZENE
Conversion (%)	80-82	>97
Selectivity (%)	72-74	72-74
Molar yield (%)	58-60	70-72
Weight yield (%p/p)	95-100	88-92
Catalyst lifetime (years)	>5	3-4

The selective oxidation of *n*-butane also presents disadvantages, which are described below.

- The recovery of unreacted C4 hydrocarbon is much more difficult than the recovery of benzene. Gaseous residues from the reaction have to pass through an incineration unit.[287]

- A small portion of **MA** can be recovered by partial condensation, but most of the **MA** (65-70%) is recovered as maleic acid, which is then dehydrated. This drawback can be resolved by replacing water washing with organic solvent washing.[287]

- CO and CO_2 are formed in parallel and consecutive reactions, and oxidative degradation of *n*-butane to acetic acid and acrylic acid occurs.[309]

- The air/*n*-butane mixture is highly flammable. The composition of the reaction mixture must be carefully controlled and kept below the flammability limit. The hydrocarbon concentration should be no more than 1.8 %mol for fixed-bed technology.[287] In a fluidized bed, the concentration can range from 3.0 to 4.5 %mol.[286]

For optimization of this industrial process, fine-tuning of the catalyst and reactor technology used is necessary. Some of the configurations developed for commercial production of maleic anhydride include fixed beds and fluidized beds.

Fixed-bed technology is used by Huntsman (formerly Monsanto), Scientific Design, Technobell, and BASF. Some advantages of this technology include higher yields, the possibility of larger industrial plants, and ease of conversion of old benzene-based plants to *n*-butane. In this process, the catalyst is embedded in the reactor piping, similar to what happens in benzene oxidation.[310]

Fluidized-bed technology is used by Polynt (formerly Lonza) and Ineos (formerly BP). Some advantages of this technology include lower investment costs, higher energy efficiency, and shorter downtime for catalyst replacement. The use of fluidized beds allows for uniform temperature profiles, reducing hot spots. On the other hand, due to fluidization, there is mixing of the product with the reagents, which partly reduces selectivity. Additionally, there is a problem of catalyst degradation and erosion associated with this type of technology.[287]

The main factor that allowed the expansion of *n*-butane utilization as a raw material for **MA** production was the development of VPO catalysts. In fact, VPOs are still the only catalysts used industrially to convert *n*-butane into **MA**.[287]

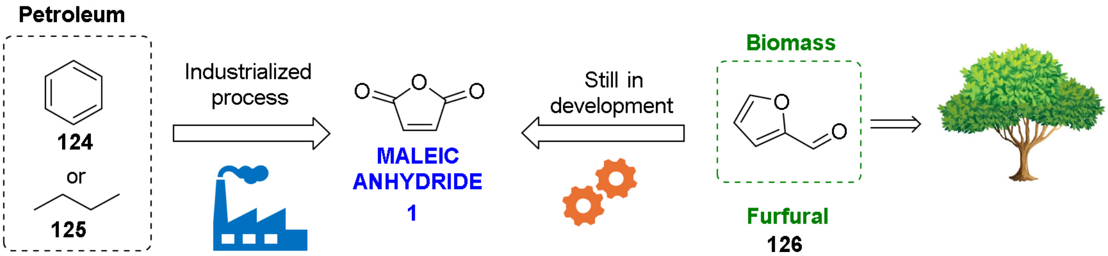
Recently, with the increase in environmental concern and need to reduce the employment of petroleum derivatives, alternative raw materials have been studied to replace or decrease the consumption of benzene and *n*-butane in **MA** production (Scheme 53). Examples of biomass derivatives are 5-hydroxymethylfurfural,[311] levulinic acid [312] and furfural **126**.[313] These starting materials are renewable, and they can be used as raw materials in the synthesis of **MA**. Furfural and furfuraldehyde have gained more attention due to their plentiful availability and better performance, both economically and environmentally, in transforming waste into valuable commodities.[314] 2-Furaldehyde is produced in large quantities, around 370 Kt per year, mostly from China.[315] The production occurs through the degradation of carbohydrates from lignocellulosic biomass such as sugarcane bagasse, oat hulls and corn stalks, among other materials that would otherwise be discarded. However, the current technology for **MA** production from biomass is still limited and needs further study. Several factors must be considered for the industrial use of this process, including selectivity, yield, reaction time, energy, stability and catalyst recycling, among others.[316]

Not all of these factors have been adequately addressed. For example, Shi and colleagues reported an optimized yield of 49% with 52% selectivity to **MA**; however, the removal of maleic acid from the reaction medium and catalyst recycling were not mentioned in this study.[317] More recently, Garcia and colleagues conducted a study on the feasibility of using furfural as a raw material in the production of maleic anhydride in a pilot plant. In this work, the need for optimizations became evident, since according to their calculations, remains more competitive from an environmental standpoint. This is because, considering the overall process, furfural production is still environmentally inadequate (e.g., the Huaxia process), especially regarding carbon emissions. This results in the carbon footprint for **MA** production from biomass not yet being environmentally and economically advantageous in comparison with petroleum-based production.[318]

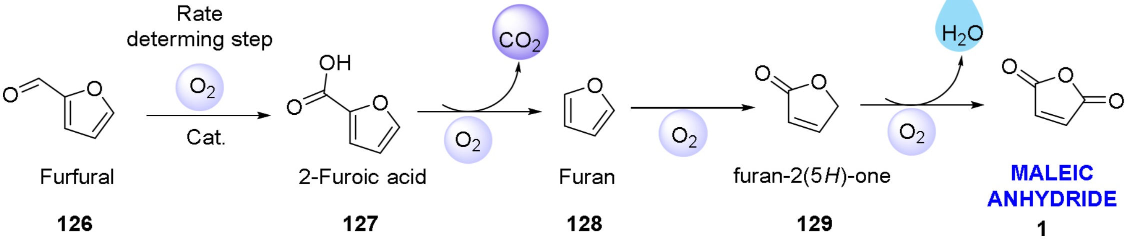
Currently, the oxidation of furfural to maleic acid, and consequently to maleic anhydride, can occur in both liquid [319] and gas phases.[320] Most researchers have found that when oxidation occurs in the liquid phase, hydrogen peroxide must be used as the oxidant.[319] This reagent, although considered a "green" oxidant,[321] is unstable and can cause explosions when concentrated. Oxygen can also be used as an oxidant; but in this case temperatures between 90-110 °C and high pressures of 10-20 bar are required.[317,322]

In the gas phase, furfural is converted into maleic anhydride with the assistance of vanadium oxide catalysts at temperatures between 200 and 360 °C.[313,320] The temperature, pressure and structure of the catalyst affect the reaction yield. Zhang *et al.* proposed that furan be converted to maleic anhydride through the following route: furfural **126** is oxidized to furan-2-carboxylic acid **127** by molecular oxygen; then, rapid decarboxylation occurs, forming furan **128**, which is oxidized twice, ultimately yielding maleic anhydride (Scheme 54). In this study, the conversion of furfural to maleic anhydride was evaluated using different vanadium oxide catalysts.[320]

In one of the earliest reports of the conversion of furfural **126** to maleic anhydride **1** found in the literature, a 70% yield was obtained using a continuous gas phase where the $H_5PMo_{10}V_2O_{40}$ was combined with $Cu(CF_3SO_3)_2$ as the catalytic system.[323] In 2016, Li and colleagues described the synthesis of maleic anhydride in the presence of Mo_4VO_{14}, using acetic acid as a solvent, which resulted in maleic anhydride with a 62% isolated yield. This yield was optimized by the group by replacing the Mo-V catalyst with



Scheme 53. Production of maleic anhydride from biomass



Scheme 54. Proposed gas-phase reaction route for furfural oxidation to MA

a vanadium-phosphorus oxide (VPO) catalyst. In this case, maleic anhydride was obtained with 90% yield and 90.8% selectivity at a temperature of 360 °C.[320]

6. Conclusions

Maleic anhydride is a highly reactive cyclic molecule containing a double bond that can react in various ways, yielding a variety of industrially relevant products such as solvents, monomers for polymers, addition polymers, condensation polymers, and more. Maleic anhydride is used to functionalize various materials, including vegetable oils and solid surfaces to be employed as catalysts and materials for gas storage, among others. Additionally, the anhydride function allows for the production of a diversity of products suitable for applications in various fields. The anhydride function undergoes hydrolysis, reaction with alcohols, amines or thiols, producing materials with uses as pesticides, reagents in proteomics and condensation polymers (polyester resins), among others. Several industrially relevant products, such as malic acid and addition polymers are produced through reactions at **MA**'s double bond. Maleic anhydride is industrially produced by the oxidation of butane or benzene with catalysts called VPOs (vanadium-phosphorus), with most industrial plants currently employing the oxidation of n-butane. Due to petroleum's non-renewability and environmental concerns related to the use of fossil fuels, research is currently being conducted to obtain maleic anhydride from biomass. In this case, furfural is the most evaluated material as a renewable feedstock for obtaining **MA**. However, an economically and environmentally viable process for obtaining maleic anhydride from furfural that is in commercial production has not yet been developed.

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