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In Focus

Zinc Chloride

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Cloreto de Zinco

Resumo: O cloreto de zinco (II) é um sólido cristalino branco, higroscópico e deliquescente. O $ZnCl_2$ é utilizado como catalisador, atuando como ácido de Lewis, em uma grande variedade de reações em síntese orgânica. As maiores vantagens de $ZnCl_2$ são o baixo custo do reagente, a facilidade de manuseio, a toxicidade moderada e o amplo espectro de atuação como catalisador. Nessa revisão foram selecionadas algumas metodologias a fim de se ilustrar o poder catalítico do $ZnCl_2$.

Palavras-chave: $ZnCl_2$; cloreto de zinco; catalisador; síntese orgânica.

Abstracts

Zinc(II) chloride is a white crystalline solid, strongly hygroscopic and deliquescent. $ZnCl_2$ is used as Lewis acid catalyst in a wide variety of reactions in organic synthesis. The biggest advantages of $ZnCl_2$ are its low cost, easy to handle, moderate toxicity and broad spectrum acting as a catalyst. In this review some reactions were selected in order to illustrate the catalytic power of $ZnCl_2$.

Keywords: $ZnCl_2$; zinc(II) chloride; catalyst; organic synthesis.

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Zinc Chloride

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1. Introduction

Zinc(II) chloride is a white crystalline solid, strongly hygroscopic and deliquescent. So it is common $ZnCl_2$ anhydrous or hydrated. Zinc(II) chloride is used as Lewis acid catalyst in a wide variety of reactions in organic synthesis.[1-10] The biggest advantages of $ZnCl_2$ are its low cost, easy to handle, moderate toxicity and broad spectrum acting as a catalyst.

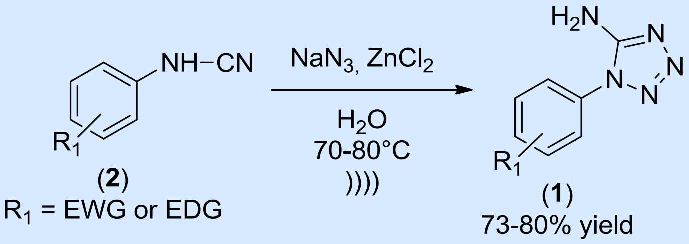
Although this reagent is available for purchase, there are classic methods for its synthesis. Addition of metallic zinc (Zn) to 35% hydrochloric acid (HCl) leads to the synthesis of anhydrous $ZnCl_2$ and hydrogen gas (H_2)[1] (Scheme 1).

$$Zn(s) + 2\,HCl(aq) \rightarrow ZnCl_2(s) + H_2(g)$$

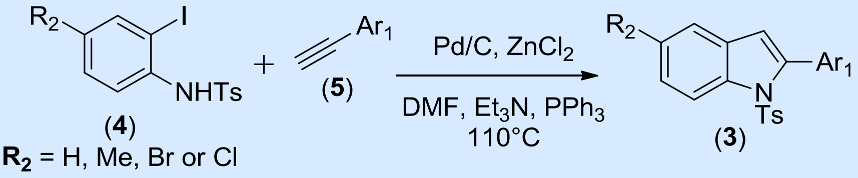
Scheme 1. $ZnCl_2$ synthesis

2. Applications

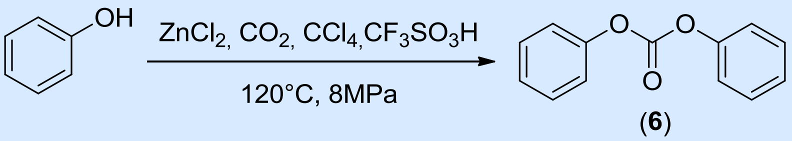
Synthesis of 1-Aryl-5-amino-1*H*-tetrazoles. 1-Aryl-5-amino-1*H*-tetrazoles (**1**) can be successfully obtained via a regioselective reaction from aryl-cyanamides (**2**) with sodium azide (NaN_3) in $ZnCl_2$ catalyst and water at 70-80°C under ultrasound irradiation. Tetrazoles (**1**) were obtained in high yields and without purification by column chromatography. Furthermore, it is a green protocol with simple methodology, easy workup and without use of hazardous reagents.[2]



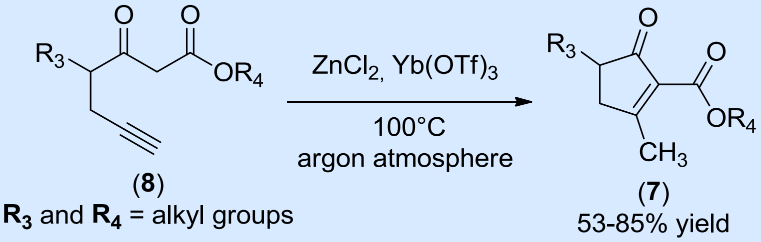
Synthesis of 2-substituted indoles. Synthesis of 2-substituted indoles (**3**) from mono-substituted aromatic alkynes (**5**) and *N*-substituted 2-iodo-aniline (**4**) using Pd/C and $ZnCl_2$ as catalyst in the presence of triethylamine (Et_3N) and phosphine (PPH_3) in *N,N*-dimethylformamide (DMF) was described. This is an efficient and mild methodology which involves a domino Sonogashira coupling/cyclization reaction, with formation of new C-C and C-N bonds with yields higher than 90%.[3]



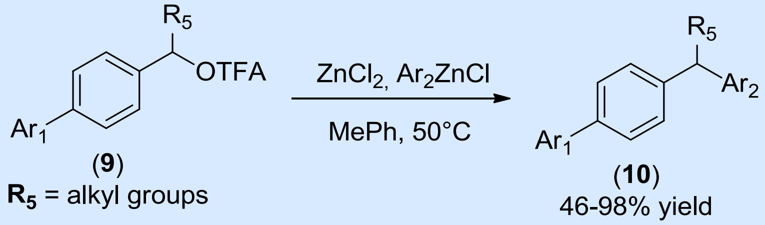
Green chemistry. Fan and colleagues (2012) developed a new, efficient and environmentally friendly homogeneous catalytic system to synthesize diphenyl carbonate (**6**, DPC) from carbon dioxide (CO_2), phenol, carbon tetrachloride (CCl_4) with $ZnCl_2$ and trifluoromethanesulfonic acid (CF_3SO_3H) as catalyst at 120°C and pressure of 8MPa.[4]



Conia-Ene Reaction. $ZnCl_2$ and $Yb(OTf)_3$ at 100 °C and under argon atmosphere were able to promote Conia-Ene reaction from linear β-Alkynic β-Dicarbonyls (**8**) to generated only *exo*-product (**7**) in good yields. It is an atom-economical and solvent-free methodology capable to promote construction of five-membered ring carbocycles.[5]



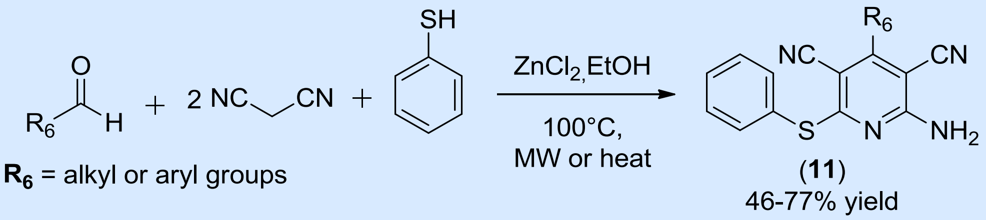
Arylation of Secondary Benzyl Trifluoroacetates. Duan and coworkers (2010) developed a methodology of arylation, via coupling Csp_3-Csp_2, between secondary benzyl trifluoroacetates (**9**) and aryl zinc reagents (ArZnCl) with $ZnCl_2$ as catalyst in toluene at 50°C to generated diarylalkanes (**10**). Despite the great power of palladium to catalyze a big variety of C-C bond-formation reactions, in this case it did not work. This is a versatile and quite tolerable synthesis, including substrates containing β-hydrogens.[6]



(**9**)
R_5 = alkyl groups

(**10**)
46-98% yield

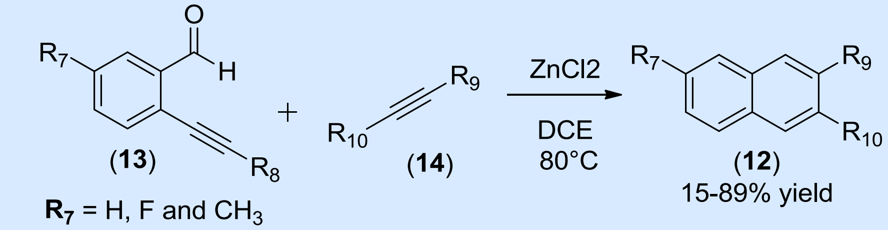
Multicomponent reaction. $ZnCl_2$ is also capable to catalyze multicomponent reactions (MCR). Sridhar and coworkers (2009) describes synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines (**11**) from a variety of aldehydes, benzenethiol and malonitrile under $ZnCl_2$ catalyst in ethanol at 100°C. Products can be obtained under microwave irradiation or with usual heating, with no significant difference in yields.[7]



R_6 = alkyl or aryl groups

(**11**)
46-77% yield

[4 + 2] Benzannulation. Synthesis of naphthalene derivatives (**12**) via [4 + 2] benzannulation with only $ZnCl_2$ as catalyst was reported. This protocol use 2-ethynylbenzaldehydes (**13**), terminal or substituted alkynes (**14**) in dichloroethane (DCE) and $ZnCl_2$ at 80°C. Scope of methodology was investigated with several aldehydes and alkynes, all with moderate to good yields. Fortunately, in spite of steric hindrance problems, there was no great difference in yields of substituted or terminal alkynes.[8]



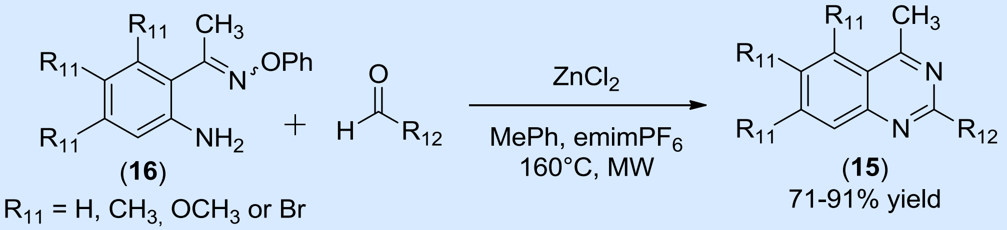
(**13**)

(**14**)

(**12**)
15-89% yield

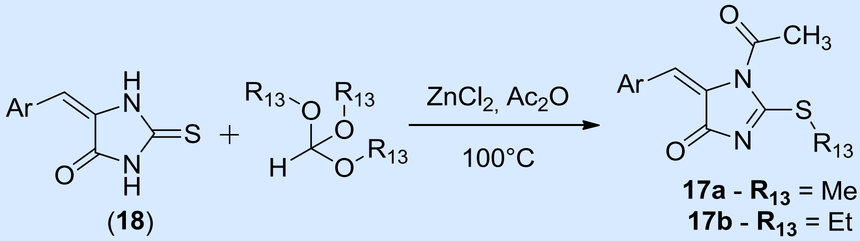
R_7 = H, F and CH_3
R_8 , **R_9** and **R_{10}** = H, aryl, heteroaryl or aryl groups

Synthesis of 4-methyl-2-substituted quinazolines. 4-methyl-2-substituted quinazolines (**15**) were obtained in good yields by treatment of 1-(2-aminophenyl)ethanone *o*-phenyl oxime (**16**) with a range of aldehydes in the presence of $ZnCl_2$ and emimPF_6 in toluene at 160°C under microwave irradiation. Aromatic aldehydes containing electron-withdrawing substituents gave better yields than aromatic aldehydes containing electron-releasing substituents; reaction involves the nucleophilic addition to the carbonyl, and this is favored by electron-withdrawing substituents.[9]



R_{11} = H, CH_3, OCH_3 or Br
R_{12} = aryl or aryl group

***S*-alkylation and *N*-acetylation of 2-thiohydantoins**. Kumar and Chauhan (2008) reported a one-pot *S*-alkylation and *N*-acetylation of 2-thiohydantoins (**18**), with trimethyl or triethyl orthoformates in the presence of $ZnCl_2$ and Ac_2O at 100°C, to generate, respectively, *S*-methyl *N*-acetyl (**17a**) or *S*-ethyl *N*-acetyl derivatives (**17b**). Products were obtained in 40-90% yield. Additionally, this was the first published methodology involving each one of these two reactions in one-pot procedure[10].



17a - **R_{13}** = Me
17b - **R_{13}** = Et
58-91% yield

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