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$ZrOCl_2 \cdot 8H_2O$ as a highly efficient and the moisture tolerant Lewis acid catalyst for Michael addition of amines and indoles to α, β-unsaturated ketones under solvent-free conditions

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Abstract

The 1,4-conjugate addition of indoles and amines to cyclic and acyclic α, β-unsaturated ketones for C–N bond formation was efficiently carried out under solvent-free conditions at 50 °C using a catalytic amount of $ZrOCl_2 \cdot 8H_2O$ as a moisture tolerant Lewis acid. The reusability of the catalyst has been successfully examined without noticeable loss of its catalytic activity.

Keywords: $ZrOCl_2 \cdot 8H_2O$; Michael reaction; Amine; Indole; α, β-Unsaturated ketones; Solvent-free

1. Introduction

In recent years, considerable attention has been focused on the development of efficient and operationally simple protocols for carbon–carbon and carbon–heteroatom bonds formation for the construction of valuable molecules. For example, carbon–carbon bond formation through the addition of electrophiles to the C-3 position of the indoles leading to the bioactive indole alkaloids [1]. However, the carbon–heteroatom bond-forming reactions especially are of concern, since the resulting functionality can be readily manipulated to produce many classes of compounds of especial importance [2]. In addition, nitrogen-containing compounds are of significant importance in human life and also they are useful as biologically active substances, dyes, and fine chemicals [3]. For instance, the β-amino carbonyl group is a common moiety in a large variety of biologically active compounds such as alkaloids and polyketides [4–7]. They are also attractive precursors in preparation of γ-amino alcohols, β-lactams, β-aminoacid derivatives and chiral auxiliaries [8–13], many of which serve as powerful antibiotics or other drugs [14]. The acid or base-induced conjugate addition of nucleophiles to α, β-unsaturated carbonyl compounds, Michael reaction, is among the most useful carbon–carbon and carbon–heteroatom bond forming reaction. To avoid problems rising from the addition of stoichiometric amounts of the acidic or basic catalysts or reagents [15], a number of methods has been developed. Thus, in this regard, Lewis acids such as $FeCl_3$, LiCl, $HgCl_2$ [16,17], lantanide salts (Ln = La, Sm, Yb) [18], $InCl_3$ and $InBr_3$ [19], Pd [20], $CeCl_3$ [21], $Bi(NO_3)_3$ [22], $Bi(OTf)_3$ [23], $Sc(DS)_3$ [24], copper salts [25] and acidic clays [26], have attracted much attention because of their unique reactivities and selectivities. However, the requirement of anhydrous conditions in most of cases and also the practice of expensive and toxic metal precursors such as lantanide triflates has restricted the use of some Lewis acids in the conjugate addition of nucleophiles to α, β-unsaturated compounds. Recently, the use of $CeCl_3$/NaI [27] supported on silica-gel has been introduced as a relatively non-toxic and a rather inexpensive catalytic system for Michael addition of indoles, but, the use of high percentage of $CeCl_3$/NaI (30 mol%) combined with the relatively harsh reaction conditions accompanied with the long reaction times, present disadvantages of this catalytic system. Thus, the addition of a safe and a cheap catalytic system, which is not a moisture and air sensitive system with high catalytic activity is of practical value. Very recently, we have developed two efficient catalytic methods for Michael addition of indoles [28], amines and thiols [29] to α, β-unsaturated ketones in an aqueous media. In continuation of our work upon new applications of Zr(IV) com-

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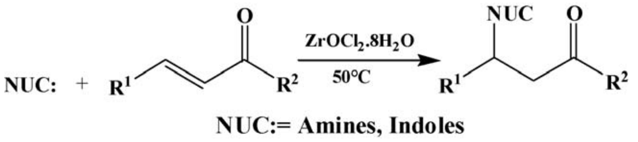
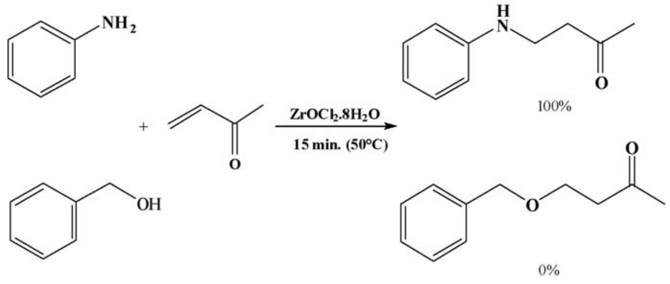


Scheme 1.

pounds [30], we first examined the conjugate addition of amines and indoles to α, β-unsaturated ketones in the presence of catalytic amounts of $ZrCl_4$ in the absence of solvent. We found that the reactions in the presence of catalytic amounts of this compound did not proceed cleanly and a mixture of unidentified products was produced. Then we used zirconyl chloride octahydrate ($ZrOCl_2{\cdot}8H_2O$) as a catalyst for the addition of amines and indoles to α, β-unsaturated ketones under non-solvent conditions with success. The reactions proceeded smoothly at 50 °C and the desired Michael adducts were produced in high yields in short reaction times (Scheme 1). Reports on the safety of Zr(IV) salts show that their LD_{50} is high [LD_{50} [$ZrOCl_2{\cdot}8H_2O$, oral rat] = 2950 mg/Kg] [31]. $ZrOCl_2{\cdot}8H_2O$ with a rather high LD_{50} and low toxicity should not be that much harmful to mammalians. $ZrOCl_2{\cdot}8H_2O$ is a highly water tolerant material therefore, its handling does not need especial precautions. This material is a commercially available and a cheap compound. Literature survey shows that only a very few reports are available dealing with the catalytic activity of this compound [32].

2. Results and discussion

Initial studies to examine the effect of temperature as well as catalyst loading were carried out using methyl vinyl ketone and aniline as a model reaction. Investigation of the different amounts of $ZrOCl_2{\cdot}8H_2O$ at different temperatures under solvent-free conditions led us to methyl vinyl ketone (1.1 mmol), aniline (1 mmol) and $ZrOCl_2{\cdot}8H_2O$ (2 mol%) at 50 °C as the optimized condition. The data presented in Table 1, show the promising feature of this method in terms of molar ratio of the catalyst, reaction rate and the yield of the product compared with those reported in the literature [18,19,21,27,33]. The work-up was easy and the catalyst was simply filtered from the reaction mixture. Then the generality of the procedure was evaluated by the reaction of a number of α, β-unsaturated cyclic and acyclic ketones with structurally and electronically diverse amines. The reactions proceeded easily and the adducts were isolated in good to excellent yields in short reaction times (Table 2, entries 1–12). Surprisingly, in the presence of this catalyst, 4-nitroaniline which is a rather weak nucleophile, reacted with both methyl vinyl ketone and cyclohexenone in short reaction times 12 and 20 min, respectively, and the adducts were isolated in excellent yields (Table 2, entries 10 and 11). However, the addition of indole and 2-methyl indole to methyl vinyl ketone was also investigated. We found that indole reacted with methyl vinyl ketone after 120 min and the adduct was isolated in 77% yield. 2-Methyl indole was reacted with methyl vinyl ketone in a shorter reaction time (30 min) and the adduct was isolated in 95% yield. Reaction of 2-methyl indole with cyclohexenone was also proceeded well within a short reaction time (50 min) and the corresponding adduct was isolated in 94% yield (Table 2, entries 13–15).



Scheme 2.

The addition of thiols and alcohols to methyl vinyl ketone, as a reaction model, under similar condition, was also investigated. The reaction of thiols with this α, β-unsaturated ketone was a non-selective and the two unidentified products were produced (1,2-addition and 1,4-addition). Alcohols, under similar condition, remained almost intact in appropriate reaction times. Therefore, addition of amines in the presence of alcohols would be a highly selective reaction. For this purpose, the reaction of aniline in the presence of equimolar amount of benzyl alcohol was studied. The results show that the reaction proceeded with absolute chemoselectivity and the amino-adduct was produced quantitatively whereas, the alcohol was remained intact (GC). This chemoselectivity is presented by Scheme 2.

Recycling of the catalyst is important for the large-scale operation and industrial point of view. To check the possibility of the catalyst recycling, addition of methyl vinyl ketone with aniline at 50 °C under solvent-free conditions in the presence of 2 mol% of $ZrOCl_2{\cdot}8H_2O$ was studied. After completion of the reaction and

Table 1
Comparison of catalytic activity of $ZrOCl_2{\cdot}8H_2O$ with respect to the other catalysts used for the addition of amines and 2-methylindole to methyl vinyl ketone

Catalyst	mol%	Solvent	2-Methylindole		Pipiridine		Aniline	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
$ZrOCl_2{\cdot}8H_2O$	2	None	30	95	3	95	8	94
SmI_3 [18]	10	CH_3CN	60	95	–	–	–	–
$InCl_3$ [19]	10	CH_2Cl_2	150	92				
$CeCl_3{\cdot}7H_2O$ [21,27]	30	None	1200	98	360	87	–	–
Nafion SAC-13 [33]	10	CH_3CN	–	–	–	–	720	98