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Short communication

$ZrOCl_2 \cdot 8H_2O$/silica gel as a new efficient and a highly water–tolerant catalyst system for facile condensation of indoles with carbonyl compounds under solvent-free conditions

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Abstract

$ZrOCl_2 \cdot 8H_2O$/silica gel as a highly water–tolerant catalyst system has been applied for the preparation of bis(indolyl)methanes via electrophilic substitution reactions of indoles with carbonyl compounds under solvent-free conditions. The yields of the isolated products are from good to excellent.

Keywords: Zr(IV) compounds; $ZrOCl_2 \cdot 8H_2O$; Silica gel; Bis(indolyl)methanes; Indole derivatives; Solvent-free

1. Introduction

Indole frameworks have attracted a plethora of research areas due to the vast applications in material sciences [1], agrochemicals [2], and pharmaceuticals [3]. Particularly, the substrates including bis(indolyl)methane moieties such as secondary metabolites [4], and marine sponge alkaloids [5], are of remarkable significant. The acid-catalyzed condensations of indole with carbonyl compounds have been of concern as a useful route for preparation of bis(indolyl)methanes. The protic acids [6], and Lewis acids [7], have been usually used in excess and drastic conditions are required. To abate the environmental pollution of the disposal of the excess acids and improvement of the condensation reactions of indole and carbonyl compounds, a number of catalytic systems such as $NaHSO_4 \cdot SiO_2$ [8], Amberlyst-15 [8], Yb-Amberlyst XN-1010 [9], Zeolites [10], ionic liquids [11], I_2 [12], and $LiClO_4$ [13], have been successfully utilized. Alternative catalytic protocols promoted by solid Lewis and Bronsted acids such as montmorillonite clay [14], have received a great deal of attention, especially for industrial requirements. The use of rare earth catalysts such as $La(OTf)_3$ [15], $In(OTf)_3$ [7a], $InCl_3$ [7a] and $La(PFO)_3$ [16] have been also reported for the promotion of this reaction.

Very recently, we have developed and reported an efficient catalytic method using aluminumdodecatungstophosphate ($AlPW_{12}O_{40}$) for the preparation of bis(indolyl)methanes via electrophilic substitution reactions of indoles with carbonyl compounds in CH_3CN at room temperature[17]. Solvent-free condensation of indoles with carbonyl compounds is scarce in the literature [14]. Along this line and in continuation of our interest to explore new applications of Zr(IV) compounds [18–24], we now introduce $ZrOCl_2 \cdot 8H_2O$/silica gel as a new efficient catalytic system for carbon–carbon bond formation between indoles and carbonyl compounds under solvent-free conditions in good to high yields (Scheme 1).

$ZrOCl_2 \cdot 8H_2O$ is a highly water–tolerant compound, which its handling does not need especial precautions. $ZrOCl_2 \cdot 8H_2O$ is a commercially available and a cheap compound. 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] [25]. $ZrOCl_2 \cdot 8H_2O$ with a rather high LD_{50} and low toxicity should not be expected that much harmful to mammalians. Literature survey shows that only a very few reports are available dealing with the catalytic activity of this compound [24,26–28].

2. Results and discussion

In order to optimize the reaction conditions, we first used zirconyl chloride octahydrate ($ZrOCl_2 \cdot 8H_2O$) as a catalyst for

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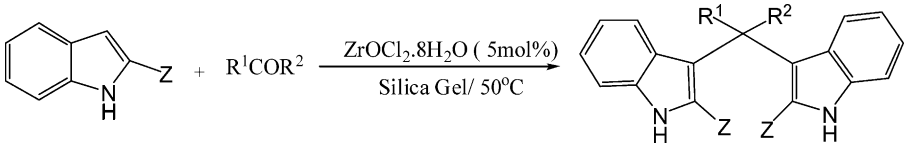
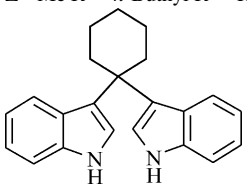
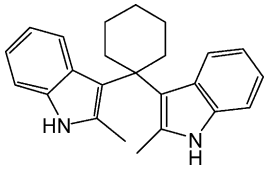
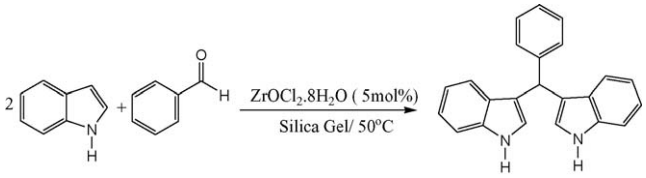
Table 1
Condensation of indoles with carbonyl compounds catalyzed by $ZrOCl_2{\cdot}8H_2O$/silica gel system under solvent-free conditions



Entry	Indole	Carbonyl compounds	Product	Time (min)	Isolated yield (%)	References to known compounds
1	Z = H	$R^1 = C_6H_5$ $R^2 = H$	Z = H $R^1 = C_6H_5$ $R^2 = H$	40	84	13
2	Z = H	$R^1 = p$-MeC_6H_5 $R^2 = H$	Z = H $R^1 = p$-MeC_6H_5 $R^2 = H$	75	75	13
3	Z = H	$R^1 = p$-OHC_6H_5 $R^2 = H$	Z = H $R^1 = p$-OHC_6H_5 $R^2 = H$	120	76	17
4	Z = H	$R^1 = p$-$NO_2C_6H_5$ $R^2 = H$	Z = H $R^1 = p$-$NO_2C_6H_5$ $R^2 = H$	30	94	10b
5	Z = Me	$R^1 = C_6H_5$ $R^2 = H$	Z = Me $R^1 = C_6H_5$ $R^2 = H$	20	85	10b
6	Z = Me	$R^1 = p$-OHC_6H_5 $R^2 = H$	Z = Me $R^1 = p$-OHC_6H_5 $R^2 = H$	120	75	17
7	Z = Me	$R^1 = p$-$NO_2C_6H_5$ $R^2 = H$	Z = Me $R^1 = p$-$NO_2C_6H_5$ $R^2 = H$	15	90	10b
8	Z = H	$R^1 = n$-Buthyl $R^2 = H$	Z = H $R^1 = n$-Buthyl $R^2 = H$	60	90	13
9	Z = Me	$R^1 = n$-Buthyl $R^2 = H$	Z = Me $R^1 = n$-Buthyl $R^2 = H$	40	93	13
10	Z = H	Cyclohexanone		180	80	13
11	Z = Me	Cyclohexanone		150	85	13
12	Z = Me	Acetophenone	No reaction	180	–	–

Pure product was obtained after plate chromatography. All products were identified by their spectroscopic data and their comparison with known samples.

the condensation of indole (2.1 mmol), benzaldehyde (1 mmol) in the absence of solvent. A highly sticky orange reaction mixture was obtained with the formation of the desired bis(indolyl)methane in 70% yield after several h. Increasing reaction time to 24 h did not also affect the yield of the product. However, we studied the catalytic effect of $ZrOCl_2{\cdot}8H_2O$ powder (5 mol%) dispersed on molecular sieves, alumina, or silica gel (0.15 g) for the similar reaction in the absence of solvent. The reaction proceeded cleanly well at 50 °C and the desired bis(indolyl)methane was isolated in 84% yield after 40 min. We have also tried a similar reaction in the presence of molecular sieves, alumina or silica gel without using $ZrOCl_2{\cdot}8H_2O$. The reaction was not successful and 50% of the starting materials remained intact plus an undesired product, which its structure has not been identified. In order to apply this catalyst for the preparation of other bis(indolyl)methanes, we have used $ZrOCl_2{\cdot}8H_2O$ dispersed on silica gel.



Scheme 1. .

The catalyst has been applied successfully for the condensation of a variety of aromatic and aliphatic carbonyl compounds with indoles. However, cyclohexanone needed longer reaction time in comparison with the aliphatic and aromatic aldehydes (Table 1, entry 10, 11). We have noticed that the reaction of indole with acetophenone in the presence of this catalyst was not successful and after a prolonged reaction time, most of the starting materials were observed intact (Table 1, entry 12).

3. Conclusions

We have introduced a highly efficient catalytic system for condensation of aldehydes and cyclohexanone with indoles in the absence of solvent under a rather mild reaction condition. The use of a relatively safe catalyst to mammalians and also its tolerance towards moisture combined with an easy work-up procedure are the promissing points for the presented methodology.

4. Experimental

$ZrOCl_2{\cdot}8H_2O$, indoles, carbonyl compounds and silica gel were purchased from Merck or Fluka Chemical Companies. Purity determinations of the products were accomplished by GLC on a Shimadzu model GC-14A instrument or by TLC on silica-gel polygram SIL G/UV 254 plates. NMR spectra were

recorded on a Brucker Avance DPX 250 MHz instrument. Mass spectra were recorded on a Shimadzu GC–MS–QP 1000PX.

4.1. Typical procedure for condensation of indole with benzaldehyde by $ZrOCl_2{\cdot}8H_2O$/silica gel

To a mixture of indole (2.1 mmol, 0.246 g) and benzaldehyde (1 mmol, 0.106 g), silica gel [0.15 g (60, 70–230 mesh)] and $ZrOCl_2{\cdot}8H_2O$ (5 mol%, 0.016 g) were added. The resulting mixture was stirred at 50 °C for 40 min. The progress of the reaction was monitored by TLC. After completion of the reaction, acetone (10 mL) was added to the mixture and filtered. Evaporation of the solvent under vacuum afforded crude product which was purified plate chromatography eluted with ethyl acetate/petroleum ether (1/2) to give a pinkish solid product in 84% yield, 0.270 g. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (ppm) = 5.87 (s, 1H), 6.62 (s, 2H), 6.99–7.3 (m, 13H), 8.05 (br s, 2H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ (ppm) = 39.38, 110.6, 119.1, 119.5, 120, 121.2,123.1, 125.9, 126.3, 128.4, 128.9, 136.6, 143.5; MS (*m*/*e*) = 322 $[M]^+$; Anal. Calcd for ($C_{23}H_{18}N_2$): C, 85.68; H, 5.63. Found: C, 85.71; H, 5.66.

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