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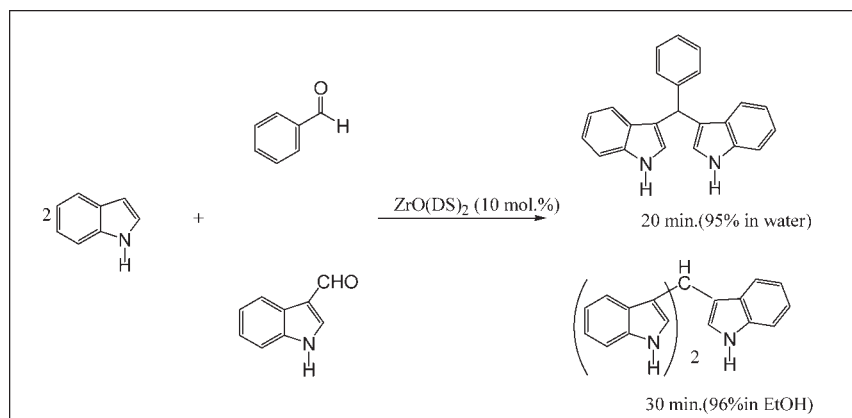
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Received April 8, 2008

DOI 10.1002/jhet.46

Published online 5 May 2009 in Wiley InterScience (www.interscience.wiley.com).



Zirconyldodecylsulfate ($\text{ZrO}(\text{DS})_2$) as a versatile Lewis acid-surfactant-combined (LASC) catalyzed ecofriendly synthesis of bis- and tris(indolyl)methanes *via* electrophilic substitution of indoles with carbonyl compounds in high yields at mild conditions.

J. Heterocyclic Chem., **46**, 535 (2009).

INTRODUCTION

Replacing current chemical processes with more environmentally benign alternatives is an increasingly attractive subject [1]. The rapid and extensive growth of synthetic procedures using materials with detrimental effects to the environment has turned the attention of chemists to the development of environmentally benign methods in order to avoid or minimize these harmful effects.

Bis(indolyl)methanes (BIM) are the most active cruciferous substances for promoting beneficial estrogen metabolism in woman and men [2]. BIM increases the body's natural metabolism of hormones and promotes good estrogen (2-hydroxyestrogen). This indole antioxidant is patented for alleviating symptoms of fibromyalgia. BIM is effective in the prevention of cancer because of its ability to modulate certain cancer causing estrogen metabolites [3]. Scientists have demonstrated that BIM induces apoptosis in human cancer cells and may also normalize abnormal cell growth associated with cervical dysplasia.

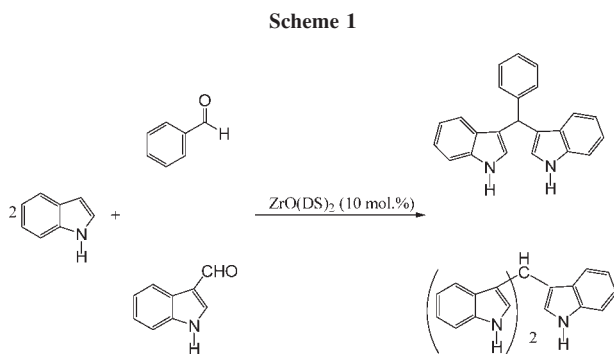
Also 1,1,1-tris(3,3',3''-indolyl)ethane was found in bacterial metabolites [4], and the triarylmethanes (TIMs)

could be converted into important cage molecules [5]. It is reported that the cationic form of TIMs could be used as acceptors of hydride ions.

Thus, indole and its derivatives have been a topic of research interest [6]. Because of their intriguing physiological activities, many synthetic procedures have been reported so far [7–12], where development of environmentally benign methods are currently of interest in process chemistry by using green catalysts.

Green catalysts require high catalytic activity and atom efficiency, as well as low toxicity, low cost, and ease of handling. Fortunately, Zr(IV) compounds generally have low toxicity and are not considered particularly poisonous. Reports on the safety of Zr(IV) salts show that their LD_{50} is high [LD_{50} [$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$, oral rat] = 3500 mg/Kg] [13]. Although $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ has a rather high LD_{50} , it should not be very harmful to mammals. Also, this material is commercially available and is an inexpensive compound.

In continuation of our ongoing interest on development of new applications of zirconium salts [8,14–18] in synthetic methods, we herein report the use of $\text{ZrO}(\text{DS})_2$ as LASC in the electrophilic substitutions of



indoles with a variety of aldehydes and ketones in H₂O and EtOH, both of which are green solvents, affording excellent yields of bis- and tris(indolyl)methanes under mild condition (Scheme 1).

RESULTS AND DISCUSSION

Optimized reaction conditions were investigated using a reaction of benzaldehyde and indole (1:2.2), with respect to temperature, time, and the molar ratio of ZrO(DS)₂ to the substrate in water. We found that 10 mol % of ZrO(DS)₂ was sufficient to obtain the desired bisindolylmethane in 96% yield within 20 min at 60°C.

Based on the optimized reaction conditions, the present protocol was applied to a variety of carbonyl compounds (Table 1). As shown in Table 1 aryl aldehydes with both electron-donating and electron-withdrawing characteristics afforded bis(indolyl)methane in excellent yields. Not only aryl aldehydes but also aliphatic aldehydes provided the desired bis(indolyl)methane (Table 1, entry 9).

We have found that the reaction of both activated and deactivated aromatic aldehydes with 2-methyl indole is faster than indole (Table 1, entries 10,11).

When 3-formylindole was used as a carbonyl compound, the corresponding trisindolylmethanes are formed. The reaction proceeded at room temperature in EtOH and the time required for the conversion was short (Table 1, entries 12,13).

The reaction of acetophenone with indole is slower than with aldehydes, and unreacted ketone and indole remains (Table 1, entry 14).

To show the merit of ZrO(DS)₂ in comparison with other catalysts used for the similar reactions in green solvents, we have tabulated some of the results in Table 2.

CONCLUSION

We have developed a highly convenient, efficient, and green catalytic system for the preparation of biolog-

ically important bis- and trisindolylmethanes in high yields through the electrophilic substitution reaction of indoles with carbonyl compounds using ZrO(DS)₂ as new LASC. This protocol will contribute to reducing the use of harmful organic solvents.

EXPERIMENTAL

General. ZrOCl₂·8H₂O, SDS, carbonyl compounds, and indoles were purchased from Merck or Fluka Chemical Companies. Progress of the reactions was monitored by TLC using silica-gel SIL G/UV 254 plates. NMR spectra were recorded on a Bruker Avance DPX 300 MHz and 500 MHz instruments. Mass spectra were recorded on a Shimadzu GC-MS-QP 5050A.

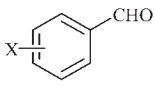
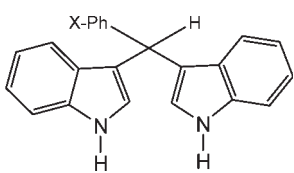
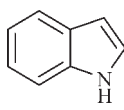
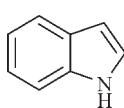
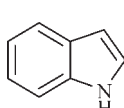
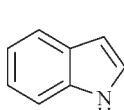
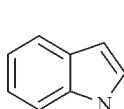
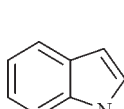
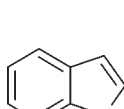
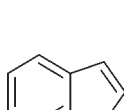
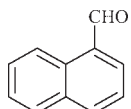
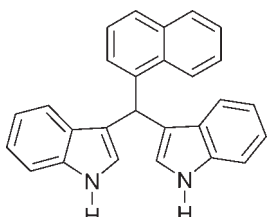
Preparation of ZrO(DS)₂ from ZrOCl₂·8H₂O and sodium dodecyl sulfate (SDS). A solution of ZrOCl₂·8H₂O (5 mmol, 1.61 g in 50 mL of water) was added to a solution of sodium dodecyl sulfate (SDS) (10 mmol, 2.88 g in 50 mL of distilled water) while stirring at room temperature. A white precipitate was appeared immediately and the mixture was stirred for another 30 min. The white solid was collected by filtration and washed with water (2 × 100 mL). The isolated solid was dried under reduced pressure and ZrO(DS)₂ was obtained as a white powder in 90% yield (2.87 g). M.p: 125°C; ¹H NMR (DMSO, 500 MHz): δ 0.82 (t, 6H, *J* = 6.8 Hz), 1.1–1.35 (m, 36H), 1.45 (m, 4H), 3.69 (t, 4H, *J* = 6.6 Hz) ppm; ¹³C NMR (DMSO, 125.77 MHz): 13.90, 22.14, 25.58, 28.78, 28.90, 29.04, 29.11, 29.13, 31.37, 32.63, 60.83, 65.99 ppm.

General procedure for condensation of indoles with carbonyl compounds catalyzed by ZrO(DS)₂. Indole (2.2 mmol) and carbonyl compound (1 mmol) was added to a suspension of ZrO(DS)₂ (10 mol %, 0.0638 g in 2 mL of water or EtOH) (see Table 1). The reaction mixture was stirred at 60°C for appropriate time which was monitored by TLC (Table 1). After completion of the reaction, EtOAc (5 mL) was added to the reaction mixture; organic phase was separated and dried over CaCl₂ followed by filtration and evaporation of the solvent. The desired product was secured in high purity (Table 1). Further purification was performed by plate chromatography eluted with *n*-hexan/EtOAc (3/1). Structural assignments of the products are based on their ¹H NMR, ¹³C NMR, MS spectra and elemental analysis.

Selected spectral data. Table 1, entry 2: Solid; mp: 97–98°C; ¹H NMR (CDCl₃, TMS, 300 MHz): δ 2.37 (s, 3H), 5.83 (s, 1H), 6.70(d, 2H, *J* = 2.45 Hz), 7.02(t, 2H, *J* = 8.2 Hz), 7.12(d, 2H, *J* = 8.2 Hz), 7.21–7.3(m, 6H), 7.45(d, 2H, *J* = 8.2 Hz), 7.9(br, s, 2H) ppm; ¹³C NMR (CDCl₃, TMS, 62.9 MHz): 21, 40.25, 110.9, 112, 119.5, 120.2, 121.6, 122.6, 129.5, 131.5, 134.3, 136.8 ppm; MS (70 eV), *m/e*: 336 [M⁺]. Anal. Calcd for (C₂₄H₂₀N₂): C, 85.68; H, 5.99; N, 8.33. Found: C, 85.70; H, 5.96; N, 8.35.

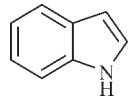

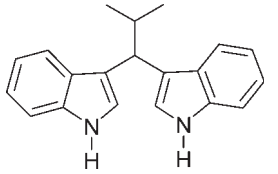
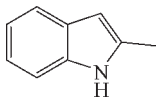
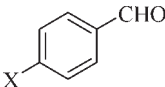
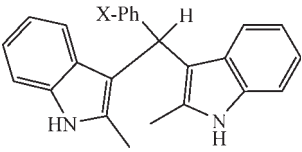
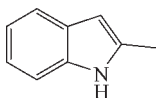
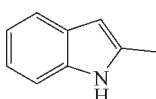
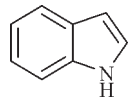
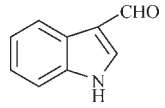
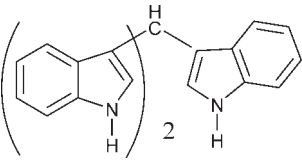
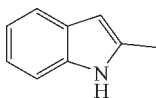
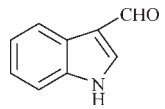
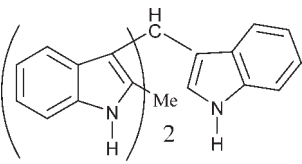
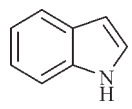
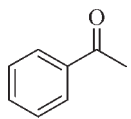
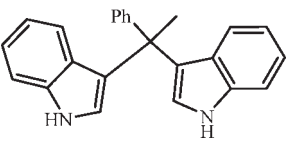
Table 1, entry 12: Solid; mp: 161°C(dec.); ¹H NMR (DMSO, 300 MHz): δ 6.08 (s, 1H), 6.89 (s, 3H), 6.87(t, 3H, *J* = 7.45 Hz), 7.02 (t, 3H, *J* = 7.25 Hz), 7.44 (d, 3H, *J* = 7.83 Hz), 7.56 (d, 3H, *J* = 7.83 Hz), 10.72 (s, 3H) ppm; ¹³C NMR (DMSO, 62.9 MHz): 30.8, 111.4, 117.5, 118, 119, 120.6, 124, 126.8, 136.5 ppm; MS (70 eV), *m/e*: 361 [M⁺]. Anal. Calcd. for (C₂₅H₁₉N₃): C, 83.08; H, 5.30; N, 11.63. Found: C, 83.10; H, 5.32; N, 11.65.

Table 1
Condensation of indoles with carbonyl compounds catalyzed by ZrO(DS)₂.

Entry	Indole	Substrate	Product	Time (min)	Isolated Yield%
					
1 ^a		X = H	X = H	20	95
2 ^a		X = 4-Me	X = 4-Me	30	95
3 ^a		X = 4-OMe	X = 4-OMe	45	96
4 ^a		X = 4-OH	X = 4-OH	25	94
5 ^a		X = 2-Me	X = 2-Me	45	96
6 ^a		X = 4-Br	X = 4-Br	15	95
7 ^a		X = 4-NO ₂	X = 4-NO ₂	15	97
8 ^b				20	96

(continued)

Table 1
(Continued)

Entry	Indole	Substrate	Product	Time (min)	Isolated Yield%
9 ^a				60	94
					
10 ^b		X = 4-OMe	X = 4-OMe	15	97
11 ^a		X = 4-NO ₂	X = 4-NO ₂	5	96
12 ^b				30	96
13 ^b				20	97
14 ^b				75	50

^a Reactions were carried out in water at 60°C.

^b Reactions were carried out in EtOH at room temperature.

All products were identified by their spectroscopic data and their comparison with known samples [7–12].

Table 2
Reaction of indole with benzaldehyde in the presence of different catalysts.

Entry	Catalyst/solvent	Catalyst (mol %)	Time (h)	Yield (%)	Reference
1	ZrO(DS) ₂ /H ₂ O	10	20 min	97	
2	Dy(OTf) ₃ / EtOH.H ₂ O	10	12	95	[19]
3	HMTAB ^a /H ₂ O	0.1 g	2.5	86	[20]
4	FeCl ₃ .6H ₂ O/[omim]PF ₆	5	1.5	98	[21]

^a Hexamethylenetetraamine-bromine.

Acknowledgment. Support for this work by Research Council of University of Birjand is highly appreciated.

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