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Zirconium oxy dichloride octahydrate: a green Lewis acid catalyst for the synthesis of novel 3-[(alkyl/arylthio)(aryl)methyl]-1H-indoles

Kobra Nikoofar[1] · **Samareh Gorji**[1]

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Abstract Some novel 3-[(alkyl/arylthio)(aryl)methyl]-1H-indoles (**4a–h**) are prepared via a one-pot, three-component, and domino reaction of indoles, aromatic aldehydes, and various (hetero) aromatic thiols in the presence of zirconium oxy dichloride octahydrate as an efficient green Lewis acid catalyst. Mild reaction conditions, simple reaction procedure, good yields of products, inexpensive and eco-friendly catalyst usage, lack of by-products formation, such as dithioacetals from aromatic aldehydes, as well as bis(indolyl)methanes, are the highlighted points of the presented protocol.

Keywords Multi-component reaction · Indoles · Thiophenols · $ZrOCl_2 \cdot 8H_2O$ · Aromatic aldehydes

Introduction

Indole and its derivatives have attracted much interest in the recent century owing to their extensive biological activities [1]. This nucleus has also appeared in various naturally occurring compounds such as alkaloids and tryptophan metabolites [2]. The indole moiety has also frequently been found in agrochemicals such as auxins and plant growth regulators [3, 4]. The 3-Substitited indoles have played major roles in the preparation of privileged medicinal scaffolds [5–7]. They possess a wide range of biological activities such as antioxidants, antibacterials, anti-insecticidals, and anticancer activity as well as antibiotic central nervous system modulation [8–10]. In addition, compounds with indole motifs can be utilized as enzyme inhibitors and receptor antagonists, anti-inflammatories and fr anti-swelling tumors [11–13]. In addition, they have obtained a critical role in the areas of bioorganic materials,

✉ Kobra Nikoofar
kobranikoofar@yahoo.com

[1] Department of Chemistry, Faculty of Physics & Chemistry, Alzahra University, Tehran, Iran

electro materials, and optomaterials [14, 15]. More importantly, indole derivatives have also pronounced effects in many physiological processes [16].

Functionalization of indoles is an important branch in organic chemistry that allows them to be utilized as important synthons. Interestingly, 3-substituted indole compounds owning sulfur atoms are very rare [17, 18]. As a matter of fact, the synthesis of sulfur-containing compounds is highly desirable because they might exhibit novel pharmacological activities [19, 20].

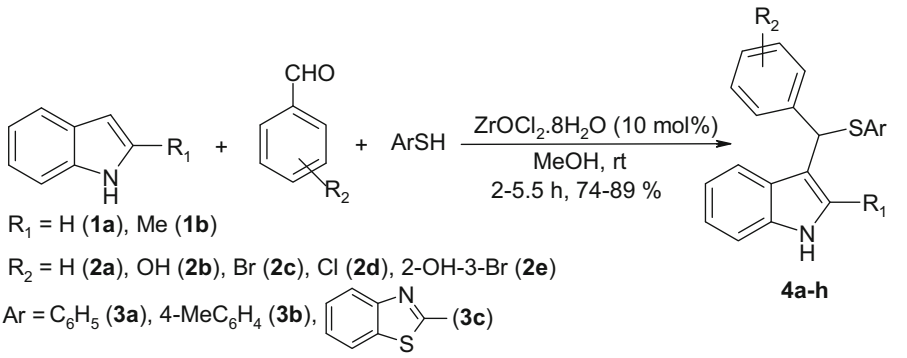
Multicomponent reactions (MCRs) in which three or more compounds have combined together to prepare a product, are a straightforward and atom-economic synthetic approach that offers highlighted advantages over conventional multi-step reaction sequences. In these protocols a complex library of compounds could be prepared without the need of intermediates isolation, which minimize waste, time, and cost [21–24]. In recent years there are many publications based on MCRs that have been observed, which affirms their highlighted applications in organic and medicinal chemistry [25–27]. Among them, electrophilic condensation of a carbonyl group with two different nucleophiles (various activated methylene compounds such as 1,3-cyclohexanedione, dimedone, 4-hydroxycoumarin, and 2-hydroxy-1,4-naphthoquinone, and some nucleophilic substrates like indoles, and thiophenols) are in highlighted demand as the conditions must be in a manner that no symmetrical by-products must appear via the reaction of aldehyde with two molecules of the same nucleophile [28, 29].

Zirconium(IV) oxy dichloride octahydrate ($ZrOCl_2{\cdot}8H_2O$) is an eco-friendly Lewis acid with the LD_{50} (oral rat) = 2950 mg kg^{-1} [30]. Zr^{4+} with high charge-to-size ratio (22.22 e^2 m^{-10}), that helps this salt to possess high coordinating ability which helps it to exhibit strong Lewis acid behavior and high catalytic activity [31]. The low toxicity, availability, low cost, moisture stability, ease of handling, recovery and reusability, safe potential catalytic activity, insensitivity to air, and good general stability make this salt a green Lewis acid catalyst for various useful organic transformations with increasing environmental concerns [32, 33].

On the basis of our research activity about indole derivatives [34–44], herein we report a mild and efficient procedure for the one-pot, three-component, and domino condensation of indoles, aromatic aldehydes, and (hetero) aromatic thiols in the presence of $ZrOCl_2{\cdot}8H_2O$ as efficient Lewis acids in methanol at room temperature to yield the corresponding 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles (Scheme 1).

Experimental

All the chemicals, and solvents were purchased from Merck, Aldrich, and Alfa Aesar and used without further purification. IR spectra were recorded from a KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were determined on a Shimadzu DSC-50 thermal analyzer and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker drx (400 MHz) machine. Elemental analyses were determined using a Thermo-Finnigan Flash EA 1112 Series. Progress of the reaction was monitored by thin layer chromatography (TLC) techniques using commercially available silica gel sheets. Preparative layer chromatography (PLC)



Scheme 1 Synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1H-indoles **4**

was carried out on 20 × 20 cm^2 plates, coated with a 1 mm layer of Merck silica gel $PF2_{54}$, prepared by applying the silica as slurry and drying in air. The products were characterized by their melting points and also FT-IR, ^{1}H NMR, and CHN analysis.

General procedure for the synthesis of 4a–h

In a round bottom flask (50 mL), a solution of indoles **1** (1 mmol) and aldehydes **2** (1 mmol) in methanol (5 mL) was stirred for 30 min in the presence of $ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), to obtain the imine intermediate, which was detected by TLC. Then, thiols **3** (1 mmol) was added to the mixture and continuously stirred for the appropriate time. The progress of the reaction was monitored by TLC (eluent: *n*-hexane–EtOAc, 2:1). After completion of the reaction, the solvent was evaporated, and the catalyst was isolated by extraction with EtOAc (2 × 10 mL). The organic layer was subjected to preparative thin-layer chromatography on silica gel to afford the pure products **4**. Spectral data of new commands are given below.

*3-[(p-Hydroxyphenyl)(phenylthio)methyl]-1H-indole (**4c**)*

M.p. 84 °C. IR (KBr, cm^{-1}): 3442 (NH, OH), 2925, 2856, 1685, 1553, 1428, 656 (C–S). ^{1}H NMR (400 MHz, DMSO-d_6): 7.72 (d, J = 11.04 Hz, 1H), 7.56 (d, J = 11.12 Hz, 1H), 7.51–7.46 (m, 1H), 7.45 (s, 1H, OH), 7.27–7.13 (m, 5H), 7.23 (s, 1H, NH), 6.86 (t, J = 10.08 Hz, 2H), 6.78 (s, 1H), 6.73–6.75 (m, 2H), 6.64 (t, J = 9.91 Hz, 2H). Anal. calcd. for $C_{21}H_{17}NSO$: C, 76.10; H, 5.17; N, 4.22 %, Found: C, 76.05; H, 5.11; N, 4.12 %.

*3-[(p-Chlorophenyl)(phenylthio)methyl]-1H-indole (**4e**)*

M.p. 152 °C. IR (KBr, cm^{-1}): 3414 (NH), 3148, 3054, 2925, 2858, 1596, 1486, 746 (C–Cl), 650 (C–S). ^{1}H NMR (400 MHz, DMSO-d_6): 7.79 (d, J = 11.16 Hz, 1H),

7.59 (d, $J = 11.24$ Hz, 1H), 7.52–7.47 (m, 1H), 7.25–7.19 (m, 5H), 7.29 (s, 1H, NH), 6.89 (t, $J = 10.04$ Hz, 2H), 6.77 (s, 1H), 6.73–6.75 (m, 2H), 6.60 (t, $J = 9.95$ Hz, 2H). Anal. calcd. for $C_{21}H_{16}NSCl$: C, 72.09; H, 4.61; N, 4.00 %, Found: C, 71.98; H, 4.52; N, 3.91 %.

*3-[(o-Hydroxy-m-bromophenyl)(4-methylphenylthio)methyl]-1H-indole (**4f**)*

M.p. Liquid. IR (KBr, cm^{-1}): 3416 (NH, OH), 3023, 2921, 2863, 1648, 1486, 1307, 626 (C–Br), 703 (C–S). ^{1}H NMR (400 MHz, DMSO-d_6): 2.25 (s, 3H, CH_3), 5.93 (s, 1H), 6.75–6.78 (m, 1H), 7.08–7.11 (m, 4H), 7.17–7.21 (m, 6H), 7.15 (s, 1H, NH), 7.36 (s, 1H), 7.38 (s, 1H, OH). Anal. calcd. for $C_{22}H_{18}NSOBr$: C, 62.26; H, 4.27; N, 3.30 %, Found: C, 61.97; H, 4.15; N, 3.15 %.

*3-[(o-Hydroxy-m-bromophenyl)(4-methylphenylthio)methyl]-1H-2-methylindole (**4g**)*

M.p. Liquid. IR (KBr, cm^{-1}): 3369 (NH, OH), 3025, 2922, 2860, 1484, 1411, 626 (C–Br), 696 (C–S). ^{1}H NMR (400 MHz, DMSO-d_6): 2.26 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 5.91 (s, 1H), 6.74–6.77 (m, 1H), 7.05–7.12 (m, 4H), 7.18–7.22 (m, 5H), 7.33–7.36 (m, 2H), 7.16 (s, 1H, NH), 7.40 (s, 1H, OH). Anal. calcd. for $C_{23}H_{20}NSOBr$: C, 63.01; H, 4.59; N, 3.19 %, Found: C, 62.90; H, 4.52; N, 3.01 %.

*3-[(p-Chlorophenyl)(2-mercaptobenzothiazolothio)methyl]-1H-indole (**4h**)*

M.p. 112 °C. IR (KBr, cm^{-1}): 3407 (NH), 3053, 2925, 1617, 1456, 1412, 1092, 742 (C–Cl), 590 (C–S). ^{1}H NMR (400 MHz, DMSO-d_6): 7.61 (s, 1H, NH), 7.28–7.19 (m, 2H), 7.18–7.15 (m, 1H), 7.02–6.15 (m, 10H), 4.7 (s, 1H). Anal. calcd. for $C_{22}H_{15}N_2S_2Cl$: C, 64.93; H, 3.71; N, 6.88 %, Found: C, 64.72; H, 3.61; N, 6.54 %.

Results and discussion

Initial studies were performed using indole (**1a**), 4-chlorobenzaldehyde (**2d**), and 2-mercapto benzimidazole (**3c**) as a model reaction. All the checking tests on this model reaction, have been fulfilled as in a domino manner in which **1a** and **2d** were added to the flask and, after a time, **3c** was imported to the reaction mixture. Accordingly, preliminary experiments were carried out in the presence of $ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%) in different solvents and also under solvent-free conditions at room temperature (Table 1, entries 1–4). The results confirmed that MeOH is the best media. Next, the effect of temperature has been examined on the model reaction. The reaction was accomplished well at room temperature (entries 4–7). Finally, the catalyst amount was investigated for the model reaction progress in methanol at room temperature. The data of entries 8–10 show that the best amount is 10 mol% of the Lewis acid catalyst usage. Surprisingly, we found that increasing the catalyst amount from 10 mol% to upper dosages, decreased the reaction promotion (entries 8–10). The model reaction was also repeated in a one-

Table 1 Screening the reaction conditions for the synthesis of 3-[(*p*-Chlorophenyl)(2-mercaptobenzothiazolothio)methyl]-*1H*-indole (**4h**)

Entry	Conditions[a]	Yield (%)[b]	Time (h)
1	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), solvent-free, rt	54	3
2	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), C_2H_5OH, rt	40	3
3	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), CH_3CN, rt	62	4.30′
4	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), CH_3OH, rt	87	2
5	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), CH_3OH, 40 °C	35	5
6	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), CH_3OH, 60 °C	50	5.30′
7	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), CH_3OH, reflux	50	4
8	$ZrOCl_2{\cdot}8H_2O$ (0.002 g, 20 mol%), CH_3OH, rt	70	3.15′
9	$ZrOCl_2{\cdot}8H_2O$ (0.003 g, 30 mol%), CH_3OH, rt	60	3
10	$ZrOCl_2{\cdot}8H_2O$ (0.0005 g, 5 mol%), CH_3OH, rt	37	5
11[c]	$ZrOCl_2{\cdot}8H_2O$ (0.001 g, 10 mol%), CH_3OH, rt	31	5
12	$FeCl_3$ (0.016 g, 10 mol%), CH_3OH, rt	78	4
13	$AlCl_3$[d] (0.013 g, 10 mol%), CH_3OH, rt	64	5

[a] All the reactions were performed in an indole/4-chlorobenzaldehyde/2-mercapto benzimidazole mole ratio of 1:1:1. For this, 5 mL of each solvent were used

[b] Isolated yields

[c] All the substrates and catalyst were added in a one-step mode

[d] The sublimated form was used

step mode, but the results were not satisfactory (entry 11). Different by-products have been observed, which could be due to dithioacetals and bis(indolyl)methanes. For comparison, some other Lewis acids such as $FeCl_3$ and $AlCl_3$ have also been examined. The results confirmed that $ZrOCl_2{\cdot}8H_2O$ is a better choice (entries 13, 14).

Next, using optimized conditions (indoles/aldehydes/thiols mole ratio of 1:1:1 in methanol in the presence of 10 mol% of $ZrOCl_2{\cdot}8H_2O$ at room temperature) various 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles, as novel sulfur containing heterocycles, were prepared (Table 2).

According to Table 2, the one-pot domino condensation of indole (**1a**), benzaldehyde (**2a**), and thiophenol (**3a**) provided the corresponding heterocycle successfully (entry 1). The 4-Methyl thiophenol, as an electron donating aromatic thiol, produced the corresponding sulfur-heterocycle in better yield in comparison to thiophenol (entry 2). 4-Hydroxy- and 4-chloro benzaldehdye condensed with indole and thiophenol in shorter reaction times than bezaldehdye (entries 3 and 5). The 3-[(*p*-bromophenyl)(4-methylphenylthio)methyl]-1*H*-indole (**4d**) was also been gained within 3 h (entry 4). The reaction of 2-hydroxy-5-bromo-benzaldehdye (**2e**), 4-methyl thiophenol (**3b**) with both indole (**1a**) and 2-methylindole (**1b**) led their corresponding products successfully. Using 2-mercaptobenzothiazole, as a heteroaromatic thiol, also produced **4h** within 2 h by 87 % yield (entry 8). According to data of Table 2, no significant relationship for electron donating as well as electron withdrawing substituents have been observed.

Table 2 Preparation of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles (**4a–h**)

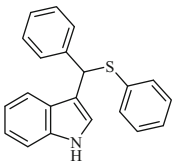
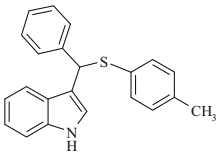
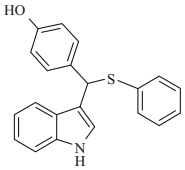
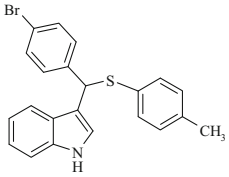
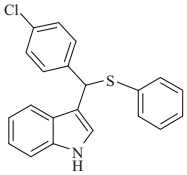
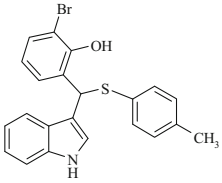
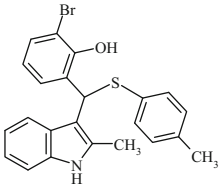
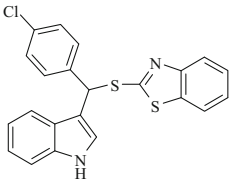
Entry	Indole	Aldehyde	Thiol	Product[a]		Time (h)	Yield (%)[b]	Mp (°C)[c]
1	**1a**	**2a**	**3a**		**4a**	5	74	Semi solid [15]
2	**1a**	**2a**	**3b**		**4b**	4.30′	82	Semi solid [15]
3	**1a**	**2b**	**3a**		**4c**	3	78	84
4	**1a**	**2c**	**3b**		**4d**	3	79	Oil [15]
5	**1a**	**2d**	**3a**		**4e**	3	89	152
6	**1a**	**2e**	**3b**		**4f**	5.30′	85	Liquid
7	**1b**	**2e**	**3b**		**4g**	5.25′	85	Liquid

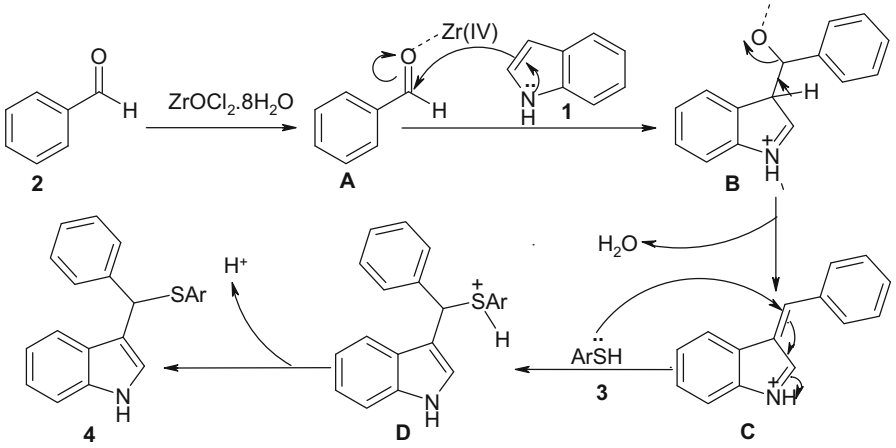
Table 2 continued

Entry	Indole	Aldehyde	Thiol	Product[a]		Time (h)	Yield (%)[b]	Mp (°C)[c]
8	**1a**	**2d**	**3c**		**4h**	2	87	112

[a] The products were identified from their spectral data and by comparison with authentic samples

[b] Isolated yields

[c] Refrence of known compounds



Scheme 2 The plausible mechanism for the synthesis of 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles

A plausible mechanism for this reaction is proposed in Scheme 2. It has been postulated that $ZrOCl_2{\cdot}8H_2O$ activated the carbonyl group of the aldehyde to form **A**. This activated complex could be attacked by indole as a nucleophile to obtain the iminium ion **B** that followed by dehydration and thia-Michael addition of thiol **3** to create the intermediate **D**. Finally deprotonation produced the product **4**.

Conclusions

In conclusion, the one-pot, three-component, and domino condensation of indoles, aldehydes, and thiols to afford the correspondence 3-[(alkyl/arylthio)(aryl)methyl]-1*H*-indoles has been performed. This successful condensation showed highlighted advantages such as (1) using eco-friendly, commercially available, non-toxic, and

water tolerant $ZrOCl_2 \cdot 8H_2O$ as effective Lewis acid catalysts for progression of the reaction, (2) avoidance of the formation of dithioacetals and bis(indolyl)methans as by-products, (3) a one-pot MCR affording excellent yields under mild conditions, and (4) preparing a class of novel sulfur-containing indole heterocycles, which could be a potent candidate for medicinal chemistry. These noteworthy points make the method a green, convenient, and efficient method in organic transformations.

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