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$ZrOCl_2.8H_2O$ as an Efficient Catalyst for the Three-Component Synthesis of Triazoloindazoles and Indazolophthalazines

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ABSTRACT. An efficient and environmentally benign protocol for the three-component synthesis of triazoloindazoles and indazolophthalazines via condensation of dimedone, aldehydes and urazole or phthalhydrazide catalyzed by $ZrOCl_2.8H_2O$ as an inexpensive and eco-friendly catalyst with high catalytic activity under solvent-free conditions is reported. This protocol provides a new and improved method for obtaining triazoloindazoles and indazolophthalazines in terms of good yields, simple experimental procedure and short reaction time.

Key words: Solvent-free, $ZrOCl_2.8H_2O$, Indazolophthalazines, Triazoloindazoles

INTRODUCTION

Functionalized nitrogen-heterocycles play a prominent role in medicinal chemistry and they have been intensively used as scaffolds for drug development.[1,2] In this context heterocycles containing urazole or phthalazine moiety are of particular interest because of their pharmacological profile. Some urazole derivatives were found to have some biological as well as pharmaceutical activity, such as anti-cancer and hypolipidemic.[3] Urazole derivatives also exhibit anticonvulsant[4] or fungicidal activity.[5] These compounds are also used in the preparation of herbicides,[6] pesticides,[7] and insecticides.[8] Similarly, phthalazine derivatives were reported to possess anticonvulsant,[9] cardiotonic,[10] and vasorelaxant[11] activities. These compounds have also proved to be promising luminescence materials and fluorescence probes.[12] Thus, the synthesis of urazole and phthalazine derivatives is an important and useful task in organic chemistry.

The use of zirconium(IV) salts as an efficient Lewis acid for various transformations, has been well documented in the literature, because of their easy availability, moisture stability and low toxicity.[13–15] Among the various types of Zr(IV) salts, particularly, $ZrOCl_2.8H_2O$ has advantages of moisture stability, readily availability and easy handling.[14] Also, the low toxicity of $ZrOCl_2.8H_2O$ is evident from their LD50 [LD50 ($ZrOCl_2.8H_2O$, oral rat) = 3500 mg/kg].[15] Therefore, the application of $ZrOCl_2.8H_2O$ in organic synthesis is of renewed interest.

As part of our research aimed at developing new methods for the preparation of biologically interesting heterocycles,[16,17] recently, for the first time we have reported synthesis of triazoloindazoles and indazolophthalazines via condensation of dimedone, aldehydes and urazole or phthalhydrazide in the presence of *p*-TSA as an acidic catalyst.[18,19] Very recently, these three-component protocols utilizing different types of catalysts have been reported.[20–25] The reported methods show varying degrees of successes as well as limitations. Therefore, there still remains a high demand for the development of more general, efficient, economically viable, and eco-compatible protocol to assemble such scaffolds. Due to unique advantages of $ZrOCl_2.8H_2O$, the aim of our research described here was to develop the three-component synthesis of triazoloindazoles and indazolophthalazines employing $ZrOCl_2.8H_2O$ as an efficient and mild Lewis acid catalyst.

EXPERIMENTAL

General Procedure

A mixture of dimedone (1 mmol), aldehyde (1 mmol), urazole or phthalazide (1 mmol) and $ZrOCl_2.8H_2O$ (30 mol%) was stirred at 80 ºC for 1 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was washed with H_2O (5 ml) and EtOH (5 ml) to afford pure product **4**.

All the products are known and were fully characterized by a comparison with authentic samples (melting point) and IR spectra.[18,19]

Selected characterization data:

6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-chlorophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4b). White powder (87%); mp 164–166 °C. IR (KBr) (ν_{max}, cm^{-1}): 2932, 1725, 1646, 1381; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (6H, s, $2CH_3$), 2.33 (2H, s, CH_2), 2.88 (2H, AB system, J = 18.7 Hz, CH_2), 6.19 (1H, s, CH), 7.34–7.50 (9H, m, H-Ar). MS *m*/*z*: 421 (M^+). Anal. Calcd for $C_{23}H_{20}ClN_3O_3$: C, 65.48; H, 4.78; N, 9.96%. Found: C, 65.40; H, 4.74; N, 9.89%.

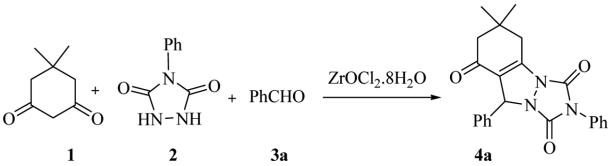
6,7-Dihydro-6,6-dimethyl-2-phenyl-9-(4-nitrophenyl)-[1,2,4]-triazolo[1,2-*a*]indazole-1,3,8(2*H*,5*H*,9*H*)-trione (4d). White powder (86%); mp 176–178 °C. IR (KBr) (ν_{max}, cm^{-1}): 2957, 1786, 1714, 1660. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.19 (3H, s, CH_3), 1.22 (3H, s, CH_3), 2.31 (2H, s, CH_2), 2.88 (2H, AB system, J = 18.7 Hz, CH_2), 6.32 (1H, s, CH), 7.40–8.18 (9H, m, H-Ar). MS *m*/*z*: 432 (M^+). Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96%. Found: C, 63.81; H, 4.73; N, 12.90%.

3,4-Dihydro-3,3-dimethyl-13-phenyl-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (6a). Yellow powder (82%). Mp 205–207 °C; IR (KBr) (ν_{max}, cm^{-1}): 2952, 1666, 1571; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (6H, s, 2Me), 2.36 (2H, s, CH_2), 3.23 and 3.43 (2H, AB system, J = 18.4 Hz, CH_2), 6.42 (1H, s, CHN), 7.33–8.35 (9H, m, Ph); MS, *m*/*z*: 372 (M^+). Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%. Found: C, 74.24; H, 5.46; N, 7.44%.

3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (6b). White powder (89%); mp 261–263 °C; IR (KBr) (ν_{max}, cm^{-1}): 2925, 1653, 1620; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.22 (3H, s, Me), 1.24 (3H, s, Me), 2.32 (2H, s, CH_2), 3.22 and 3.39 (2H, AB system, J = 18.6 Hz, CH_2), 6.45 (1H, s, CHN), 7.29–8.30 (8H, m, Ph); MS, *m*/*z*: 406 (M^+). Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%. Found: C, 67.97; H, 4.65; N, 6.83%.

RESULTS AND DISCUSSION

Initially, the reaction of dimedone 1 (1 mmol), urazole 2 (1 mmol) and benzaldehyde 3a (1 mmol) as a simple model substrate in the presence of $ZrOCl_2.8H_2O$ in different solvents and under solvent-free conditions was investigated to optimize the reaction conditions (*Scheme* 1). It was found that the reaction under solvent-free conditions after 1 h resulted in the higher isolated yield (*Table* 1). Similarly, the molar ratio of $ZrOCl_2.8H_2O$ was studied with the optimum amount being 30 mol% (entry 5). When this reaction was carried out without $ZrOCl_2.8H_2O$ the yield of the expected product was trace (entry 8).



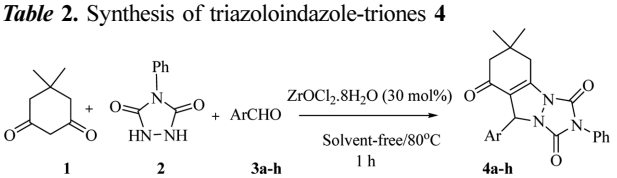
***Scheme* 1.**

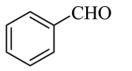
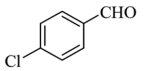
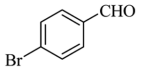
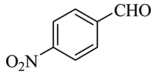
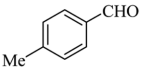
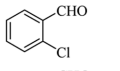
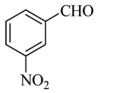
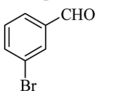
***Table* 1.** Screening of the reaction conditions

Entry	Solvent	$ZrOCl_2.8H_2O$ (Mol%)	Time (h)	Yield (%)
1	H_2O	30	8	Trace
2	EtOH	30	8	53
3	CH_3CN	30	8	<30
4	$CHCl_3$	30	8	Trace
5	S.F.	30	1	85
6	S.F.	35	15	85
7	S.F.	25	1	73
8	S.F.	-	6	Trace

Using the optimized conditions, the generality of this reaction was examined using several types of aromatic aldehydes **3a–h**. In all cases, the reactions gave the corresponding products in good isolated yields (*Table* 2). These reactions proceeded very cleanly under mild con-

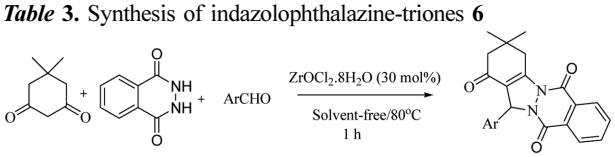
***Table* 2.** Synthesis of triazoloindazole-triones **4**



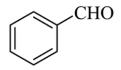
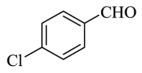
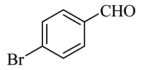
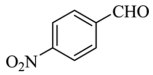
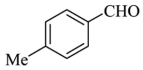
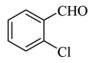
Product **4**	Aldehyde **3**	Yield (%)
a		85(85,83)[a]
b		83
c		81
d		86
e		79
f		84
g		88
h		83

[a]Isolated yield after recycling of catalyst

***Table* 3.** Synthesis of indazolophthalazine-triones **6**



1 5 3 6

Product **6**	Aldehyde **3**	Yield (%)
a		82
b		89
c		84
d		88
e		80
f		85
h		82

ditions and no side reactions were observed.

Another advantage of this approach could be related to the reusability of the catalyst. We found that the catalyst could be separated from the reaction mixture simply by washing with water and reused after washing with CH_2Cl_2 and dried at 60 °C. The reusability of the catalyst was checked by the reaction of dimedone **1**, urazole **2** and benzaldehyde **3a** under optimized reaction conditions. The results show that the catalyst can be used effectively three times without any loss of its activity (*Table* 2, entry 1). Therefore, the recyclability of the catalyst makes the process economically and potentially viable for commercial applications.

To further explore the potential of $ZrOCl_2.8H_2O$, we investigated reaction of phthalhydrazide **5** and dimedone **1** with aldehydes **3** and obtained 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione **6** in good isolated yields under the same reaction conditions (*Table* 3).

CONCLUSION

In conclusion, we have demonstrated that $ZrOCl_2.8H_2O$ can be used as green and reusable catalyst for efficient synthesis of triazoloindazoles and indazolophthalazines under solvent-free conditions. Moreover, the cheapness, easy availability of the reagent, easy and clean workup makes this method attractive for organic chemist.

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