

12-20-2020

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Recommended Citation

Mohamadpour, Farzaneh (2020) "Efficient and Mild Four-component Process for the Synthesis of Highly Substituted Dihydro-2-oxopyrroles using $ZrOCl_2 \cdot 8H_2O$ as an Environmental-ly Friendly Catalyst," *Makara Journal of Science*: Vol. 24 : Iss. 4 , Article 2.

DOI: 10.7454/mss.v24i4.1212

Available at: <https://scholarhub.ui.ac.id/science/vol24/iss4/2>

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Efficient and Mild Four-component Process for the Synthesis of Highly Substituted Dihydro-2-oxopyrroles using $ZrOCl_2 \cdot 8H_2O$ as an Environmentally Friendly Catalyst

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Received May 15, 2019 | Accepted August 5, 2020

Abstract

This study investigated the catalytic ability of $ZrOCl_2 \cdot 8H_2O$ as a mild, environmentally benign nature, and economical catalyst for the multi-component efficient synthesis of biologically active highly substituted dihydro-2-oxopyrrole derivatives with excellent yields and short reaction times. This procedure has several advantages, including use of mild, nontoxic, and inexpensive catalysts, one-pot synthesis, environmentally benign nature, simple operational procedure, and highly efficient conditions.

Keywords: $ZrOCl_2 \cdot 8H_2O$, highly substituted dihydro-2-oxopyrroles, environmentally friendly catalyst, high atom economy

Introduction

Recent studies have focused on the synthesis of heterocyclic compounds. Organic compounds containing nitrogen-heterocyclic rings are important compounds in medicinal chemistry. The synthesis of biologically active pyrrole rings has received considerable attention because of their advantages in biological and pharmaceutical products, such as cytomegalovirus protease [1], CD45 protein tyrosinphosphatase [2], anti-cancer [3], thiomarinol A4 antibiotic [4], alkaloids [5], UCS1025A [6], and oteromycin [7]. These rings have been used in HIV integrase [8], and they also show herbicidal [9] activities. In recent years, various catalysts have been utilized to prepare compounds. These catalysts include $Cu(OAc)_2 \cdot H_2O$ [10], $InCl_3$ [11], I_2 [12], $AcOH$ [13], $[n-Bu_4N][HSO_4]$ [14], $Al(H_2PO_4)_3$ [15], oxalic acid [16], $ZrCl_4$ [17], glutamic acid [18], caffeine [19], and glycine [20]. However, these catalysts have some disadvantages, such as difficult work-up, toxicity, and high cost. Moreover, they cause long reactions and low yields.

Multi-component domino reactions have recently attracted considerable interest [21–27] as powerful tools in the synthesis of organic compounds with biological and pharmaceutical properties because of their notable advantages, such as atom economy, environmental friendliness, low cost, one-pot, and simple work-up.

During the past decades, the use of zirconium compounds as catalysts in organic synthesis has attracted great interest because of their notable advantages, such as nontoxicity, environmental friendliness, easy to handle, high efficiency, and low cost [28]. The advantages of using $ZrOCl_2 \cdot 8H_2O$ as a catalyst [29–30] in the synthesis of organic compounds are mild, inexpensive, nontoxicity, environmentally benign nature, and high activity. In addition, we carried out one-pot multi-component condensations using $ZrOCl_2 \cdot 8H_2O$ as catalyst and obtained excellent yields in short reaction times.

On the basis of these findings, the development of a simple, clean, economical, and environmentally safe method for the synthesis of these compounds has become the major aim of our research. Results revealed that $ZrOCl_2 \cdot 8H_2O$ is an efficient, environmentally benign, and economical catalyst for the one-pot, four-component synthesis of highly substituted dihydro-2-oxopyrrole derivatives.

Materials and Methods

General. The melting points of all compounds were determined using an Electro thermal 9100 apparatus. The 1H NMR spectra were recorded on Bruker DRX-400 Avance and Bruker DRX-300 Avance instruments with $CDCl_3$ as solvent. All reagents and solvents purchased from Merck, Fluka, and Acros chemical companies were used without further purification.

General procedure for the preparation of highly substituted dihydro-2-oxopyrroles (5a-t). A mixture of amine 1 (1.0 mmol) and dialkyl acetylenedicarboxylate 2 (1.0 mmol) was stirred in MeOH (3 mL) for 15 min. Then, amine 3 (1.0 mmol), formaldehyde 4 (1.5 mmol), and $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (15 mol%) were added, and the reaction was stirred for an appropriate time. After completion of the reaction (by thin layer chromatography), the mixture was separated with filtration and the solid washed with ethanol (3×2 mL) with no column chromatographic separation to produce pure compounds (5a-t). The catalyst is solvable in ethanol and was removed from the reaction mixture. Products were characterized by comparison of spectroscopic data (^1H NMR). Supporting Information associated with this article can be found in the online version.

Results and Discussion

The generality of this four-condensation reaction was studied under optimized conditions, and the reaction

between aniline, dimethyl acetylenedicarboxylate, and formaldehyde was investigated as a model reaction. The effect of different amounts of catalyst in MeOH as a solvent was studied in this protocol. In the absence of a catalyst, a trace amount of this product was detected after 12 h (Table 1, entry 1). Good yields were obtained in the presence of a catalyst. The optimum catalyst amount was 15 mol% (Table 1, entry 4). Increasing further the catalyst amount did not increase the product yield (Table 1, entry 12). In addition, the effect of various solvents, including H_2O , EtOH, DMF, CHCl_3 , CH_3CN , and CH_2Cl_2 , was investigated for this protocol. Among these solvents, MeOH was the best for this methodology (Table 1, entry 4). Finally, a convenient, expedient and efficient procedure for the synthesis of highly substituted dihydro-2-oxopyrroles was described *via* the one-pot four-condensation of amines (aromatic or aliphatic 1 and 3), dialkyl acetylenedicarboxylate 2, and formaldehyde 4 under ambient temperature in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (Scheme 1).



Scheme 1. Synthesis of Highly Substituted Dihydro-2-oxopyrroles

Table 1. Optimization of the Reaction Condition in the Presence of Different Amounts of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ and Different Solvents on the Synthesis of 5a^a

Entry	$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (mol %)	Solvent	Time (h)	Isolated Yield (%)
1	Catalyst free	MeOH	12	trace
2	5	MeOH	7	41
3	10	MeOH	4	63
4	15	MeOH	3	88
5	15	Solvent free	8	30
6	15	H_2O	6	37
7	15	EtOH	4	69
8	15	DMF	5	52
9	15	CHCl_3	8	26
10	15	CH_3CN	5	58
11	15	CH_2Cl_2	8	21
12	20	MeOH	3	89

^aReaction conditions: aniline (2.0 mmol), dimethyl acetylenedicarboxylate (1.0 mmol) and formaldehyde (1.5 mmol) and catalyst in various solvents at room temperature.

Table 2. Synthesis of Highly Substituted Dihydro-2-oxopyrroles

Entry	R ¹	R ²	Ar	Product	Time (h)	Yield (%) ^a	M.p. °C	Lit.M.p. °C
1	Ph	Me	Ph	5a	3	88	154-156	155-156 ¹²
2	Ph	Et	Ph	5b	3	86	138-140	138-140 ¹³
3	4-OMe-C ₆ H ₄	Me	4-OMe-C ₆ H ₄	5c	3.5	87	175-177	172-175 ¹⁴
4	4-OMe-C ₆ H ₄	Et	4-OMe-C ₆ H ₄	5d	4	83	153-155	152-154 ¹⁵
5	4-Cl-C ₆ H ₄	Me	4-Cl-C ₆ H ₄	5e	4	81	171-173	171-173 ¹⁴
6	4-Cl-C ₆ H ₄	Et	4-Cl-C ₆ H ₄	5f	4	84	166-168	168-170 ¹⁴
7	4-F-C ₆ H ₄	Me	4-F-C ₆ H ₄	5g	2	90	163-165	163-165 ¹⁶
8	4-F-C ₆ H ₄	Et	4-F-C ₆ H ₄	5h	3	87	170-172	172-174 ¹⁴
9	4-Me-C ₆ H ₄	Me	4-Me-C ₆ H ₄	5i	2.5	85	177-179	177-178 ¹²
10	4-Me-C ₆ H ₄	Et	4-Me-C ₆ H ₄	5j	2.5	88	132-134	131-132 ¹³
11	4-Br-C ₆ H ₄	Me	4-Br-C ₆ H ₄	5k	4.5	78	176-178	175-177 ¹⁴
12	4-Br-C ₆ H ₄	Et	4-Br-C ₆ H ₄	5l	5	75	171-173	169-171 ¹³
13	n-C ₄ H ₉	Me	Ph	5m	3.5	84	58-60	60 ¹²
14	n-C ₄ H ₉	Me	3,4-Cl ₂ -C ₆ H ₃	5n	4	80	95-97	97-99 ¹⁵
15	n-C ₄ H ₉	Et	4-Br-C ₆ H ₄	5o	5	76	96-98	94-96 ¹⁵
16	PhCH ₂	Me	Ph	5p	4	85	140-142	140-141 ¹³
17	PhCH ₂	Me	4-F-C ₆ H ₄	5q	3	82	164-166	166-168 ¹⁵
18	PhCH ₂	Me	4-Br-C ₆ H ₄	5r	5	79	119-121	120-121 ¹²
19	PhCH ₂	Me	4-Cl-C ₆ H ₄	5s	5	81	145-147	147-148 ¹²
20	PhCH ₂	Et	Ph	5t	5	84	131-133	130-132 ¹³

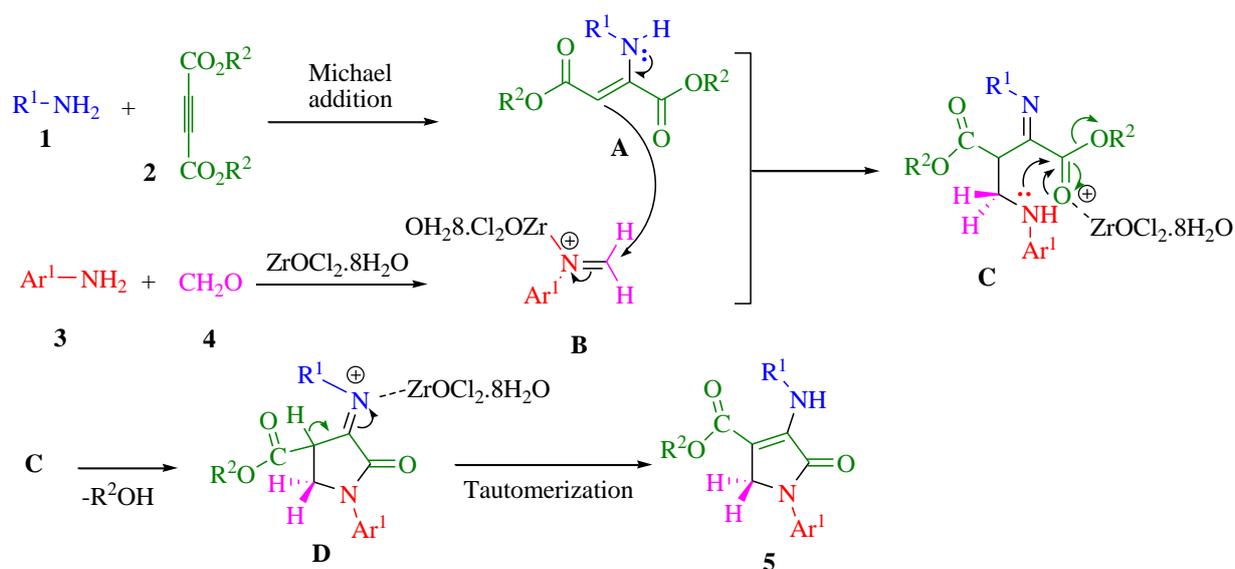
^a Isolated yield

Both classes of aromatic or aliphatic amines containing electron-releasing and electron-withdrawing substituent gained the appropriate products in excellent yields and short reaction times. The reaction times of aromatic or aliphatic amines having electron-withdrawing groups and electron-donating groups were similar. We also applied dialkyl acetylenedicarboxylate (methyl or ethyl). In each of these substitutions, no significant difference in reaction rate and product yield was found. The results are summarized in Table 2.

The proposed mechanism for the synthesis of highly substituted dihydro-2-oxopyrroles [17] in the presence of $ZrOCl_2 \cdot 8H_2O$ is illustrated in scheme 2. First, an amine (1) reacts with dialkyl acetylenedicarboxylate (2) to yield intermediate A. Second, condensation between amine 3 and formaldehyde 4 in the presence of $ZrOCl_2 \cdot 8H_2O$ produces imine B. Intermediate A possesses

an enamine character and can thus readily react with imine B in the presence of $ZrOCl_2 \cdot 8H_2O$ to generate intermediate C. Cyclization of intermediate C yields intermediate D, which tautomerizes to the corresponding highly substituted dihydro-2-oxopyrroles (5) in the final step.

A comparison of the catalytic ability of some of the catalysts as reported in the literature for the synthesis of highly substituted dihydro-2-oxopyrroles is shown in Table 3. Results demonstrate that $ZrOCl_2 \cdot 8H_2O$ shows extraordinary potential as an alternative environmentally friendly, inexpensive, and efficient catalyst for the one-pot synthesis of these biologically active heterocyclic compounds. Excellent yields and short reaction times are other notable advantages of this present methodology.



Scheme 2. Proposed Mechanistic Route for the Synthesis of Highly Substituted Dihydro-2-oxopyrroles

Table 3. Comparison of the Catalytic Ability of some of the Catalysts as Reported in the Literature for use in the Synthesis of Highly Substituted Dihydro-2-oxopyrroles

Entry	Compound	Catalyst	Condition	Time/Yield (%)	Reference
1	5a	Cu(OAc) ₂ ·H ₂ O	MeOH, r.t.	6h/91	[10]
2	5a	InCl ₃	MeOH, r.t.	3h/85	[11]
3	5a	I ₂	MeOH, r.t.	1 h/82	[12]
4	5a	[n-Bu ₄ N][HSO ₄]	MeOH, r.t.	4 h/88	[14]
5	5a	Al(H ₂ PO ₄) ₃	MeOH, r.t.	5 h/81	[15]
6	5a	ZrCl ₄	MeOH, r.t.	4 h/84	[17]
7	5a	ZrOCl₂·8H₂O	MeOH, r.t.	3 h/88	This work
8	5b	Cu(OAc) ₂ ·H ₂ O	MeOH, r.t.	5h/85	[10]
9	5b	InCl ₃	MeOH, r.t.	3h/85	[11]
10	5b	I ₂	MeOH, r.t.	1 h/81	[12]
11	5b	[n-Bu ₄ N][HSO ₄]	MeOH, r.t.	4 h/86	[14]
12	5b	Al(H ₂ PO ₄) ₃	MeOH, r.t.	5 h/80	[15]
13	5b	ZrCl ₄	MeOH, r.t.	3.5 h/83	[17]
14	5b	ZrOCl₂·8H₂O	MeOH, r.t.	3 h/86	This work

Conclusion

We have studied an efficient, environmentally benign nature and economical catalyst for the one-pot four-component synthesis of highly substituted dihydro-2-oxopyrrole derivatives. ZrOCl₂·8H₂O has catalyzed the synthesis of these bioactive compounds under mild reaction conditions. Notable advantages of this procedure include use of mild, nontoxic, and inexpensive catalysts, one-pot synthesis, environmentally benign nature, simple operational procedure, and highly efficient conditions.

Acknowledgements

We gratefully acknowledge the financial support from the Research council of the Apadana Institute of Higher Education.

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