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Chemistry

$ZnCl_2$-CATALYZED FOUR-COMPONENT DOMINO REACTION FOR ONE-POT ECO-SAFE AND CONVENIENT SYNTHESIS OF POLYFUNCTIONALIZED DIHYDRO-2-OXOPYRROLES AT AMBIENT TEMPERATURE

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Abstract. In this study, $ZnCl_2$ was applied as an environmentally friendly and efficient Lewis acid catalyst for the one-pot four-component synthesis of polysubstituted dihydro-2-oxopyrroles from the reaction between dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at ambient temperature. This methodology has a number of advantages such as use of inexpensive, eco-safety of catalyst, short reaction times, high yields, easy work-up (just simple filtration), and simplicity of operation**.** All products are characterized by comparison of FT-IR and ^{1}H NMR spectroscopic data.

Keywords: $ZnCl_2$, polysubstituted dihydro-2-oxopyrroles, catalyst, one-pot synthesis, FTIR, ^{1}H NMR spectroscopy.

1. Introduction

The development of novel methodologies that reduce pollution during chemical synthesis has received considerable attention due to increasing environmental concerns. In this context, one active area is the utilization of eco-friendly solid catalysts instead of conventional toxic and polluting catalysts. These solid catalysts have many other advantages such as operational simplicity, low cost, nontoxicity, and ease of preparation, handling and isolation. On the other hand, multi-component reactions (MCRs) [1-6] are the most powerful tools to access diverse complex molecular scaffolds. MCRs have merits over conventional multistage syntheses in several aspects including time and energy saving, high yields, no separation of intermediates and, consequently, the reduction of solvents and waste. Therefore, the development of new MCRs using eco-friendly solid catalysts is highly valuable. Synthesis of nitrogen containing heterocycles such as pyrroles and its derivatives is very important because of their pharmacology and biological properties. In this context, dihydro-2-oxopyrroles exhibit diverse biological activity such as inhibitors of the anneexin A2-S100A10 protein interaction [7], they have been used as Pl-091 [8], many of number alkaloids with biological activities have pyrrole rings [9], cardiac cAMP phosphodiesterase [10]. In addition, these rings have been used HIV integrase [11], have anti-cancer [12] activities and have been used as UCS1025A [13], Oteromycin [14]. Some example containing a heterocyclic dihydro-2-oxopyrrole rings with biological activities have been shown in Fig. 1.

Recently, some methods have been reported for the synthesis of polyfunctionalized dihydro-2 oxopyrroles by means of one-pot four-component reactions of dialkyl acetylenedicarboxylate, formaldehyde and amines using catalyst such as I_2 [15], $InCl_3$ [16], [*n*-Bu_4N][HSO_4] [17], $Al(H_2PO_4)_3$ [18], AcOH [19], oxalic acid [20], $Cu(OAC)_2{\cdot}H_2O$ [21]. However, many of these methods suffer from long reaction times, expensive reagents, and strong acidic conditions. During the past decades, the use of zinc compounds as environmental safe catalysts in organic synthesis have attracted great interest due to their notable advantages such as non-toxic, environmental friendliness, ease of handling, high efficient and low cost [22, 23]. Therefore, considering the importance of pyrrole derivatives, and in continuation of our ongoing program for the synthesis of heterocyclic compounds, herein, we report the eco-safe and highly effective formation of polyfunctionalized dihydro-2-oxopyrroles through a domino, one-pot, four-component condensation reaction between amines (aromatic or aliphatic **1** and **3**), dialkylacetylenedicarboxylate **2** and formaldehyde **4** in the presence of $ZnCl_2$ as a highly reactive, non-toxic, and easy to handle eco-friendly Lewis acid catalyst under ambient temperature (Scheme 1).

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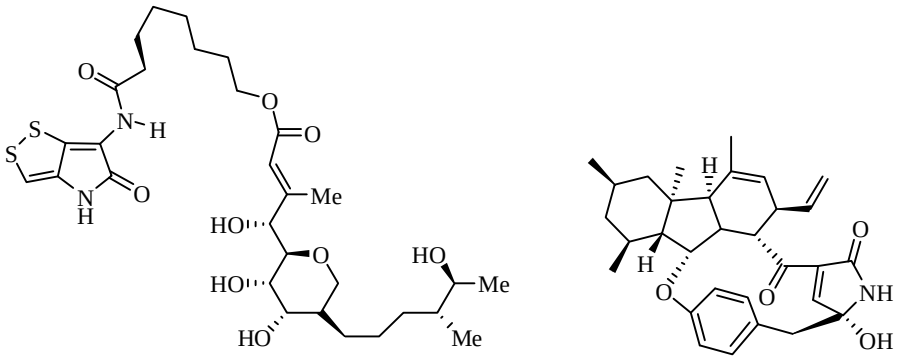
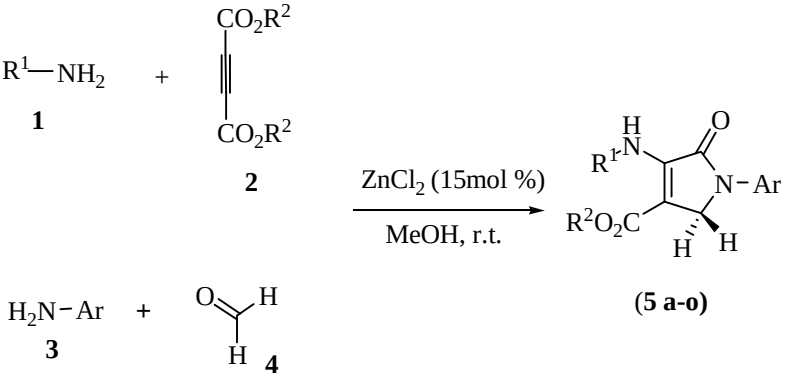


Thiomarinol A 4 **Pyrrocidine A**

Fig. 1. Biologically active compounds with dihydro-2-oxopyrrole rings



Scheme 1. Synthesis of polysubstituted dihydro-2-oxopyrroles

2. Experimental

Melting points and IR spectra of all compounds were determined using an Electro thermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer. Also, nuclear magnetic resonance, ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent. All reagents and solvents were purchased from Merck, Fluka and Across chemical companies and were used without further purification.

2.1. General Preparation Procedure for Polysubstituted Dihydro-2-oxopyrroles (5a-o)

A mixture of amine **1** (1.0 mmol) and dialkyl acetylenedicarboxylate **2** (1.0 mmol) was stirred in MeOH (3 ml) for 15 min. Next, amine **3** (1.0 mmol), formaldehyde **4** (1.5 mmol) and $ZnCl_2$ (15 mol %) were added and the mixture was stirred for appropriate time. After completion of the reaction (by thin layer chromatography TLC), the mixture was separated by filtration and the solid was washed with ethanol (3×2 ml) with no column chromatographic separation to give pure compounds (**5a-o**). The formulae of **5a-o** are given below in Table 3. Some of the components are characterized by comparison of spectroscopic data (FT-IR, ^{1}H NMR). Due to the fact that all the synthesized compounds in this paper were known, spectral data (^{1}H NMR) were used only to identify some of these compounds. The rest of the compound is identified using a FT-IR and melting point. Spectra data of some products are represented below:

Methyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5h): solid powder; yield 82 %; m.p. 447–449 K. IR (KBr, cm^{-1}): *ν* 3288 (NH), 1675 (C=O), 1649 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 2.36 (6H, s, $2CH_3$), 3.77 (3H, s, OCH_3), 4.52(2H, s, $C\underline{H}_2$-N), 7.06 (2H, d, *J*=8.4 Hz, ArH), 7.14 (2H, d, *J*=8.4 Hz, ArH), 7.21(2H, d, *J*=8.4 Hz, ArH), 7.68 (2H, d, *J*=8.8 Hz, ArH), 8.03 (1H, s, NH).

Ethyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5i): solid powder; yield: 81 %; m.p. 402–405 K. IR (KBr, cm^{-1}): *ν* 3290 (NH), 1687 (C=O), 1643 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (3H, t, *J*=7.2 Hz, $CH_2\underline{CH_3}$), 2.37

(6H, s, $2CH_3$), 4.23 (2H, q, *J*=7.2 Hz, $2\underline{CH_2}CH_3$), 4.53 (2H, s, $C\underline{H_2}$-N),7.06 (2H, d, *J*=8.4 Hz, ArH), 7.14 (2H, d, *J*=8.4 Hz, ArH), 7.21 (2H, d, *J*=8.4 Hz, ArH), 7.69 (2H, d, *J*=8.4 Hz, ArH), 8.01 (1H, s, NH).

Methyl4-(4-fluoroyphenylamino)-1-(4-fluoro-phenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5j): solid powder; yield 91 %; m.p. 435–437 K. IR (KBr, cm^{-1}): *ν* 3285 (NH), 1673 (C=O), 1652 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 3.79 (3H, s, OCH_3), 4.52 (2H, s, $C\underline{H_2}$-N), 7.04 (2H, t, *J*=8.4 Hz, ArH), 7.08-7.16 (4H, m, ArH), 7.73-7.76 (2H, m, ArH), 8.05 (1H, s, NH).

Methyl4-(4-methoxyphenylamino)-1-(4-methoxy-phenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5l): solid powder; yield 86 %; m.p. 444–446 K. IR (KBr, cm^{-1}): *ν* 3279 (NH), 1687 (C=O), 1642 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 3.77 (3H, s, CH_3), 3.83 (6H, s, $2OCH_3$), 4.50 (2H, s, $C\underline{H_2}$-N), 6.89 (4H, d, *J*=17.6 Hz, ArH), 7.13 (1H, s, ArH), 7.68 (1H, s, ArH), 8.03 (1H, s, NH).

Ethyl4-(4-methoxyphenylamino)-1-(4-methoxy-phenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5m): solid powder; yield 82 %; m.p. 424–426 K. IR (KBr, cm^{-1}): *ν* 3266 (NH), 1703 (C=O), 1652 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (3H, t, *J*=7.2Hz, $CH_2\underline{CH_3}$), 3.83 (6H, s, $2OCH_3$), 4.23 (2H, q, *J*=7.2 Hz, $\underline{CH_2}CH_3$), 4.50 (2H, s, $C\underline{H_2}$-N), 6.87 (2H, d, *J*=8.8 Hz, ArH), 6.93 (2H, d, *J*=8.8 Hz, ArH), 7.12 (2H, d, *J*=8.8 Hz, ArH), 7.69 (2H, d, *J*=8.8 Hz, ArH), 8.02 (1H, s, NH).

3. Results and Discussion

The generality of this four-component condensation was studied under optimized conditions and the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was investigated as a model reaction.

The effect of different amount of catalyst was studied. A trace amount of the product was detected after 10 h, indicating that the catalyst is necessary for this transformation. (Table 1, entry 1). The optimized conditions were determined by the number of the equivalents of catalyst. Various loadings of catalysts, including 5, 10, 15, and 20 mol % were screened in our model reaction. By lowering the catalyst loading to 5 mol %, the corresponding product was obtained with lower yield (Table 1, entry 2). By increasing the amount of catalyst from 5 to 10 and 15 mol %, the reaction time is reduced and the yield of the product increases (Table 1, entry 2-4). So, among them, 15 mol % of $ZnCl_2$ was proven to be the most efficient catalyst for this reaction (Table 1, entry 4). The larger amount of the catalyst did not improve the yields (Table 1, entry 5). Also, the increase in time has no appreciable effect on the reaction yield.

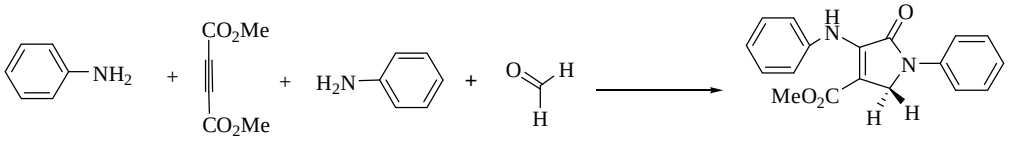


Table 1

Optimization of the reaction condition in the presence of different amounts of $ZnCl_2$

Entry	$ZnCl_2$, mol %	Time, h	Product	Isolated yield, %
1	0	10	5a	traces
2	5	8	5a	46
3	10	7	5a	72
4	**15**	**4**	**5a**	**87**
5	20	4	5a	89

Notes: aniline (2.0 mmol), dialkyl acetylenedicarboxylate (1.0 mmol), formaldehyde (1.5 mmol); room temperature.

Table 2

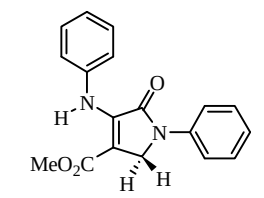
Optimization of the reaction condition in the presence of different solvents

Entry	Solvent	Time, h	Product	Isolated yield, %
1	–	8	5a	42
2	CH_2Cl_2	6	5a	23
3	$CHCl_3$	6	5a	19
4	**MeOH**	**4**	**5a**	**87**
5	H_2O	7	5a	16
6	CH_3CN	6	5a	38
7	EtOH	4	5a	71

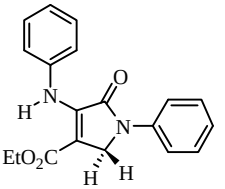
Notes: aniline (2.0 mmol), dialkyl acetylenedicarboxylate (1.0 mmol), formaldehyde (1.5 mmol), $ZnCl_2$ (15 mol %); room temperature.

Table 3

$ZnCl_2$ catalyzed synthesis of polysubstituted dihydro-2-oxopyrroles



5a



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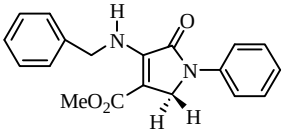
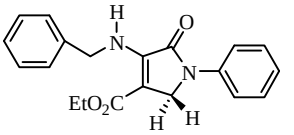
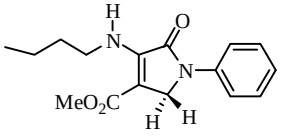


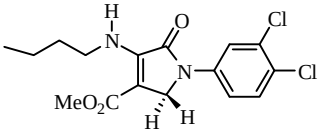
5c



5d



5e



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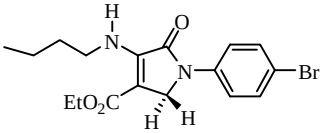
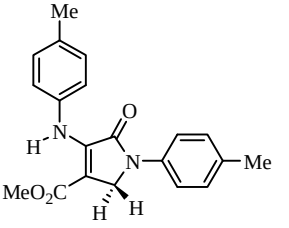
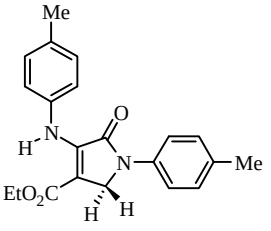


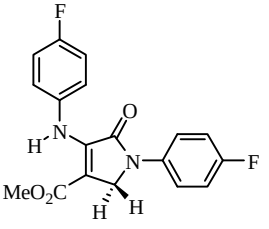
5g



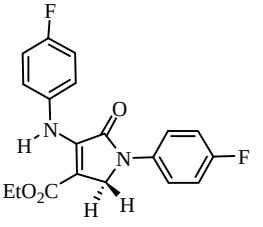
5h



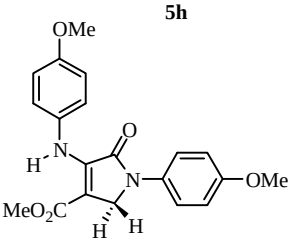
5i



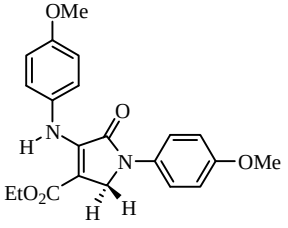
5j



5k



5l



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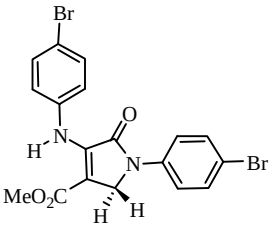
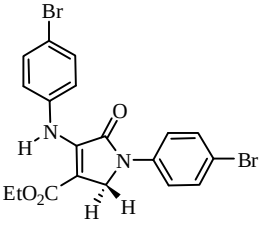


5n

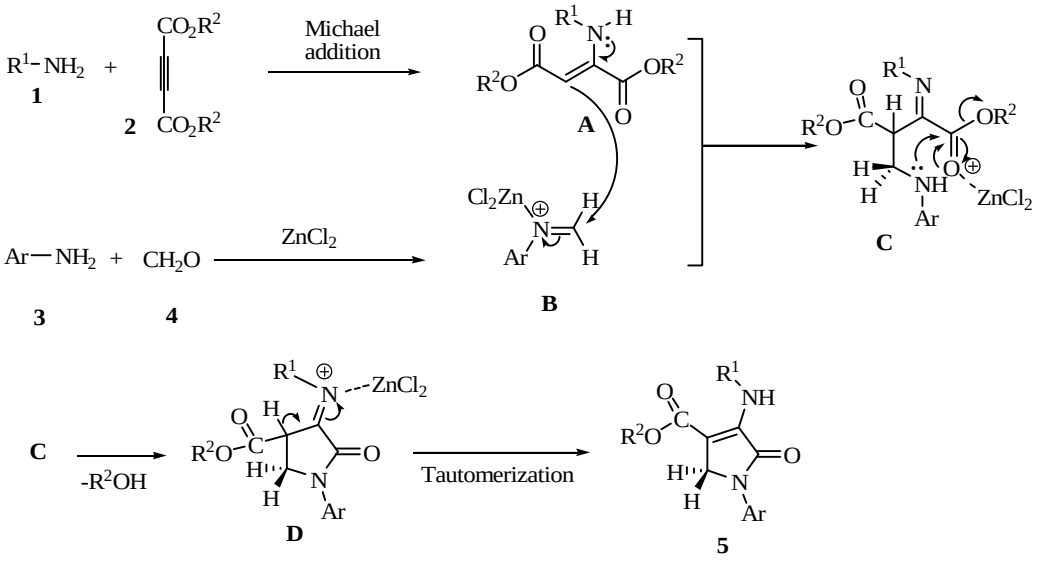


5o

Entry	R^1	R^2	Ar	Product	Time, h	Isolated yield, %	m.p., K	m.p. [lit], K
1	Ph	Me	Ph	**5a**	4	87	426–428	428–429 [15]
2	Ph	Et	Ph	**5b**	4	85	410–412	411–413 [19]
3	$PhCH_2$	Me	Ph	**5c**	4.5	83	414–416	413–414 [19]
4	$PhCH_2$	Et	Ph	**5d**	5	80	404–407	403–405 [19]
5	*n*-C_4H_9	Me	Ph	**5e**	4	89	335–337	333 [15]
6	*n*-C_4H_9	Me	3,4-Cl_2-C_6H_3	**5f**	5	84	368–371	370–372 [18]
7	*n*-C_4H_9	Et	4-Br-C_6H_4	**5g**	4	86	366–368	367–369 [18]
8	4-Me-C_6H_4	Me	4-Me-C_6H_4	**5h**	4	82	447–449	450–451 [15]
9	4-Me-C_6H_4	Et	4-Me-C_6H_4	**5i**	4	81	402–405	404–405 [19]
10	4-F-C_6H_4	Me	4-F-C_6H_4	**5j**	3	91	435–437	436–438 [20]
11	4-F-C_6H_4	Et	4-F-C_6H_4	**5k**	3.5	88	446–448	445–447 [17]
12	4-OMe-C_6H_4	Me	4-OMe-C_6H_4	**5l**	4	86	444–446	445–448 [17]
13	4-OMe-C_6H_4	Et	4-OMe-C_6H_4	**5m**	4.5	82	424–426	425–427 [18]
14	4-Br-C_6H_4	Me	4-Br-C_6H_4	**5n**	5	79	445–447	427–429 [17]
15	4-Br-C_6H_4	Et	4-Br-C_6H_4	**5o**	6	76	443–445	442–444 [19]

Also, the effect of various solvents such as CH_2Cl_2, $CHCl_3$, MeOH, H_2O, CH_3CN, and EtOH was investigated. Among them MeOH was found to be the best solvent for this methodology (Table 2, entry 4), the results are shown in Table 2.Finally, we reported $ZnCl_2$ (15 mol %) as an economical, non-toxic and inexpensive Lewis acid catalyst for one-pot four-component condensation of amines (aromatic or aliphatic), dialkyl acetylenedicarboxylate and formaldehyde in MeOH as a solvent at room temperature. In order to study this procedure, various substituted anilines, dimethyl and diethyl acetylenedicarbixylate and formaldehyde were employed successfully to generate the desired polysubstituted dihydro-2-oxopyrroles under ambient temperature in MeOH. The results are shown in Table 3 and the proposed mechanism for the synthesis of polysubstituted dihydro-2-oxopyrroles is shown in Scheme 2.

Comparison of catalytic ability of some of catalysts reported in the literature for synthesis of polysubstituted dihydro-2-oxopyrroles is shown in Table 4. This study reveals that $ZnCl_2$ has shown extraordinary potential to be an alternative eco-friendly, nontoxic, inexpensive, and highly an efficient catalyst for the one-pot synthesis of these heterocyclic compounds. In addition, good to high yields and short reaction times at room temperature are the notable advantages of this methodology.



Scheme 2. Proposed mechanistic route for the synthesis of polysubstituted dihydro-2-oxopyrroles

Table 4

Comparison of catalytic ability of some of catalysts reported in the literature for the synthesis of polysubstituted dihydro-2-oxopyrroles[a]

Entry	Product	Catalyst	Conditions	Time, h/Yield, %	References
1	**5a**	I_2	MeOH, r.t.	1/82	[15]
2	**5a**	$InCl_3$	MeOH, r.t.	3/85	[16]
3	**5a**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4/88	[17]
4	**5a**	$Al(H_2PO_4)_3$	MeOH, r.t.	5/81	[18]
5	**5a**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	6/91	[21]
6	**5a**	$ZnCl_2$	MeOH, r.t.	4/87	This work
7	**5b**	I_2	MeOH, r.t.	1/81	[15]
8	**5b**	$InCl_3$	MeOH, r.t.	3/85	[16]
9	**5b**	[n-Bu_4N][HSO_4]	MeOH, r.t.	4/86	[17]
10	**5b**	$Al(H_2PO_4)_3$	MeOH, r.t.	5/80	[18]
11	**5b**	$Cu(OAc)_2.H_2O$	MeOH, r.t.	5/85	[21]
12	**5b**	$ZnCl_2$	MeOH, r.t.	4/85	This work

Note: [a] Based on the four-component reaction of aniline, dimethylacetylenedicarboxylate, formaldehyde

4. Conclusions

A cost effective and eco-friendly approach for the synthesis of polysubstituted dihydro-2-oxopyrroles *via* one-pot four-component reaction of various substituted anilines, dimethyl and diethyl acetylenedicarbixylate and formaldehyde in the presence of $ZnCl_2$ as a Lewis acid catalyst at room temperature has been developed. The important aspects of this protocol are simple procedure, cleaner reaction and easy work up with no column chromatographic separation, short reaction times and good to high yields, use of inexpensive, non-toxic and environmentally friendly catalyst.

Acknowledgements

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ЧОТИРИКОМПОНЕНТНА ЛАНЦЮГОВА РЕАКЦІЯ НА $ZnCl_2$ КАТАЛІЗАТОРІ ДЛЯ ОДНОСТУПЕНЕВОГО ЕКОБЕЗПЕЧНОГО СИНТЕЗУ ПОЛІФУНКЦІОНАЛЬНИХ ДИГІДРО-2-ОКСОПІРОЛІВ ЗА КІМНАТНОЇ ТЕМПЕРАТУРИ

Анотація. *В присутності екологічно безпечного і ефективного каталізатора Фріделя-Крафта $ZnCl_2$ проведено одноступеневий чотирикомпонентний синтез полізаміщеного дигідро-2-оксопіролу за кімнатної температури з використанням діалкилацетилендикарбоксилату, формальдегіду та амінів (ароматичних та аліфатичних). Показаний ряд переваг такого синтезу: легкість, дешевизна, екологічно безпечний каталізатор, короткий час реакції, високі виходи, легке оброблення (тільки звичайна фільтрація) та простота експлуатації. Визначено характеристику одержаних продуктів за допомогою Фур'є- та ЯМР-спектроскопії.*

Ключові слова: *$ZnCl_2$, полізаміщені дигідро-2-оксопіроли, каталізатор, одноступеневий синтез, Фур'є- та ЯМР спектроскопія.*