

Al₂(SO₄)₃•18H₂O AS AN ECO-SAFE CATALYST PROMOTING SYNTHESIS OF POLYSUBSTITUTED DIHYDROPYRROL-2-ONES

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Abstract. Aluminum sulfate octadecahydrate (Al₂(SO₄)₃•18H₂O) as an efficient, mild and eco-safe catalyst for one-pot four-component synthesis of polysubstituted dihydropyrrol-2-ones from reaction between dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature with good to high yields and short reaction times is reported. The most benefits of this synthetic method are efficiency, environmentally benign nature, inexpensive and non-toxic catalyst, operational simplicity, clean reaction profile and ease of product isolation with no necessity of chromatographic purification steps. Products have been characterized by melting points and ¹H NMR spectroscopy.

Keywords: polysubstituted dihydropyrrol-2-ones, aluminum sulfate octadecahydrate, eco-safe and efficient catalyst, one-pot and facile procedure, multi-component reaction.

1. Introduction

Recently, the study of the synthesis of nitrogen-containing heterocyclic compounds, such as pyrrole rings, has attracted considerable interest among organic chemists because of their special biological and pharmaceutical activities [1-9]. In the past decades, considerable attention has been paid to the design of efficient and environmental friendly synthetic route by using of multi-component reactions (MCRs) [10-17] due to a wide range of points, such as atom-economy, simple work-up, mildness and environmental friendliness, one pot, and low cost. Due to the importance of polysubstituted dihydropyrrol-2-ones, various methodologies for the preparation of these

compounds have been developed, such as Cu(OAc)₂•H₂O [18], InCl₃ [19], I₂ [20], AcOH [21], [*n*-Bu₄N][HSO₄] [22], Al(H₂PO₄)₃ [23], oxalic acid [24], ZrCl₄ [25], [Hpyro][HSO₄] [26], and *p*-TsOH•H₂O [27] can be used as catalysts for this transformation. Some of these methodologies have limitations such as long reaction time, low yields, toxic and expensive catalysts, complex work-up, and use of strongly acidic conditions. Thus, there is still a need to develop a highly efficient and convenient method for the synthesis of these biologically active heterocyclic compounds.

During the past decades, the use of alum compounds as environmental safe catalysts in organic synthesis [28, 29] have attracted a great interest due to their notable advantages such as non-toxicity, environmental friendliness, ease to handle, high efficiency and low cost. Furthermore, one of the sources of environmental pollutions is the usage of organic solvents under reflux conditions and the need for column chromatography to purify the products. In this work, the products were obtained through simple filtering with no need of column chromatographic separation.

Based on the above considerations and our interest in the design of efficient and environmentally benign methodologies, attempts were directed to synthesize polysubstituted dihydropyrrol-2-ones by using a non-toxic, eco-safe and mild catalyst.

Therefore, we reported an efficient and capable protocol for the preparation of polysubstituted dihydropyrrol-2-ones in the presence of aluminum sulfate octadecahydrate (Al₂(SO₄)₃•18H₂O) as an environmental friendly, inexpensive and efficient catalyst by reaction of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) under ambient temperature. High effectiveness, environmentally benign nature, ready-to-use, low-cost and non-toxic catalyst, good to high yields, short reaction times, and economy is what makes our protocol an alternative to some of the earlier reported methods.

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2. Experimental

2.4. Determination of Total Fluorine

Melting points of all compounds were determined using an Electro thermal 9100 apparatus. Also, nuclear magnetic resonance, ¹H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with CDCl₃ as solvent. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies and used without further purification.

General procedure for preparation of polysubstituted dihydropyrrol-2-ones (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. Next, amine **3** (1.0 mmol), formaldehyde **4** (1.5 mmol) and Al₂(SO₄)₃·18H₂O (15 mol %) were added and the reaction was stirred for appropriate time. After completion of the reaction (by thin layer chromatography TLC), the mixture was separated with filtration and the solid was washed with ethanol (3×2 ml) with no column chromatographic separation to give pure compounds (**5a-t**). The catalyst is soluble in ethanol and was removed from the reaction mixture. Products were characterized by comparison of spectroscopic data (¹H NMR).

2.2. Physical and Spectral Data for Selected Products:

Methyl-4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5c):

White solid; Yield: 89 %; M.p. 449–451 K; ¹H NMR (400 MHz, CDCl₃): 2.36 (6H, s, 2CH₃), 3.77 (3H, s, OCH₃), 4.52 (2H, s, CH₂-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).

Ethyl-4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5d):

White solid; Yield: 87 %; M.p. 402–404 K; ¹H NMR (400 MHz, CDCl₃): 1.25 (3H, t, *J*=7.2 Hz, CH₂CH₃), 2.37 (6H, s, 2CH₃), 4.23 (2H, q, *J*=7.2 Hz, 2CH₂CH₃), 4.53 (2H, s, CH₂-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).

Methyl-4-(4-fluorophenylamino)-1-(4-fluorophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5e):

White Solid; Yield: 93 %; M.p. 437–439 K; ¹H NMR (400 MHz, CDCl₃): 3.79 (3H, s, OCH₃), 4.52 (2H, s, CH₂-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).

Methyl-4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5g):

White solid; Yield: 88 %; M.p. 447–448 K; ¹H NMR (400 MHz, CDCl₃): 3.77 (3H, s, CH₃), 3.83 (6H, s, 2OCH₃), 4.50 (2H, s, CH₂-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).

Ethyl-4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5h):

White solid; Yield: 85 %; M.p. 427–429 K; ¹H NMR (400 MHz, CDCl₃): 1.26 (3H, t, *J*=7.2 Hz, CH₂CH₃), 3.83 (6H, s, 2OCH₃), 4.23 (2H, q, *J*=7.2 Hz, CH₂CH₃), 4.50 (2H, s, CH₂-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

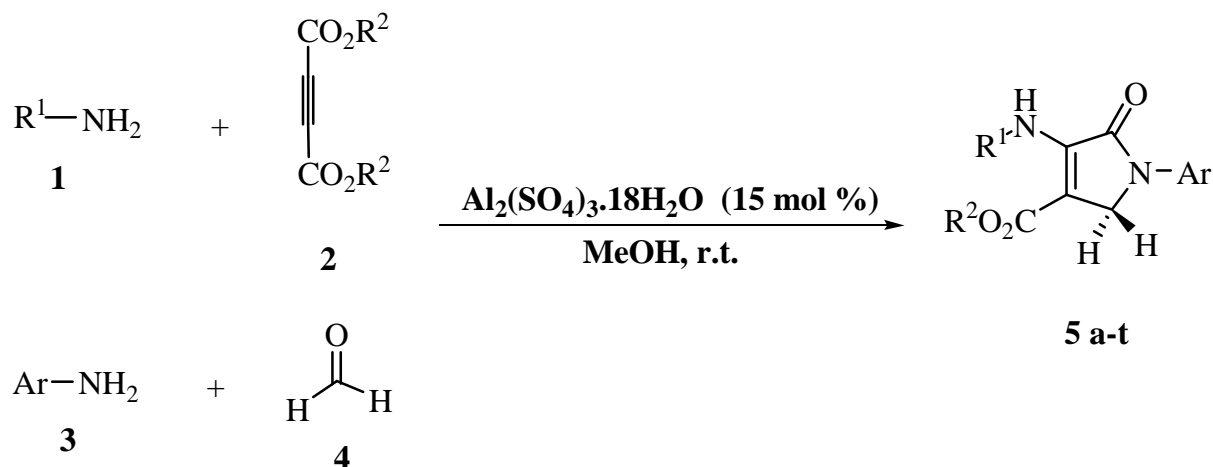
To optimize the reaction conditions, reaction between aniline, dimethyl acetylenedicarboxylate (DMAD), and formaldehyde was used as model reaction. The initially catalytic activity of Al₂(SO₄)₃·18H₂O was tested in a model system using four-component reaction of aniline (2 mmol), dimethyl acetylenedicarboxylate (DMAD) (1 mmol) and formaldehyde (1.5 mmol). In the absence of a catalyst, only a trace of product was obtained at rt for a reaction time of about 10 h (Table 1, entry 1), which indicated that the catalysts should be necessary for this transformation. The optimized conditions were determined by the number of the equivalents of catalyst and varying the solvents. 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). 15 mol % of Al₂(SO₄)₃·18H₂O 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 12). The reaction was also investigated in the absence of solvent, in the presence of 15 mol % of the catalyst and at rt, which resulted in the production of a reaction product with low yield and longer reaction time, indicating that the solvent plays an effective role in the development of this reaction (Table 1, entry 11). The results indicated that a low yield of the desired product was obtained when EtOH, H₂O, CHCl₃, CH₂Cl₂, DMF and CH₃CN were used as solvents. The best yield was obtained when the reaction was performed in MeOH and it accelerated the reaction compared with other solvents and solvent-free condition (Table 1, entry 4). Therefore, we employed the optimized conditions 15 mol % of Al₂(SO₄)₃·18H₂O as an efficient catalyst in MeOH at rt for the condensation reaction of amine **1**, **3** (2.0 mmol) and

dialkyl acetylenedicarboxylate **2** (1.0 mmol) and formaldehyde **4** (1.5 mmol) into the corresponding polysubstituted dihydropyrrol-2-one derivatives (Scheme 1 and Table 2). Aromatic or aliphatic amines with electron donating groups such as Me and OMe, as well as electron withdrawing groups including F, Cl, and Br were converted into the corresponding products with good to high yields and short reaction times. We also applied dimethyl/ethyl acetylenedicarboxylate. The results are summarized in Table 2. In general, at the beginning of reactions, the reagents were completely soluble in reaction medium to form a mixture. However, at the end of the reactions, the product **5** was precipitated and separated by simple filtration. No column chromatography technique was used for products purification. This avoids the use of large amounts of volatile organic solvents, as the solvent is generally the main source of waste and environmental pollution. The structure of the products was characterized by their melting points and nuclear magnetic resonance ($^1\text{H NMR}$) spectral data. For example, the structure of known product **5g** was deduced on the basis of $^1\text{H NMR}$ spectroscopy and its structural assignment is described below. The $^1\text{H NMR}$ spectrum of compound **5g** in CDCl_3 exhibits two singlets at 3.77 and 3.83 ppm for methyl and methoxy groups. A singlet at 4.50 ppm appeared for methylene protons of dihydropyrrol-2-one ring. The NH proton exhibited as a broad singlet at

8.03 ppm and 6 aromatic protons which appeared as a doublet at 6.89 and two singlets at 7.13 and 7.68 ppm, respectively.

Proposed mechanism for the synthesis of polysubstituted dihydropyrrol-2-ones derivatives in the presence of $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ are shown in Scheme 2. Firstly, the reaction of amine **1** with dialkyl acetylenedicarboxylate **2** leads to intermediate **A**. Secondly, condensation between amine **3** and formaldehyde **4** in the presence of $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ produces imine **B**. Intermediate **A** possesses an enamine character and, thus, can readily react with imine **B** in the presence of $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ to generate intermediate **C**. Cyclization reaction of intermediate **C** leads to intermediate **D**, which in the final step tautomerizes to the corresponding polysubstituted dihydropyrrol-2-ones **5**.

Comparison of catalytic ability of some of catalysts reported in the literature for the synthesis of polysubstituted dihydropyrrol-2-ones are shown in Table 3. This study reveals that $\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$ has shown its extraordinary potential to be an alternative, inexpensive, of environmentally benign nature, and efficient catalyst for the one-pot synthesis of these biologically active heterocyclic compounds. Additionally, good to high yields and short reaction times are the notable advantages of this methodology.



$\text{R}^1 = \text{C}_6\text{H}_5, 4\text{-Me-C}_6\text{H}_4, 4\text{-F-C}_6\text{H}_4, 4\text{-OMe-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_4, \text{PhCH}_2, n\text{-C}_4\text{H}_9.$

$\text{R}^2 = \text{CH}_3, \text{C}_2\text{H}_5.$

$\text{Ar} = \text{C}_6\text{H}_5, 4\text{-Me-C}_6\text{H}_4, 4\text{-F-C}_6\text{H}_4, 4\text{-OMe-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_4, 4\text{-Cl-C}_6\text{H}_4, 3, 4\text{-Cl}_2\text{-C}_6\text{H}_3.$

Scheme 1. Synthesis of polysubstituted dihydropyrrol-2-ones

Table 1

Optimization of the reaction condition in the presence of different amounts of $Al_2(SO_4)_3 \cdot 18H_2O$ and different solvents for the synthesis of 5a

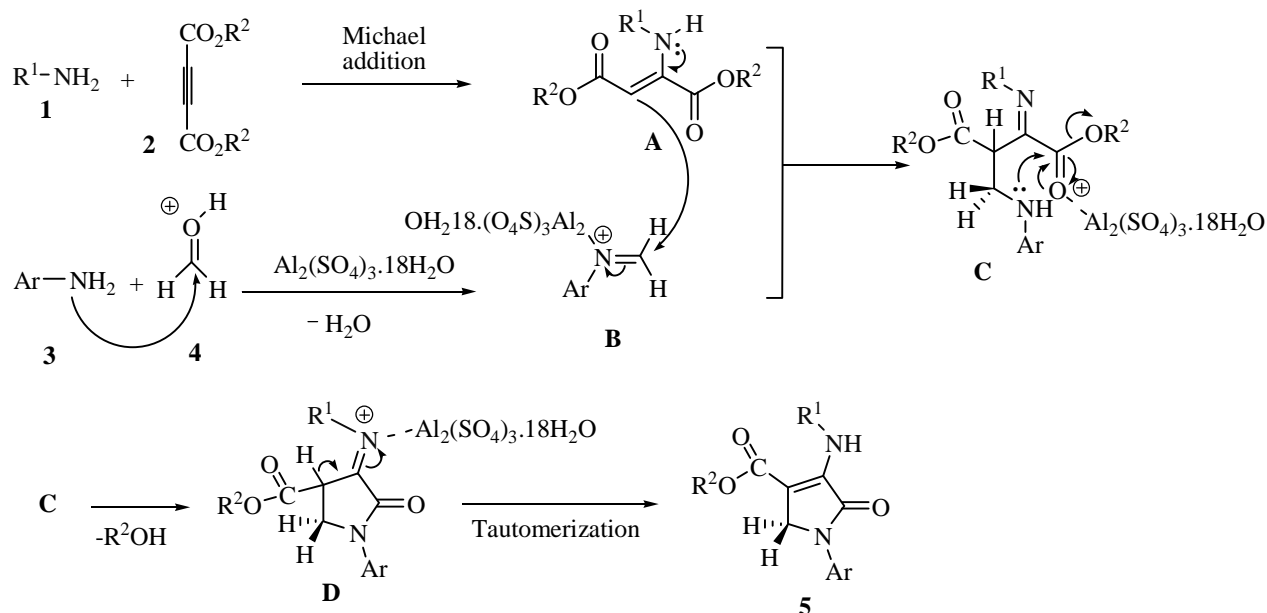
Entry	$Al_2(SO_4)_3 \cdot 18H_2O$, mol %	Solvent	Time, h	Isolated yield, %
1	Catalyst free	MeOH	10	trace
2	5	MeOH	6	45
3	10	MeOH	4	73
4	15	MeOH	3	91
5	15	H ₂ O	10	31
6	15	CH ₃ CN	6	43
7	15	EtOH	4	65
8	15	DMF	10	37
9	15	CHCl ₃	12	16
10	15	CH ₂ Cl ₂	12	14
11	15	Solvent free	6	42
12	20	MeOH	3	92

Note: 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 polysubstituted dihydropyrrol-2-ones

Entry	R ¹	R ²	Ar	Product	Time, h	Isolated yield, % ^a	M.p., K	Lit. M.p., K
1	Ph	Me	Ph	5a	3	91	426–428	428–429 [19]
2	Ph	Et	Ph	5b	3	88	412–414	411–413 [20]
3	4-Me-C ₆ H ₄	Me	4-Me-C ₆ H ₄	5c	3	89	449–451	450–451 [19]
4	4-Me-C ₆ H ₄	Et	4-Me-C ₆ H ₄	5d	3	87	402–404	404–405 [20]
5	4-F-C ₆ H ₄	Me	4-F-C ₆ H ₄	5e	2.5	93	437–439	436–438 [23]
6	4-F-C ₆ H ₄	Et	4-F-C ₆ H ₄	5f	3	92	444–446	445–447 [21]
7	4-OMe-C ₆ H ₄	Me	4-OMe-C ₆ H ₄	5g	4	88	447–448	445–448 [21]
8	4-OMe-C ₆ H ₄	Et	4-OMe-C ₆ H ₄	5h	4	85	427–429	425–427 [22]
9	4-Br-C ₆ H ₄	Me	4-Br-C ₆ H ₄	5i	5	83	446–448	448–450 [21]
10	4-Br-C ₆ H ₄	Et	4-Br-C ₆ H ₄	5j	5.5	80	444–446	442–444 [20]
11	PhCH ₂	Me	Ph	5k	4	84	412–414	413–414 [20]
12	PhCH ₂	Et	Ph	5l	4	82	405–407	403–405 [20]
13	PhCH ₂	Me	4-Cl-C ₆ H ₄	5m	4.5	78	417–419	417–420 [26]
14	PhCH ₂	Me	4-F-C ₆ H ₄	5n	3.5	89	440–442	439–441 [22]
15	PhCH ₂	Me	4-Br-C ₆ H ₄	5o	4	81	394–396	396–398 [26]
16	<i>n</i> -C ₄ H ₉	Me	Ph	5p	4	82	312–314	313 [19]
17	<i>n</i> -C ₄ H ₉	Me	4-Cl-C ₆ H ₄	5q	5	79	366–368	365–367 [26]
18	<i>n</i> -C ₄ H ₉	Me	3,4-Cl ₂ -C ₆ H ₃	5r	5.5	76	368–370	370–372 [22]
19	<i>n</i> -C ₄ H ₉	Me	4-F-C ₆ H ₄	5s	4	84	353–355	354–356 [25]
20	<i>n</i> -C ₄ H ₉	Et	4-Br-C ₆ H ₄	5t	5.5	75	369–371	367–369 [22]



Scheme 2. Proposed mechanistic route for the synthesis of polysubstituted dihydropyrrol-2-ones

Table 3

Comparison of catalytic ability of some of catalysts reported in the literature for the synthesis of polysubstituted dihydropyrrol-2-ones

Entry	Compound	Catalyst	Conditions	Time, h/Yield, %	References
1	5a	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	MeOH, r.t.	6/91	[17]
2	5a	InCl_3	MeOH, r.t.	3/85	[18]
3	5a	I_2	MeOH, r.t.	1/82	[19]
4	5a	$[\text{n-Bu}_4\text{N}][\text{HSO}_4]$	MeOH, r.t.	4/88	[21]
5	5a	$\text{Al}(\text{H}_2\text{PO}_4)_3$	MeOH, r.t.	5/81	[22]
6	5a	ZrCl_4	MeOH, r.t.	4/84	[24]
7	5a	$[\text{Hpyro}][\text{HSO}_4]$	MeOH, r.t.	6/82	[25]
8	5a	$p\text{-TsOH} \cdot \text{H}_2\text{O}$	MeOH, r.t.	3/84	[26]
9	5a	$\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$	MeOH, r.t.	3/91	This work
10	5b	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	MeOH, r.t.	5/85	[17]
11	5b	InCl_3	MeOH, r.t.	3/85	[18]
12	5b	I_2	MeOH, r.t.	1/81	[19]
13	5b	$[\text{n-Bu}_4\text{N}][\text{HSO}_4]$	MeOH, r.t.	4/86	[21]
14	5b	$\text{Al}(\text{H}_2\text{PO}_4)_3$	MeOH, r.t.	5/80	[22]
15	5b	ZrCl_4	MeOH, r.t.	3.5/83	[24]
16	5b	$[\text{Hpyro}][\text{HSO}_4]$	MeOH, r.t.	6/80	[25]
17	5b	$p\text{-TsOH} \cdot \text{H}_2\text{O}$	MeOH, r.t.	4/84	[26]
18	5b	$\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$	MeOH, r.t.	3/88	This work

4. Conclusions

A clean and mild protocol for the one-pot preparation of polysubstituted dihydropyrrol-2-ones *via* a one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at room temperature conditions using aluminum sulfate octadecahydrate ($\text{Al}_2(\text{SO}_4)_3 \cdot 18\text{H}_2\text{O}$) as the catalyst

with short reaction times is studied. The present procedure provides economic, mild and convenient methodology for the synthesis of target compounds. The notable advantages of the present methodology are environmentally benign nature, inexpensiveness, non-toxicity, easy to handle and versatile catalyst, good to high yields, one-pot, high efficiency, and simplicity of operation with no necessity of chromatographic purification steps.

Acknowledgments

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$Al_2(SO_4)_3 \cdot 18H_2O$ ЯК ЕКО-БЕЗПЕЧНИЙ КАТАЛІЗАТОР ДЛЯ СИНТЕЗУ ПОЛІЗАМЩЕНИХ ДИГІДРОПІРОЛ-2-ОНІВ

Анотація. Досліджено октадекагідрат алюмінію сульфату ($Al_2(SO_4)_3 \cdot 18H_2O$) як ефективний та екологічно безпечний каталізатор для одностадійного чотирикомпонентного синтезу багатозаміщених дигідропірол-2-онів за реакцією діалкілацетиленидикарбоксилату, формальдегіду та амінів (ароматичних та аліфатичних) за температури навколишнього середовища. Встановлено, що в присутності такого каталізатора виходи продуктів є високими, а час реакції малий. Показано, що найбільшими перевагами такого синтезу є ефективність, екологічність, недорога вартість та нетоксичність каталізатора, простота експлуатації, чіткий перебіг реакції та легкість виділення продукту без необхідності хроматографічного очищення. Визначено температури топлення продуктів та проведено 1H ЯМР-спектроскопічні дослідження.

Ключові слова: багатозаміщені дигідропірол-2-они, октадекагідрат алюмінію сульфату, екологічно безпечний та ефективний каталізатор, одностадійний синтез, багатокомпонентна реакція.