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Recommended Citation

Mohamadpour, Farzaneh (2018) "ZnSO4.7H2O Catalyzed One-pot and Facile Synthesis of Highly Substituted Dihydro-2-oxopyrroles at Room Temperature," Makara Journal of Science: Vol. 22 : Iss. 2 , Article 4.
DOI: 10.7454/mss.v22i2.8792
Available at: https://scholarhub.ui.ac.id/science/vol22/iss2/4

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Cover Page Footnote
We gratefully acknowledge financial support from the Research Council of the Young Researchers and Elite Club of Islamic Azad University of Shiraz.

This article is available in Makara Journal of Science: https://scholarhub.ui.ac.id/science/vol22/iss2/4
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Received December 17, 2017 | Accepted May 9, 2018

Abstract

A mild and facile ZnSO₄.7H₂O-catalyzed procedure is developed for the convenient one-pot synthesis of highly substituted dihydro-2-oxopyrroles under mild reaction conditions. In this procedure, dihydro-2-oxopyrroles are synthesized via the four-component reactions of amines, dialkyl acetylenedicarboxylates and formaldehyde. The present procedure is an economical and mild approach that offers numerous advantages, including good to high yields, simplicity, inexpensive and readily available catalyst, and high atom economy.

Introduction

Pyrrole rings are an important class of heterocyclic compounds with extensive biological activities. For example, pyrrole rings are present in human cytomegalovirus protease [1] and CD45 protein tyrosinophosphatase [2]. Moreover, these structures are present in compounds with anticancer activities [3]. Pyrrole rings are present in thiomarinol A4, an antibiotic [4]; numerous biologically active alkaloids [5]; UCS1025A [6], Oteromycin [7]; and HIV integrase [8]. They also exhibit herbicidal [9] activities. Numerous protocols have been developed to exploit the biological, pharmacological, and synthetic importance of highly substituted dihydro-2-oxopyrroles. Among these various protocols, the most widely used are the one-pot multi-component condensation of dialkylacetylenedicarboxylate, formaldehyde, and amines. Cu(OAc)₂·H₂O [10], InCl₃ [11], I₂ [12], AcOH [13], [n-Bu₄N][HSO₄] [14], Al(H₂PO₄)₃ [15], oxalic acid [16], and ZrCl₄ [17] are applied as catalysts in the synthesis of dihydro-2-oxopyrroles. However, some of the pathways for the synthesis of pyrrole rings suffer from one or more drawbacks, such as poor yields and long reaction times. In addition, these pathways require the use of toxic catalysts at excessively high loadings. Therefore, the development of a simple and economical procedure for the synthesis of highly substituted dihydro-2-oxopyrroles is necessary. Over the past decades, the use of zinc compounds as environmentally safe catalysts [18-21] in organic synthesis has attracted considerable interest because of the notable advantages of zinc. These advantages include nontoxicity, facile handling, high efficiency, and low cost. In addition, zinc compounds can be successfully used to generate carbon–carbon bonds under mild reaction conditions. Furthermore, the usage of organic solvents under reflux conditions and the need for column chromatography to purify products are sources of environmental pollution. In this present work, products were obtained through simple filtration without the need for column chromatographic separation.

Keywords: Highly substituted dihydro-2-oxopyrroles, ZnSO₄.7H₂O, inexpensive and readily available catalyst, high atom economy
As a part of our research on the identification and development of efficient and economical catalysts for multicomponent reactions [22–29] and in consideration of the above, herein, we report an efficient and simple procedure for the synthesis of highly substituted dihydro-2-oxopyrroles via a one-pot four-condensation domino reaction among amines (aromatic or aliphatic 1 and 3), dialkyl acetylenedicarboxylate 2, and formaldehyde 4 in the presence of ZnSO$_4$.7H$_2$O at room temperature. Compared with some of the earlier reported methods, our protocol, which requires the use of a nontoxic catalyst, is more efficient, facile, inexpensive, and environmentally friendly. Moreover, it provides good to high yields and requires a short reaction time.

Materials and Methods

**General.** The melting points of all compounds were determined by using an Electro thermal 9100 apparatus. Nuclear magnetic resonance and $^1$H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with CDCl$_3$ as a solvent. All reagents and solvents were purchased from Merck, Fluka, and Acros chemical companies and were used without further purification.

**General procedure for the preparation of highly substituted dihydro-2-oxopyrroles (5a–q).** 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 ZnSO$_4$.7H$_2$O (20 mol%) were added to the mixture, and the reaction was stirred for the appropriate duration. After the reaction was completed, the mixture was separated through filtration with thin layer chromatography (TLC). The recovered solid was washed with ethanol (3 times $\times$ 2 mL) to obtain the pure compounds 5a–q without the need for column chromatographic separation [12, 14]. The catalyst is soluble in ethanol and removable from the reaction mixture. The products were characterized through the comparison of spectroscopic data ($^1$H NMR). The spectral data of the products are presented below.

**Ethyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5f):** Yield: 85%; M.p. 150 $^\circ$C–152 $^\circ$C; $^1$H NMR (400 MHz, CDCl$_3$): 1.26 (3H, t, $J$ = 7.2 Hz, CH$_2$CH$_3$), 3.83 (6H, s, 2OCH$_3$), 4.23 (2H, q, $J$ = 7.2 Hz, CH$_2$(CH)$_3$), 4.50 (2H, s, CH$_2$–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).

**Methyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5k):** Yield: 88%; M.p. 178 $^\circ$C–180 $^\circ$C; $^1$H NMR (400 MHz, CDCl$_3$): 2.36 (6H, s, 2CH$_3$), 3.77 (3H, s, OCH$_3$), 4.52 (2H, s, CH$_2$–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).

Results and Discussion

The reaction conditions of this four-condensation reaction were optimized. The reaction among aniline, dimethyl acetylenedicarboxylate (DMAD), and formaldehyde was investigated as the model reaction. Then, the effects of different amounts of catalyst in MeOH solvent on the protocol were investigated. A trace amount of the product was detected after 10 h in the absence of the catalyst (Table 1, entry 1), and good yields were obtained in the presence of the catalyst. The optimal amount of the catalyst was 20 mol% (Table 1, entry 5). Increasing the amount of the catalyst did not increase product yields (Table 1, entry 14). The results are summarized in Table 1. In addition, the effect of various solvents, namely, H$_2$O, EtOH, H$_2$O/EtOH, CH$_2$Cl$_2$, CHCl$_3$, CH$_3$CN and DMF, on the protocol was investigated, and MeOH was identified as the optimal solvent for this methodology (Table 1, entry 5). Finally, a convenient, expedient, and efficient procedure for the synthesis of highly substituted dihydro-2-oxopyrroles 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 ZnSO$_4$.7H$_2$O (Scheme 1) was described. The results are summarized in Table 2.

The proposed mechanism for the synthesis of highly substituted dihydro-2-oxopyrroles in the presence of ZnSO$_4$.7H$_2$O 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 ZnSO₄·7H₂O produces imine B. Intermediate A possesses an enamine character and can thus readily react with imine B to in the presence of ZnSO₄·7H₂O to generate intermediate C. The cyclization of intermediate C yields intermediate D, which tautomerizes to the corresponding highly substituted dihydro-2-oxopyrrole (5) in the final step.

![Scheme 1. Synthesis of Highly Substituted Dihydro-2-oxopyrroles](image)

| Entry | ZnSO₄·7H₂O (mol %) | Solvent       | Time (h) | Isolated Yields (%) |
|-------|---------------------|---------------|----------|---------------------|
| 1     | Catalyst free       | MeOH          | 10       | trace               |
| 2     | 5                    | MeOH          | 8        | 34                  |
| 3     | 10                   | MeOH          | 8        | 51                  |
| 4     | 15                   | MeOH          | 5        | 73                  |
| 5     | 20                   | MeOH          | 4        | 86                  |
| 6     | 20                   | Solvent free  | 10       | 27                  |
| 7     | 20                   | H₂O           | 7        | 24                  |
| 8     | 20                   | EtOH          | 4        | 61                  |
| 9     | 20                   | H₂O/EtOH      | 6        | 45                  |
| 10    | 20                   | CH₂Cl₂        | 12       | 11                  |
| 11    | 20                   | CHCl₃         | 12       | 16                  |
| 12    | 20                   | CH₃CN         | 6        | 47                  |
| 13    | 20                   | DMF           | 6        | 43                  |
| 14    | 25                   | MeOH          | 4        | 88                  |

*Reaction 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 | R¹ | R² | Ar | Product | Time (h) | Yield (%) | M.p. °C | Lit. M.p. °C |
|-------|----|----|----|---------|----------|-----------|---------|--------------|
| 1     | Ph | Me | Ph | 5a      | 4        | 86        | 156–158 | 155–156³⁴   |
| 2     | Ph | Et | Ph | 5b      | 4        | 85        | 139–141 | 138–140³⁴   |
| 3     | 4-Cl-C₆H₄ | Me | 4-Cl-C₆H₄ | 5c      | 5        | 78        | 170–172 | 171–173³⁴   |
| 4     | 4-Cl-C₆H₄ | Et | 4-Cl-C₆H₄ | 5d      | 5        | 76        | 168–170 | 168–170³⁴   |
| 5     | 4-F-C₆H₄ | Me | 4-F-C₆H₄ | 5e      | 3        | 89        | 164–166 | 163–165³⁶   |
| 6     | 4-F-C₆H₄ | Et | 4-F-C₆H₄ | 5f      | 3        | 88        | 173–175 | 172–174³⁴   |
| 7     | 4-Br-C₆H₄ | Me | 4-Br-C₆H₄ | 5g      | 5        | 75        | 177–179 | 175–177³⁴   |
| 8     | 4-Br-C₆H₄ | Et | 4-Br-C₆H₄ | 5h      | 5        | 73        | 167–170 | 169–171³³   |
| 9     | 4-OMe-C₆H₄ | Me | 4-OMe-C₆H₄ | 5i      | 4        | 82        | 172–174 | 172–175³⁴   |
| 10    | 4-OMe-C₆H₄ | Et | 4-OMe-C₆H₄ | 5j      | 4.5      | 85        | 150–152 | 152–154³⁵   |
| 11    | 4-Me-C₆H₄ | Me | 4-Me-C₆H₄ | 5k      | 3        | 88        | 178–180 | 177–178³¹²   |
| 12    | 4-Me-C₆H₄ | Et | 4-Me-C₆H₄ | 5l      | 3.5      | 86        | 131–133 | 131–132³¹³   |
| 13    | PhCH₂ | Me | Ph | 5m      | 4.5      | 82        | 138–140 | 140–141³¹³   |
| 14    | PhCH₂ | Et | Ph | 5n      | 5.5      | 79        | 132–134 | 130–132³¹³   |
| 15    | PhCH₂ | Me | 4-F-C₆H₄ | 5o      | 4        | 84        | 167–169 | 166–168³¹⁵   |
| 16    | n-C₄H₉ | Me | Ph | 5p      | 4.5      | 80        | 60–62   | 60³¹²       |
| 17    | n-C₄H₉ | Me | 3,4-Cl₂-C₆H₃ | 5q     | 5        | 75        | 99–101  | 97–99³¹⁵     |

* Isolated yield

Scheme 2. Proposed Mechanistic Route for the Synthesis of Highly Substituted Dihydro-2-oxopyrroles
The comparison of the catalytic ability of some previously reported catalysts in the synthesis of highly substituted dihydro-2-oxopyrroles is shown in Table 3. ZnSO₄·7H₂O has extraordinary potential as an alternative, inexpensive, readily available, and efficient catalyst for the one-pot synthesis of biologically active heterocyclic compounds. Good to high yields and short reaction times are the notable advantages of the present methodology.

**Conclusion**

ZnSO₄·7H₂O was used as a readily available, economical, and efficient catalyst in the simple synthesis of highly substituted dihydro-2-oxopyrroles under mild reaction conditions. Results showed that the efficiency of ZnSO₄·7H₂O is higher than those of other reported catalysts, especially in the terms of reaction times and yields. The important aspects of this protocol are simplicity, environmental friendliness, and ease while requiring the use of an inexpensive and readily available catalyst.

**Acknowledgments**

We gratefully acknowledge financial support from the Research Council of the Young Researchers and Elite Club of Islamic Azad University of Shiraz.

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