Makara Journal of Science

Volume 24
Issue 3 *September*

Article 7

9-18-2020

# Malonic Acid as A Green and Efficient Catalyst for the Mass-scale Synthesis of Pyrrole Medicinal Drugs

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Makara Journal of Science, 24/3 (2020), 188–193
doi: 10.7454/mss.v24i3.1203

# Malonic Acid as A Green and Efficient Catalyst for the Mass-scale Synthesis of Pyrrole Medicinal Drugs

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Received May 18, 2019 | Accepted June 14, 2020

## Abstract

A green and naturally biodegradable malonic acid synthesis of highly substituted dihydro-2-oxopyrrole derivatives has been accomplished *via* one-pot four-condensation of amines (aromatic or aliphatic), dialkyl acetylenedicarboxylate, and formaldehyde under mild reaction conditions. The notable advantages of the present procedure are a green, low cost, and efficient catalyst; operational simplicity; no need for chromatographic purification steps; short reaction times; and good to high yields.

*Keywords: highly substituted pyrrole derivatives, malonic acid, green catalyst, mild reaction*

## Introduction

The synthesis of highly substituted dihydro-2-oxopyrroles and their derivatives has received much attention because of the importance of these compounds in various fields of biology and pharmacology. Some of these compounds exhibit cytomegalovirus (HCMV) protease [1], CD45 protein tyrosinphosphatase [2], anti-cancer [3] properties. The antibiotic thiomarinol A4 [4] and biologically active alkaloids have pyrrole rings [5], and these rings have been used as UCS1025A [6] and oteromycin [7].

Due to the importance of highly substituted dihydro-2-oxopyrrole derivatives, various methodologies, such as the ones using $Cu(OAc)_2.H_2O$ [8], $InCl_3$ [9], $I_2$ [10], AcOH [11], $[n\text{-}Bu_4N][HSO_4]$ [12], $Al(H_2PO_4)_3$ [13], oxalic acid [14], $ZrCl_4$ [15] ethylenediammonium diformate (EDDF) [16], $Fe_3O_4$@nano-cellulose–$OPO_3H$ [17], $BiFeO_3$ nanoparticles [18], nano-$Fe_3O_4$@$SiO_2$/$SnCl_4$ [19], $TiCl_4$/nano-sawdust [20], graphene oxide [21], $CoFe_2O_4$@$SiO_2$@IRMOF-3 [22], caffeine [23], glutamic acid [24], and $ZnCl_2$ [25] catalysts, have been developed for the preparation of these compounds. The limitations of these methodologies include low yields, toxic catalysts, energy intensive reaction conditions, expensive materials, and long reaction times.

Therefore, as a part of our research aimed at developing efficient methodologies for preparing organic compounds using efficient and eco-safe catalysts [26-31], we report herein a simple, eco-safe, and clean protocol for the four-component synthesis of highly substituted dihydro-2-oxopyrrole derivatives in the presence of the green and naturally biodegradable malonic acid catalyst [32] via the reaction of amines (aromatic or aliphatic), dialkyl acetylenedicarboxylate, and formaldehyde under mild reaction conditions.

## Materials and Methods

The melting points of all dihydro-2-oxopyrrole derivatives synthesized herein were determined using an Electrothermal 9100 apparatus. $^1$H NMR spectra were recorded on a Bruker DRX-400 Avance instrument with $CDCl_3$ as solvent. All the reagents and solvents were purchased from Merck, Fluka, and Acros and were used without further purification.

***General procedure preparing highly substituted dihydro-2-oxopyrrole derivatives (5a-p).*** A mixture of amine **1** (1.0 mmol) and dialkyl acetylenedicarboxylate **2** (1.0 mmol) was stirred in methanol (3 mL) for 15 min. This solution was labeled A. Amine **3** (1.0 mmol), formaldehyde **4** (1.5 mmol), and malonic acid (10 mol %) were added to solution A, and the reaction was stirred for X minutes. This solution was labeled B. After the completion of the reaction [24] {via thin layer chromatography (TLC) [*n*-hexane /EtOAc (4: 1)]}, solution B was separated via filtration, and the solid was washed with ethanol (3×2 mL) to obtain pure compounds (**5a-p**). The ethanol-soluble catalyst was removed from the reaction mixture. The products were characterized by comparing spectroscopic data ($^1$H NMR). The spectroscopic data of the products are shown below:

***Methyl4-(4-methylphenylamino)-1-(4-methylphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5e):*** Yield: 85%; M.p. 177–179°C; $^1$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 (5f):*** Yield: 88%; M.p. 130–132°C; $^1$H NMR (400 MHz, $CDCl_3$): 1.25 (3H, t, *J* = 7.2 Hz, $CH_2CH_3$), 2.37 (6H, s, $2CH_3$), 4.23 (2H, q, *J* = 7.2 Hz, $2CH_2CH_3$), 4.53 (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), 7.69 (2H, d, *J* = 8.4 Hz, ArH), 8.01 (1H, s, NH).

***Methyl4-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5i):*** Yield: 87%; M.p. 173–174°C; $^1$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-methoxyphenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5j):*** Yield: 88%; M.p. 154–156°C; $^1$H NMR (400 MHz, $CDCl_3$): 1.26 (3H, t, *J* = 7.2 Hz, $CH_2\underline{CH}_3$), 3.83 (6H, s, $2OCH_3$), 4.23 (2H, q, *J* = 7.2 Hz, $\underline{CH}_2CH_3$), 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).

## Results and Discussion

Initially, the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD), and formaldehyde was investigated as a model reaction. In the absence of a catalyst, only a trace amount of product was obtained at room temperature for a reaction time of approximately 10 h (Table 1, entry 1), indicating that a catalyst is necessary for this transformation. The optimized conditions were determined by changing the parameters affecting the reaction, such as the amount of catalyst and type of solvent. To determine the optimum quantity of catalyst, the model reaction was performed in the presence of different amounts of malonic acid. Catalyst loadings of 5, 10, and 15 mol%, were screened in our model reaction. By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in a lower yield (Table 1, entry 2). By increasing the amount of catalyst from 5 to 10 mol%, the reaction time was reduced and the product yield was increased (Table 1, entry 3). Thus, among these loadings, 10 mol% of malonic acid was proven to be the most efficient amount of catalyst for this reaction (Table 1, entry 3). The larger amount of catalyst did not improve the yields (Table 1, entry 12). Performing the reaction at room temperature in the absence of solvent and in the presence of 10 mol% of the catalyst resulted in a low product yield and a longer reaction time, indicating that the solvent plays an effective role in the development of this reaction (Table 1, entry 7). Therefore, choosing an appropriate solvent is crucial for a successful synthesis. To determine the optimal solvent, the model reaction was investigated in 10 mol% malonic acid using various solvents. The results indicated that a low yield of the desired product is obtained when $CH_3CN$, $H_2O$, EtOH, $H_2O$/EtOH, $CHCl_3$, DMF, $CH_2Cl_2$, and MeOH are used as solvents. The best yield was obtained in MeOH, which increased the reaction rate compared with the other solvents and the solvent-free condition. The results of these comparative experiments are summarized in Table 1. In light of these results, we used the optimized conditions of 10 mol% malonic acid as an eco-safe catalyst in MeOH at room temperature for the condensation reaction of amines (aromatic or aliphatic, **1** and **3**), dialkyl acetylenedicarboxylate **2,** and formaldehyde **4** into the corresponding highly substituted dihydro-2-oxopyrroles (Table 2 and Figure 1). Encouraged by the remarkable results obtained from the above conditions, and in order to show the generality and scope of this protocol, we used various aromatic or aliphatic amines bearing either electron-withdrawing functional groups or electron-donating groups for the synthesis of the corresponding highly substituted dihydro-2-oxopyrroles. The results are summarized in Table 2. The attractive features of this catalyst are ease of handling, mild, and environmentally benign conditions, operational simplicity, high reaction yields, and short reaction times.

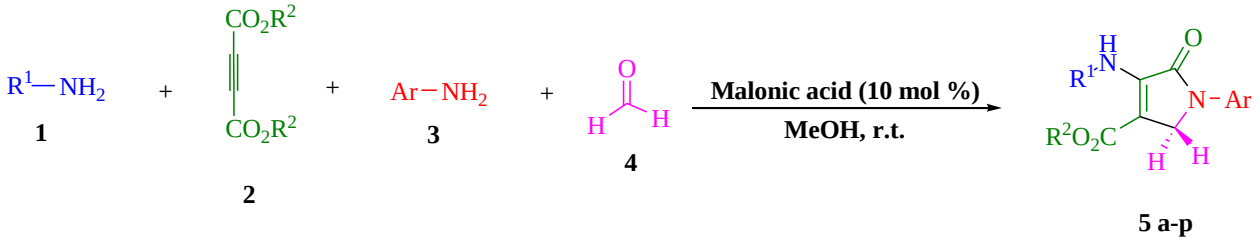



**Figure 1. Synthesis of Highly Substituted Dihydro-2-Oxopyrrole Derivatives**

**Table 1. Optimization of the Reaction Conditions in Terms of the Amount of Malonic Acid and the Type of Solvent for the Synthesis of 5a** [a]

| Test | Malonic Acid (mol%) | Solvent (3 mL) | Time (h) | Isolated Yields (%) |
|---|---|---|---|---|
| 1 | Catalyst-free | MeOH | 10 | Trace |
| 2 | 5 | MeOH | 5 | 34 |
| 3 | 10 | MeOH | 4 | 82 |
| 4 | 10 | $CH_3CN$ | 6 | 39 |
| 5 | 10 | Distilled water | 7 | 31 |
| 6 | 10 | EtOH | 4 | 53 |
| 7 | 10 | Solvent-free | 6 | 41 |
| 8 | 10 | $H_2O$/EtOH | 6 | 49 |
| 9 | 10 | $CHCl_3$ | 10 | 17 |
| 10 | 10 | DMF | 5 | 47 |
| 11 | 10 | $CH_2Cl_2$ | 10 | 28 |
| 12 | 15 | MeOH | 4 | 83 |

[a] Reaction conditions: aniline (2.0 mmol), dimethyl acetylenedicarboxylate (1.0 mmol), formaldehyde (1.5 mmol), and catalyst in various solvents at room temperature.

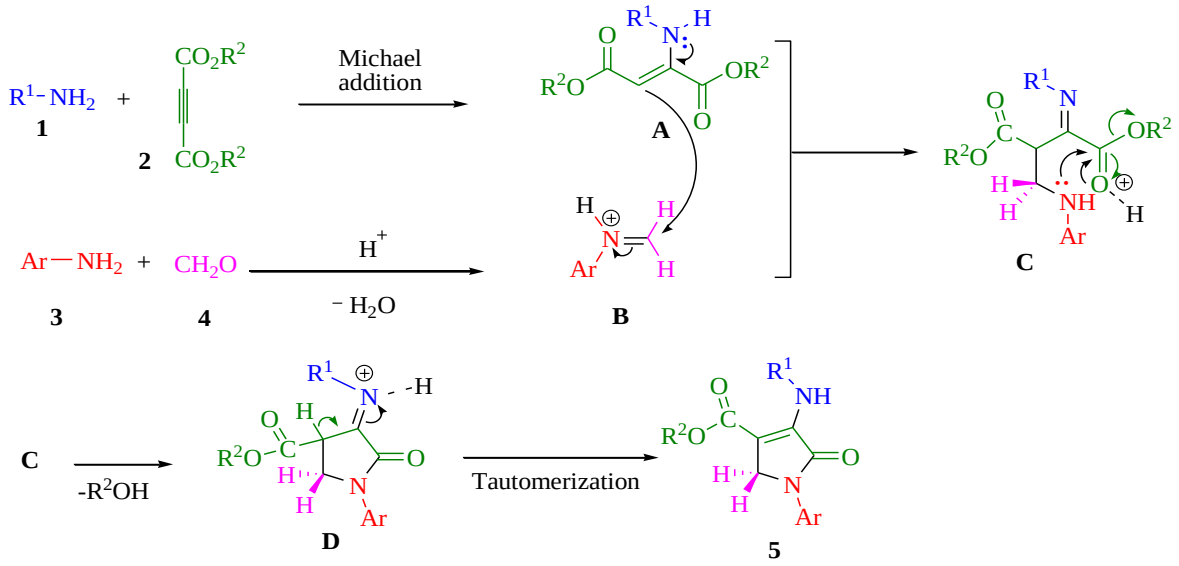
**Table 2. Synthesis of Highly Substituted Dihydro-2-Oxopyrrole Derivatives**

| Entry | $R^1$ | $R^2$ | Ar | Product | Time (h) | Yield (%)[a] | Melting point ˚C | Lit. Melting point ˚C |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Me | Ph | **5a** | 4 | 82 | 153–155 | 155–156[10] |
| 2 | Ph | Et | Ph | **5b** | 4 | 84 | 137–139 | 138–140[11] |
| 3 | 4-F-$C_6H_4$ | Me | 4-F-$C_6H_4$ | **5c** | 3 | 92 | 165–167 | 163–165[8] |
| 4 | 4-F-$C_6H_4$ | Et | 4-F-$C_6H_4$ | **5d** | 3 | 86 | 174–176 | 172–174[12] |
| 5 | 4-Me-$C_6H_4$ | Me | 4-Me-$C_6H_4$ | **5e** | 3 | 85 | 177–179 | 177–178[10] |
| 6 | 4-Me-$C_6H_4$ | Et | 4-Me-$C_6H_4$ | **5f** | 3 | 88 | 130–132 | 131–132[11] |
| 7 | 4-Cl-$C_6H_4$ | Me | 4-Cl-$C_6H_4$ | **5g** | 4.5 | 75 | 173–175 | 171–173[12] |
| 8 | 4-Cl-$C_6H_4$ | Et | 4-Cl-$C_6H_4$ | **5h** | 5.5 | 73 | 166–168 | 168–170[12] |
| 9 | 4-OMe-$C_6H_4$ | Me | 4-OMe-$C_6H_4$ | **5i** | 4 | 87 | 173–174 | 172–175[12] |
| 10 | 4-OMe-$C_6H_4$ | Et | 4-OMe-$C_6H_4$ | **5j** | 5 | 88 | 154–156 | 152–154[13] |
| 11 | $PhCH_2$ | Me | Ph | **5k** | 5 | 87 | 140–142 | 140–141[11] |
| 12 | $PhCH_2$ | Me | 4-Br-$C_6H_4$ | **5l** | 5.5 | 72 | 118–120 | 120–121[10] |
| 13 | $PhCH_2$ | Me | 4-F-$C_6H_4$ | **5 m** | 4 | 88 | 168–170 | 166–168[13] |
| 14 | $PhCH_2$ | Et | Ph | **5n** | 5 | 84 | 131–133 | 130–132[11] |
| 15 | n-$C_4H_9$ | Me | Ph | **5o** | 4 | 86 | 61–63 | 60[10] |
| 16 | n-$C_4H_9$ | Et | 4-Br-$C_6H_4$ | **5p** | 5.5 | 79 | 95–97 | 94–96[13] |

[a] Isolated yield.

The proposed mechanism for the synthesis of highly substituted dihydro-2-oxopyrrole derivatives in the presence of malonic acid is shown in scheme 1. First, the reaction of amine **1** with dialkyl acetylenedicarboxylate **2** leads to intermediate **A**. Second, condensation between amine **3** and formaldehyde **4** in the presence of malonic acid produces imine **B**. Intermediate **A** possesses enamine character and, thus, can readily react with imine **B** in the presence of malonic acid to generate intermediate **C**. The cyclization reaction of intermediate **C** leads to intermediate **D**, which in the final step tautomerizes to the corresponding highly substituted dihydro-2-oxopyrrole derivative **5**.

A comparison of catalytic abilities reported in the literature for the synthesis of polysubstituted dihydro-2-oxypyrroles is shown in Table 3. The present study reveals that malonic acid has extraordinary potential as an alternative, natural, green, readily available mildly




**Scheme 1. Proposed Mechanistic Route for the Synthesis of Highly Substituted Dihydro-2-Oxopyrrole Derivatives**

**Table 3. Comparison of Catalytic Abilities Reported in the Literature for the Synthesis of Polysubstituted Dihydro-2-Oxypyrroles**

| Entry | Compound | Catalyst | Conditions | Time/Yield (%) | References |
|---|---|---|---|---|---|
| 1 | **5a** | $Cu(OAc)_2.H_2O$ | MeOH, r.t. | 6 h/91 | [8] |
| 2 | **5a** | $InCl_3$ | MeOH, r.t. | 3 h/85 | [9] |
| 3 | **5a** | $I_2$ | MeOH, r.t. | 1 h/82 | [10] |
| 4 | **5a** | $[n\text{-}Bu_4N][HSO_4]$ | MeOH, r.t. | 4 h/88 | [12] |
| 5 | **5a** | $Al(H_2PO_4)_3$ | MeOH, r.t. | 5 h/81 | [13] |
| 6 | **5a** | $ZrCl_4$ | MeOH, r.t. | 4 h/84 | [15] |
| 7 | **5a** | EDDF | EtOH, Reflux | 3 h/89 | [16] |
| 8 | **5a** | Malonic acid | MeOH, r.t. | 4 h/82 | This work |
| 9 | **5b** | $Cu(OAc)_2.H_2O$ | MeOH, r.t. | 5 h/85 | [8] |
| 10 | **5b** | $InCl_3$ | MeOH, r.t. | 3 h/85 | [9] |
| 11 | **5b** | $I_2$ | MeOH, r.t. | 1 h/81 | [10] |
| 12 | **5b** | $[n\text{-}Bu_4N][HSO_4]$ | MeOH, r.t. | 4 h/86 | [12] |
| 13 | **5b** | $Al(H_2PO_4)_3$ | MeOH, r.t. | 5 h/80 | [13] |
| 14 | **5b** | $ZrCl_4$ | MeOH, r.t. | 3.5 h/83 | [15] |
| 15 | **5b** | EDDF | EtOH, Reflux | 3.5 h/84 | [16] |
| 16 | **5b** | Malonic acid | MeOH, r.t. | 4 h/84 | This work |

acidic, and highly efficient catalyst for the one-pot synthesis of these biologically active heterocyclic compounds. In addition, good to high yields and short reaction times are notable advantages of the present methodology. Furthermore, in the present work, the products were obtained through simple filtering and washing with ethanol (thus avoiding the use of organic solvents under reflux conditions, which is a source of environmental pollution) and column chromatographic separation was not needed to purify the products.

## Conclusion

We have introduced malonic acid as an economical and highly efficient catalyst for facile one-pot synthesis of highly substituted dihydro-2-oxopyrrole derivatives via a four-component reaction of amines (aromatic or aliphatic), dialkyl acetylenedicarboxylate, and formaldehyde. The promising features that distinguish this approach from other reported methods are the use of a low cost and readily available catalyst with high catalytic

ability as well as a simple reaction work-up, which make the present methodology more economical and industrially important. Additional advantages of the present protocol include good to high reaction yields, short reaction times, and mild reaction conditions.

## Acknowledgements

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

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