Eco-friendly and Convenient Synthesis of Biologically Active Polysubstituted Dihydro-2-Oxypyrroles Using Manganese (II) Nitrate Tetrahydrate at Ambient Temperatures

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Eco-friendly and Convenient Synthesis of Biologically Active Polysubstituted Dihydro-2-Oxypyrroles Using Manganese (II) Nitrate Tetrahydrate at Ambient Temperatures

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Abstract

A convenient, expedient and efficient method for the synthesis of polysubstituted dihydro-2-oxypyrroles is described via the one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde, and amines (aromatic and aliphatic) at ambient temperature in the presence of Manganese (II) Nitrate Tetrahydrate (Mn(NO$_3$)$_2$.4H$_2$O) as a cost effective and inexpensive catalyst. The present methodology provides a simple and eco-safe procedure for the synthesis of polysubstituted dihydro-2-oxypyrroles with some additional advantages, such as good to high yields, short reaction times, avoidance of hazardous or toxic catalysts, simplicity of operating and work-up procedures with no necessity for chromatographic purification steps.

Keywords: Polysubstituted dihydro-2-oxypyrroles, Manganese (II) Nitrate Tetrahydrate (Mn(NO$_3$)$_2$.4H$_2$O), eco-safe procedure, one-pot synthesis

Introduction

Synthesis of pyrrole rings has attracted great interest due to their biological and pharmaceutical properties. They have been used as human cytomegalovirus (HCMV) protease [1], CD45 protein tyrosinphosphatase [2], and an anti-cancer agent [3]. In addition, Thiomarinol A4 used as an antibiotic has pyrrole rings [4], and a number of alkaloids performing biological activities have pyrrole rings [5], which have been used as UCS1025A [6], and Oteromycin [7]. Furthermore, these rings have been used with HIV integrase [8], and they also have also herbicidal [9] properties. Some of those with biologically properties are shown in Figure 1.

In recent years, considerable attention has been paid to the design of an efficient and eco-friendly synthetic route through the use of multi-component domino reactions (MCRs) [10–13] due to their wide range of advantages, such as their atom-economy, simple work-up, mild and environmentally-friendly, one-pot, and low-cost. Cu(OAc)$_2$.H$_2$O [14], InCl$_3$ [15], I$_2$ [16], AcOH [17], [n-Bu$_4$N][HSO$_4$] [18], Al(H$_2$PO$_4$)$_3$ [19], oxalic acid [20], ZrCl$_4$ [21], Fe$_3$O$_4$@nano-cellulose–OPO$_3$H [22], -

Figure 1. Biologically Active Compounds with Dihydro-2-Oxypyrrole Rings
ethylenediammonium formate (EDDF) [23], tartaric acid [24], Phthalic acid [25], and ZnSO₄·7H₂O [26] can all be used as catalysts in this transformation. Some of these methodologies have limitations, such as using an expensive catalyst for the reflux condition, a longer reaction time, lower yield, tedious work-up procedure, or the use of a large amount of the catalyst. Thus, as part of our ongoing research program that aims for the development of efficient methodologies, we here report a mild and facile protocol for the synthesis of polysubstituted dihydro-2-oxo-pyrroles in the presence of Mn(NO₃)₂·4H₂O as being a readily available and non-toxic catalyst, using a one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at ambient temperature.

**Material and Methods**

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

**General procedure for preparation of polysubstituted dihydro-2-oxo-pyrroles (5a-q) [16]:** 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 Mn(NO₃)₂·4H₂O (20 mol%) were added and the reaction was stirred for an appropriate time. After completion of the reaction (ascertained 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-q). The catalyst is soluble in ethanol and was thus removed from the reaction mixture. The products were characterized by comparison of the spectroscopic data (¹H NMR). The ¹H NMR data of the products were compared with the literature (Table 4). The spectra data of the products are represented below:

**Methyl 4-(4-bromophenylamino)-1-(4-bromophenyl)-2,5-dihydro-5-oxo-1H-pyrrole-3-carboxylate (5c):**

Yield: 78%; M.p. 176-178 °C; ¹H NMR (400 MHz, CDCl₃): 3.81 (3H, s, OCH₃), 4.52 (2H, s, CH₂-N), 7.04 (2H, d, J= 11.2 Hz, ArH), 7.46 (2H, d, J= 11.6 Hz, ArH), 7.53 (2H, d, J= 12.0 Hz, ArH), 7.71 (2H, d, J= 12.0 Hz, ArH), 8.06 (1H, s, NH) ppm.

**Ethyl 3-(4-bromophenylamino)-1-(4-bromophenyl)-2,5-dihydro-2-oxo-1H-pyrrole-4-carboxylate (5d):**

Yield: 79%; M.p. 167-169 °C; ¹H NMR (400 MHz, CDCl₃): 1.29 (3H, t, J= 9.6 Hz, OCH₂CH₃), 4.28 (2H, q, J= 9.6 Hz, OCH₂CH₃), 4.53 (2H, s, CH₂-N), 7.04 (2H, d, J= 11.6 Hz, ArH), 7.45 (2H, d, J= 11.2 Hz, ArH), 7.53 (2H, d, J= 12.0 Hz, ArH), 7.72 (2H, d, J= 11.6 Hz, ArH), 8.05 (1H, s, NH) ppm.

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

Yield: 86%; M.p. 178-179 °C; 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) ppm.

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

Yield: 83%; M.p. 132-134 °C; 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), 7.72 (2H, d, J= 11.6 Hz, ArH), 8.05 (1H, s, NH) ppm.
Results and Discussion

The generalizability of this four-condensation reaction was studied under optimized conditions and the reaction between aniline, dimethyl acetylenedicarboxylate (DMAD) and formaldehyde was investigated as a model reaction, and then the effect of different amounts of the catalyst in MeOH as the solvent was studied in this protocol. In the absence of the catalyst, a trace amount of this product was detected after 12 h (Table 1, entry 1). Good yields were obtained in the presence of catalyst. The most effective amount of the catalyst was 20 mol % (Table 1, entry 5). Higher amounts of catalyst did not increase the products’ yields (Table 1, entry 12). The results are summarized in Table 1. The effect of various solvents was also investigated for this protocol, including H2O, EtOH, CH2Cl2, CHCl3 and CH3CN. Of the solvents, MeOH was found to be the most effective for this methodology (Table 1, entry 5). Finally, a convenient, expedient and efficient procedure for the synthesis of polysubstituted dihydro-2-oxypyrrroles was described via the one-pot four-condensation of (aromatic or aliphatic 1 and 3), dialkyl acetylenedicarboxylate 2 and formaldehyde 4 under ambient temperature in the presence of Mn(NO3)2·4H2O (Scheme 1). The results are summarized in Table 2.

The proposed mechanism for the synthesis of polysubstituted dihydro-2-oxypyrrroles in the presence of Mn(NO3)2·4H2O 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 Mn(NO3)2·4H2O produces imine B. Intermediate A

Figure 1. Synthesis of Polysubstituted Dihydro-2-Oxypyrrroles

R1 = C6H5, 4-Br-C6H4, 4-OMe-C6H4, 4-F-C6H4, 4-Me-C6H4, 4-Et-C6H4, n-C4H9, PhCH2.

R2 = CH3, C2H5.

Ar = C6H5, 4-Br-C6H4, 4-OMe-C6H4, 4-F-C6H4, 4-Me-C6H4, 4-Et-C6H4, 3,4-Cl2-C6H4.

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Table 1. Optimization of the Reaction Conditions in the Presence of Different Amounts of Mn(NO₃)₂·4H₂O and Different Solvents in the Synthesis of 5a *

![Chemical structure](image)

| Entry | Mn(NO₃)₂·4H₂O (mol%) | Solvent   | Time (h) | Isolated Yields (%) |
|-------|----------------------|-----------|----------|--------------------|
| 1     | Catalyst free        | MeOH      | 12       | trace              |
| 2     | 5                    | MeOH      | 9        | 26                 |
| 3     | 10                   | MeOH      | 7        | 43                 |
| 4     | 15                   | MeOH      | 6        | 68                 |
| 5     | 20                   | MeOH      | 5        | 84                 |
| 6     | 20                   | Solvent free | 8     | 35                 |
| 7     | 20                   | EtOH      | 5        | 67                 |
| 8     | 20                   | H₂O       | 8        | 28                 |
| 9     | 20                   | CH₂Cl₂    | 10       | 18                 |
| 10    | 20                   | CHCl₃     | 10       | 13                 |
| 11    | 20                   | CH₃CN     | 7        | 39                 |
| 12    | 25                   | MeOH      | 5        | 84                 |

* Reaction conditions: aniline (2.0 mmol), dimethyl acetylenedicarboxylate (1.0 mmol) and formaldehyde (1.5 mmol) with catalyst in various solvents at room temperature

Table 2. Synthesis of Dihydro-2-Oxypyrrole Derivatives

| Entry | R¹ | R² | Ar   | Product | Time (h) | Yield (%) | M.p. (°C) | Lit. M.p. (°C) |
|-------|----|----|------|---------|----------|-----------|-----------|----------------|
| 1     | Ph | Me | Ph   | 5a      | 5        | 84        | 154-156   | 155-156²⁰      |
| 2     | Ph | Et | Ph   | 5b      | 5        | 82        | 140-141   | 138-140²⁷      |
| 3     | 4-Br-C₆H₄ | Me | 4-Br-C₆H₄ | 5c     | 7        | 78        | 176-178   | 175-177²⁸      |
| 4     | 4-Br-C₆H₄ | Et | 4-Br-C₆H₄ | 5d     | 7        | 79        | 167-169   | 169-171¹⁷      |
| 5     | 4-O-Me-C₆H₄ | Me | 4-O-Me-C₆H₄ | 5e     | 5        | 85        | 175-177   | 172-175²⁸      |
| 6     | 4-O-Me-C₆H₄ | Et | 4-O-Me-C₆H₄ | 5f     | 5        | 81        | 153-155   | 152-154²⁹      |
| 7     | 4-F-C₆H₄ | Me | 4-F-C₆H₄ | 5g     | 4        | 87        | 161-163   | 163-165²⁰      |
| 8     | 4-F-C₆H₄ | Et | 4-F-C₆H₄ | 5h     | 4        | 88        | 170-172   | 172-174²⁸      |
| 9     | 4-Me-C₆H₄ | Me | 4-Me-C₆H₄ | 5i     | 4        | 86        | 178-179   | 177-178²⁶      |
| 10    | 4-Me-C₆H₄ | Et | 4-Me-C₆H₄ | 5j     | 4        | 83        | 132-134   | 131-132²⁷      |
| 11    | 4-Et-C₆H₄ | Me | 4-Et-C₆H₄ | 5k     | 4        | 82        | 126-128   | 124-125²²      |
| 12    | n-C₆H₅ | Me | Ph    | 5l     | 4        | 84        | 58-60     | 60²⁶          |
| 13    | n-C₆H₅ | Me | 3,4-Cl₂-C₆H₃ | 5m    | 6        | 78        | 96-98     | 97-99²⁹      |
| 14    | n-C₆H₅ | Et | 4-Br-C₆H₄ | 5n     | 5        | 81        | 93-95     | 94-96²⁹      |
| 15    | PhCH₂ | Me | Ph    | 5o     | 6        | 85        | 141-143   | 140-141²⁷      |
| 16    | PhCH₂ | Me | 4-F-C₆H₄ | 5p     | 5        | 87        | 165-167   | 166-168²⁹      |
| 17    | PhCH₂ | Et | Ph    | 5q     | 6        | 84        | 128-130   | 130-132²⁷      |

* Isolated yield.
Eco-Friendly and Convenient Synthesis of Biologically Active

Table 3. Comparison of the Catalytic Ability of Some of the Catalysts as Reported in the Literature for use in the Synthesis of Polysubstituted Dihydro-2-Oxypyrroles

| Entry | Compound | Catalyst | Conditions | Time/Yield (%) | Reference |
|-------|----------|----------|------------|----------------|-----------|
| 1     | 5a       | Cu(OAc)$_2$·H$_2$O | MeOH, r.t. | 6h/91          | [14]      |
| 2     | 5a       | InCl$_3$   | MeOH, r.t. | 3h/85          | [15]      |
| 3     | 5a       | I$_2$      | MeOH, r.t. | 1 h/82         | [16]      |
| 4     | 5a       | [n-Bu$_3$N][HSO$_4$] | MeOH, r.t. | 4 h/88         | [18]      |
| 5     | 5a       | Al(H$_2$PO$_4$)$_3$ | MeOH, r.t. | 5 h/81         | [19]      |
| 6     | 5a       | ZrCl$_4$   | MeOH, r.t. | 4 h/84         | [21]      |
| 7     | 5a       | EDDF       | EtOH, Reflux | 3 h/89         | [23]      |
| 8     | 5a       | Mn(NO$_3$)$_2$·4H$_2$O | MeOH, r.t. | 5 h/84         | This work |
| 9     | 5b       | Cu(OAc)$_2$·H$_2$O | MeOH, r.t. | 5h/85          | [14]      |
| 10    | 5b       | InCl$_3$   | MeOH, r.t. | 3h/85          | [15]      |
| 11    | 5b       | I$_2$      | MeOH, r.t. | 1 h/81         | [16]      |
| 12    | 5b       | [n-Bu$_3$N][HSO$_4$] | MeOH, r.t. | 4 h/86         | [18]      |
| 13    | 5b       | Al(H$_2$PO$_4$)$_3$ | MeOH, r.t. | 5 h/80         | [19]      |
| 14    | 5b       | ZrCl$_4$   | MeOH, r.t. | 3.5 h/83       | [21]      |
| 15    | 5b       | EDDF       | EtOH, Reflux | 3.5 h/84       | [23]      |
| 16    | 5b       | Mn(NO$_3$)$_2$·4H$_2$O | MeOH, r.t. | 5 h/82         | This work |

Table 4. Comparison of $^1$HNMR Data for the Synthesis of Polysubstituted Dihydro-2-Oxypyrroles

| Entry | Product | H Shift (found) | H Shift (lit) | Reference |
|-------|---------|----------------|---------------|-----------|
| 1     | 5c      | 3.81 (3H, s, OCH$_3$) | 3.79 (3H, s, NH) | 14        |
|       |         | 4.52 (2H, s, CH$_2$-N) | 4.48 (2H, s, CH$_2$-N) |           |
|       |         | 8.06 (1H, s, NH) | 8.06 (1H, s, OCH$_3$) |           |
Table 4. Continue

| Entry | Product | H Shift (found) | H Shift (lit) | Reference |
|-------|---------|----------------|---------------|-----------|
| 2     | 5d      | 1.29 (3H, t, \(J = 9.6 \text{ Hz}, \) OCH(CH)\(\_\)_2) | 1.29 (3H, t, \(J = 7.1 \text{ Hz}, \) OCH(CH)\(\_\)_2) | 14        |
|       |         | 4.28 (2H, q, \(J = 9.6 \text{ Hz}, \) OCH(CH)\(\_\)_2) | 4.27 (2H, q, \(J = 7.1 \text{ Hz}, \) OCH(CH)\(\_\)_2) |           |
|       |         | 4.53 (2H, s, CH\(\_\)_2-N) | 4.52 (2H, s, CH\(\_\)_2-N) |           |
|       |         | 8.05 (1H, s, NH) | 8.05 (1H, s, NH) |           |
| 3     | 5i      | 2.36 (6H, s, 2CH\(\_\)_3) | 2.38 (6H, d, 2CH\(\_\)_3) | 14        |
|       |         | 3.77 (3H, s, OCH\(\_\)_3) | 3.77 (3H, s, OCH\(\_\)_3) |           |
|       |         | 4.52 (2H, s, CH\(\_\)_2-N) | 4.50 (2H, s, CH\(\_\)_2-N) |           |
|       |         | 8.03 (1H, s, NH) | 8.06 (1H, s, NH) |           |
| 4     | 5j      | 1.25 (3H, t, \(J = 7.2 \text{ Hz}, \) CH\(\_\)_2) | 1.25 (3H, t, \(J = 7.1 \text{ Hz}, \) OCH(CH)\(\_\)_2) | 14        |
|       |         | 2.37 (6H, s, 2CH\(\_\)_3), | 2.37 (6H, s, 2CH\(\_\)_3), |           |
|       |         | 4.23 (2H, q, \(J = 7.2 \text{ Hz}, \) 2CH\(\_\)_2) | 4.24 (2H, q, \(J = 7.1 \text{ Hz}, \) OCH(CH)\(\_\)_2) |           |
|       |         | 4.53 (2H, s, CH\(\_\)_2-N) | 4.51 (2H, s, CH\(\_\)_2-N) |           |
|       |         | 8.01 (1H, s, NH) | 8.04 (1H, s, NH) |           |

possesses an enamine character and can thus readily react with imine B in the presence of Mn(NO\(_3\))\(_2\).4H\(_2\)O to generate intermediate C. The cyclization of intermediate C yields intermediate D, which tautomerizes to the corresponding polysubstituted dihydro-2-oxypyrroles (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 polysubstituted dihydro-2-oxypyrroles is shown in Table 3. In Table 4, the \(^1\)HNMR data for the products is compared with that in the literature. This study reveals that Mn(NO\(_3\))\(_2\).4H\(_2\)O has shown extraordinary potential as an alternative, inexpensive, eco-safe, and efficient catalyst for the one-pot synthesis of these biologically active heterocyclic compounds. In addition, good to high yields and short reaction times are other notable advantages of this present methodology.

Conclusions

In conclusion, we have introduced a simple and efficient protocol for the synthesis of a wide range of biologically and pharmacologically polysubstituted dihydro-2-oxypyrroles in the presence of Manganese (II) Nitrate Tetrahydrate (Mn(NO\(_3\))\(_2\).4H\(_2\)O) via a one-pot four-condensation of dialkyl acetylenedicarboxylate, formaldehyde and amines (aromatic and aliphatic) at room temperature conditions. The promising advantages of the methodology presented are its generalizability, the avoidance of hazardous byproducts in production, good to high yields, short reaction times, clean reaction profiles and ease of product isolation.

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