A Mild and Facile One-Pot Synthesis of N-Methyl-3-Acyl-Pyrroles

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Received: 28 February 2010; in revised form: 23 March 2010 / Accepted: 18 April 2010 / Published: 27 April 2010

Abstract: N-Methyl-3-acylpyrroles were synthesized via a multicomponent reaction of dimethylacetylene dicarboxylate (DMAD), N-methylhydroxylamine and acylchlorides in the presence of KHCO₃. For comparison both conventional and microwave protocols were examined in this procedure. The reaction is clean and gives the products in good to excellent yields under conventional heating conditions at 40 °C in anhydrous dichloromethane.

Keywords: 3-acylpyrrole; multicomponent reaction; dimethylacetylene dicarboxylate

1. Introduction

Pyrrrole is one of the most important heterocyclic compounds, having become increasingly important in medicinal chemistry and organic synthesis [1-5]. Some of the recently isolated pyrrole-containing marine natural products have been found to exhibit considerable cytotoxicity and function as multi drug resistant (MDR) reversal agents. Many of these biologically active compounds have emerged as chemotherapeutic agents [6]. Heterocyclic compounds containing a 3-acylpyrrole fragment are of interest for making new pharmacological preparations. For example, the cannabinoid activity of 1-alkyl-3-(naphthoyl)pyrroles [7] and 1-alkyl-3-(naphthoyl)indoles [8] is known, as is the antibiotic activity of verrucarin E (3-acetyl-4-hydroxymethylpyrrole) isolated from Myrothecium verrucaria [9]. 3-Acylpyrroles and other 3-substituted pyrroles obtained from them are precursors of liquid crystal materials [10] and polypyrroles [11], possessing high electrical conductivity in comparison with their
1-substituted analogs [12]. Such conjugated polymers may be used, for example, to construct gas sensors [13], and also sensors capable of distinguishing DNA molecules [14]. Many methods for the synthesis of diversely substituted pyrroles have been developed [15]. Conjugate addition reactions [16], transition metal-mediated reactions [17], reductive couplings [18], aza-Wittig reactions [19], and other multistep operations [20] have all been performed for the synthesis of pyrroles. Despite these huge developments, the Paal-Knorr [21] reaction is still considered to be the most attractive method for the synthesis of pyrroles. In the present work, we describe a simple method for the KHCO$_3$-catalyzed synthesis of 3-acylpyrroles in good yields starting from commercially available DMAD, N-methylhydroxylamine and various acylchlorides.

2. Results and Discussion

Our research group has reported several studies directed toward the synthesis of some heterocyclic compounds under solvent-free conditions [22-27]. Because of the biological activities of pyrrole derivatives, we became interested in the one-pot synthesis of $N$-methyl-3-acylpyrroles under mild and solvent-free conditions.

Electrophilic substitution in pyrrole occurs predominantly at the C$_2$-position [28-30]. Thus, the investigation of efficient methods for preparing C$_3$-substituted pyrroles is one of the important goals in pyrrole chemistry because of their frequent use for obtaining various biologically active compounds like porphyrins. For the substitution on β-(C$_3$) position, Friedel-Crafts acylation or alkylation on pyrrole bearing an electron withdrawing substituent at C$_2$ [31-32] or N$_1$ [33-34] has been widely investigated. Direct Friedel-Crafts acylation on 2,5-dimethylpyrrole also gives 3,4-symmetric acyl compounds, but normally the yields are very low (<5%) when no electron withdrawing groups are on the substituted pyrroles [18]. Very recently we prepared pentasubstituted pyrroles via the reaction of DMAD with N-methylhydroxylamine under mild solvent-free conditions, so we studied the possibility of synthesizing $N$-methyl-3-acylpyrroles 4a-e using a multicomponent reaction in anhydrous dichloromethane of DMAD (1), N-methylhydroxylamine (2) and various acylchlorides 3a-e in the presence of KHCO$_3$ (Scheme 1).

**Scheme 1.** One-pot synthesis of $N$-methyl-3-acylpyrroles.

We tried several different reaction conditions under microwave irradiation and conventional heating, and found that the reaction took place efficiently and in good yield at 40°C in CH$_2$Cl$_2$. Firstly, benzoyl chloride (3a) was chosen as a model for the reaction with DMAD and $N$-
methylhydroxylamine to optimize reaction conditions. It was observed that a low yield of 4a was obtained in the absence of KHCO₃ when the reaction was stirred at room temperature for 10 h. The reaction in the presence of the KHCO₃ at room temperature in CH₂Cl₂, afforded the corresponding product in 61% yield (Table 1, entry 1). The reaction was also examined at 40 ºC and found to be faster and to give higher yield (81%) than at room temperature (Table 1, entry 2). The procedure was examined under microwave-assisted conditions and found that the yield of product was very low in comparison with conventional heating in anhydrous CH₂Cl₂ (Table 1, entries 7-8). In another experiment, for the same reaction, several common solvents were examined in the presence of KHCO₃ at 40 ºC. The results showed that the reaction in CH₂Cl₂ resulted in higher yields in comparison with the other tested solvents (Table 1, entries 2-5). There is no significant difference in the results using different bases such as Na₂CO₃, K₂CO₃, KHCO₃, NH₄OAc, NaOH, and NH₄Cl as the catalyst in this procedure. The reaction of enamine, derived from addition of an N-methylhydroxylamine to DMAD, and benzoylchloride proceeds by a smooth 1:1:1 addition reaction in anhydrous dichloromethane at 40 ºC to produce N-methyl-3-benzoylpyrrole (4a) in 81% yield.

Table 1. Study of the synthesis of 3-benzoylpyrrole 4a under different conditions.

| Entry | Solvent/Solid support | Mode of heating | Temperature (ºC) | Time (h) | Yield a(%) |
|-------|-----------------------|-----------------|------------------|----------|------------|
| 1     | CH₂Cl₂                | Conventional    | 25               | 3        | 61         |
| 2     | CH₂Cl₂                | Conventional    | 40               | 2.5      | 81         |
| 3     | CHCl₃                 | Conventional    | 40               | 3        | 63         |
| 4     | Dioxane               | Conventional    | 40               | 2.5      | 60         |
| 5     | THF                   | Conventional    | 40               | 2.5      | 63         |
| 6     | Neat                  | Conventional    | 40               | 3        | 53         |
| 7     | Neat                  | MW              | Not detected     | 10 min   | <30        |
| 8     | Basic alumina         | MW              | Not detected     | 10 min   | <30        |

*a Isolated yields after column chromatography.

Having established the reaction conditions, various acyl chlorides were examined in this procedure to investigate the reaction scope, and several representative examples are summarized in Table 2. The reaction was clean and proceeded smoothly to give the corresponding 3-acylpyrroles in good to excellent yields. There were no remarkable differences in yields and reaction times between aromatic and aliphatic acyl halides in this procedure.

Table 2. One-pot synthesis of 3-acylpyrroles.

| Entry | Product | Time (h) | Yield a(%) |
|-------|---------|----------|------------|
| 1     | 4a      | 2.5      | 81         |
| 2     | 4b      | 3        | 83         |
| 3     | 4c      | 3        | 73         |
| 4     | 4d      | 3.5      | 78         |
| 5     | 4e      | 2.5      | 76         |

*a Isolated yields after column chromatography.
The structures of compounds \(4a-4e\) were deduced from their elemental analyses and their IR, \(^1\)HNMR, and \(^{13}\)C-NMR spectroscopic data and no side products were identified. For example, the \(^1\)HNMR spectrum of \(4a\) exhibited one singlet identified as the \(N\)-methyl moiety (\(\delta\) 3.50), phenyl proton multiplets (\(\delta\) 7.30, 3H and \(\delta\) 7.41, 2H), along with multiplets [\(\delta\) 7.51, 1H, \(\delta\) 7.60, 1H and \(\delta\) 7.81, 1H], for the pyrrole protons. The \(^1\)H-decoupled \(^{13}\)C-NMR spectrum of \(4a\) showed 10 distinct resonances that confirm the proposed structure. The IR spectrum of \(4a\) displayed a characteristic carbonyl (1,732 cm\(^{-1}\)) stretching vibration.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the enamine \(5\) formed from \(N\)-methyl-hydroxylamine and DMAD attacked to acyl chloride to furnish intermediate \(6\), which is converted to intermediate \(7\). Subsequent reaction of \(7\) with DMAD yields intermediate \(8\), which undergoes an intramolecular cyclization reaction to generate \(9\). Finally, products \(4a-e\) were formed from intermediate \(9\).

**Scheme 2.** Plausible mechanism for the formation of the products \(4a-e\).

3. Experimental

3.1 General

All reagents were purchased from Merck and used without further purification. \(^1\)H- and \(^{13}\)C-NMR spectra were recorded on a Bruker Avance AC-400 MHz instrument using CDCl\(_3\) as the deuterated solvent and TMS as internal standard. Elemental analyses were carried out on a Perkin-Elmer 240C
elemental analyzer and are reported in percent atomic abundance. All melting points are uncorrected and measured in open glass-capillaries using Stuart melting point apparatus. Microwave experiments were conducted in a Milestone MicroSYNTH apparatus.

3.2. General procedure for preparation of 3-acylpyrroles 4a-e

Dimethylacetylene dicarboxylate (2 mmol) was added to a stirred solution of N-methylhydroxylamine hydrochloride (2 mmol) and KHCO₃ (3 mmol) in anhydrous CH₂Cl₂ (10 mL). The mixture was stirred for 15 min, and then a solution of an acyl chloride (2 mmol) and dimethylacetylene dicarboxylate (2 mmol) in CH₂Cl₂ (5 mL) was added slowly at 40 °C. After completion of the reaction (2.5–3.5 h) as indicated by TLC on silica gel F₂₅⁴ (n-hexane/EtOAc 6:1), the solvent from the reaction mixture was evaporated under reduced pressure to leave a residue that was purified by column chromatography (n-hexane/EtOAc 6:1) to afford pure desired products 4a-e.

**N-Methyl-3-benzoyl pyrrole (4a):** IR (KBr) (ν max, cm⁻¹): 1732 (C=O); ¹H-NMR δH (ppm): 7.81 (m, 1H), 7.60 (m, 1H), 7.51 (m, 1H), 7.41 (m, Ph-H, 2H), 7.30 (m, Ph-H, 3H), 3.50 (s, 3H, N-Me); ¹³C-NMR δC (ppm): 163.32, 133.14, 132.24, 129.92, 128.77, 127.62, 127.10, 126.84, 125.75, 36.24; Anal. Calcd (%) for C₁₂H₁₁NO: C, 77.81; H, 5.99; N, 7.56. Found (%): C, 77.90; H, 5.91; N, 7.48.

**N-Methyl-3-acetyl pyrrole (4b):** IR (KBr) (ν max, cm⁻¹): 1727 (C=O); ¹H-NMR δH (ppm): 7.75 (m, 1H), 7.48-7.55 (m, 2H), 3.53 (s, 3H, N-Me), 2.09 (s, 3H, COMe); ¹³C-NMR δC (ppm): 160.22, 131.33, 129.12, 126.12, 124.78, 33.45, 27.50; Anal. Calcd (%) for C₇H₉NO: C, 68.27; H, 7.37; N, 11.37. Found (%): C, 69.05; H, 7.29; N, 11.31.

**N-Methyl-3-(4-chlorobenzoyl)-pyrrole (4c):** IR (KBr) (ν max, cm⁻¹): 1720 (C=O); ¹H-NMR δH (ppm): 7.77 (m, 1H), 7.51-7.58 (m, 2H), 7.38 (d, J=7.56Hz, 2H), 7.31 (d, J=7.56Hz, 2H), 3.47 (s, 3H, N-Me); ¹³C-NMR δC (ppm): 164.56, 135.66, 134.32, 131.11, 129.32, 128.09, 127.99, 126.25, 126.15, 33.36; Anal. Calcd (%) for C₁₂H₊ClNO: C, 65.61; H, 4.59; N, 6.38. Found (%): C, 65.65; H, 4.53; N, 6.34.

**N-Methyl-3-(2-methoxybenzoyl)-pyrrole (4d):** IR (KBr) (ν max, cm⁻¹): 1721 (C=O); ¹H-NMR δH (ppm): 7.83 (m, 1H), 7.49-7.54 (m, 2H), 7.31-7.38 (m, Ph-H, 4H), 3.87 (s, 3H, OMe), 3.50 (s, 3H, N-Me); ¹³C-NMR δC (ppm): 162.21, 137.62, 136.54, 135.66, 134.10, 133.22, 132.20, 130.34, 129.79, 127.94, 127.40, 126.15, 67.71, 34.16; Anal. Calcd (%) for C₁₃H₁₃NO₂: C, 72.54; H, 6.09; N, 6.51. Found (%): C, 72.58; H, 5.98; N, 6.48.

**N-Methyl-3-(4-nitrobenzoyl)-pyrrole (4e):** IR (KBr) (ν max, cm⁻¹): 1717 (C=O); ¹H-NMR δH (ppm): 7.70 (m, 1H), 7.66 (d, J=7.87Hz, 2H), 7.45-7.53 (m, 2H), 7.37 (d, J=7.87Hz, 2H), 3.54 (s, 3H, N-Me); ¹³C-NMR δC (ppm): 160.06, 133.06, 133.02, 131.21, 129.70, 128.56, 127.65, 127.05, 126.55, 37.09; Anal. Calcd (%) for C₁₂H₁₀N₂O₃: C, 62.60; H, 4.38; N, 12.17. Found (%): C, 62.80; H, 4.35; N, 12.08.
4. Conclusions

In summary, we have described a highly efficient one-pot procedure for the preparation of \(N\)-methyl-3-acylpyrroles by a three component reaction in \(CH_2Cl_2\) using KHCO\(_3\) as catalyst. The reaction products were prepared in moderate to good yield, even with different substituted acyl halides. We believe that this procedure provides a valuable addition to current methodologies.

Acknowledgements

The partial financial assistance from the Research Vice Chancellor of Azarbaijan University of Tarbiat Moallem is gratefully acknowledged.

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*Sample Availability:* Samples of compounds 4a-e are available from the authors.

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