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Solvent-free synthesis of substituted pyrroles and pyridones via multicomponent reaction of primary amines

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Abstract: Substituted pyrroles and pyridones have easily synthesized by the three-component reactions involving alkyl propiolates and primary amines in the presence of catalytic amount of *N*-methylimidazole or malonyl chloride at 50 °C under solvent-free conditions.

Keywords: Solvent-free conditions, primary amines, *N*-methyl imidazol, Pyrroles, Pyridone, Alkyl propiolates.

Introduction

At the beginning of the new century, a move in importance in chemistry is obvious with the longing to extend environmentally gentle routes to a numerous of materials [1]. Green chemistry approaches hold out momentous potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies [2]. Of all of the existing areas of chemistry, medicinal and pharmaceutical chemistry, with their traditionally large volume of waste/product ratio, are maybe the most developed for greening [3]. Multicomponent reactions (MCRs) have been commonly employed by synthetic chemists as a too easy means to produce molecular diversity from bifunctional substrates that react successively in a intramolecular way [4]. Five and/or six membered, nitrogen-containing heterocycles are main building blocks in a broad number of biologically active compounds [5]. Among them, pyrroles and pyridones are heterocycles of enormous importance. Pyrroles presence in several natural products like heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes is important [6]. Some of the recently isolated pyrrole-containing marine natural products have been set up to display considerable cytotoxicity and function as multidrug resistant reversal agents [7]. Many of these biologically active compounds have appeared as chemotherapeutic agents. In addition, substituted pyrroles are molecular skeleton having enormous importance in material science [8]. They have been also applied as antioxidants, antibacterial, ionotropic, antitumor, anti inflammatory, and antifungal agents [9-14]. Also, substituted pyridones have been used in many filed such as biological and natural products [15-20].

As part of our current studies on the development of new routes in heterocyclic compounds, we report an efficient three component reaction between alkyl propiolate 1, primary amines 2 and alkyl propiolate 3 in the presence of catalytic amount of *N*-methylimidazole at 50 °C under solvent-free conditions which lead to pyrrole derivatives 4 in good yield (Scheme **1**). In addition in this work, functionalized 2-pyridones 6 synthesize *via* the reaction of methyl propiolate 1 and alkyl amines 2 in the presence of malonyl dichloride **5** under solvent-free conditions at 50°C (Scheme **2**).

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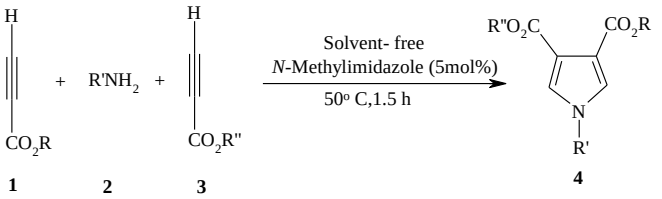
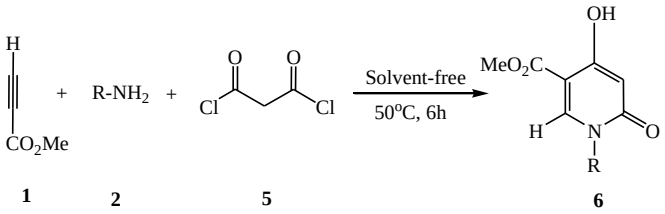


1 **2** **3** **4**

Scheme 1: Reaction of alkyl propiolates and primary amines in the presence of catalytic amount of *N*-methylimidazole.



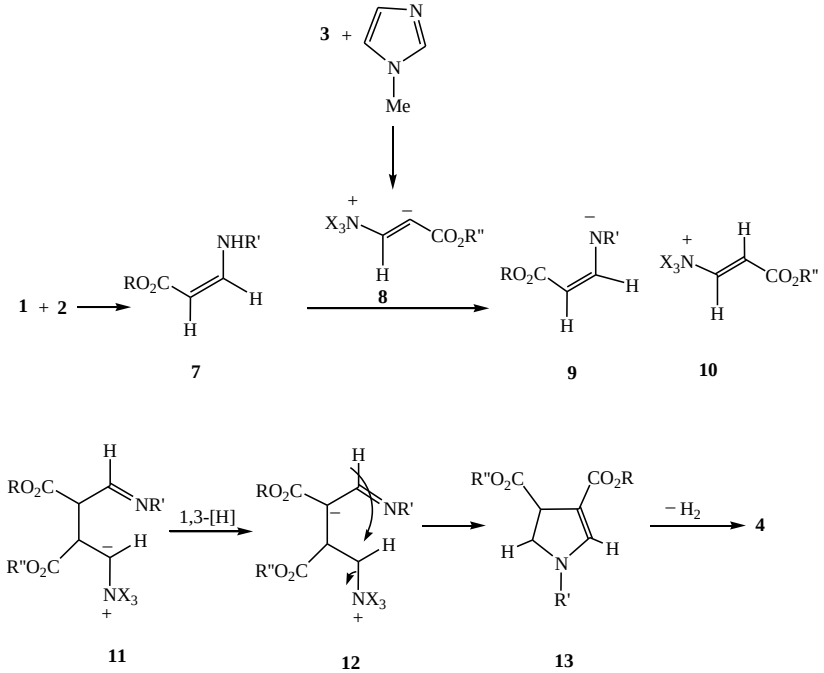
1 **2** **5** **6**

Scheme 2: Three component reaction of alkyl amines with methyl propiolate in the presence of malonyl dichloride.

Results and discussion

Three component reaction between alkyl propiolate 1, primary amine 2 and alkyl propiolate 3 in the presence of catalytic amount of *N*-methylimidazole at 50 °C under solvent-free conditions produced functionalized pyrroles 4 in 85-92% yields (Table **1**).

The structures of compounds 4 were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of 4a exhibited one singlet for two methoxy protons at (δ 3.78 ppm), one singlet for NMe protons at (δ 3.58 ppm) and one singlet for two methin groups at (δ 6.92 ppm). The ^{13}C NMR spectrum of 4a exhibited 9 distinct resonances which further confirmed the proposed structure. The IR spectrum of 4a displayed characteristic C=O bands. The mass spectra of 4a displayed the molecular ion peak at the appropriate m/z. Presumably, the zwitterionic intermediate 8, formed from *N*-methylimidazole (X_3N) and alkyl propiolate 3, is protonated by the enaminoester 7, generated in situ from primary amine 2 and alkylpropiolate 1, to produce intermediates 9 and 10 (Scheme **3**). Nucleophilic attack of the conjugate base 9 on intermediate 10 leads to adduct 11, which undergoes twice proton shifts to afford new zwitterionic intermediate 12. Finally, intramolecular cyclization affords 13 by elimination of *N*-methylimidazole, which is converted into 4 by elimination of hydrogen (Scheme **3**).



7 **8** **9** **10** **11** **12** **13**

Scheme 3: Proposed mechanism for the formation of **4**.

Under similar conditions we describe an efficient synthesis of functionalized 2-pyridones 6 *via* the reaction of alkyl amines **2** with methyl propiolate 1 in the presence of malonyl dichloride **5** under solvent-free conditions at 50°C in 87-92% yileds (Table **2**).

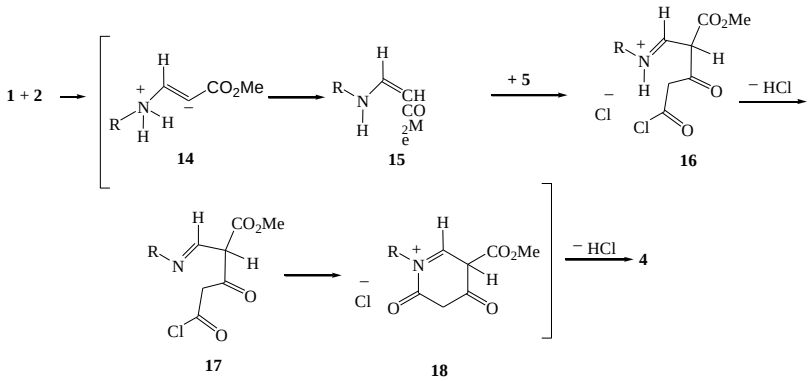
A tentative mechanism for this transformation is proposed in Scheme 4. It is conceivable that the initial event is the formation of enaminone 15 from the amine and propiolate which is subsequently attacked by malonyl dichloride to produce 16. Intermediate 16 undergoes cyclization reaction, HCl elimination and keto-enol tautomerism carry out to generate 6.

Table 1: Functionalized pyrroles 4.

Compound 4	R	R′	R″	Yield (%) of 4
a	Me	Me	Me	92
b	Me	Et	Me	87
c	Me	*n*-butyl	Me	85

Table 2. Functionalized pyridones 6.

1, **2**, **5**	R	Yield (%) of **6**
a	Bn	92
b	4-Me-C_6H_4-CH_2	90
c	4-MeO-C_6H_4-CH_2	87



Scheme 4: Proposed mechanism for the one-pot synthesis of 2-pyridones.

Conclusion

We report two reactions involving alkyl propiolates and primary amines in the presence of catalytic amount of *N*-methylimidazole or malonyl chloride at 50 °C under solvent-free conditions which affords a new route to the synthesis of functionalized pyrroles and pyridones. The present procedures have the advantage that, not only is the reaction performed under solvent-free conditions, but also the reactants can be mixed without any prior activation or modification.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H, and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

General procedure for the preparation of compounds pyrroles:

To a mixture of alkyl propiolate 1 (2 mmol) and primary amine 2 (2 mmol) was added mixture of alkyl propiolate 3 (2 mmol) and *N*-methylimidazole (5 mol%) at 50 °C. The reaction mixture was then stirred for 1.5 h. After completion of the reaction [1.5h; TLC (AcOEt/hexane 1:4) monitoring], the reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using *n*-hexane–EtOAc as eluent to afforded pure compounds 4.

Dimethyl 1-methyl-1H-pyrrole-3,4-dicarboxylate (4a): Pale yellow oil, Yield: 0.36 g (92%) IR (KBr): 1735, 1729, 1587, 1435, 1295, 1126 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_4$ (197.19): C 54.82, H 5.62, N 7.10; Found: C 54.93, H 5.74, N 7.22. ^{1}H NMR*:* 3.58 (3 H, s, NMe), 3.78 (6 H, s, 2 MeO), 6.92 (2 H, s, 2 CH) ppm. ^{13}C NMR: 35.8 (NMe), 51.8 (2 MeO), 137.2 (2 C), 138.3 (2 CH), 165.4 (2 C=O) ppm.

Dimethyl 1-ethyl-1H-pyrrole-3,4-dicarboxylate (4b): Yield: 0.37 g (87%). Yellow oil. IR (KBr): 1730, 1727, 1562, 1454, 12876 cm^{-1}. ^{1}H NMR*:* 1.23 (3 H, t, ^3J = 7.4 Hz, Me), 3.58 (2 H, q, ^3J = 7.4 Hz, NCH_2), 3.82 (6 H, s, 2 MeO), 6.87 (2 H, s, 2 CH) ppm. ^{13}C NMR: 14.2 (Me), 48.3 (NCH_2), 52.4 (2 MeO), 137.5 (2 C), 139.0 (2 CH), 166.2 (2 C=O) ppm.

Dimethyl 1-butyl-1H-pyrrole-3,4-dicarboxylate (4c). Pale yellow oil, Yield: 0.41 g (85%) IR (KBr): 1728, 1725, 1545, 1378, 1268, 1226 cm^{-1}. Anal. Calcd for $C_{12}H_{17}NO_4$ (239.27): C 60.24, H 7.16, N 5.85; Found: C 60.33, H 7.25, N 5.92. ^{1}H NMR*:* 0.92 (3 H, t, ^3J = 7.3 Hz, Me), 1.27 (2 H, m, CH_2), 1.52 (2 H, m, CH_2),

3.62 (2 H, t, ^3J = 7.3 Hz, NCH_2), 3.75 (6 H, s, 2 MeO), 6.86 (2 H, s, 2 CH) ppm. ^{13}C NMR: 13.2 (Me), 18.6 (CH_2), 32.4 (CH_2), 52.2 (2 MeO), 53.3 (NCH_2), 135.4 (2 C), 137.6 (2 CH), 167.0 (2 C=O) ppm.

General procedure for the preparation of compounds 6a-c:

To a mixture of alkyl propiolate (2.5 mmol) and primary amine (2.5 mmol), malonyl dichloride (0.19 mL, 2 mmol) was added slowly at 50°C. The reaction mixture was then stirred for 6 h. The reaction mixture was purified by flash column chromatography on silica gel (Merck 230–400 mesh) using *n*-hexane–EtOAc as eluent to afforded pure compounds.

Methyl 1-benzyl-4-hydroxy-6-oxo-1,6-dihydro-2-pyridinedicarboxylate (6a): White powder; mp 114-116 °C; yield: 0.48 g (92%). IR (KBr): 3442 (OH), 1730, 1627, 1542, 1385 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.75 (s, 3 H, MeO), 5.20 (s, 2 H, CH_2), 6.12 (s, 1 H, CH), 6.27 (s, 1 H, CH), 7.14 (d, 2 H, ^3J = 7.0 Hz, 2 CH), 7.24–7.30 (m, 3 H, 3 CH), 10.75 (s, 1 H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 47.8 (NCH_2), 52.8 (MeO), 97.8 (CH), 100.2 (CH), 102.6 (C), 127.4 (2 CH), 128.0 (CH), 128.6 (2□CH), 135.5 (C), 162.5 (C), 165.3 (C=O), 167.1 (C=O). MS: *m/z* (%) = 259 (15) [M^+], 228 (64), 168 (15), 91 (100), 77 (20), 31 (28). Anal. Calcd for $C_{14}H_{13}NO_4$ (259.26): C, 64.86; H, 5.05; N, 5.40. Found: C, 64.92; H, 5.12; N, 5.45.

Methyl 1-(4-methylbenzyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate (6b): White powder; mp 119-121 °C; yield: 0.49 g (90%). IR (KBr): 3445 (OH), 1734, 1635, 1584, 1373 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 2.45 (s, 3H, Me), 3.82 (s, 3 H, MeO), 5.24 (s, 2 H, CH_2), 6.15 (s, 1 H, CH), 6.34 (s, 1 H, CH), 7.15 (d, 2 H, ^3J = 7.3 Hz, 2 CH), 7.30 (d, 2 H, ^3J = 7.3 Hz, 2 CH), 10.68 (s, 1 H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.5 (CH_3), 48.2 (NCH_2), 53.0 (MeO), 98.2 (CH), 100.4 (CH), 105.7 (C), 127.5 (2 CH), 128.4 (2□CH), 130.7 (C), 135.4 (C), 160.7 (C), 165.5 (C=O), 167.6 (C=O).

Methyl 1-(4-methoxylbenzyl)-4-hydroxy-6-oxo-1,6-dihydro-2-pyridine dicarboxylate (6c). White powder; mp 128-130°C; yield: 0.50 g (87%). IR (KBr): 3440 (OH), 1737, 1636, 1580, 1287 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ 3.83 (s, 3H, MeO), 3.89 (s, 3 H, MeO), 5.25 (s, 2 H, CH_2), 6.08 (s, 1 H, CH), 6.23 (s, 1 H, CH), 7.08 (d, 2 H, ^3J = 7.5 Hz, 2 CH), 7.45 (d, 2 H, ^3J = 7.6 Hz, 2 CH), 10.75 (s, 1 H, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 48.5 (NCH_2), 52.8 (CH_3O), 53.3 (OMe), 98.5 (CH), 99.7 (CH), 104.8 (C), 117.4 (2 CH), 131.7 (2□CH), 135.4 (C), 154.4 (C), 158.7 (C), 164.6 (C=O), 168.2 (C=O).

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