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Application of Water for Synthesis of Cyclopentadienes via Multi-component Reactions of *N*-methyl imidazole

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Abstract

A water-accelerated multi-component synthesis of organic target molecules was used as a key method for the preparation of cyclopentadiene derivatives. The three-component condensation reactions of primary amines with alkyl propiolates in the presence of *N*-methylimidazole in water at room temperature were developed as efficient and clean green synthetic procedures for the high-yielding preparation of 4-oxo-2,5-cyclopentadiene-1,2-dicarboxylate derivatives.

Key words: *Primary amines, N-methylimidazole, Alkyl propiolates, Multi-component reaction, Water.*

Introduction

At the beginning of the 21st century, a move of 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]. Since the discovery of ferrocene in which a cyclopentadiene ring is bonded to a transition metal, [4] the cyclopentadiene ring and/or cyclopentadienyl system have enjoyed considerable research interest for more than half a century in organic chemistry and the other research fields [4-11]. Herein, we report an efficient three component reaction between *N*-methylimidazole **1**, alkyl propiolate **2, 3** and primary amines **4** in water at 80 °C which lead to cyclopentadiene derivatives **5** in good yield (Scheme 1).

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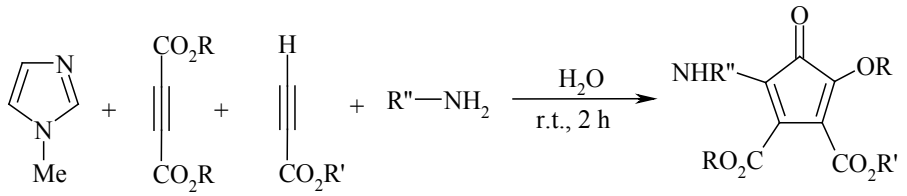


1 **2** **3** **4** **5**

2, 3, 4, 5	R	R'	R"	Yield (%) of **5**
a	Me	Me	Bn	90
b	Me	Et	Et	95
c	Me	Et	4-Me-$C_6H_4CH_2$	95
d	Et	Me	Me	90

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

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 preparation of compounds **5a-g**

To a magnetically stirred mixture of alkyl propiolate **3** (2 mmol) and N-methylimidazole **1** (2 mmol) in water (5 mL) was added mixture of alkyl propiolate **2** and primariy amine **4** (2 mmol) at r.t. after 30 min. The reaction mixture was then stirred for 2h. After completion of the reaction [TLC (AcOEt/hexane 1:4) monitoring], solid residue was filtered and washed with cold Et_2O to afforded pure compounds **5**.

Dimethyl 3-(benzylamino)-5-methoxy-4-oxo-2,5-cyclopentadiene-1,2-dicarboxylate **(5a)**

Yellow oil, yield: 0.59g (90%), IR (KBr) (ν_{max}/ cm^{-1}): 1764, 1695, 1547, 1435, 1352, 1247 cm^{-1} . ^{1}H NMR (500.1 Hz, $CDCl_3$): σ = 3.75 (3 H, s, MeO), 3.86 (3 H, s, MeO), 3.92 (3 H, s, MeO), 5.23 (2 H, s, NCH_2), 6.17 (1 H, broad, NH), 7.32 (1 H, t, ^3J = 7.3 Hz, CH), 7.38 (2 H, t, ^3J = 7.6 Hz, 2 CH), 7.46 (2 H, d, ^3J = 7.3 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 48.6 (NCH_2), 52.3 (MeO), 53.4 (MeO), 59.6

(MeO), 113.4 (C), 121.7 (C), 128.2 (2 CH), 129.4 (2 CH), 135.3 (C), 138.2 (CH), 148.4 (C), 150.2 (C), 162.4 (C=O), 163.2 (C=O), 187.4 (C=O) ppm. MS: *m/z* (%) = 331 [M^+, 10], 300 (86), 91 (100), 77 (56), 31 (100). Anal. Calc. for $C_{17}H_{17}NO_6$ (331.32): C, 61.63; H, 5.17; N, 4.23. found: C, 61.72; H, 5.24; N, 4.35%.

Ethy 3-(ethylamino)l-5-methoxy-4-oxo-2,5-cyclopentadiene-1,2-dicarboxylate **(5b)**

Pale yellow oil, yield: 0.54g (95%), IR (KBr) (ν_{max}/cm^{-1}): 1756, 1735, 1687, 1656, 1524, 1482, 1363 cm^{-1} . ^{1}H NMR (500.1 Hz, $CDCl_3$): σ = 1.15 (3 H, t, ^3J = 7.3 Hz, Me), 1.35 (3 H, t, ^3J = 7.5 Hz, Me), 3.34 (2 H, q, ^3J = 7.3 Hz, NCH2), 3.74 (3 H, s, MeO), 3.83 (3 H, s, MeO), 4.26 (2 H, q, ^3J = 7.5 Hz, CH_2O), 4.67 (1 H, broad, NH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.7 (Me), 14.3 (Me), 39.2 (NCH_2), 51.7 (MeO), 58.5 (MeO), 62.0 (CH_2O), 113.7 (C), 132.4 (C), 147.2 (C), 150.6 (C), 162.8 (C=O), 163.7 (C=O), 186.4 (C=O) ppm. MS: *m/z* (%) = 283[M^+, 15], 252 (88), 31 (100). Anal. Calc. for $C_{13}H_{17}NO_6$ (283.28): C, 55.12; H, 6.05; N, 4.94. found: C, 55.24; H, 6.17; N, 5.07%.

Ethyl-5-methoxy-3-(4-methylbenzylamino)-4-oxo-2,5-cyclopentadiene-1,2-dicarboxylate **(5c)**

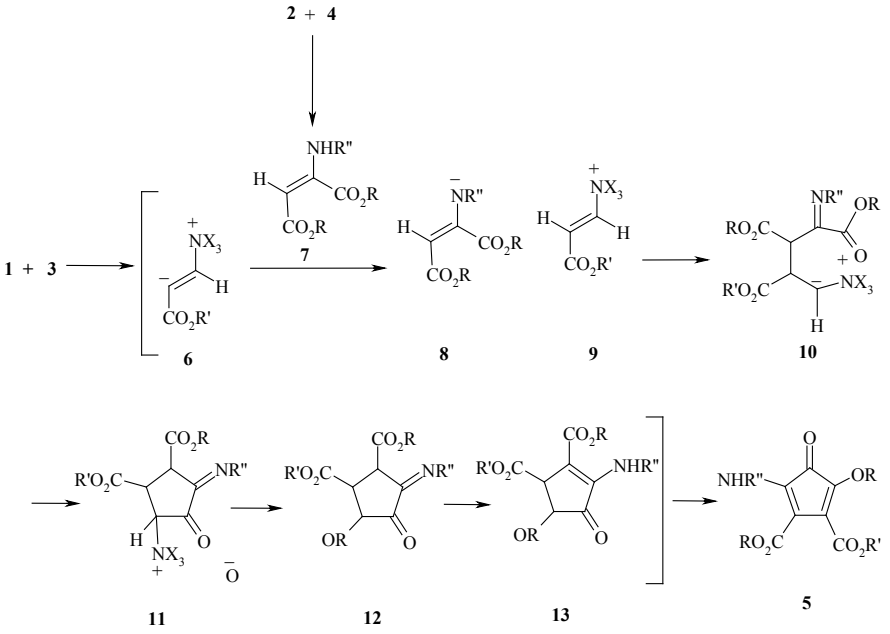
Yellow oil, yield: 0.68g (95%), IR (KBr) (ν_{max}/ cm^{-1}):1764, 1735, 1670, 1445, 1340 cm^{-1} . ^{1}H NMR (500.1 Hz, $CDCl_3$): σ = 1.27 (3 H, t, ^3J = 7.4 Hz, Me), 2.32 (3 H, s, Me), 3.76 (3 H, s, MeO), 3.87 (3 H, s, MeO), 4.24 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.18 (2 H, s, NCH_2), 6.12 (1 H, broad, NH), 7.32 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.40 (2 H, d, ^3J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.7 (Me), 21.4 (Me), 47.8 (NCH_2), 52.3 (MeO), 59.7 (MeO), 62.5 (CH_2O), 113.6 (C), 124.5 (C), 128.6 (2 CH), 130.4 (2 CH), 131.4 (C), 135.7 (C), 138.5 (C), 151.2 (C), 163.2 (C=O), 164.2 (C=O), 186.4 (C=O) ppm. Anal. Calc. for $C_{19}H_{21}NO_6$ (359.38): C, 63.50; H, 5.89; N, 3.90. found: C, 63.62; H, 5.93; N, 3.98%.

Methyl-5-ethoxy-3-(methylamino)-4-oxo-2,5-cyclopentadiene-1,2-dicarboxylate **(5d)**

Yellow oil, yield: 0.51g (90 %). IR (KBr) (ν_{max}/ cm^{-1}): 1752, 1740, 1694, 1487, 1365 cm^{-1} . ^{1}H NMR (500.1 Hz, $CDCl_3$): σ = 1.28 (3 H, t, ^3J = 7.5 Hz, Me), 1.35 (3 H, t, ^3J = 7.4 Hz, Me), 3.45 (NMe), 3.78 (3 H, s, MeO), 4.25 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.32 (2 H, q, ^3J = 7.5 Hz, CH_2O), 4.74 (1 H, broad, NH) ppm. ^{13}C NMR (125.7 Hz, $CDCl_3$): δ = 13.6 (Me), 14.8 (Me), 32.6 (NCH_3), 52.4 (MeO), 65.4 (CH_2O), 68.4 (CH_2O), 115.2 (C), 125.2 (C), 138.5 (C), 149.6 (C), 163.5 (C=O), 164.7 (C=O), 185.6 (C=O) ppm. Anal. Calc. for $C_{13}H_{17}NO_6$ (283.28): C, 55.12; H, 6.05; N, 4.94. found: C, 55.23; H, 6.15; N, 5.08%.

Results and discussion

The structures of compounds **5** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **5a** exhibited four singlets for methoxy and NCH_2 group at 3.75 (3 H, s, MeO), 3.86 (3 H, s, MeO), 3.92 (3 H, s, MeO), 5.23 (2 H, s, NCH_2) and one broad singlet for NH proton at (δ 6.17 ppm). The ^{13}C NMR spectrum of 5a exhibited 17 distinct resonances which further confirmed the proposed structure. The IR spectrum of **5a** displayed characteristic C=O bands. The mass spectra of **5a** displayed the molecular ion peak at the appropriate *m/z*. Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterionic intermediate **6**, generated from *N*-methylimidazole and alkyl propiolate **3**, is trapped by the enaminoester **7**, generated in situ from the corresponding amine **4** and alkyl propiolate **3** to produce intermediates **8** and 9 (Scheme 2). Nucleophilic attack of the conjugate base 8 on intermediate 9 leads to an adduct **10**, which undergoes intramolecular Wittig reaction to afford imino-cyclopentene derivative **11**. Intermediate **11** undergoes a [1, 5] H-shift to generate **5** (Scheme 2).



Scheme 2. Proposed mechanism for the formation of 5.

Conclusion

In summary, we report a reaction involving acetylenic compounds and primary amines in the presence of *N*-methylimidazole at room temperature in water as the solvent which affords a new route to the synthesis of functionalized cyclopentadienes. The present procedure has the advantage that, not

only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

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