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Green synthesis of lactone derivatives in *N*-formylmorpholine as green solvent

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Abstract: The reaction between dimethyl acetylenedicarboxylate and various OH-acids in N-formylmorpholine leads to butyrolactone derivatives in nearly good yields. The present protocol offers the advantages of clean reaction, short reaction time, high yield, easy purification and affordability of the catalyst.

Keywords: Butyrolactone, 8-Hydroxyquinoline, Cathechol, Dialkyl acetylenedicarboxylates.

Introduction

Green chemistry techniques continue to grow in importance, and alternative processes are developed with the aim to conserve resources and reduce costs [1-3]. A major challenge in modern chemistry is the design of highly efficient chemical reactions with the minimum number of synthetic steps and short reaction times. Butyrolactones are an important structure unit in natural products and intermediates in organic synthesis [4, 5]. There has been considerable work on the synthesis of these compounds due to the discovery of many naturally occurring cytotoxic or antitumor agents. Although this ring system has been the objective of synthetic projects in a number of laboratories, the number of basically different approaches is not large [6-9].

Results and discussion

We now report a synthesis of butyrolactone derivatives **2** through the reaction of dimethyl acetylenedicarboxylate (DMAD) with phenols in *N*-formylmorpholine.

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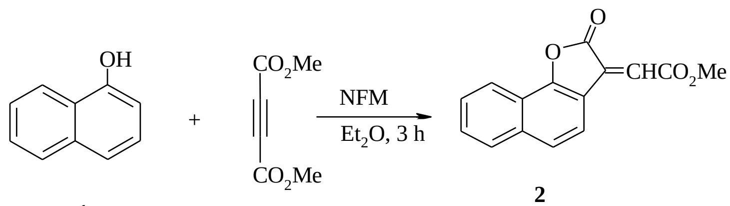
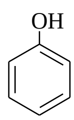
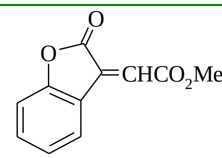
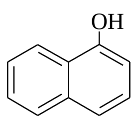
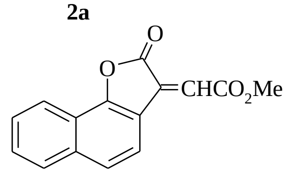
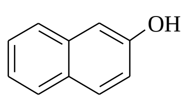
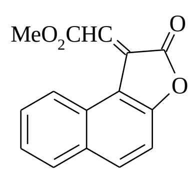
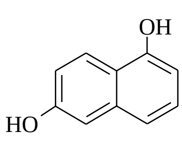
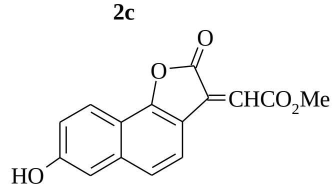
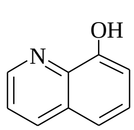
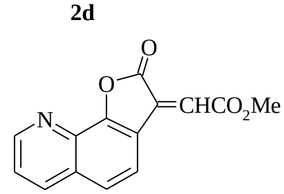
Our results are summarized in Table **1**. The reaction of phenol (**1a**) with DMAD in *N*-formylmorpholine at room temperature leads to the butyrolactone derivative **2a** in 93% yield (Table **1**). No other compound was obtained from the residue by column chromatography. The structure of the product was deduced from its elemental analyses and its IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The ^{1}H NMR spectrum of **2a** exhibited two singlets identified as methoxy (δ = 3.72 ppm) and olefinic (δ = 7.01 ppm) protons along with multiplets (δ = 6.65, 7.23, 7.31, and 7.48 ppm) for the aromatic protons. The ^{13}C NMR spectrum of **2a** showed eleven distinct resonances in agreement with the proposed structure. Also, The ^{1}H NMR spectrum of **2d** exhibited two singlets identified as methoxy (δ = 3.88 ppm) and olefinic (δ = 6.67 ppm) protons along with multiplets (δ = 7.27-8.46 ppm) for the aromatic protons. The OH proton resonance appears at δ = 9.34 ppm. The ^{13}C NMR spectrum of **2d** showed 15 distinct resonances in agreement with the proposed structure.

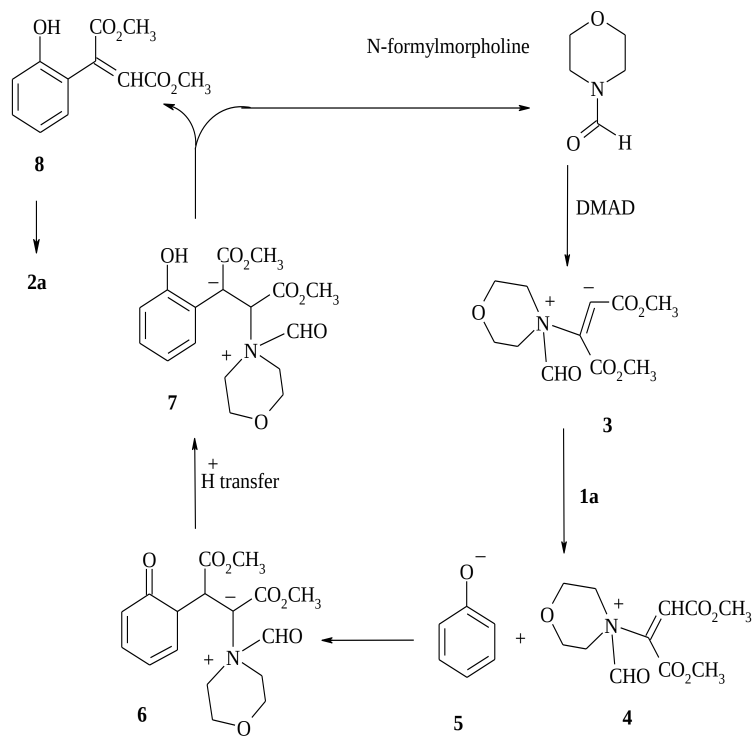
A possible mechanism for the formation of **2a** is proposed in Scheme **1**. It is reasonable to assume that **2a** results from initial addition of NFM as green solvent to the acetylenic ester and subsequent protonation of the 1,3-dipolar intermediate **3** by **1a**. Then, the positively charged ion **4** might be attacked by the conjugated base of the OH-acid to produce the nitrogen ylide **6**, which undergoes proton-transfer reaction to produce **7**. The 1,3-dipolar ion **7** is converted to **8** by elimination of NFM. The product **2a** is formed by intramolecular lactonization of **8**. Similar mechanism can be proposed for the formation of **2b-2e**.



1 **2**

Table 1: Reaction of DMAD with phenols *N*-formylmorpholine.

Entry	Starting materials	Product	Yield (%)
1	 **1a**	 **2a**	**93**
2	 **1b**	 **2b**	**94**
3	 **1c**	 **2c**	**90**
4	 **1d**	 **2d**	**85**
5	 **1e**	 **2e**	**86**



Scheme1: Proposed mechanism for formation of **2**

Experimental section

Typical procedure for the synthesis of **2a**: To a stirred solution of **1a** (0.19 g, 2 mmol) and DMAD (0.28 g, 2 mmol) in 10 mL dry ether was added NFM (5 mL) as green solvent at room temperature. The reaction mixture was then stirred for 3 h. The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (Merck 230-400 mesh) using *n*-hexane-EtOAc (4:1) as eluent to give **2a**.

Yellow oil; yield 0.38 g, 93%. IR (KBr) (ν_{max}/cm^{-1}): 1735 and 1650 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ= 3.72 (3 H, s, OMe), 6.65 (1 H, d, $^3J_{HH}$ =7.9 Hz, CH), 7.01 (1 H, s, CH), 7.23 (1 H, dd, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ = 7.5 Hz, CH), 7.31(1 H, dd, $^3J_{HH}$ = 7.8 Hz, $^3J_{HH}$ = 7.5 Hz, CH), 7.48 (1 H, d, $^3J_{HH}$ =7.8 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.6 (OCH_3), 111.2 (CH), 122.1 (CH), 123.1 (CH), 123.5 (C), 124.3 (CH), 130.6 (CH), 138.2 (C), 153.5 (C), 165.3 (C=O), 166.5 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 204 (M$^+$, 12), 189 (17), 160 (47), 145 (73), 144 (36), 132 (100), 91 (14), 76 (68), 59 (42). Anal. Calcd for $C_{11}H_8O_4$ (204.2): C, 64.71; H, 3.95%. Found: C, 65.18; H, 3.99%.

Compound **2b**: Brown crystals, mp 176-178 °C, yield 0.48 g, 94%. IR (KBr) (ν_{max}/cm^{-1}): 1715 and 1616 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.02 (3 H, s, OMe), 6.94 (1 H, s, CH), 7.59 (1 H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 6.9 Hz, CH), 7.62 (1 H, dd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 5.1 Hz CH), 7.63 (1 H, d, $^3J_{HH}$ = 5.1 Hz, CH), 7.81 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH), 8.10 (1 H, d, $^3J_{HH}$ = 6.9 Hz, CH), 8.46 (1 H, d, $^3J_{HH}$ = 6.3 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 53.2 (OCH_3), 111.4 (CH), 118.2 (C), 121.7 (CH), 122.5 (CH), 122.9 (C), 124.5 (CH), 127.2 (CH), 127.6 (CH), 129.2 (CH), 134.8 (C), 143.2 (C), 151.7 (C-O), 159.9 (C=O), 164.5 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 (M$^+$, 5), 251 (22), 223 (100), 195 (38), 135 (56), 113 (84), 109 (54), 55 (78). Anal. Calcd for $C_{15}H_{10}O_4$ (254.2): C, 70.86; H, 3.96%. Found: C, 70.40; H, 3.81%.

Compound **2c**: Green powder, mp 113-115 °C, yield 0.46 g, 90%. IR (KBr) (ν_{max}/cm^{-1}): 1724 and 1620 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.06 (3 H, s, OMe), 6.59 (1 H, s, CH), 7.46 (1 H, d, $^3J_{HH}$ = 8.1 Hz, CH), 7.55 (1H, dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 6.1 Hz, CH), 7.64 (1 H, dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 8.1 Hz, CH), 7.77 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH), 7.92 (1 H, d, $^3J_{HH}$ = 6.1 Hz, CH), 8.02 (1 H, d, $^3J_{HH}$ = 8.4 Hz, CH) ppm. ^{13}C

NMR (125.7 MHz, $CDCl_3$): *δ* = 53.5 (OCH_3), 110.1 (CH), 115.5 (CH), 117.3 (CH), 123.3 (C), 126.1 (CH), 127.9 (CH), 128.1 (CH), 129.4 (C), 130.9 (C), 134.6 (CH), 145.9 (C), 154.9 (C), 159.5 (C=O), 167.8 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 (M^+, 10), 251 (45), 223 (100), 135 (50), 113 (84), 109 (65), 55 (75). Anal. Calcd for $C_{15}H_{10}O_4$ (254.2): C, 70.86; H, 3.96%. Found: C, 70.39; H, 3.82%.

Compound **2d**: Orange powder, mp 187-189 °C, yield 0.46 g, 85%. IR (KBr) (ν_{max}/cm^{-1}): 3435 (OH), 1712 and 1617 (C=O). ^1H NMR (500 MHz, $CDCl_3$): *δ* = 3.89 (3 H, s, OMe), 6.67 (1 H, s, CH), 7.27 (1 H, d, $^4J_{HH}$ = 3.2 Hz, CH), 7.29 (1 H, dd, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 3.2 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 7.96 (1 H, d, $^3J_{HH}$ = 8.7 Hz, CH), 8.45 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 9.34 (1 H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): *δ* = 52.6 (OCH_3), 111.3 (CH), 114.2 (C), 114.4 (CH), 120.5 (CH), 121.9 (C), 123.0 (CH), 124.7 (CH), 124.9 (CH), 124.9 (C), 134.9 (C), 139.7 (C), 151.7 (C), 159.9 (C=O), 164.4 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 270 (M^+, 20), 242 (100), 239 (26), 211 (78), 155 (100), 126 (42), 77 (26). Anal. Calcd for $C_{15}H_{10}O_5$ (270.2): C, 66.67; H, 3.73%. Found: C, 66.91; H, 3.65%.

Compound **2e**: Pale yellow crystals, mp 155-157 °C, yield 0.44 g, 86%. IR (KBr) (ν_{max}/cm^{-1}): 1714 and 1619 (C=O). ^1H NMR (500 MHz, $CDCl_3$): *δ* = 3.91 (3 H, s, OMe), 7.2 (1 H, s, CH), 7.35 (1 H, d, $^3J_{HH}$ = 8.5 Hz, CH), 7.45 (1 H, dd, $^3J_{HH}$ =8.5 Hz, $^3J_{HH}$ = 6.7 Hz, CH), 7.50 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH), 8.15 (1 H, d, $^3J_{HH}$ = 6.7 Hz, CH), 8.78 (1 H, d, $^3J_{HH}$ = 7.2 Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): *δ* = 52.8 (OCH_3), 112.7 (CH), 116.9 (C), 117.6 (CH), 122.1 (CH), 127.9 (C), 129.4 (C), 136.1 (CH), 137.95 (C), 148.2 (CH), 148.2 (CH), 150.4 (C), 159.5 (C=O), 164.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 255 (M^+, 5), 224 (100), 195 (45), 128 (65), 109 (54), 77 (24), 59 (78), 31 (52). Anal. Calcd for $C_{14}H_9NO_4$ (255.2): C, 65.88; H, 3.55%. Found: C, 65.50; H, 3.46%.

Conclusion

In summary, the reaction between DMAD and phenols *N*-formylmorpholine leads to butyrolactone derivatives in excellent yields. The presented one-pot reaction carries the advantage that not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification.

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