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Synthesis of fused α-methylene-γ-butyrolactone derivatives through pyridine-induced addition of phenols to dimethyl acetylenedicarboxylate

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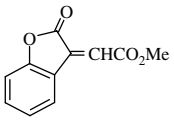
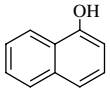
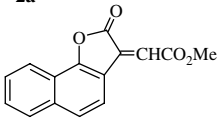
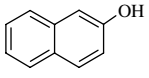
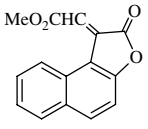
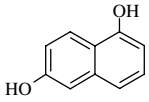
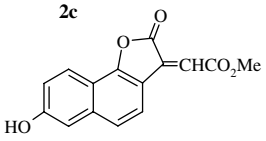
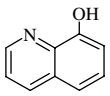
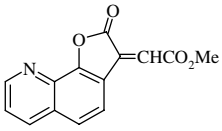
Abstract—The reaction between dimethyl acetylenedicarboxylate and various phenols including phenol, 1-naphthol, 2-naphthol, 8-hydroxyquinoline, 1,6-dihydroxynaphthalene, cathechol, hydroquinone and resorcinol in the presence of catalytic amounts of pyridine leads to fused α-methylene-γ-butyrolactone derivatives in good yields.

α-Methylene-γ-butyrolactones are an important structural unit in natural products and are intermediates in organic synthesis.[1–6] There has been considerable work on the synthesis of these compounds due to the discovery of many naturally occurring cytotoxic or antitumour agents containing this structural unit. Although this ring system has been the objective of synthetic projects in several laboratories,[1–6] the number of different approaches is not large. We now report a synthesis of fused α-methylene-γ-butyrolactone derivatives **2** through the reaction of dimethyl acetylenedicarboxylate (DMAD) with phenols in the presence of a catalytic amount of pyridine.[7] Our results are summarized in Table 1.

The reaction of phenol **1a** with DMAD in the presence of a catalytic amount of pyridine at room temperature in dry ether led to the fused α-methylene-γ-butyrolactone derivative **2a** in 93% yield (see Table 1). No other compound was obtained from the residue by column chromatography. The structure of the product was deduced from its elemental analysis and IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.[8]

The ^{1}H NMR spectrum of **2a** exhibited two singlets identified as methoxy ($\delta = 3.72$ ppm) and olefinic ($\delta = 7.01$ ppm) protons along with signals at $\delta = 6.65$,

Table 1. Reaction of DMAD with phenols in the presence of pyridine

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

(*continued on next page*)

Keywords: Pyridine; Naphthofuran; Naphthol; Acetylenic ester; Butyrolactone; Furanone.
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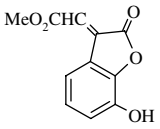
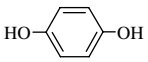
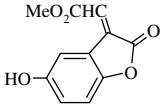
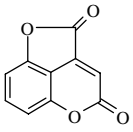
Table 1 (*continued*)

Entry	Starting material	Product	Yield (%)
6	 **1f**	 **2f**	80
7	 **1g**	 **2g**	88
8	 **1h**	 **2h**	84

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.[8]

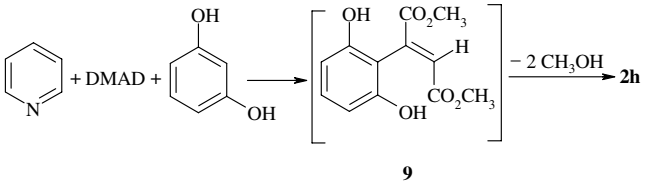
A possible mechanism for the formation of **2a** is proposed in Scheme 1. It is reasonable to assume that **2a** results from initial addition of pyridine to DMAD and subsequent protonation of the 1,3-dipolar[9–13] intermediate **3**, by **1a**. Then, the resulting positively charged ion **4** could be attacked by the phenoxide to produce the nitrogen ylide **6**, which undergoes a proton-transfer reaction to produce **7**. The 1,3-dipolar ion **7** is converted to **8** by elimination of pyridine. The product **2a** is then formed by intramolecular lactonization of **8**. A similar mechanism can be proposed for the formation of **2b**–**h**.

The reaction of dihydroxy compounds such as 1,6-dihydroxynaphthalene, catechol and hydroquinone with 1 equiv of DMAD in the presence of catalytic amounts of pyridine gave butyrolactones **2d**, **2f** and **2g** (see Table 1).

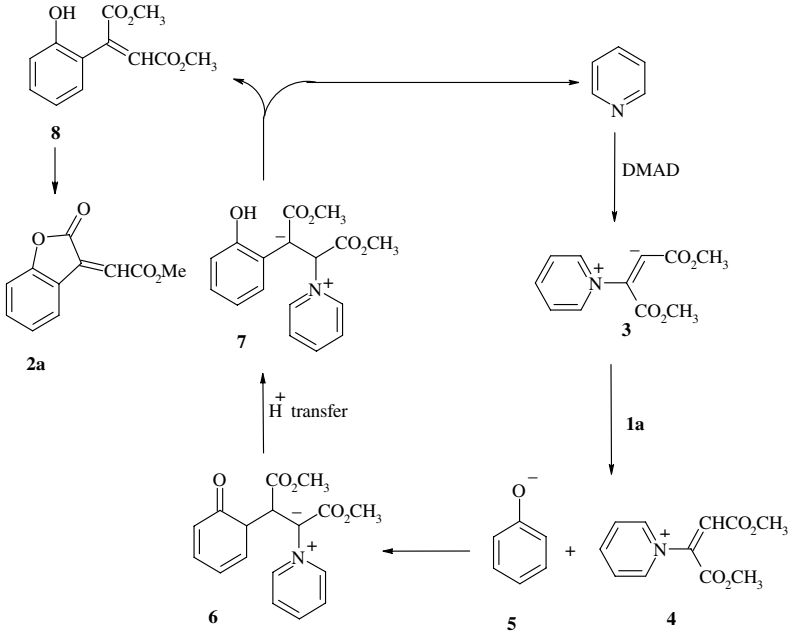
The ^{1}H NMR spectrum of **2d** exhibited two singlets identified as methoxy ($\delta = 3.89$ ppm) and olefinic ($\delta = 6.67$ ppm) protons along with resonances at $\delta = 7.27$–8.45 ppm for the aromatic protons. The OH proton resonance appeared at $\delta = 9.34$ ppm. The ^{13}C NMR spectrum of **2d** showed 15 distinct resonances in agreement with the proposed structure. The spectral data of **2b**, **2c**, **2e**, **2f** and **2g** were in agreement with the proposed structures.

Addition of a catalytic amount of pyridine to a mixture of resorcinol and DMAD led to furo[4,3,2-*de*]chromene-2,4-dione **2h** via double lactonization of intermediate **9** (see Table 1 and Scheme 2).

The ^{1}H NMR spectrum of **2h** exhibited a singlet ($\delta = 6.98$ ppm) for the olefinic proton along with resonances between $\delta = 6.32$–6.34 ppm for the aromatic protons. The ^{13}C NMR spectrum of **2h** showed 10 distinct resonances.



Scheme 2.



Scheme 1.

In summary, the reaction between DMAD and phenols in the presence of a catalytic amount of pyridine gave fused α-methylene-γ-butyrolactone derivatives in good to excellent yields. The presented one-pot reaction carries the advantage that not only is the reaction performed under neutral conditions, but the substances can also be mixed without any activation or modification.

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8. 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 of dry ether was added dropwise, 0.02 g pyridine (0.2 mmol) at room temperature. The reaction mixture was then stirred for 24 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, $CDCl_3$): $\delta = 3.72$ (3H, s, OMe), 6.65 (1H, d, $^3J_{HH} = 7.9$ Hz, CH), 7.01 (1H, s, CH), 7.23 (1H, dd, $^3J_{HH} = 7.8$ Hz, $^3J_{HH} = 7.5$ Hz, CH), 7.31 (1H, dd, $^3J_{HH} = 7.8$ Hz, $^3J_{HH} = 7.5$ Hz, CH), 7.48 (1H, d, $^3J_{HH} = 7.8$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 52.6$ (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, $CDCl_3$): $\delta = 4.02$ (3H, s, OMe), 6.94 (1H, s, CH), 7.59 (1H, dd, $^3J_{HH} = 7.6$ Hz, $^3J_{HH} = 6.9$ Hz, CH), 7.62 (1H, dd, $^3J_{HH} = 7.6$ Hz, $^3J_{HH} = 5.1$ Hz CH), 7.63 (1H, d, $^3J_{HH} = 5.1$ Hz, CH), 7.81 (1H, d, $^3J_{HH} = 6.3$ Hz, CH), 8.10 (1H, d, $^3J_{HH} = 6.9$ Hz, CH), 8.46 (1H, d, $^3J_{HH} = 6.3$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 53.2$ (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, $CDCl_3$): $\delta = 4.06$ (3H, s, OMe), 6.59 (1H, s, CH), 7.46 (1H, d, $^3J_{HH} = 8.1$ Hz, CH), 7.55 (1H, dd, $^3J_{HH} = 7.2$ Hz, $^3J_{HH} = 6.1$ Hz, CH), 7.64 (1H, dd, $^3J_{HH} = 7.2$ Hz, $^3J_{HH} = 8.1$ Hz, CH), 7.77 (1H, d, $^3J_{HH} = 8.4$ Hz, CH), 7.92 (1H, d, $^3J_{HH} = 6.1$ Hz, CH), 8.02 (1H, d, $^3J_{HH} = 8.4$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 53.5$ (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). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.89$ (3H, s, OMe), 6.67 (1H, s, CH), 7.27 (1H, d, $^4J_{HH} = 3.2$ Hz, CH), 7.29 (1H, dd, $^3J_{HH} = 8.7$ Hz, $^4J_{HH} = 3.2$ Hz, CH), 7.50 (1H, d, $^3J_{HH} = 8.5$ Hz, CH), 7.96 (1H, d, $^3J_{HH} = 8.7$ Hz, CH), 8.45 (1H, d, $^3J_{HH} = 8.5$ Hz, CH), 9.34 (1H, s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 52.6$ (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). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.91$ (3H, s, OMe), 7.20 (1H, s, CH), 7.35 (1H, d, $^3J_{HH} = 8.5$ Hz, CH), 7.45 (1H, dd, $^3J_{HH} = 8.5$ Hz, $^3J_{HH} = 6.7$ Hz, CH), 7.50 (1H, d, $^3J_{HH} = 7.2$ Hz, CH), 8.15 (1H, d, $^3J_{HH} = 6.7$ Hz, CH), 8.78 (1H, d, $^3J_{HH} = 7.2$ Hz, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 52.8$ (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.

   Compound **2f**: Brown oil, yield 0.35 g, 80%. IR (KBr) (ν_{max}/cm^{-1}): 3440 (OH), 1739 and 1645 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.78$ (3H, s, OMe), 6.30 (1H, br s, OH), 6.68 (1H, d, $^3J_{HH} = 8.3$ Hz, CH), 6.89 (1H, s, CH), 7.20 (1H, dd, $^3J_{HH} = 8.3$ Hz, $^3J_{HH} = 7.4$ Hz, CH), 7.48 (1H, d, $^3J_{HH}$=7.4 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 53.4$ (OCH_3), 104.8 (CH), 109.5 (CH), 120.7 (CH), 123.0 (C), 125.3 (CH), 129.6 (C) 131.9 (C) 146.9 (C), 163.9 (C=O), 166.5 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 220 (M^+, 15), 189 (100), 160 (45), 119 (80), 31 (100), 60 (25), 77 (10). Anal. Calcd for $C_{11}H_8O_5$ (220.2): C, 60.01; H,3.66. Found: C, 60.41; H, 3.50.

   Compound **2g**: Yellow powder, mp 117–119 °C, yield 0.39 g, 88%. IR (KBr) (ν_{max}/cm^{-1}): 3440 (OH), 1712 and 1640 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.78$ (3H, s, OMe), 6.67 (1H, d, $^3J_{HH} = 6.5$ Hz, CH), 6.79 (1H, dd, $^3J_{HH} = 6.5$ Hz, $^4J_{HH} = 4.4$ Hz CH), 6.82 (1H, d, $^4J_{HH} = 4.4$ Hz, CH), 6.95 (1H, s, CH), 7.71 (1H, br s, OH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 51.9$ (OCH_3), 114.3 (CH), 116.5 (CH), 118.3 (C), 127.9 (CH), 129.4 (C), 150.5 (C), 151.1 (CH), 154.3 (C), 163.3 (C=O), 168.1 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 220 (M^+, 10), 189 (100), 160 (26), 119 (78), 31 (100), 60 (42), 77 (26). Anal. Calcd for $C_{11}H_8O_5$ (220.2): C, 60.01; H, 3.66. Found: C, 60.54; H, 3.54.

   Compound **2h**: Yellow oil; yield 0.32 g, 84%. IR (KBr) (ν_{max}/cm^{-1}): 1694 and 1596 (C=O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.32$ (1H, d, $^3J_{HH} = 6.2$ Hz, CH), 6.35 (1H, dd, $^3J_{HH} = 6.6$ Hz, $^3J_{HH} = 6.2$ Hz, CH), 6.34 (1H, d, $^3J_{HH} = 6.6$ Hz, CH), 6.98 (1H, s, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 103.4$ (CH), 107.5 (CH), 117.6 (CH), 122.1 (C), 125.3 (C), 130.6 (CH), 137.9 (C), 146.9 (C), 159.3 (C=O), 167.7 (C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 188 (M^+, 15), 119 (85), 69 (45), 77 (26), 45 (100).

Anal. Calcd for $C_{10}H_4O_4$ (188.1): C, 63.84; H, 2.14. Found: C, 63.53; H, 2.26.
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