A Convenient One-Pot Method for the Construction of Tetrasubstituted Phenols through a Michael Addition−Aldol Cyclization Sequence†

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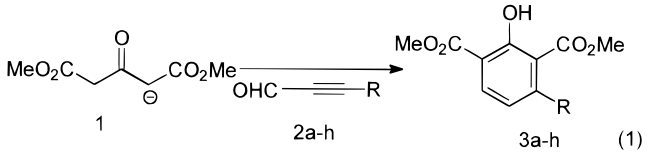
Received March 14, 1997[⊗]

The sodium salt of dimethyl 1,3-acetonedicarboxylate (**1**) readily reacts with certain alkynals under mild conditions in THF to give a tetrasubstituted aromatic ring with regiocontrol at the meta-position through a Michael addition−aldol cyclization sequence. Thus the reaction of I with propynal, 2-butynal, 2-pentynal, 2-octynal, 4-(benzoyloxy)-2-butynal, and 4-((tetrahydropyranyl)-oxy)-2-butynal at 25 °C gave the following products: dimethyl 2-hydroxybenzene-1,3-dicarboxylate (11%), dimethyl 2-hydroxy-4-methylbenzene-1,3-dicarboxylate (45%), dimethyl 4-ethyl-2-hydroxy-benzene-1,3-dicarboxylate (46%), dimethyl 2-hydroxy-4-pentylbenzene-1,3-dicarboxylate (42%), dimethyl 2-hydroxy-4-((pivaloyloxy)methyl)benzene-1,3-dicarboxylate (88%), dimethyl 2-hydroxy-4-((benzoyloxy)methyl)benzene-1,3-dicarboxylate (74%), and dimethyl 2-hydroxy-4-(((tetrahydro-pyranyl)oxy)methyl)benzene-1,3-dicarboxylate (70%).

In the present work, we describe an easy one-pot synthesis of phenols, employing the dimethyl 1,3-acetone-dicarboxylate anion (**1**) (formed with NaH in THF). We have observed that anion **1** readily reacts with alkynals **2** under mild conditions to give tetrasubstituted aromatic ring products (eq 1).



(1)

We have found that this transformation is a general one, and several β-substituted propynals can be converted to the corresponding aromatic products (Table 1). The reactions were carried out using 3 mmol of the dimethyl 1,3-acetonedicarboxylate, 3.6 mmol of NaH, and 3 mmol of the corresponding alkynal in THF (4 mL).

This reaction can be explained by a sequence of steps involving Michael addition[1] followed by aldol cyclization[2] through the enolate intermediates[3] (Scheme 1). The analogous reaction with alkynones has been described.[4]

The reactions afford phenols in moderate to high yields, and only in the case of propynal as Michael acceptor, is the yield low, probably due to anionic polymerization.[5]

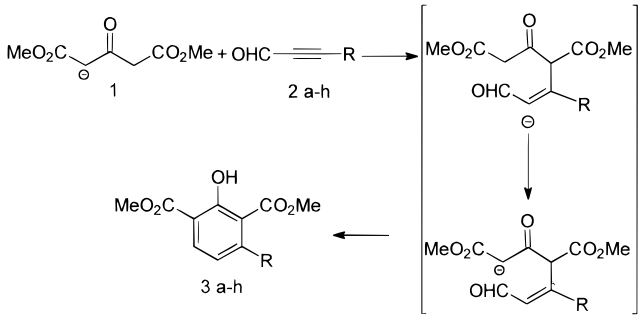
The supply of phenols is of significant importance in synthetic chemistry,[6] because numerous biologically active and naturally occurring compounds have this moiety in their framework.[7] The simple, general, one-pot method described here for the construction of the phenolic system should be useful in the synthesis of these natural products.

Table 1

no.	alkynal (R)	*t* (°C)	product[a] (yield, %)
1	**2a** (H)	−10	**3a** (11)
2	**2b** (Me)	−10	**3b** (45)
3	**2c** (Et)	25	**3c** (46)
4	**2d** $(CH_2)_4CH_3$	25	**3d** (42)
5	**2e** (CH_2OPv)	25	**3e** (88)
6	**2f** (CH_2OBz)	25	**3f** (76)
7	**2g** CH_2OTHP)	25	**3g** (70)

[a] Products were characterized by common spectroscopic techniques (IR, ^{1}H NMR, ^{13}C NMR, MS). In addition, HRMS data (EI) were obtained for products in entries 4−6.

Scheme 1



Experimental Section

All reactions were carried out under an argon atmosphere. Tetrahydrofuran was freshly distilled over benzophenone−sodium. Propynal, 2-butynal, and 2-pentynal were synthesized from the commercially available alcohols by oxidation with the Jones reagent;[8] 4-(benzoyloxy)-2-butynal and 4-(pivaloyloxy)-2-butynal were synthesized from 2-butyn-1,4-diol by mono-protection with BzCl and PvCl, respectively, and Et_3N in CH_2Cl_2[9,10] followed by oxidation with the Jones reagent.[8] 4-((Tetrahydropyranyl)oxy)-2-butynal[10] was obtained by oxida-

† Contribution No. 1574 of the Instituto de Química, UNAM.

⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

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S0022-3263(97)00466-0 CCC: $14.00

tion with MnO_2[11] in CH_2Cl_2; 2-octynal and dimethyl 1,3-acetonedicarboxylate were purchased from Aldrich Inc.

Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60 F_{254} plates and visualized by UV irradation. ^{1}H NMR spectra were recorded either at 200 or 300 MHz, while ^{13}C NMR spectra were run at 75 MHz. Low- and high-resolution mass spectra were measured at 70 eV (EI). Elemental analyses were performed by Galbraith Laboratories, Inc.; column chromatography was carried out using silica gel (70−230 mesh).

General Procedure for the Preparation of Dimethyl 2-Hydroxy 1,3-Dicarboxylate Derivatives 3a−g. Dimethyl 2-Hydroxy-4-((pivaloyloxy)methyl)benzene-1,3-dicarboxylate (3e). Dimethyl 1,3-acetonedicarboxylate (97%; 0.4 g, 2.23 mmol) was added dropwise to a mixture of NaH (60%; 0.107 g, 2.67 mmol) in dry THF (4 mL) with magnetic stirring. 4-(Pivaloyloxy)-2-butynal (0.38 g 2.26 mmol) was added to the resulting solution. After 2 h, the mixture was poured into dilute HCL (15 mL), the organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was subjected to column chromatography. The phenol **3e** (88%, 0.63g) was eluted using 3% ethyl acetate in hexane: mp 54−56 °C; IR (neat) 3147, 1730, 1683, 1156 cm^{-1}; ^{1}H NMR δ ppm 1.21 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 5.16 (s, 2H), 6.95 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.2, 1H), 11.29 (s, 1H); ^{13}C NMR δ ppm 27.1, 38.8, 52.5, 52.6, 63.6, 112.3, 112.8, 118.69, 131.7, 142.3, 151.6, 159.1, 166.5, 169.7; MS (EI) m/z (relative intensity) 324 (M^+, 14), 292 (23), 208 (100), 207 (72); HRMS calcd for $C_{16}H_{20}O_7$ 324.1209, found 324.1199. Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.17. Found: C, 58.87; H, 6.22.

A similar procedure was followed for the other substrates (Table 1). The physical constants and spectral data obtained for other phenols (entries 1−4 and 6−8) are summarized below.

Dimethyl 2-hydroxybenzene-1,3-dicarboxylate (3a): yield 11%; mp 72 °C (lit.[12] mp 70−71 °C); IR (KBr) 3441, 1728, 1614, 1262 cm^{-1}; ^{13}C NMR δ 20.1, 52.2, 52.3, 110.6, 121.0, 130.9, 144.2, 158.8, 167.6, 170.1; MS (EI) m/z (relative intensity) 210 (M^+, 76), 178 (56), 147 (94), 120 (100). Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.56; H, 4.76. Found: C, 57.56; H, 5.04.

Dimethyl 2-hydroxy-4-methylbenzene-1,3-dicarboxylate (3b): yield 45%; mp 44−46 °C; IR (neat) 3138, 1735, 1676, 1265 cm^{-1}; ^{1}H NMR δ ppm 2.31 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.70 (d, J = 8.7 Hz,1H), 7.73 (d, J = 8.7 Hz, 1H), 11.11 (s, 1H); ^{13}C NMR δ ppm 20.1, 52.2, 52.3, 110.6, 121.0, 123.0, 130.9, 144.2, 158.8, 167.6, 170.1; MS (EI) m/z (relative intensity) 224 (M^+, 36), 192 (100), 161 (96), 134 (93). Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.35. Found: C, 59.03; H, 5.41.

Dimethyl 4-ethyl-2-hydroxybenzene-1,3-dicarboxylate (3c): yield 46%; oil; IR (neat) 3151, 1732, 1677, 1621 cm^{-1}; ^{1}H NMR δ ppm 1.21 (t, J = 7.6 Hz, 3H), 2.63 (q, J = 7.6 Hz, 2H), 3.94 (s, 6H), 6.78 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 11.12 (s, 1H); ^{13}C NMR δ ppm 14.9, 27.1, 29.6, 52.24, 52.29, 110.4, 119.4, 130.9, 150.0, 158.6, 167.6, 170.1; MS (EI) m/z (relative intensity) 238 (M^+, 25), 206 (100), 175 (75), 148 (52). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88. Found: C, 60.65; H, 5.99.

Dimethyl 2-hydroxy-4-pentylbenzene-1,3-dicarboxylate (3d): yield 42%; oil; IR (neat) 3151, 1735, 1677, 1261 cm^{-1}; ^{1}H NMR δ ppm 0.86 (m, 3H), 1.28 (m, 4H), 1.6 (m, 2H), 2.58 (t, J = 7.6, 1H), 3.91 (s, 3H), 3.92 (s, 3H), 6.74 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 11.10 (s, 1H); ^{13}C NMR δ ppm 170.0, 167.6, 158.6, 148.8, 130.6, 122.9, 120.0, 110.3, 52.24, 52.13, 33.8, 31.5, 30.3, 22.2, 13.7; MS (EI) m/z (relative intensity) 280 (M^+, 26), 248 (100), 205 (99); HRMS calcd for $C_{15}H_{28}O_5$ 280.1311, found 280.1314. Anal. Calcd for $C_{15}H_{28}O_5$: C, 64.28; H, 7.14. Found: C, 64.59; H, 7.47.

Dimethyl 2-hydroxy-4-((benzoyloxy)methyl)benzene-1,3-dicarboxylate (3f): yield 76%; oil; IR (neat) 3075, 1725, 1678, 1266 cm^{-1}; ^{1}H NMR δ ppm 3.87 (s, 3H), 4.97 (s, 3H), 5.42 (s, 2H), 7.02 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1 H), 7.8−8.3 (m, 3H), 8.1−8.3 (m, 2H), 11.31 (s, 1H); ^{13}C NMR δ ppm 3.87 (s, 3H), 3.97 (s, 3H), 5.42 (s, 2H), 7.02 (d, J = 4 Hz, 1H), 7.92 (d, J = 4 Hz, 1H), 7.92 (d, J = 4 Hz, 1H), 7.8−8.3 (m, 3H), 8.1−8.3 (m, 2H), 11.31 (s, 1H); ^{13}C NMR δ ppm 52.6, 52.7, 113.0, 118.8, 121.6, 128.4, 129.5, 129.8, 130.1, 131.8, 133.3, 142.0, 159.2, 165.9, 166.9, 169.8; MS (EI) m/z (relative intensity) 344 (M^+, 7), 312 (13), 207 (27), 105 (100), HRMS calcd for $C_{18}H_{16}O_7$ 344.0896, found 344.0907. Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.79, H, 4.65. Found: C, 62.90; H, 4.27.

Dimethyl 2-hydroxy-4-[((tetrahydropyran-2-yl)oxy)-methyl]benzene-1,3-dicarboxylate (3g): yield 70%; oil; IR (neat) 3138, 1733, 1678, 1263 cm^{-1}; ^{1}H NMR δ ppm 1.45−1.98 (m, 6H), 3.45−3.60 (m, 1H), 3.80−3.95 (m, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.57 and 4.82 (AB sys, J = 13.6 Hz, 2H), 4.64 (t, J = 3.4 Hz, 1H), 7.01 (d, J = 8.2 Hz), 7.87 (d, J = 8.2 Hz), 11.22 (s, 1H); ^{13}C NMR δ ppm 19.1, 25.3, 30.2, 52.2, 52.4, 62.0, 66.4, 98.1, 112.1, 118.4, 121.3, 131.4, 144.8, 158.9, 166.9, 169.9; MS (EI) m/z (relative intensity) 324 (M^+, 2), 208 (69), 191 (100). Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.17. Found: C, 58.88; H, 6.24.

Acknowledgment. This research was supported by a Grant-in-aid for scientific research No. 40361-5-3352E from CONACYT, México.

JO9704669

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