Chemoselective Carbon−Carbon Coupling of Organocuprates with (Bromomethyl)methylmaleic Anhydride: Synthesis of Chaetomellic Acid A†

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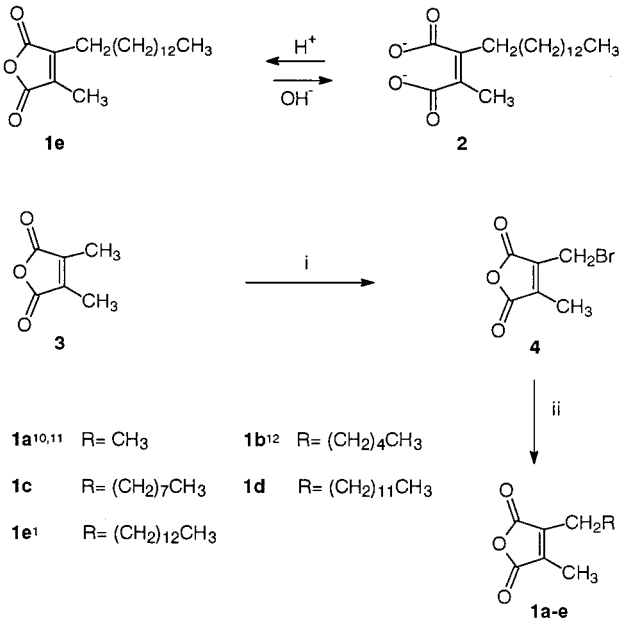
Chaetomellic anhydrides A and B have been recently isolated[1] from *Chaetomella acutiseta*, and their dianionic forms are potent and highly specific inhibitors of ras farnesyl-protein transferase. The provision of facile synthetic approaches to this bioactive natural product, Chaetomellic acid A anhydride (tetradecylmethylmaleic anhydride, **1e**), is a task of current interest.[2−9] Seven alternate syntheses of **1e**, including two from our group,[6,7] have recently been accomplished using elegant strategies.[2−8] In recent years, a number of 2-alkyl-3-methyl-substituted maleic anhydrides have been isolated as natural products,[10−15] and some of them exhibit a specific biological activity.[1,14] In an attempt to have easy access to substituted maleic anhydrides of this type, we herein report a simple two-step approach to *n*-alkylmethylmaleic anhydrides **1a**−**e** via copper(I) iodide (CuI) induced, highly chemoselective, carbon−carbon coupling of Grignard reagents with (bromomethyl)methylmaleic anhydride (**4**) (Scheme 1).

Chemoselective Grignard reactions, with preservation of substrate functional groups such as ester,[5,17,18] carboxylic acid,[19] nitrile,[17] and epoxide[20] are known in the literature. The unsymmetrical anhydride **4** has five alternate sites available for nucleophilic reactions,[21] viz (i) two carbonyl carbons for 1,2-addition (with or without ring opening), (ii) two sites for Michael addition, and (iii) allylic halide for displacement reaction, and such chemoselective carbon−carbon coupling reaction of organocuprates and **4** with preservation of the maleic anhydride moiety has not been reported.[22] Reaction of dimethylmaleic anhydride (**3**)[23] with NBS/benzoyl peroxide in carbon tetrachloride under reflux gave (bromomethyl)-methylmaleic anhydride (**4**)[24] (68%), accompanied by 2,3-di(bromomethyl)maleic anhydride (2%) and starting material (30%) (^{1}H NMR). Vacuum distillation of this mixture using a Kugelrohr apparatus yielded 60% of **4** with 98% purity (by ^{1}H NMR). The reactions of (bromomethyl)methylmaleic anhydride (**4**) with excess (5 equiv) of freshly prepared Grignard reagents derived from methyl iodide, *n*-pentyl iodide, *n*-octyl bromide, *n*-dodecyl bromide, and *n*-tridecyl bromide, in the presence of catalytic amount of CuI in ether (or THF) and HMPA as solvent system at −5 to 0 °C furnished exclusively the corresponding anhydrides **1a**−**e** in 55−60% yields via chemoselective nucleophilic displacement of allylic bromide. Optimization of the coupling reaction was carried out by changing reaction temperature, mode of addition, and molar amounts of Grignard reagents, CuI and HMPA. The observed chemoselectivity could be ascribed to the controlled reactivity of cuprates generated from Grignard reagents and CuI in the presence of

Scheme 1[a]



[a] Key: (i) NBS, Benzoyl peroxide, CCl_4, reflux, 10 h. (ii) RMgX, Et_2O/THF, HMPA, CuI, −5 to 0 °C, 8 h.

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HMPA[20a] and will be useful for the tailor-made synthesis of a wide range of alkylmethylmaleic anhydride derivatives.

In summary, we have demonstrated for the first time a simple chemoselective carbon−carbon coupling reaction of **4** and organocuprates for the synthesis of **1a**−**e** in 55−60% yields with preservation of the dialkyl-substituted maleic anhydride moiety.

Experimental Section

Column chromatographic separations were done on ACME silica gel (60−120 mesh). Copper(I) iodide, HMPA, and the alkyl halides were obtained from Aldrich Chemical Co.

3-(Bromomethyl)-4-methyl-2,5-furandione (4). A mixture of dimethylmaleic anhydride[23] (**3**, 5.04 g, 50 mmol), NBS (14.24 g, 100 mmol), and a catalytic amount of benzoyl peroxide (200 mg, 0.83 mmol) in carbon tetrachloride (300 mL) was gently refluxed for 5 h in a 500 mL round-bottom flask. The reaction mixture was allowed to cool to room temperature, a second portion of benzoyl peroxide (200 mg, 0.83 mmol) was added, and again the refluxing was continued 5 h longer. The mixture was left overnight at room temperature and then filtered. The residue was washed with CCl_4 (25 mL × 2); the combined organic layer was washed with water (100 mL × 2) and brine (100 mL), and then dried over Na_2SO_4 and concentrated in vacuo to furnish thick yellow oil, which was purified by chromatography on a silica gel column [elution with petroleum ether/ethyl acetate (8:2)] to obtain a crude product (7.0 g) and then further purified by distillation using Kugelrohr apparatus. The first fraction (2.5 g) was a mixture of **3** and **4** while the second fraction obtained at 120−125 °C (2 mm) was the anhydride **4**, 4.2 g, (60% yield, 98% purity by ^{1}H NMR): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.18 (s, 3H), 4.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.2, 16.2, 139.4, 144.0, 163.9, 165.2; MS (*m*/*e*) 206, 204, 125, 80, 53; IR (neat) ν_{max} 1775, 1675 cm^{-1}. Anal. Calcd for $C_6H_5BrO_3$: C, 35.15; H, 2.46. Found: C, 35.01; H, 2.49.

General Procedure for the Synthesis of Alkylmethylmaleic Anhydrides (1a−e). A freshly prepared solution of Grignard reagent (10 mmol) in ether (15 mL) was added dropwise to the solution of (bromomethyl)methylmaleic anhydride (**4**, 410 mg, 2 mmol) and CuI (38 mg, 0.2 mmol) in ether (10 mL) and HMPA (4 mL) under argon at −5 to 0 °C over 15 to 20 min under stirring. The reaction mixture was allowed to reach rt and further stirred for 8 h. It was diluted with ether (15 mL) and acidified with 4 N H_2SO_4 (10 mL), and the aqueous layer was further extracted with ether (15 mL × 3). The combined organic layer was washed with water (20 mL × 2), brine (20 mL), and dried over Na_2SO_4. Concentration in vacuo followed by silica gel column chromatographic purification of the crude product using petroleum ether/ethyl acetate (19:1) as eluent furnished pure alkylmethylmaleic anhydrides **1a**−**e** in 55−60% yields. These reactions were also carried out under identical conditions in THF without any loss of yield.

The products obtained can also be purified by chemical treatment. The crude products were basified with 5% aqueous NaOH solution (10 mL) and then extracted with ether (10 mL × 3). Subsequent acidification of the aqueous layer, followed by ether extraction (15 mL × 3), washing of extract with water (15 mL) and brine (15 mL), drying over Na_2SO_4, and concentration in vacuo furnished pure product with similar yield.

3-Ethyl-4-methyl-2,5-furandione (1a):[10,11] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 8 Hz, 3H), 2.09 (s, 3H), 2.52 (q, J = 8 Hz, 2H); IR (neat) ν_{max} 1765, 1660 cm^{-1}. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.76; H, 5.83.

3-Hexyl-4-methyl-2,5-furandione (1b):[12] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (m, 3H), 1.15−1.45 (m, 6H), 1.45−1.70 (m, 2H), 2.08 (s, 3H), 2.46 (t, J = 7 Hz, 2H); MS (*m*/*e*) 196, 168, 139, 126, 98, 81, 70, 55; IR (neat) ν_{max} 1765, 1655 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.57; H, 8.51.

3-Nonyl-4-methyl-2,5-furandione (1c): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, J = 6 Hz, 3H), 1.15−1.48 (bs, 12H), 1.48−1.70 (m, 2H), 2.10 (s, 3H), 2.48 (t, J = 8 Hz, 2H); MS (*m*/*e*) 238, 210, 193, 178, 153, 140, 126, 98, 81, 55; IR (neat) ν_{max} 1765, 1670 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.63; H, 9.39.

3-Tridecyl-4-methyl-2,5-furandione (1d): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7 Hz, 3H), 1.10−1.45 (bs, 20H), 1.45−1.70 (m, 2H), 2.08 (s, 3H), 2.46 (t, J = 7 Hz, 2H); MS (*m*/*e*) 294, 276, 249, 221, 192, 163, 150, 140, 126, 98, 55; IR (neat) ν_{max}, 1770, 1675 cm^{-1}. Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.11; H, 10.10.

3-Tetradecyl-4-methyl-2,5-furandione (Chaetomellic Acid A Anhydride, 1e):[1] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7 Hz, 3H), 1.15−1.45 (bs, 22H), 1.46−1.69 (m, 2H), 2.07 (s, 3H), 2.45 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.6, 14.3, 22.9, 24.6, 27.7, 29.0−31.0 ($9CH_2$), 32.1, 140.6, 144.9, 166.0, 166.4; MS (*m*/*e*) 308, 290, 191, 150, 126, 91, 81, 69; IR (neat) ν_{max} 1770, 1680 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.73; H, 10.39.

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Supporting Information Available: ^{1}H NMR and mass spectra of **1b**−**e** and **4**, ^{13}C NMR of **1e** and **4** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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