A New Strategy for the Synthesis of Furan-3,4-dicarboxylic Acid[1]

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Abstract: A facile route to furan-3,4-dicarboxylic acid is described. Dimethylmaleic anhydride (**1**) on NBS-bromination followed by aqueous KOH treatment gave bis(hydroxymethyl)maleic anhydride (**3**), which on intramolecular Mitsunobu ring closure followed by esterification and DDQ-oxidation furnished the desired esters of furan-3,4-dicarboxylic acid **7a**/**b**.

Key words: 2,3-bis(bromomethyl)maleic anhydride, intramolecular Mitsunobu ring closure, DDQ-oxidation, furan-3,4-dicarboxylic acid

The applications of furan-3,4-dicarboxylic acid and its esters have been well known in practice.[2] They are used as starting materials in the synthesis of several bioactive natural products such as zargocic acid,[3] confertin,[4] aromaticin,[5] lactral,[6] freelingyne,[7] biotin,[8] nectriafurone[9] and perrilin.[9] They are also used in the synthesis of several pharmacologically useful molecules,[10] preparation of complexes with rare earth metal ions[11] and as a potential dienes in Diels–Alder reactions for the synthesis of several novel heterocycles.[12] The development of new facile synthetic routes to this potential building block is a challenging task.[13–17] To date five multi-step synthesis of **7a**/**b** are known in the literature via partial decarboxylation of furan tetracarboxylic acid,[13] thermal decomposition of partially reduced Diels–Alder adduct of furan and acetylenedicarboxylic acid/ester,[14] cyclisation of 1,4-dicarbonyl systems,[15] regioselective lithiation of 2-silylated-3-furoic acid[16] and involving condensation of methyl glycolate with methyl acrylate as the key step.[17] Very recently we prepared the (bromomethyl)methylmaleic anhydride and used it for synthesis of chaetomellic acid A,[18a] fulgenic acid,[18b] heterocycles,[18c] maleic anhydride segment of tautomycin,[18d] telfairic anhydride[19] and graphenone.[19] Now, we herein report the preparation of bis(bromomethyl)maleic anhydride (**2**) and its application for the new synthesis of esters of furan-3,4-dicarboxylic acid **7a**/**b** (Scheme).

The reaction of dimethylmaleic anhydride (**1**) with excess of NBS in the presence of catalytic amounts of dibenzoyl peroxide in refluxing CCl_4 gave the bis(bromomethyl)maleic anhydride (**2**) in 62% yield. The dibromoanhydride **2** on treatment with 4 N aqueous KOH at room temperature followed by acidification afforded exclusively the substitution product bis(hydroxymethyl)maleic anhydride (**3**) in 98% yield. The isolated anhydride **3** was quite stable and did not show any tendency for intramolecular/intermolecular dehydration, Michael addition and nucleophilic ring opening of anhydride moiety. The anhydride **3** on intramolecular Mitsunobu ring closure in THF at room temperature followed by aqueous work up furnished dihydrofuran-3,4-dicarboxylic acid (**5**) in 91% yield. The diacid **5** on reaction with methanol/ethanol and a catalytic amount of sulfuric acid gave the corresponding esters **6a**/**b**, respectively, in 88–90% yield. These esters **6a**/**b**, in presence of excess of DDQ in refluxing 1,4-dioxane, furnished the desired 3,4-furandicarboxylic acid esters **7a**/**b** in 80–85% yield (Scheme). The overall yield of **7a**/**b** in five-steps was 39–42% and the analytical and spectral data obtained for **7a**/**b** were in complete agreement with the reported data.[2,14c] The present practical approach to design **7** from suitably substituted dicarboxylic acid/cyclic anhydride to generate furan ring has several advantages over others in the literature (furan to furan-3,4-dicarboxylic acid).

In our hands all our attempts to transfer **2** to dihydropyrrole-3,4-dicarboxylic acid/dihydrothiophene-3,4-dicarboxylic acid (**8a**/**b**) using ammonia and sodium sulfide met with failure, and only polymeric/decomposed gums were obtained. The conditions to obtain **8a**/**b** from **2** are still elusive to us and the work is in progress in our laboratory.

In summary, starting from dimethylmaleic anhydride (**1**), we have demonstrated an elegant 5-step practical approach to esters of furan-3,4-dicarboxylic acid **7a**/**b** with 39–42% overall yield via two new anhydrides **2** and **3**.

Melting points are uncorrected. The IR spectra were recorded on FT IR-8400 IR spectrophotometer. The ^{1}H NMR spectra were recorded on Bruker ACF 200 NMR spectrometer (200 MHz). The ^{13}C NMR spectra were recorded on Bruker ACF 200 NMR spectrometer (50 MHz). The Mass spectra were recorded on Finnigan Mat 1020 mass spectrometer at 70 eV. Column chromatographic separations were done on ACME silica gel (60–120 mesh). Petroleum ether with a bp range of 60–80 °C was used. Dimethylmaleic anhydride, Ph_3P, diethyl azodicarboxylate (DEAD) and dibenzoyl peroxide (DBP) were obtained from Aldrich Chemical Co.

Bis(bromomethyl)maleic Anhydride (2)

A mixture of dimethylmaleic anhydride (**1**; 5.04 g, 40 mmol), *N*-bromosuccinimide (14.24 g, 80 mmol) and a catalytic amount of dibenzoyl peroxide (200 mg, 0.83 mmol) in CCl_4 (300 mL) was gently refluxed for 12 h in a 500 mL round-bottom flask. The reaction mixture was allowed to cool to r.t. and a second portion of *N*-bromosuccinimide (14.24 g, 80 mmol) and dibenzoyl peroxide (200 mg, 0.83 mmol) was added and again the refluxing was continued

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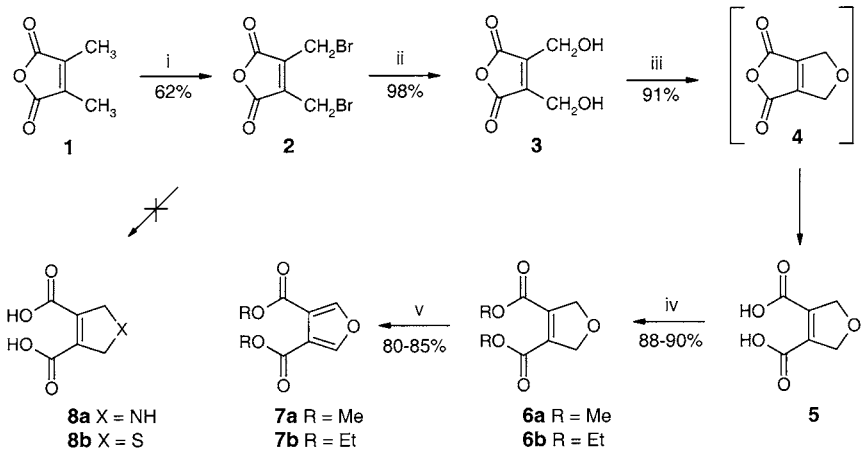

Scheme *Reagents and conditions*: i) NBS, DBP, CCl_4, reflux, 24; ii) (a) aq KOH, r.t., 3 h, (b) H^+/2 N HCl; iii) DEAD, TPP, THF, r.t., 3 h; iv) ROH, H^+/H_2SO_4, r.t., 24 h; v) DDQ, 1,4-dioxane, reflux, 24 h

for another 12 h. The mixture was left overnight at r.t. and then filtered. The residue was washed with CCl_4 (2 × 25 mL), the combined organic layer was washed with H_2O (2 × 100 mL), brine (100 mL), then dried (Na_2SO_4) and concentrated in vacuo to furnish a thick yellow oil. Chromatography of the oil on a silica gel column with petroleum ether–EtOAc (8:2) as eluent gave the crude product (9.7 g) which was further purified by distillation using a Kugelrhor apparatus. The first fraction (2.2 g) was a mixture of a small amount of starting material and major portion of (bromomethyl)methylmaleic anhydride, whereas the second fraction obtained at 145–150 °C/2 mm was the pure dibromoanhydride **2**; yield: 7.1 g (62%, 98% purity by ^{1}H NMR); mp 84–86 °C [benzene–petroleum ether (1:3)].

IR (Nujol): 1784, 1664 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.28 (s).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 15.1, 141.1, 162.7.

MS: *m*/*z* (%) = 286 (9), 284 (21), 282 (9), 205 (93), 203 (100), 161 (36), 159 (39), 133 (58), 131 (59), 124 (22), 80 (83), 66 (85).

Anal. Calcd for $C_6H_4Br_2O_3$: C, 25.38; H, 1.42. Found: C, 25.62; H, 1.26.

Bis(hydroxymethyl)maleic Anhydride (3)

To an ice-cold solution of 4 N aq KOH (25 mL) was added bis(bromomethyl)maleic anhydride (**2**; 5.68 g, 20 mmol) and the mixture was stirred at r.t. for 3 h. The mixture was slowly acidified with aq 2 N HCl and saturated with solid NaCl and stirred at r.t. for 30 min. The aqueous layer was extracted with EtOAc (3 × 25 mL), the organic layer was washed with brine (25 mL) and dried (Na_2SO_4). Concentration of the organic layer in vacuo gave pure **3**; yield: 3.01 g (98%); mp 174–176 °C [benzene–petroleum ether (1:3)].

IR (Nujol): 3429, 1769, 1693 cm^{-1}.

^{1}H NMR (acetone-d_6, 200 MHz): δ = 4.96 (s, 4 H), 8.00–9.00 (br s, 2 H).

^{13}C NMR (acetone-d_6, 50 MHz): δ = 77.7, 139.9, 164.4.

MS: *m*/*z* (%) = 158 (2), 140 (52), 113 (36), 112 (39), 96 (41), 95 (39), 91 (7), 84 (100), 69 (83), 66 (85), 55 (24).

Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.83. Found: C, 45.73; H, 3.67.

2,5-Dihydrofuran-3,4-dicarboxylic Acid (5)

To a solution of **3** (1.58 g, 10 mmol) and Ph_3P (2.88 g, 11 mmol) in THF (20 mL) was added a solution of DEAD (1.92 g, 11 mmol) in THF (10 mL) in a dropwise fashion with continuous stirring at r.t. and the reaction mixture was further stirred for 3 h. The mixture was concentrated in vacuo and the residue was dissolved in aq 5% $NaHCO_3$ solution (25 mL). The aqueous layer was washed with EtOAc (2 × 20 mL); subsequent acidification of the aqueous layer with aq 2 N HCl followed by extraction with EtOAc (3 × 10 mL). The organic extracts were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4) and concentrated to furnish the pure product **5**; yield: 1.44 g (91%); mp 191–193 °C (EtOAc).

^{1}H NMR (acetone-d_6, 200 MHz): δ = 4.96 (s, 4 H), 8.75–9.75 (br s, 2 H).

^{13}C NMR (DMSO-d_6, 50 MHz): δ = 77.3, 139.9, 164.2.

MS: *m*/*z* (%) = 158 (2), 140 (12), 112 (14), 96 (23), 84 (35), 69 (47), 66 (100), 55 (28).

Anal. Calcd for $C_6H_6O_5$: C, 45.58; H, 3.83. Found: C, 45.76; H, 3.58.

Dimethyl 2,5-Dihydrofuran-3,4-dicarboxylate (6a); Typical Procedure

A solution of **5** (790 mg, 5 mmol) in MeOH and H_2SO_4 (19:1, 20 mL) was stirred at r.t. for 24 h under N_2 and the reaction mixture was concentrated in vacuo. The residue was diluted with H_2O and extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with H_2O (25 mL), brine (25 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the crude product using petroleum ether–EtOAc (7:3) as eluent furnished the pure dimethyl ester **6a** as a thick oil; yield: 837 mg (90%).

IR (neat): 1726, 1666, 1279 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.82 (s, 6 H), 4.93 (s, 4 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 52.1, 76.3, 136.2, 162.4.

Anal. Calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41. Found: C, 51.86; H, 5.54.

Diethyl 2,5-Dihydrofuran-3,4-dicarboxylate (6b)

Similarly the diethyl ester was prepared from **5** (790 mg, 5 mmol) using EtOH and H_2SO_4 (19:1, 20 mL); thick oil; yield: 941 mg (88%).

IR (neat): 1726, 1666, 1273 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.32 (t, *J* = 8 Hz, 6 H), 4.27 (q, *J* = 8 Hz, 4 H), 4.93 (s, 4 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.0, 61.4, 76.5, 136.2, 162.2.

MS: *m*/*z* (%) = 214 (2), 213 (8), 201 (4), 189 (19), 168 (35), 157 (7), 140 (31), 123 (8), 112 (49), 95 (53), 84 (88), 69 (100), 55 (19).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.36; H, 6.29.

Dimethyl Furan-3,4-dicarboxylate (7a); Typical Procedure

To a solution of **6a** (744 mg, 4 mmol) in 1,4-dioxane (15 mL) was added DDQ (2.724 g, 12 mmol) and the reaction mixture was refluxed for 24 h. The mixture was concentrated in vacuo and the residue was dissolved in EtOAc (30 mL), washed with H_2O (15 mL), brine (15 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the crude product using petroleum ether–EtOAc (7.5:2.5) as eluent furnished the pure dimethyl ester **7a**; yield: 618 mg (84%); mp 48–50 °C.

IR (Neat): 2955, 1736, 1286 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.87 (s, 6 H), 7.95 (s, 2 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 51.9, 118.2, 148.7, 162.0.

MS: *m*/*z* (%) = 184 (23), 153 (100), 123 (70), 95 (5), 69 (4), 59 (10), 53 (10).

Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.27; H, 4.34.

Diethyl Furan-3,4-dicarboxylate (7b)

Similarly reaction of **6b** (856 mg, 4 mmol) on DDQ oxidation (2.724 g, 12 mmol) furnished **7b** as a thick oil; yield: 687 mg (81%).

IR (neat): 2951, 1732, 1281 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.32 (t, *J* = 8 Hz, 6 H), 4.33 (q, *J* = 8 Hz, 4 H), 7.93 (s, 2 H).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 6.70. Found: C, 56.43; H, 6.89.

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