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The Regiospecific C-3 Lithiation of 5-Ethyl-2-furoic acid: An Approach to Key Natural Product Intermediates

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Treatment of 5-ethyl-2-furoic acid with *n*-butyllithium in tetrahydrofuran gave regiospecific C-3 lithiation, whereas treatment of the same acid with lithium di-isopropylamide (LDA) afforded only starting material. The synthetic utility of dilithiated 5-ethyl-2-furoic acid has been demonstrated with the synthesis of two substituted 3-benzyl-5-ethyl-2-furoic acid derivatives which are key intermediates for the preparation of naturally occurring cytotoxic 2-ethylfuronaphthoquinones. Reaction of the C-3 lithiated species with two equivalents of benzaldehyde and subsequent reduction afforded the corresponding 3-benzyl-5-ethyl-2-furoic acids. An alternative route to 5-ethyl-2-furoic acid has been described allowing for a more convenient preparation of longer-chain 5-alkyl-2-furoic acids.

Keywords: regiospecific lithiation; 2-furoic acid; 5-ethyl-2-furoic acid; butyl-lithium; lithium di-isopropylamide (LDA); furonaphthoquinone

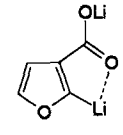
INTRODUCTION

The ability of furan carboxylic acids to form dilithiated species (**1** and **2**) upon treatment with lithium di-isopropylamide (LDA) is well known.[1] When heteroaromatic systems contain a single heteroatom, lithiation almost always occurs at an adjacent site, but a limitation is that lithiation may occur at either of two vacant α-positions. Many functional groups have been identified which are capable of directing lithiation to a specific α-position.[2] Such groups generally contain a heteroatom that can coordinate to an incoming base, with the resulting complex induced proximity effect giving rise to lithiation at the corresponding α-position. When such effects are combined, as with 3-furoic acid, lithiation is found to occur exclusively at the (C-2) α-position. Such lithiated intermediates are amongst the most useful for the rapid and often regiospecific homologation of heteroaromatic systems and we have recently demonstrated the synthetic utility of **1** in the synthesis of cytotoxic, naturally occurring furonaphthoquinone analogues **3**.[3] Both our own studies[4] and those of others[5] have identified benzylfuran carboxylic acids analogous to **4** to be key intermediates in such syntheses.

Following the isolation of 2-ethylfuronaphthoquinone from the heartwood of *Paratecoma peroba* (Bignoniaceae)[6] we sought to expand our present methodology[3] to allow the preparation of analogues of this naturally occurring compound. Herein we report the regiospecific C-3 lithiation of 5-ethyl-2-furoic acid, making possible the preparation of substituted 3-benzyl-5-ethyl-2-furoic acids, key intermediates in the synthesis of 2-ethylfuronaphthoquinones.

RESULTS AND DISCUSSION

Treatment of 2-furoic acid **5** (Scheme 1) with two equivalents of LDA in tetrahydrofuran (THF) and quenching of the resulting dilithio intermedi-



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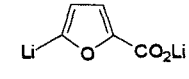

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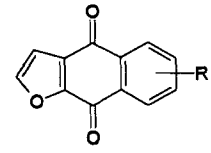

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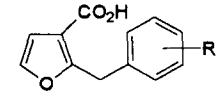

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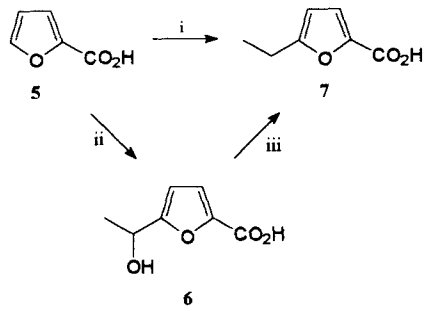


Scheme 1 Reagents and conditions: i, lithium di-isopropylamide, tetrahydrofuran, −78 °C to −40 °C, ethyl iodide, 6 h; ii, lithium di-isopropylamide, tetrahydrofuran, −78 °C acetaldehyde, 2 h; iii, iodotrimethylsilane, acetonitrile, 24 h.

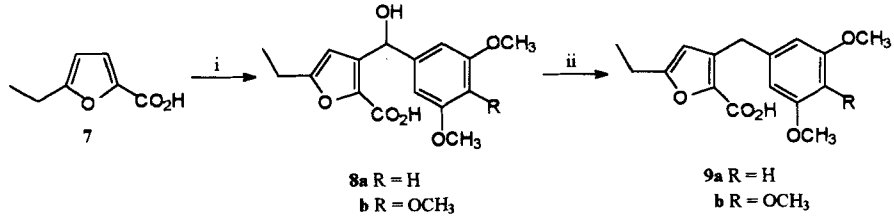
ate with D_2O afforded the expected 5-deuterio-2-furoic acid in 96% yield by ^1H NMR.[1] However, reaction with ethyl iodide (−20 °C, 6 h) afforded a mixture of 5-ethyl-2-furoic acid **7** and unreacted **5** in 70 and 30% yield, respectively, by ^1H NMR. Given the longer reaction time required and lower yield, probably due to protonation at higher temperatures, an alternative route was sought. Treatment of the dilithio intermediate of **5** with acetaldehyde smoothly afforded 5-(1-hydroxyethyl)-2-furoic acid **6** in 77% yield (Scheme 1). Subsequent reduction with iodotrimethylsilane afforded 5-ethyl-2-furoic acid **7** (Scheme 1) in quantitative yield.[7] Besides affording the required product in excellent yield, this route also allows for the preparation of other 5-alkyl derivatives that would be impractical by reaction with longer-chain alkyl halides.

We then sought to investigate whether the carboxylic acid moiety of 5-ethyl-2-furoic acid **7** could direct lithiation towards the relatively less acidic proton at the C-3 position. Treatment of the acid **7** with two equivalents of LDA in THF at both −78 and −20 °C, and subsequent quenching with D_2O failed to yield any of the C-3 or C-4 deuterated product. Given the failure to isolate any deuterated product using LDA as the base, we decided to investigate the action of n-butyl-lithium on the acid **7**. It is generally accepted that the carboxylic acid moiety is not a good α-directing group when butyl-lithium is employed as the base,[2] the second equivalent of butyl-lithium usually adds to the initially formed lithium carboxylate to give the corresponding butyl ketone. There are, however, two notable exceptions. Treatment of thiophene-2-carboxylic acid with two equivalents of butyl-lithium afforded the C-3 lithiated product[8] whilst 2-(*t*-butyldimethylsilyl)-3-furoic acid has been regiospecifically lithiated at the C-4 position.[9]

Treatment of 5-ethyl-2-furoic acid **7** with 2 equivalents of n-butyl-lithium in THF (−78 °C, 0.5 h) and quenching of the resulting intermediate dilithio species with D_2O afforded 3-deuterio-5-ethyl-2-furoic acid in *ca* 60% yield and unchanged starting material. Treatment of the intermediate dilithio species with 3,5-dimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde afforded the corresponding hydroxyfuroic acids **8a** and **8b** in 53 and 55% yield respectively (Scheme 2). Subsequent reduction with iodotrimethylsilane in acetonitrile[4] afforded the required 3-benzyl-5-ethyl-2-furoic acids **9a** and **9b** in near quantitative yield (Scheme 2).

CONCLUSION

We have demonstrated regiospecific C-3 lithiation of 5-ethyl-2-furoic acid with n-butyl-lithium in the preparation of substituted 3-benzyl-5-ethyl-2-furoic acids as key intermediates for the synthesis of 2-ethylfuronaphthoquinones. This reaction provides another example of α-directed lithiation of an aromatic acid as opposed to the more commonly observed butyl ketone addition product. An alternative route to 5-alkyl-2-furoic acids has been described. Investigations into the



8a R = H
b R = OCH_3

9a R = H
b R = OCH_3

Scheme 2 Reagents and conditions: i, n-Butyl-lithium, tetrahydrofuran, −78 °C, appropriate benzaldehyde, 3 h; ii, iodotrimethylsilane, acetonitrile, 0.5 h.

lithiation of other 5-substituted 2-furoic acids are in progress.

EXPERIMENTAL

Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were recorded as potassium bromide discs using a Perkin–Elmer 683 IR spectrometer and values are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Brüker AC250 spectrometer at 303.3 K in $CDCl_3$. Chemical shifts (ppm) are given downfield of tetramethylsilane. Coupling constants (*J*) are given in Hertz. Electron impact mass spectra were determined on a VG Trio-3 mass spectrometer at an ionization energy of 70 eV. Diisopropylamine was freshly distilled from solid potassium hydroxide prior to use. Acetonitrile was distilled and stored over 0.4 nm molecular sieves prior to use. Organic solutions were dried over anhydrous magnesium sulphate. Ether refers to diethyl ether.

5-Ethyl-2-furoic acid (7)

From the reaction of 2-furoic acid with ethyl iodide
To di-isopropylamine (7 ml, 5 mmol) at −10 °C under nitrogen was added n-butyl-lithium (32 ml of a 1.6 M solution in hexanes, 50 mmol) with stirring. After 15 min the resulting viscous solution was diluted with THF (50 ml), cooled to −78 °C, and a solution of 2-furoic acid (2.8 g, 25 mmol) in THF (50 ml) was added. The solution was stirred at −78 °C for 30 min and then allowed to warm to −40 °C. Ethyl iodide (2.6 ml, 32 mmol) was added and the solution stirred at −40 to −20 °C for 6 h and then warmed to room temperature. The resulting solution was diluted with water and washed with ether (2 × 50 ml). The aqueous portion was acidified (2 M HCl) and extracted with ether (3 × 150 ml). The combined extracts were washed with brine, dried and evaporated to yield a crude brown solid (5-ethyl-2-furoic acid/2-furoic acid, 70:30 by ^1H NMR). Careful recrystallization from water yielded a pure sample as a cream solid (2.0 g, 57%), m.p. 88–90 °C (lit.[10] 91–92 °C). IR: ν 1690 (C=O). ^1H NMR: 10.1 (1H, br s, OH), 7.27 (1H, d, *J* 3.4, 3-H), 6.19 (1H, dd, *J* 3.4, 0.7, 4-H), 2.76 (2H, q, *J* 7.6, CH_2), 1.30 (3H, t, *J* 7.6, CH_3). ^{13}C NMR: 163.9, 163.4, 142.0, 121.4, 107.2, 21.6, 11.6.

Via 5-(1-Hydroxyethyl)-2-furoic acid (6)
To di-isopropylamine (7 ml, 50 mmol) at −10 °C under nitrogen was added n-butyl-lithium (32 ml of a 1.6 M solution in hexanes, 50 mmol) with stirring. After 15 min the resulting viscous solution was diluted with THF (50 ml), cooled to −78 °C, and a solution of 2-furoic acid (2.8 g, 25 mmol) in THF (50 ml) was added. The solution was stirred at −78 °C, and a solution of 2-furoic acid (2.8 g, 25 mmol) in THF (50 ml) was added. The solution was stirred at −78 °C for 30 min and acetaldehyde (25 mmol) was added. The solution was allowed to warm slowly to room temperature over *ca* 2 h. The resulting solution was diluted with water and washed with ether (2 × 50 ml). The aqueous portion was acidified (2 M HCl) and extracted with ether (3 × 100 ml). The combined extracts were washed with brine, dried and evaporated to yield 5-(1-hydroxyethyl)-2-furoic acid (**6**) as a brown oil (3.0 g, 77%). ^1H NMR: 7.89 (1H, br s, OH), 7.17 (1H, d, *J* 3.4, 3-H), 6.36 (1H, d, *J* 3.4, 4-H), 4.94 (1H, q, *J* 6.6, C*H*OH), 1.54 (3H, d, *J* 6.6, CH_3). ^{13}C NMR: 162.7, 162.4, 142.8, 120.5, 107.6, 63.6, 20.9.

To a suspension of NaI (4.5 g, 30 mmol) in acetonitrile (10 ml) under nitrogen was added Me_3SiCl (3.86 ml, 30 mmol) with stirring. A solution of 5-(1-hydroxyethyl)-2-furoic acid (5 mmol) in acetonitrile (50 ml) was added and the solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined extracts were washed with aqueous sodium thiosulphate solution (2 × 50 ml), saturated brine (50 ml), and dried. Evaporation and recrystallization from hexane yielded the title compound (0.67 g, 96%). m.p. 92 °C (hexanes) (lit.[10] 91–92 °C). IR: ν 1690 (C=O). ^1H NMR: 10.1 (1H, br s, OH), 7.27 (1H, d, *J* 3.4, 3-H), 6.19 (1H, dd, *J* 3.4, 0.7, 4-H), 2.76 (2H, q, *J* 7.6, CH_2), 1.30 (3H, t, *J* 7.6, CH_3). ^{13}C NMR: 163.9, 163.4, 142.0, 121.4, 107.2, 21.6, 11.6.

3-[(3,5-Dimethoxyphenyl)-hydroxymethyl]-5-ethyl-2-furoic acid (8a) and 3-[(3,4,5-trimethoxyphenyl)-hydroxymethyl]-5-ethyl-2-furoic acid (8b)

To a solution of 5-ethyl-2-furoic acid (2.45 g, 17.5 mmol) in THF (100 ml) at −78 °C under

nitrogen was added n-butyl-lithium (24 ml of a 1.6 M solution in hexanes, 38.5 mmol). The solution was stirred for 30 min at −78 °C and a solution of either 3,5-dimethoxybenzaldehyde (2.9 g, 17.5 mmol), or 3,4,5-trimethoxybenzaldehyde (3.43 g, 17.5 mmol) in THF (100 ml) was added. The solution was allowed to reach room temperature over *ca* 3 h. The mixture was diluted with water (200 ml), and washed with ether (2 × 50 ml). The aqueous portion was acidified (2M HCl) and extracted with ether (3 × 100 ml). The combined extracts were dried and evaporated, affording the title compounds.

3-[(3,5-Dimethoxyphenyl)hydroxymethyl]-5-ethyl-2-furoic acid (8a)
Yield: 2.85 g (53%). ^{1}H NMR: 12.95 (1H, br s, OH), 6.56 (2H, d, *J* 2.4, 2′-H, 6′-H), 6.34 (1H, t, *J* 2.4, 4′-H), 6.30 (1H, s, 3-H), 6.20 (1H, s, C*H*OH), 3.70 (6H, s, OCH_3), 2.61 (2H, q, *J* 7.5, CH_2), 1.15 (3H, t, *J* 7.5, CH_3).

3-[(3,4,5-Trimethoxyphenyl)hydroxymethyl]-5-ethyl-2-furoic acid (8b)
Yield: 3.25 g (55%). ^{1}H NMR: 6.67 (2H, s, 2′-H, 6′-H), 6.10 (1H, s, 3-H), 6.03 (1H, s, C*H*OH), 3.84 (6H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.68 (2H, q, *J* 7.6, CH_2), 1.24 (3H, t, *J* 7.6, CH_3).

3-(3,5-Dimethoxybenzyl)-5-ethyl-2-furoic acid (9a) and 3-(3,4,5-trimethoxybenzyl)-5-ethyl-2-furoic acid (9b)

To a suspension of NaI (2.25 g, 15 mmol) in acetonitrile (10 ml) under nitrogen was added Me_3SiCl (1.93 ml, 15 mmol) with stirring. A solution of either 3-[(3,5-dimethoxyphenyl)hydroxymethyl]-5-ethyl-2-furoic acid (0.765 g, 2.5 mmol) or 3-[(3,4,5-trimethoxyphenyl)hydroxymethyl]-5-ethyl-2-furoic acid (0.84 g, 2.5 mmol) in acetonitrile (50 ml) was added and the solution was stirred at room temperature for 30 min. The reaction mixture was diluted with water (50 ml) and extracted with ether (3 × 50 ml). The combined extracts were washed with aqueous sodium thiosulphate solution (2 × 50 ml), saturated brine (50 ml), and dried. Evaporation yielded the title compounds.

3-(3,5-Dimethoxybenzyl)-5-ethyl-2-furoic acid (9a)
Yield: 0.70 g (97%), m.p. 98 °C (from hexane). IR: ν 1675 (C=O). MS: *m/z* 290 (M^+, 100%), 272 (11), 245 (17). ^{1}H NMR: 6.43 (2H, d, *J* 2.3, 2′-H, 6′-H), 6.35 (1H, t, *J* 2.3, 4′-H), 6.00 (1H, s, 4-H), 4.11 (2H, s, CH_2), 3.79 (6H, s, OCH_3) 2.68 (2H, q, *J* 7.6, CH_2), 1.25 (3H, t, *J* 7.6, CH_3). ^{13}C NMR: 164.2, 162.7, 160.8, 141.6, 137.9, 137.3, 109.7, 106.9, 98.2, 55.2, 32.2, 21.6, 11.6. Analysis: Found: C, 66.0; H, 6.1. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.2%.

3-(3,4,5-Trimethoxybenzyl)-5-ethyl-2-furoic acid (9b)
Yield: 0.76 g (95%). IR: ν 1675 (C=O). MS: *m/z* 320 (M^+, 8%), 276 (21), 212 (38), 197 (29), 181 (20), 140 (59), 125 (100), 95 (30), 79 (32), 39 (31). ^{1}H NMR: 6.47 (2H, s, 2′-H, 6′-H), 5.97 (1H, s, 4-H), 4.08 (2H, s, CH_2), 3.82, (9H, s, OCH_3) 2.67 (2H, q, *J* 7.6, CH_2), 1.23 (3H, t, *J* 7.6, CH_3). ^{13}C NMR 164.1, 162.7, 153.1, 137.9, 137.4, 136.5, 135.0, 109.6, 105.9, 60.7, 56.0, 32.2, 21.6, 11.5. Analysis: Found: C, 63.6; H, 6.3. $C_{17}H_{20}O_6$ requires C, 63.7; H, 6.3%.

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