A CONVENIENT SYNTHESIS OF BENZOFURAN-3-ACETIC ACIDS

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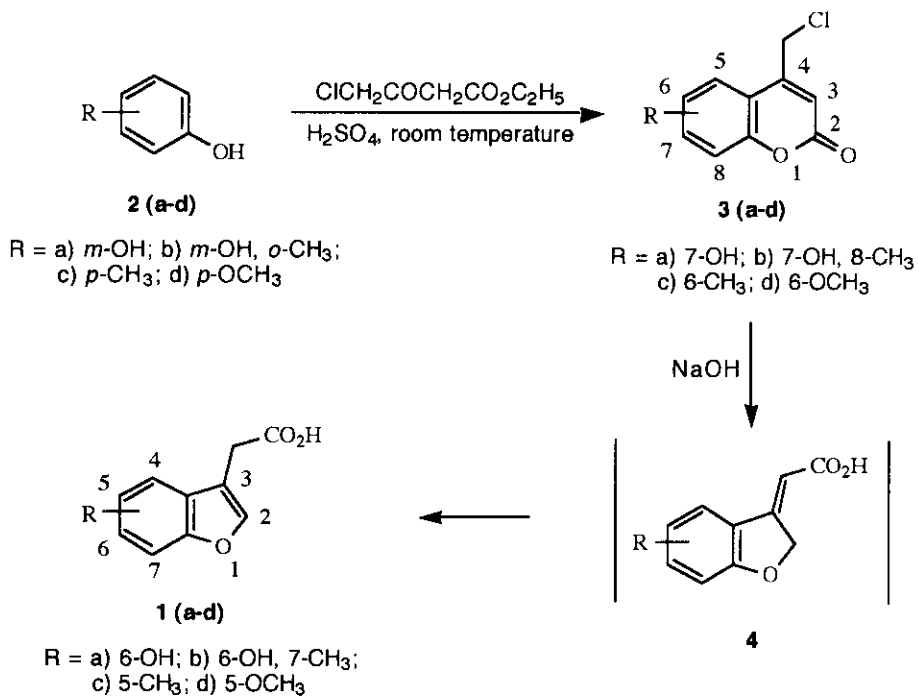
Abstract — We describe a two-step synthesis of benzofuran-3-acetic acids (**1**) from phenols (**2**) involving alkali-mediated rearrangement of 4-halomethylcoumarins (**3**) *via* α,ß-unsaturated acids (**4**). Electron-donating substituents at the *meta* position of the phenol favour high yields of the coumarin, which in all cases rearranges to afford benzofuran-3-acetic acids in near quantitative yields.

While a variety of synthetic approaches to substituted indoles are available,[1] less attention has been paid to synthesis of the corresponding benzofurans. A scan of the literature revealed only a few, in some cases rather complex, syntheses of benzofuran-3-acetic acid or its ethyl ester,[2] and 5-methylbenzofuran-3-acetic acid (**1c**) has been prepared previously from 2-hydroxy-5-methylacetophenone in a lengthy four-step synthesis involving a Wittig reaction of the corresponding benzofuran-3(2*H*)-one (overall yield, 58%).[3]

In this work we report a short and versatile synthetic route to benzofuran isosteres of some pharmacologically important indoles functionalized at position 3. We synthesized compounds (**1a-d**), which may exhibit anti-inflammatory, analgesic and antipyretic activity of the type shown by other arylalkanoic acids,[4] and which, by

virtue of the easy chemical manipulation of their carboxylic acid side chain, can also serve as intermediates in the synthesis of analogues of *e.g.* tryptamine,[5] serotonin,[6] melatonin and cholecystokinin antagonists.[7]

The reaction of base with 3-halocoumarins is well known,[8] proceeding *via* hydrolysis of the unsaturated lactone to the substituted phenol, and intramolecular reaction between the phenolate ion and the α-halocarboxyl side chain occurs to form benzofuran-2-carboxylic acids (coumarilic acids). The key step in our synthetic strategy used the same basic conditions, but involved rearrangement of 4-chloromethylcoumarins (**3**) to benzofuran-3-acetic acids (**1**).[9]



2 (a-d)

R = a) *m*-OH; b) *m*-OH, *o*-CH_3; c) *p*-CH_3; d) *p*-OCH_3

3 (a-d)

R = a) 7-OH; b) 7-OH, 8-CH_3 c) 6-CH_3; d) 6-OCH_3

4

1 (a-d)

R = a) 6-OH; b) 6-OH, 7-CH_3; c) 5-CH_3; d) 5-OCH_3

The required 4-chloromethylcoumarins were prepared by the Pechmann reaction.[10] Appropriately substituted phenols and ethyl 4-chloroacetoacetate were stirred in 1:1.2 molar ratio, in sulphuric acid for 10 h at room temperature. Phenols (**2a**) and (**2b**), with electron-donating substituents in the *meta* position, gave 7-hydroxycoumarins in moderate yields (50 and 75% for **3a** and **3b** respectively),[11] and similar substituents in the *para* position gave 6-substituted coumarins, but in poor yields (10 and 5% for **3c** and **3d** respectively).[12]

Treatment of **3a-d** (0.1 mmol) with 0.1 M NaOH (10 mL), for either 10 min under reflux or 3 h at room

temperature in the case of **3a** and **3b**, and for either 30 min under reflux or 7 days at room temperature in the case of **3c** and **3d**, gave acids (**1**) in almost quantitative yields,[13] *via* α,ß-unsaturated acids (**4**).[14]

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12. All compounds provided spectral and analytical data consistent with their structures. Purification was carried out by flash chromatography with 9:1 hexane/ethyl acetate as eluent. **3c**: yield 10%; mp 147°C. ^{1}H Nmr (300 MHz, DMSO-d_6): 2.38 (3H, s), 5.01 (2H, s), 6.65 (1H, s), 7.33 (1H, d, J = 8.45 Hz), 7.46 (1H, dd, J = 8.45 and 1.63 Hz), 7.64 (1H, d, J = 1.63 Hz) ppm. **3d**: yield 5%; mp 144°C. ^{1}H Nmr (300 MHz, DMSO-d_6): 3.82 (3H, s), 5.05 (2H, s), 6.67 (1H, s), 7.25 (2H, m), 7.39 (1H, d, J = 8.94 Hz) ppm.

13. All compounds provided spectral and analytical data consistent with their structures. **1a**: yield 100%; mp 143°C. ^{1}H Nmr (300 MHz, DMSO-d_6): 3.58 (2H, s), 6.72 (1H, dd, J = 8.40 and 2.04 Hz), 6.86 (1H, d, J = 2.04 Hz), 7.33 (1H, d, J = 8.40 Hz), 7.65 (1H, s), 9.50 (1H, s), 12.40 (1H, s) ppm. **1b**: yield 100%; mp 140°C. ^{1}H Nmr (300 MHz, DMSO-d_6): 2.22 (3H, s), 3.57 (2H, s), 6.76 (1H, d, J = 8.40 Hz), 7.15 (1H, d, J = 8.40 Hz), 7.68 (1H, s), 9.32 (1H, s), 12.40 (1H, s) ppm. **1c**: yield 100%; mp 100°C (lit.,[2a] 50°C and lit.,[2b] 82°C). **1d**: yield 100%; mp 141°C. ^{1}H Nmr (300 MHz, DMSO-d_6): 3.66 (2H, s), 3.76 (3H, s), 6.89 (1H, dd, J = 8.90 and 2.00 Hz), 7.09 (1H, d, J = 2.00 Hz), 7.44 (1H, d, J = 8.90 Hz), 7.83 (1H, s), 12.48 (1H, s) ppm.

14. Reaction of **3c** for shorter periods allowed isolation of (5-methyl-3(2*H*)-benzofuranylidene)acetic acid (**4c**), which was purified by flash chromatography with 9:1 hexane/ethyl acetate as eluent; mp 164°C. ^{1}H Nmr (300 MHz, DMSO-d_6): 2.26 (3H, s), 5.21 (2H, d, J = 2.60 Hz), 5.80 (1H, t, J = 2.60 Hz), 6.87 (1H, d, J = 8.35 Hz), 7.22 (1H, dd, J = 8.35 and 1.85 Hz), 8.51 (1H, d, J = 1.85 Hz) ppm.

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