

## A CONVENIENT SYNTHESIS OF BENZOFURAN-3-ACETIC ACIDS

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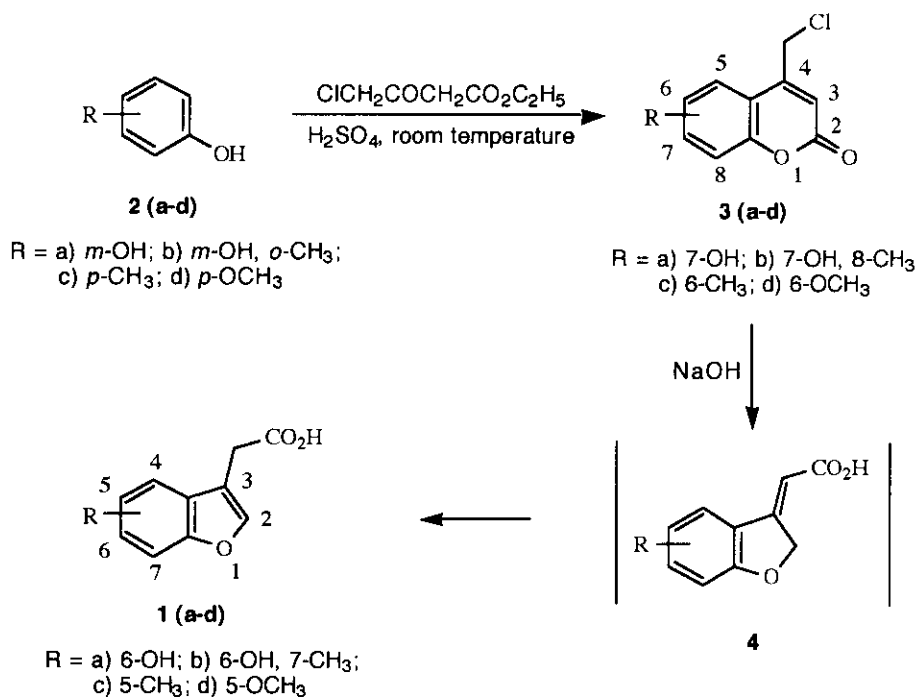
*Abstract* — We describe a two-step synthesis of benzofuran-3-acetic acids (**1**) from phenols (**2**) involving alkali-mediated rearrangement of 4-halomethylcoumarins (**3**) via  $\alpha,\beta$ -unsaturated acids (**4**). Electron-donating substituents at the *meta* position of the phenol favour high 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,<sup>1</sup> 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,<sup>2</sup> 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(*2H*)-one (overall yield, 58%).<sup>3</sup>

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,<sup>4</sup> 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,<sup>5</sup> serotonin,<sup>6</sup> melatonin and cholecystokinin antagonists.<sup>7</sup>

The reaction of base with 3-halocoumarins is well known,<sup>8</sup> proceeding *via* hydrolysis of the unsaturated lactone to the substituted phenol, and intramolecular reaction between the phenolate ion and the  $\alpha$ -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**).<sup>9</sup>



The required 4-chloromethylcoumarins were prepared by the Pechmann reaction.<sup>10</sup> 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),<sup>11</sup> and similar substituents in the *para* position gave 6-substituted coumarins, but in poor yields (10 and 5% for **3c** and **3d** respectively).<sup>12</sup>

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,<sup>13</sup> *via*  $\alpha,\beta$ -unsaturated acids (**4**).<sup>14</sup>

#### ACKNOWLEDGEMENTS

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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.  $^1\text{H Nmr}$  (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.  $^1\text{H Nmr}$  (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.  $^1\text{H Nmr}$  (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.  $^1\text{H Nmr}$  (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.,<sup>2a</sup> 50°C and lit.,<sup>2b</sup> 82°C). **1d**: yield 100%; mp 141°C.  $^1\text{H Nmr}$  (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.  $^1\text{H Nmr}$  (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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