Synthesis of 4-Arylbutanenitriles

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4-Arylbutanenitriles are valuable intermediates for the preparation, via hydrolysis to the corresponding butanoic acids and subsequent cyclization, of substituted tetralones. However, the synthetic methods presently available are either too long or require conditions so rigorous as to be incompatible with other functionalities in the molecule or even have the necessity of certain electron-withdrawing substituents. We have thus developed a simple and versatile method for the preparation of substituted 4-arylbutanenitriles 5 based on the reductive desulfonylation of α-cyanoethylated-benzyl 4-tolysulfonyls of type 4, as shown in the Scheme.

The required sulfoles 2 are easily prepared by heating together the corresponding benzyl chlorides 1 with a slight excess of sodium 4-toluenesulfinate monohydrate in absolute ethanol and all are nicely crystalline solids. Whereas the cyanoethylation reaction (2→4) is best carried out in dry acetonitrile by utilizing a catalytic amount of Triton B, the reductive desulfonylation (4→5) requires the use of methanolic 6% sodium amalgam buffered with anhydrous dipotassium hydrogen phosphate. As expected, the latter conditions cause concomitant reduction of other reducible functionalities present in the molecule, such as the nitro group (entry 5d in the Table). The method has been optimized only for the 2-methoxyphenyl derivatives (Table).

The method shown can also be utilized for the preparation of alkyl 4-arylbutanoates simply by using an appropriate acrylic ester in place of acrylonitrile (3) in the conversion 2→6. In this manner, ethyl 4-(2-methoxyphenyl)-butanoate (7) was prepared in 50% overall yield (not optimized) from 2-methoxybenzyl chloride (1a), and yielded upon basic hydrolysis the known 4-(2-methoxyphenyl)-butanoic acid (8), m.p. 40°C.

Table. Compounds 2a–e, 4a–e, 5a–e, and 6–8 prepared

<table>
<thead>
<tr>
<th>Product*</th>
<th>Yield [%]</th>
<th>m.p. [°C] or b.p. [°C/torr]</th>
<th>Molecular formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>94</td>
<td>93–95*</td>
<td>C_{6}H_{10}O_{3}S</td>
</tr>
<tr>
<td>2b</td>
<td>21</td>
<td>114–115*</td>
<td>C_{6}H_{10}O_{3}S</td>
</tr>
<tr>
<td>2c</td>
<td>47</td>
<td>126–128*</td>
<td>C_{6}H_{10}O_{3}S</td>
</tr>
<tr>
<td>2d</td>
<td>84</td>
<td>189–190*</td>
<td>185–189*</td>
</tr>
<tr>
<td>2e</td>
<td>90</td>
<td>145–146*</td>
<td>144–145*</td>
</tr>
<tr>
<td>4a</td>
<td>92</td>
<td>139–140*</td>
<td>C_{6}H_{10}NO_{3}S</td>
</tr>
<tr>
<td>4b</td>
<td>57</td>
<td>116–118*</td>
<td>C_{6}H_{10}NO_{3}S</td>
</tr>
<tr>
<td>4c</td>
<td>78</td>
<td>120–122*</td>
<td>C_{6}H_{10}NO_{3}S</td>
</tr>
<tr>
<td>4d</td>
<td>83</td>
<td>180–182*</td>
<td>C_{6}H_{10}NO_{3}S</td>
</tr>
<tr>
<td>4e</td>
<td>94</td>
<td>107–108*</td>
<td>C_{6}H_{10}NO_{3}S</td>
</tr>
<tr>
<td>5a</td>
<td>94</td>
<td>146–148* / 12</td>
<td>145–155 / 12–14*</td>
</tr>
<tr>
<td>5b</td>
<td>91</td>
<td>oil</td>
<td>C_{6}H_{10}NO</td>
</tr>
<tr>
<td>5c</td>
<td>79</td>
<td>oil</td>
<td>C_{6}H_{10}O_{3}S</td>
</tr>
<tr>
<td>5d</td>
<td>10</td>
<td>oil</td>
<td>169–173 / 6*</td>
</tr>
<tr>
<td>5e</td>
<td>84</td>
<td>oil</td>
<td>C_{6}H_{10}N_{2}</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>130–131 / 10*</td>
<td>142–145 / 6*</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>96–97*</td>
<td>C_{6}H_{10}O_{3}S</td>
</tr>
<tr>
<td>8</td>
<td>87</td>
<td>70</td>
<td>C_{6}H_{10}O_{3}S</td>
</tr>
</tbody>
</table>

* The 'H-N.M.R. and I.R. spectra were in accord with the proposed structures.

The microanalyses were in satisfactory agreement with the calculated values (C ± 0.20, H ± 0.10, N ± 0.13, S ± 0.11).

and the mixture heated under reflux overnight. Removal of the solvent under reduced pressure and pouring the residue into ice-water (100 ml) causes precipitation of a white solid. Recrystallization from ethanol affords 2a; yield: 8.24 g (94%); m.p. 93–95° C.

C_{6}H_{10}O_{3}S calc. C 65.21 H 5.84 S 11.60 (276.3)
found 65.23 5.80 11.71

I.R. (KBr): ν = 1131, 1135 cm⁻¹ (SO₂).


α-(2-Cyanoethyl)-2-methoxybenzyl-4-tolysulfone (4a):
To a solution of 2a (0.5 g, 0.002 mol) and Triton B (0.2 mol 40% methanol solution) in dry acetonitrile (10 ml) is added in one portion freshly distilled acetonitrile (3, 0.2 g, 0.004 mol). After 0.5 h stirring, the mixture is diluted with water (20 ml), acidified to Congo red with 2 normal hydrochloric acid, and partially evaporated. The suspension is extracted with ethyl acetate (4 x 20 ml), the organic extract is washed with water (2 x 10 ml), and dried with magnesium sulfate. The solvent is evaporated and the residue recrystallized from ethyl ether to give 4a; yield: 0.548 g (92%); m.p. 139–140° C.

C_{6}H_{10}O_{3}NS calc. C 65.63 H 5.81 N 4.25 S 9.73 (329.4)
found 65.70 5.74 4.18 9.69

I.R. (KBr): ν = 2240 (CN), 1320, 1140 cm⁻¹ (SO₂).

H-N.M.R. (CDCl₃): δ = 7.30 (d, J = 8 Hz, 2H arom), 7.00 (d, J = 8 Hz, 2H arom), 6.63 (4H, 4H, 2H, Ar–CH₂), 4.8 (4H, 4H, 2H, Ar–OC₂H₅), 2.7 (1H, 1H, (CH₂)₂–CN), 2.33 ppm (3H, 3H, Ar–CH₃).

4-(2-Methoxyphenyl)-butanenitrile (5a):
A solution of 3a (0.6 g, 0.002 mol) and anhydrous dipotassium hydrogen carbonate (2.2 g, 0.013 mol) in dry methanol (60 ml) is cooled to 5°C (ice-water bath) and treated portionwise with freshly prepared 6% sodium amalgam (8 g, 0.021 mol). After 0.5 h stirring, a second portion of amalgam (4 g, 0.01 mol) is added and the stirring continued for 1 h. The mixture is diluted with water (20 ml), acidified to Congo red with 2 normal sulfuric acid, filtered, and partially evaporated. The suspension is extracted with ethyl acetate (3 x 15 ml), the organic extract is washed with water (2 x 10 ml), and dried with magnesium sulfate. The solvent is evaporated and the residue separated by preparative TLC on silica gel using hexane/ethyl acetate (7:3) as eluent; yield: 0.298 g (94%); b.p. 146–148°C/12 torr (Lit., b.p. 145–155°C/12–14 torr).
1. R. (neat)  $\nu = 2240$ cm$^{-1}$ (CN).

2. $^1$H-N.M.R. (CDCl$_3$) $\delta = 7.03$ (m, 4 H$_{\text{ax}}$), 3.81 (s, 3 H, Ar-OC$_3$H$_7$); 2.30 ppm (m, 6 H, 4, 6, CH$_2$).

In the larger-scale runs (up to 0.1 mol), it is best to purify the corresponding 4-arylbutanenitriles 5 by the direct vacuum distillation of the evaporated organic extract.

3. Methoxycarboxyl-1,2-(methoxycarbonyl)-propyl-4-tolylsulfone (6):

To a solution of 2a (0.5 g, 0.002 mol) and Triton B (0.2 ml, 40% methanol solution) in dry acetonitrile (10 ml) is added in one portion freshy distilled methyl acrylate (0.348 g, 0.004 mol). After 1 h stirring at 45°C the mixture is diluted with water (20 ml), acidified to Congo red with 2 normal hydrochloric acid, and partially evaporated. The suspension is extracted with ethyl acetate (4 x 20 ml), the organic extract washed with water (2 x 10 ml), and dried with magnesium sulfate. The solvent is evaporated and the residue separated by preparative T.L.C. on silica gel using hexane/ethyl acetate (8:2) as eluent. Recrystallization of the residue from ethyl acetate/hexane gives 6 & yield 0.414 g (63%); m.p 96-97°C.

4. C$_4$H$_7$O$_2$S  calc. C 62.96 H 6.11 S 8.84
   (362.4)  found 63.03 6.15 8.87
   I.R. (KBr): $\nu = 1740$ (COOC$_3$H$_7$), 1310, 1140 cm$^{-1}$ (SO$_2$).

5. $^1$H-N.M.R. (CDCl$_3$) $\delta = 7.32$ (d, $J = 8$ Hz, 2H$_{\text{ax}}$), 7.01 (d, $J = 8$ Hz, 2H$_{\text{ax}}$), 6.6 (m, 4H$_{\text{ax}}$), 4.8 (m, 1H, Ar-C=CH$_2$), 3.56 (s, 3H, Ar-OC$_3$H$_7$), 3.36 (s, 3H, COOCH$_3$); 2.5 (m, 4H, CH$_2$), COOCH$_3$; 2.36 ppm (s, 3H, Ar-C=CH$_2$).

Ethyl 4-(2-Methoxyphenyl)-butanoate (7):

A solution of 6 (0.362 g, 0.001 mol) in dry ethanol (15 ml) is cooled to 5°C (ice/water bath) and treated with freshly prepared 6% sodium amalgam (2.4 g, 0.006 mol). After 1 h stirring, the mixture is diluted with water (20 ml), acidified to Congo red with 2 normal sulfuric acid, filtered, and partially evaporated. The suspension is extracted with ethyl acetate (4 x 15 ml), the organic extract washed with water (2 x 10 ml), and dried with magnesium sulfate. The solvent is evaporated and the residue separated by preparative T.L.C. on silica gel using hexane/ethyl acetate (7:3) as eluent to give 7 as a viscous colorless oil; yield 0.179 g (50%).

5. C$_7$H$_{14}$O$_2$  calc. C 70.24 H 8.16
   (222.2)  found 70.31 8.22
   I.R. (neat): $\nu = 1740$ cm$^{-1}$ (COOC$_3$H$_7$).

6. $^1$H-N.M.R. (CDCl$_3$) $\delta = 7.0$ (m, 4H$_{\text{ax}}$), 3.80 (s, 3H, Ar-OC$_3$H$_7$), 4.11 (q, $J = 6$ Hz, 2H, COOCH$_3$,CH$_3$); 2.24 ppm (m, $J = 6$ Hz, 3H, COOCH$_3$,CH$_3$).

4-(2-Methoxyphenyl)-butanoic Acid (8):

To a solution of 7 (5.5 g, 0.02 mol) in methanol (10 ml) is added 1 normal sodium hydroxide (6 ml) and the solution is stirred at room temperature for 4 h. The mixture is diluted with water (10 ml), acidified with 2 normal hydrochloric acid, and partially evaporated. The suspension is extracted with ethyl acetate (4 x 10 ml), the organic extract washed with water (2 x 10 ml), and dried with sodium sulfate. The solvent is evaporated and the residue recrystallized from aqueous ethanol to give 7, yield 0.411 g (94%); m.p. 40°C (Lit., m.p. 40°C); b.p. 160°C/5 torr.

7. I.R. (neat): $\nu = 3550$-2600, 1710 cm$^{-1}$ (COOH).

8. $^1$H-N.M.R. (CDCl$_3$) $\delta = 10.90$ (bs, 1H, COOH); 6.93 (m, 4H$_{\text{ax}}$), 3.87 (s, 3H, OCO$_3$H$_7$), 2.68 (t, $J = 6$ Hz, 2H, CH$_2$-COOH); 2.32 (t, $J = 6$ Hz, 2H, Ar-C=CH$_2$); 1.90 ppm (m, 2H, CH$_2$-COOCH$_3$).

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