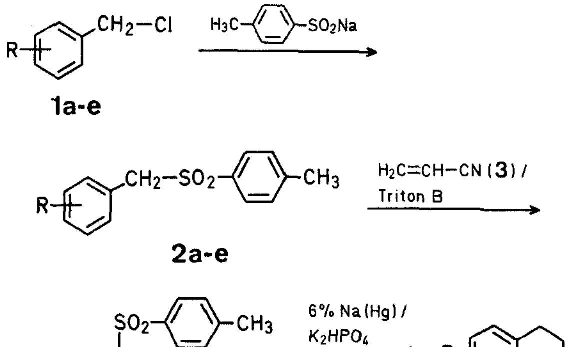
Synthesis of 4-Arylbutanenitriles[1]

Ignacio H. Sánchez*, María Antonieta Aguilar

Departamento de Química Orgánica, División de Estudios de Posgrado, Facultad de Química, Universidad Nacional Autónoma de México, México 20, D. F., México

4-Arylbutanenitriles are valuable intermediates for the preparation, via hydrolysis to the corresponding butanoic acids and subsequent cyclization[2,3], of substituted tetralones. However, the synthetic methods presently available are either too long[4] or require conditions so rigorous as to be incompatible with other functionalities in the molecule[5] or even have the necessity of certain electron-withdrawing substituents[6]. We have thus developed a simple and versatile method for the preparation of substituted 4-arylbutanenitriles **5** based on the reductive desulfonylation[7] of α-cyanoethylated-benzyl-4-tolylsulfones of type **4**, as shown in the Scheme.



1,2,4,5	a	b	c	d	e
R	2-H$_3$CO	4-H$_3$CO	3,4-O—CH$_2$—O—	4-O$_2$N	H

The required sulfones **2** are easily prepared[8] by heating together the corresponding benzyl chlorides[9] **1** with a slight excess of sodium 4-toluenesulfinate monohydrate[10] 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[11], the reductive desulfonylation (**4**→**5**) requires the use of methanolic 6% sodium amalgam[12-15] buffered with anhydrous dipotassium hydrogen phosphate[16]. 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[9,17] (**1a**), and yielded upon basic hydrolysis the known[4] 4-(2-methoxyphenyl)-butanoic acid (**8**), m.p. 40 °C.

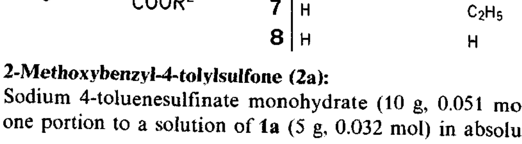


Table. Compounds **2a-e**, **4a-e**, **5a-e**, and **6-8** prepared

Product[a]	Yield [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b] or Lit. m.p. [°C] or b.p. [°C]/torr	
2a	94	93-95°	$C_{15}H_{16}O_3S$	(276.3)
2b	21	114-115°	$C_{15}H_{16}O_3S$	(276.3)
2c	47	126-128°	$C_{15}H_{14}O_4S$	(290.3)
2d	84	189-190°	185-189°[18]	
2e	90	145-146°	144-145°[19]	
4a	92	139-140°	$C_{18}H_{19}NO_3S$	(329.4)
4b	57	116-118°	$C_{18}H_{19}NO_3S$	(329.4)
4c	78	120-122°	$C_{18}H_{17}NO_4S$	(343.4)
4d	83	180-182°	$C_{17}H_{16}N_2O_4S$	(344.4)
4e	94	107-108°	$C_{17}H_{17}NO_2S$	(299.4)
5a	94	146-148°/12	145-155°/12-14[4]	
5b	91	oil	$C_{11}H_{13}NO$	(175.2)
5c	79	oil	$C_{11}H_{11}NO_2$	(189.2)
5d	10	oil	169-173°/6[6]	
5d′	84	oil	$C_{10}H_{12}N_2$	(160.2)
5e	62	130-131°/10	142-145/16[20]	
6	63	96-97°	$C_{19}H_{22}O_5S$	(362.4)
7	80	oil	$C_{13}H_{18}O_3$	(222.2)
8	94	40°	40°[4]	

[a] The ^{1}H-N.M.R. and I.R. spectra were in accord with the proposed structures.

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

2-Methoxybenzyl-4-tolylsulfone (2a):

Sodium 4-toluenesulfinate monohydrate (10 g, 0.051 mol) is added in one portion to a solution of **1a** (5 g, 0.032 mol) in absolute ethanol (20 ml) 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 gives **2a**; yield: 8.24 g (94%); m.p. 93-95 °C.

$C_{15}H_{16}O_3S$	calc.	C 65.21	H 5.84	S 11.60
(276.3)	found	65.23	5.80	11.71

I.R. (KBr): $\nu = 1313, 1135\ \text{cm}^{-1}$ (SO_2).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.51$ (d, $J = 8$ Hz, $2H_{arom}$); 7.21 (d, $J = 8$ Hz, $2H_{arom}$); 6.82 (m, $4H_{arom}$); 4.41 (s, 2H, Ar—C$\underline{H}_2$); 3.35 (s, 3H, Ar—OC$\underline{H}_3$); 2.38 ppm (s, 3H, Ar—C$\underline{H}_3$).

α-(2-Cyanoethyl)-2-methoxybenzyl-4-tolylsulfone (4a):

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 freshly distilled acrylonitrile (**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 × 20 ml), the organic extract is washed with water (2 × 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.

$C_{18}H_{19}O_3NS$	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): $\nu = 2240$ (CN), 1320, 1140 cm^{-1} (SO_2).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.30$ (d, $J = 8$ Hz, $2H_{arom}$); 7.00 (d, $J = 8$ Hz, $2H_{arom}$); 6.63 (m, $4H_{arom}$); 4.8 (m, 1H, Ar—C$\underline{H}$—); 3.36 (s, 3H, Ar—OC$\underline{H}_3$); 2.7 [m, 4H, (C$\underline{H}_2$)$_2$—CN]; 2.35 ppm (s, 3H, Ar—C$\underline{H}_3$).

4-(2-Methoxyphenyl)-butanenitrile (5a):

A solution of **3a** (0.6 g, 0.002 mol) and anhydrous dipotassium hydrogen phosphate (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 × 15 ml), the organic extract is washed with water (2 × 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; yield: 0.298 g (94%); b.p. 146-148 °C/12 torr (Lit.[4], b.p. 145-155 °C/12-14 torr).

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I.R. (neat): $\nu = 2240\ cm^{-1}$ (CN).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.03$ (m, $4\,H_{arom}$); 3.81 (s, 3H, $Ar-OC\underline{H}_3$); 2.30 ppm [m, 6H, $(C\underline{H}_2)_3$].

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-Methoxycarbonyl-1-(2-methoxyphenyl)-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 freshly 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 × 20 ml), the organic extract washed with water (2 × 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.

$C_{19}H_{22}O_5S$	calc.	C 62.96	H 6.11	S 8.84
(362.4)	found	63.03	6.15	8.87

I.R. (KBr): $\nu = 1740$ ($COOCH_3$), 1310, 1140 cm^{-1} (SO_2).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.32$ (d, $J = 8$ Hz, $2\,H_{arom}$); 7.01 (d, $J = 8$ Hz, $2\,H_{arom}$); 6.6 (m, $4\,H_{arom}$); 4.8 (m, 1H, $Ar-C\underline{H}$); 3.56 (s, 3H, $Ar-OC\underline{H}_3$); 3.36 (s, 3H, $COOC\underline{H}_3$); 2.5 [m, 4H, $(C\underline{H}_2)_2-COOCH_3$]; 2.36 ppm (s, 3H, $Ar-C\underline{H}_3$).

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 × 15 ml), the organic extract washed with water (2 × 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 (80%).

$C_{13}H_{18}O_3$	calc.	C 70.24	H 8.16
(222.2)	found	70.31	8.22

I.R. (neat): $\nu = 1740\ cm^{-1}$ ($COOC_2H_5$).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.0$ (m, $4\,H_{arom}$); 3.80 (s, 3H, $Ar-OC\underline{H}_3$); 4.11 (q, $J = 6$ Hz, 2H, $COOC\underline{H}_2CH_3$); 2.24 [m, 6H, $(C\underline{H}_2)_3$]; 1.25 ppm (t, $J = 6$ Hz, 3H, $COOCH_2C\underline{H}_3$).

4-(2-Methoxyphenyl)-butanoic Acid (8):
To a solution of **7** (0.5 g, 0.002 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 × 10 ml), the organic extract washed with water (2 × 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.[4] m.p. 40 °C); b.p. 160 °C/3 torr.

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

^{1}H-N.M.R. ($CDCl_3$): $\delta = 10.90$ (bs, 1H, $COO\underline{H}$); 6.93 (m, $4\,H_{arom}$); 3.87 (s, 3H, $OC\underline{H}_3$); 2.68 (t, $J = 6$ Hz, 2H, $C\underline{H}_2-COOH$); 2.32 (t, $J = 6$ Hz, 2H, $Ar-C\underline{H}_2$); 1.90 ppm (m, 2H, $CH_2-C\underline{H}_2-CH_2$).

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