Synthesis of (±)-3-Amino-2-(4-chlorophenyl)propanesulfonic acid (Saclofen)

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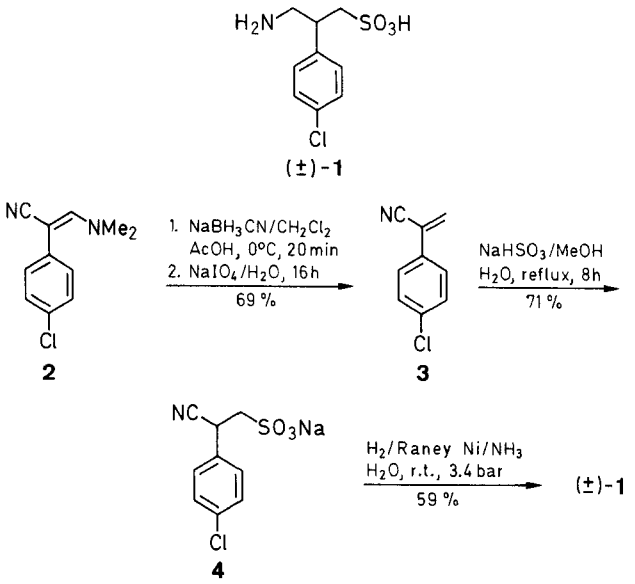
An efficient synthesis of saclofen, a putative $GABA_B$ antagonist, is reported.

Saclofen (3-amino-2-(4-chlorophenyl)propanesulfonic acid, **1**) has been described as a competitive antagonist of the $GABA_B$ receptor.[1] Our interest in this area[2] and our desire to subject **1** to pharmacological evaluation prompted us to develop a synthetic route to **1**. The preparation of this putative antagonist has not been disclosed. Herein we present an efficient synthesis of **1** which could be carried out on a multigram scale.



(*E*)-2-(4-Chlorophenyl)-3-dimethylamino-2-propenenitrile (**2**) was prepared according to Chiefari et al.,[3] from the reaction of 4-chlorophenylacetonitrile with dimethylformamide dimethyl acetal. However, transformation of **2** to 2-(4-chlorophenyl)-2-propenenitrile (**3**) could not be reproduced as described[3] and a modified one-pot procedure for the conversion of **2** to **3** was devised. Thus, 1,4-reduction of nitrile **2** with sodium cyanoborohydride in acetic acid followed by in situ oxidation with sodium periodate and elimination of the intermediate amine oxide at room temperature furnished the reactive Michael acceptor **3** in 69% yield. Nitrile **3** was purified by chromatography and used immediately in the subsequent transformation. Thus the nitrile **3** was formed in a two-step sequence from 4-chlorophenylacetonitrile in an overall yield of 50%. Other methods of preparing α-methylene benzeneacetonitriles in less steps have been described[4-7] but these generally give a mixture of regioisomers and/or low yields (< 50%). Conjugate addition of **3** with sodium bisulfite in refluxing aqueous methanol provided sodium 2-(4-chlorophenyl)-2-cyanoethylsulfonate (**4**) in 71% yield.[8] Hydrogenation of **4** using Raney nickel as catalyst in dilute aqueous ammonium hydroxide solution, followed by filtration, and neutralization with aqueous hydrochloric acid gave saclofen **1** in 59% yield (28% overall from **2**) as a white powder.

2-(4-Chlorophenyl)-2-propenenitrile (3):
To a solution of **2** (5.4 g, 26.2 mmol) in CH_2Cl_2 (8 mL) is added AcOH (90 mL). The mixture is cooled to 0°C (ice-water bath) and solid $NaBH_4CN$ (2.0 g, 31.7 mmol) is added portionwise over a period of ~ 5 min. After further stirring for 15 min, H_2O (50 mL) and $NaIO_4$ (12.3 g, 57.5 mmol) are added. The whole mixture is slowly warmed to r.t. and stirred for 16 h. TLC (silica gel, 20% EtOAc in hexanes) analysis shows a UV sensitive spot at R_f ~ 0.4. Water (200 mL) is added and the whole mixture is extracted with Et_2O (2 × 150 mL). The combined Et_2O extracts are washed with cold 1N NaOH (3 × 150 mL) and brine (150 mL). Drying (Na_2SO_4) and removal of solvent yield a pale yellow residue. Chromatography over silica gel and eluting with [petroleum ether (bp 40–60°C)/Et_2O, (4:1)] gives **3**; yield: 3.0 g (69%).

MS (70 eV): m/z = 163 (M^+)

^{1}H-NMR ($CDCl_3$): δ = 6.12 (s, 1H, CH'H), 6.32 (s, 1H, CH'H), 7.40 (d, 2H_{arom}, J = 8.0 Hz), 7.56 (d, 2H_{arom}, J = 8.0 Hz).

Sodium 2-(4-Chlorophenyl)-2-cyanoethylsulfonate (4):
A mixture of **3** (3.0 g, 18.3 mmol) and $NaHSO_3$ (1.7 g, 9.0 mmol) in 70% aq MeOH (70 mL) is refluxed for 8 h. Removal of solvent and recrystallization from 96% EtOH provides **4** as a white microcrystalline solid; yield: 3.5 g (71%); mp > 280°C (dec).

$C_9H_7ClNO_3SNa$	calc.	C 40.38	H 2.64	N 5.23
(267.7)	found	40.43	2.43	5.19

MS (FAB−): m/z (244, M-Na).

^{1}H-NMR (D_2O): δ = 3.35 (dd, 1H, J = 14.2, 4.9 Hz, CH'H), 3.58 (dd, 1H, J = 14.2, 9.5 Hz, CH'H), 4.52 (dd, 1H, J = 9.5, 4.9 Hz, CH), 7.45 (s, 5H_{arom}).

(±)-3-Amino-2-(4-chlorophenyl)propanesulfonic Acid (1):
A mixture of **4** (1.6 g, 6.0 mmol) and Raney nickel (~ 500 mg) in 6% aq NH_3 (50 mL) is hydrogenated at 3.4 bars and at r.t. (~ 2 h). The mixture is filtered and solvent removed. The residue is dissolved in H_2O (20 mL), acidified with 1N HCl (15 mL) and concentrated to dryness. Ice-cold H_2O (10 mL) is added and the mixture is filtered. The white solid collected is washed with cold H_2O (2 × 3 mL) and dried to give **1**; yield: 880 mg (59%); mp > 320°C.

$C_9H_{12}ClNO_3S$	calc.	C 43.29	H 4.84	N 5.61
(249.7)	found	43.35	4.86	5.31

MS (FAB+): m/z = (250, M + 1)
(FAB−): m/z = (248, M − 1)

^{1}H-NMR (D_2O): δ = 3.20–3.70 (m, 5H, CH_2, CH_2, CH), 7.40 (d, 2H_{arom}, J = 8.0 Hz), 7.50 (d, 2H_{arom}), J = 8.0 Hz).

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