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AN EFFICIENT SYNTHESIS OF (±)-4-AMINO-3-(4-CHLOROPHENYL)-BUTYRIC ACID. (BACLOFEN).

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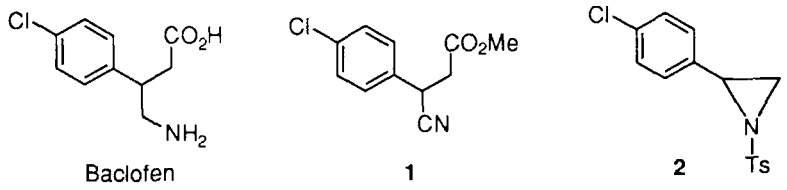
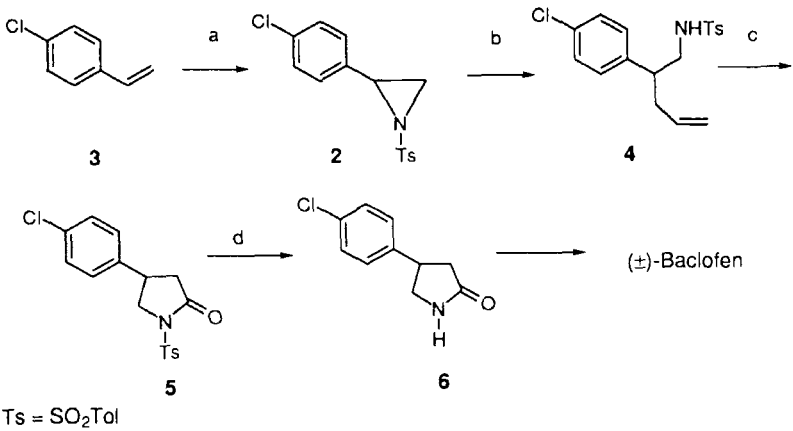
Summary: A new preparation of baclofen is proposed. The key step involved a regioselective ring opening of 2-phenylaziridine with allylmagnesium bromide. Further oxydation of the side chain give access to 4-phenyl-pyrrolidin-2-one and to baclofen.

(±)-Baclofen is a lipophilic analogue of GABA (γ-aminobutyric acid), which has been introduced several years ago as an antispastic agent.[1] In the early patent literature (±)-baclofen was obtained via a catalytic reductive hydrogenation of nitrile **1** (Scheme 1).[2] As we were embarked on a structure-activity study devoted to baclofen, we made use of this reported procedure for the preparation of analogues of baclofen.[3] But it appeared that in some cases, specially when two or more chlorine atomes were attached to the phenyl ring, partial hydrogenolysis of chlorine occurred, rendering tedious the final purification step. To avoid this complication, we explored a different route starting from N-tosyl-2-phenylaziridine (**2**) (Scheme 1).

Aziridines as latent primary amines, are versatile intermediates for the synthesis of compounds bearing nitrogen functionnality.[4] Furthermore in a pioneer work,



Scheme 1



Reagents: a.PhI=NTs, $Cu(aca)_2$, 70%; b. allylMgBr, Et_2O, 0°C, 90%; c. i.$NaIO_4$, $RuCl_3$, ii. CH_2N_2 Et_2O, 65%; d. Na-Naphtalene, THF, 70%; e. HCl 6N, 70%.

Scheme 2

Kozikowski has shown that Grignard reagents opened phenylaziridines in a regio-selective way.[5] Herein we report our results on the synthesis of baclofen starting from 2-(p-chlorophenyl)-aziridine **2** (Scheme 2).

Aziridine **2** was obtained, as a crystalline solid in 70% yield from the commercially available styrene **3,** using the copper catalysed aziridination recently described by Evans[6,7]. Excess allymagnesium bromide (4 eq.) caused ring oppening of aziridine **2**, the allyl transfer occured exclusively at the benzylic carbon and furnished adduct **4** in 91% yield. During this reaction the excess of

Grignard reagent is functioning as Lewis acid. Thus the terminal double bond in **4** was oxidized under Sharpless conditions[8] to a transient acid, which upon treatment with etheral diazomethane gave after spontaneous cyclization, lactame **5** in 65% overall yield (3 steps). It has to be mentioned that attempts to open directly aziridine **2** with the anion deriving from tert-butyl acetate, gave a complexe mixture without any trace of the desired adduct, instead reductive opening of the aziridine was the major product. The tosyl group was removed using sodium naphtalenide to yield the known lactame **6**.[9,10] Finally acidic hydrolysis of **6** afforded (±)-baclofen as hydrochloride.

As several substituted styrenes are commercially available, our synthesis provides a convenient access to not only baclofen but also to various analogues. Finally as homochiral aziridines are accessible,[11] our synthesis of baclofen can be rendered enantioselective, this is of importance because (-)-(*R*)-baclofen is the pharmacological active enantiomer.[12]

Experimental

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker AC 200 at 200 MHz and 50 MHz respectively. The melting points were measured in open capilary tubes using an Gallenkampf apparatus, and are uncorrected. Purification and separations by column chromatography were performed on silica gel, using flash chromatography. Ether and THF were distilled from sodium ketyl under argon. Tlc visualization was achieved by spraying with 2% ethanolic phosphonomolybdic acid and charring. 4-Chlorostyrene was purchased from Lancaster.

N-p-Toluenesulfonyl-2-(p-chlorophenyl)-aziridine **2**.

To a stirred suspension of N-(p-toluenesulfonyl)-imino-phenyliodinane[7] (2 g, 5.36 mmol) and $Cu(aca)_2$ (140 mg, 0.536: 10 mol %) in acetonitrile (7 mL) was added dropwise p-chlorostyrene (2.95 g, 21.44 mmol) at 0°C. The mixture was stirred for 48 h at room temperature. The mixture was concentreted under reduced pressure. Ice (15 g) and ammonium hydroxyde (28% in H_2O, 5 mL) were added to the oily residue and the mixture was stirred for 15 min. The resulting mixture was extracted with CH_2Cl_2, the extract was washed with brine and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by flash

chromatography over silica gel with hexane-ethylacetate (10 : 1) gave a crystalline residue. Recrystallization from hexane-AcOEt gave the title compound **2** as colorless crystals (1.15 g, 70 %), m.p. 113°C.

^{1}H NMR ($CDCl_3$) δ 2.35 (d, J = 4.3 Hz, 1H), 2.44 (s, 3 H), 2.98 (d, J = 7.0 Hz, 1 H), 3.74 (dd, J = 7.0 and 4.3 Hz, 1 H), 7.10-7.40 (m, 6 H), 7.80-7.90 (m, 2 H); ^{13}C ($CDCl_3$) δ 21.5, 35.9; 40.2; 122.9; 128.7; 129.7; 133.6; 134.6; 134.1; 134.8; 144.7. Anal. calcd for $C_{15}H_{14}NClO_2S$: C, 58.53; H, 4.58; N, 4.54. Found C, 58.4; H, 4.4; N, 4.4.

2-(p-Chlorophenyl)-N-(p-toluenesulfonyl)-pent-4-en-1-amine **4**.

To a stirred solution of the aziridine **2** (176 mg, 0.57 mmol) in dry THF (4 mL) was added dropwise at 0°C by syringe allylmagnesium bromide (4 mL of a 0.6 M solution in Et_2O), and the mixture was stirred at room tempertaure for 1 h. The mixture was quenched with saturated ammonium chloride, and extracted with Et_2O.The extract was washed with water and dried over Na_2SO_4. Concentration under reduced pressure followed by flash chromatography on silica gel (hexane-EtOAc: 3/1) gave a crystalline residue. Recrystallisation from hexane gave the title compound **4** (180 mg, 91 %) as colorless crystals m.p. 93°C.

^{1}H NMR ($CDCl_3$) δ 2.25-2.40 (m, 2 H), 2.44 (s, 3 H), 2.70-2.85 (m, 1 H), 2.98 (ddd, J = 12.5, 8.9 and 5.2 Hz, 1 H), 3.28 (ddd, J = 12.5, 7.5 and 5.5 Hz, 1 H), 4.42 (dd, J = 7.5 and 5.0 Hz, 1 H), 4.75-5.03 (m, 2 H), 5.45-5.67 (m, 1 H), 6.94-7.00 (m, 2 H), 7.18-7.30 (m, 4 H), 7.61-7.65 (m, 2 H); ^{13}C ($CDCl_3$) δ 21.4, 37.7, 44.7; 47.6, 117.2; 126.9, 128.8, 129.0, 129.2, 129.6, 134.9, 136.7, 139.5, 143.4.

Anal. Calcd for $C_{19}H_{20}O_2SClN$: C, 61.79; H, 5.76; N, 4.00. Found C, 61.7; H, 5.9; N, 3.9.

N-Tosyl-4-(p-chlorophenyl)-pyrrolidin-2-one **5**.

To a mixture of **4** (1.04 g, 3 mmol), CCl_4 (6 mL), MeCN (6 mL), and water (9 mL) was added successively $NaIO_4$ (5.65 g, 26.4 mmol) and $RuCl_3.H_2O$ (0.132 mmol) with vigorous stirring at room temperature for 3h. The mixture was made acidic with aqueous HCl (5%) at 0°C, and Na_2SO_3 (10 g) was added in portions with stirring. The mixture was extracted with CH_2Cl_2 and the extracts were washed with water, dried over Na_2SO_4. The organic phase was removed *in vacuo* and the residue taken up in Et_2O, and treated with an etheral solution of diazomethane. After removal of the solvent in *vacuo*, the obtained oil was purified

using silica gel chromatography (hexane-Et_2O: 4/1) to yield the lactam as colorless needles (70%), m.p. 105°C.

^1H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 2.56 (dd, J = 17.2 and 8.9 Hz, 1 H), 2.85 (dd, J = 17.2 and 8.3 Hz, 1H), 3.42 (m, 1 H), 3.76 (dd, J = 9.8 and 7.6 Hz, 1 H), 4.32 (dd, J = 9.8 and 8.0 Hz, 1 H), 7.04-7.11 (m, 2 H), 7.25-7.38 (m, 2 H), 7.90-7.96 (m, 2 H); ^{13}C ($CDCl_3$) δ 21.5; 36.4, 39.2, 53.3, 127.7, 127.9, 129.5, 129.9.

Anal. Calcd for $C_{17}H_{16}O_3SClN$;C, 58.36; H, 4.61; N, 4.00. Found C, 58.4; H, 4.7; N, 3.9.

4-(4'-Chlorophenyl)-2-pyrrolidinone. **6.**

Sodium naphtalenide was prepared in THF (10 mL) from sodium (230 mg, 10 mmol) and naphtalene (1.28 g, 10 mmol). To a solution of lactame **5** (240 mg, 0.7 mmol) in dry THF (5 ml) was added dropwise the sodium naphtalenide solution untill the persistance of the blue color. The mixture was stirred at -78°C untill no starting material was apparent on Tlc analysis. The mixture was quenched with aqueous NH_4Cl and diluted with AcOEt. The organic layer was washed with water, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with AcOEt to yield **6** (95 mg, 70%) as a white solid, m.p.115°C, (lit [8,9] m.p. 118°C).

^1H NMR ($CDCl_3$) δ 2.39-2.81 (ddd, J = 8.4, 8.7 and 16.8 Hz, 2H), 3.35-3.42 (m, 1H), 3.60-3.84 (m, 2H), 7.14-7.36 (m, 4H).

(±)-*Baclofen, hydrochloryde.*

A mixture of **6** (98 mg, 0.5 mmol) in aqueous HCl (6 N, 1 mL) was heated at 100°C during 12 h . The solvent was removed in vacuo and the residue was obtained crystalline after trituration in isopropanol to yield baclofen (87 mg, 70%), m.p. 195°C, (lit [2] m.p. 195°C)

^1H-NMR (DMSO d6) δ 2.65-2.91 (AB part from ABX, J_{AB} = 16.6 Hz, J_{AX} = 6.9 Hz, J_{BX} = 7.7 Hz, 2H), 3.10-3.39 (AB part from ABX, J_{AB},= 12.8 Hz, J_{AX} = 6.0 Hz, J_{BX} = 8.9 Hz, 2H), 3.64-3.72 (m, 1H), 7.41-7.43 (m, 4H).

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