This article was downloaded by: [University of Arizona]
On: 06 May 2013, At: 03:30
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Simple and Efficient New Approach to the Total Synthesis of (±)-4-Amino-3-(4-Chlorophenyl)-Butyric Acid (BACLOFEN)

Fernando Coelho [a], Mariangela B. M. de Azevedo [a], Roberta Boschiero [a] & Patrícia Resende [a]
[a] UNICAMP - Instituto de Química, Depto. de Química Orgânica, P.O. Box 6154, 13083-970, Campinas, SP, BRAZIL
Published online: 21 Aug 2006.

To cite this article: Fernando Coelho , Mariangela B. M. de Azevedo , Roberta Boschiero & Patrícia Resende (1997): A Simple and Efficient New Approach to the Total Synthesis of (±)-4-Amino-3-(4-Chlorophenyl)-Butyric Acid (BACLOFEN), Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:14, 2455-2465

To link to this article: http://dx.doi.org/10.1080/00397919708004109

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Downloaded by [University of Arizona] at 03:30 06 May 2013

SYNTHETIC COMMUNICATIONS, 27(14), 2455-2465 (1997)

A SIMPLE AND EFFICIENT NEW APPROACH TO THE TOTAL SYNTHESIS OF (±)-4-AMINO-3-(4-CHLOROPHENYL)-BUTYRIC ACID (BACLOFEN)

Fernando Coelho* , Mariangela B. M. de Azevedo, Roberta Boschiero and Patrícia Resende

UNICAMP - Instituto de Química/Depto. de Química Orgânica
P.O. Box 6154 - 13083-970 - Campinas, SP - BRAZIL

Downloaded by [University of Arizona] at 03:30 06 May 2013

ABSTRACT: Based on the utilization of a [2+2] cycloaddition reaction between dichloroketene and an appropriated olefin as a key step, we describe a new and simple four step approach to the total synthesis of (±)-4-amino-3-(4-chlorophenyl)-butyric acid (BACLOFEN), a selective $GABA_B$ agonist used as antispastic agent

The inhibitory neurotransmitter γ-aminobutyric acid (GABA) has two major receptor subtypes ($GABA_A$ and $GABA_B$)[1-2], which apparently play an important part in the central and peripheral nervous system through ion-channel regulation[3]. The overall physiological effects are transmission inhibitions mediated pre- and post-synaptically by the $GABA_A$ sites and presynaptically by the $GABA_B$ sites[4]. For instance, the $GABA_B$ receptor in the peripheral and central nervous

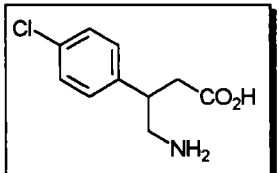
* author to whom correspondence should be addressed (e-mail: coelho@iqm.unicamp.br)

Copyright © 1997 by Marcel Dekker, Inc.

system is implicated in analgesia muscle relaxation, hypertension, increased gastric motility, and inhibition of the release of corticotropin releasing hormone[5].

During the last decade a number of specific agonists or antagonists at the $GABA_A$ receptor site have been developed[2,6]. In contrast there are only a few examples of those acting at $GABA_B$ receptor site. Among the latter, 4-amino-3-(4-chlorophenyl)-butyric acid (**1**, figure 1) (Baclofen) is the only selective and therapeutically useful $GABA_B$ agonist known[7a-c]. Baclofen is a GABA analog, but, unlike GABA, it can cross the blood/brain barrier. Racemic Baclofen (Lioresal®) is used in the treatment of spasticity caused by disease of the spinal cord, particularly traumatic lesions.

FIG.1: Baclofen



Baclofen (1)

Due to its biological and pharmacological importance, there are several reports in the literature concerning the total synthesis of Baclofen[8a-d, 9a-d]. We report herein a new approach to the total synthesis of **1**, using as key step a [2+2] cycloaddition [10,11] reaction between dichloroketene and an adequately substituted olefin.

Downloaded by [University of Arizona] at 03:30 06 May 2013

Cycloadduct **2** was obtained as the only detectable regiosomer, by the reaction between *in situ* generated dichloroketene and commercial 4-chlorostyrene in 82% yield (Scheme 1). Reductive dechlorination of **2** in acetic acid/Zn dust furnished the cyclobutanone derivative **3** in 92% yield. The preparation of the Baclofen lactam **4** was easily accomplished, in 43% yield, by the expansion of the cyclobutanone ring *via* a Beckmann rearrangement, using as nitrogen source the N-hydroxylamine-O-sulphonic acid[12]. The acid hydrolysis of lactam **4** furnished Baclofen (**1**) as a white solid in 70% yield.

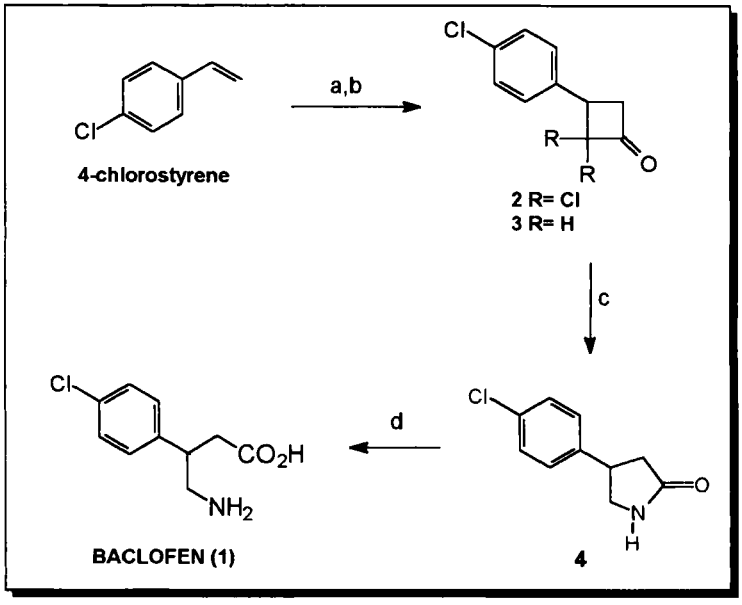
In conclusion, this reaction sequence provides a facile access to (±)-**1** in 4 steps from an easily available and cheap commercial starting material in 22% overall yield. As several substituted styrenes are commercially available or could be easily prepared[14], this approach should provide a convenient access not only to baclofen but also to various analogs. Generalizations and modifications aiming at an asymmetric version of this methodology is ongoing.

Downloaded by [University of Arizona] at 03:30 06 May 2013

EXPERIMENTAL

General: The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian GEMINI BB-300 at 300MHz and 75.1 MHz respectively. The mass spectra were recorded on CG/MS HP model 5988A. The melting points were measured

SCHEME 1



Reagents and conditions: a: Cl_3CCOCl, Zn-Cu, $POCl_3$, ether, reflux, 20 h, 82%; b: Zn/CH_3CO_2H, 70°C, 14 h, 93%; c: H_2NOSO_3H, HCO_2H 98%, reflux, 10 h, 43%; d. HCl, reflux, 12 h, 70%..

in open capilary tubes using an Electrothermal apparatus model 9100, and are uncorrected. Purification and separations by column chromatography were performed on silica gel, using flash chromatography. Ether and THF were distilled from benzophenone ketyl under nitrogen. Trichloroacetyl chloride and phosphorus oxychloride (both Aldrich) were distilled before use. Tlc visualization was achieved by spraying with 5% ethanolic phosphomolybdic acid

Downloaded by [University of Arizona] at 03:30 06 May 2013

and heating. 4-Chlorostyrene was purchased from Aldrich and used without purification.

(RS)-2,2-dichloro-3-(4'-chlorophenyl)-cyclobutanone **2**

To a stirred suspension of Zn-Cu[15] (3.10 g, 45.48 mmol) and 4-chlorostyrene (3.00 g, 21.66 mmol) in dry ether (44 mL) was added dropwise, during 1 hr at room temperature, a solution of phosphorus oxychloride (4.98 g, 3,03 mL, 32,49 mmol) and trichloroacetyl chloride (5,90 g, 3,63 mL, 32.49 mmol) in dry ether (22 mL). The suspension was stirred for 20 h at room temperature. The mixture was filtered through a pad of celite and washings were performed with hexane (100 mL). The filtrate was concentrated to one third of the original volume under reduced pressure. The residue was diluted with hexane (100 mL) and again concentrated to one third. This operation was repeated twice more. The final concentrate (~ 150 mL) was washed with cold water (200 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL) and was dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by flash chromatography on silica gel with hexane-ethyl acetate (8 : 2) gave a solid residue. Recrystallization from dichloromethane gave dichlorocyclobutanone **2** as a white solid (4.42 g, 82%).

m.p. 73-75°C.

IR (KBr, λ_{max}): 2928, 1812, 1493, 1403, 1094, 1014, 827 cm^{-1}.

Downloaded by [University of Arizona] at 03:30 06 May 2013

MS (70eV, m/e): 250 (M^+ + 2), 248 (M^+), 208, 206, 138.

^{1}H NMR (300MHz, $CDCl_3$) δ 3.51-3.73 (m, 2H), 4.21 (t, J= 10.2Hz, 1H), 7.17-7.43 (dd, J= 8.4 and 8.8Hz, 4H).

^{13}C NMR (75.1MHz, $CDCl_3$) δ 29.8, 46.0, 50.2, 129.4, 129.9, 192.2

Anal. calcd. for $C_{10}H_7Cl_3O$: C, 48.39; H, 2.84. Found C, 48.37; H, 2.83.

(RS)-3-(4'-chlorophenyl)-cyclobutanone **3**

To a stirred solution of **2** (0.472 g, 1.89 mmol) in acetic acid (5 mL) was added Zn dust (0.756 g, 11.63 mmol). The suspension was stirred at room temperature for 14 h. The mixture was diluted with ether (60 mL) and filtered. The solid was washed with ether (50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by flash chromatography on silica gel with hexane-ethyl acetate (9 : 1) gave compound **3** (0.32 g, 93%) as a yellow tinged oil.

IR (neat, λ_{max}): 2924, 1787, 1493, 1378, 1013, 821 cm^{-1}

^{1}H NMR (300MHz, $CDCl_3$) δ 3.16-3.26 (m, 2H), 3.44-3.55 (m, 2H), 3.60-3.69 (m, 1H), 7.21-7.34 (m, 4H).

^{13}C NMR (75.1MHz, $CDCl_3$) δ 27.9, 54.6, 127.9, 128.7, 142.0, 206.0.

MS (70eV, m/e): 180 (M^+), 110, 138, 103, 89, 77.

Anal. calcd. for $C_{10}H_9ClO$: C, 66.65; H, 5.04. Found C, 66.63 ; H, 5.03.

Downloaded by [University of Arizona] at 03:30 06 May 2013

(RS)-4-(4-chlorophenyl)-pyrrolidin-2-one **4**

To a stirred solution of **3** (0.219g, 1.21 mmol) in formic acid 98% (5 mL) was added 0.32g Hydroxylamine-O-sulphonic acid (2.42 mmol). The solution was stirred at reflux for 10 h, cooled to room temperature and dropped into a mixture of saturated NH_4Cl (9 mL) and water (9 mL). The aqueous solution was then extracted with $CHCl_3$ (3 x 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (3 x 30 mL) , brine, and dried over anhydrous sodium sulfate. Concentration under reduced pressure followed by flash chromatography on silica gel with hexane-ethyl acetate (6 : 4) gave compound **4** (0.102 g, 42%) as a white solid.

m.p: 115-116 (literature[8b, 14] 117-118°C)

IR (KBr, λ_{max}): 3420, 3200, 1698, 1493, 1090, 830 cm^{-1};

^1H NMR (300MHz, $CDCl_3$) δ 2.42-2.50 (dd, J= 16.9 and 8.4 Hz, 1H), 2.70-2.79 (dd, J= 16.9 and 8.7Hz, 1H), 3.36-3.41 (dd, J= 9.1 and 6.9 Hz, 1H), 3.62-3.73 (q, J= 8.3 Hz, 1H), 3.73-3.82 (dd, J= 17,5 and 8.5 Hz, 1H), 6.28 (br s, 1H NH), 7.19-7.33 (m, 4H)

^{13}C NMR (75.1MHz, $CDCl_3$) δ 38.2, 40.6, 49.3, 128.1, 129.0, 139.1, 181.0.

MS (70 eV, m/e): 197 (M^+ +2), 195 (M^+), 140, 138

(±)-Baclofen, hydrochloride **1**

A mixture of **4** (0,150 g, 0.769 mmol) in aqueous HCl (6N, 1,5 mL) was

Downloaded by [University of Arizona] at 03:30 06 May 2013

heated at 100°C during 12h. The solvent was removed *in vacuo* and the residue was triturated in isopropanol yielding crystalline baclofen (0,134 g, 70%).

M.p. 195°C (literature[8a] m.p. 195°C)

IR (KBr, λ_{max}): 3000-2500, 1620, 1550, 1490, 1090 cm^{-1}.

^{1}H NMR (300MHz, DMSO-d_6): δ 2.65-2.91 (AB part from ABX, J_{AB} = 16.6 Hz, J_{AX} = 6.9Hz, J_{BX} = 7.7Hz, 2H), 3.10-3.39 (AB part from ABX, J_{AB} = 12.8 Hz, J_{AX} = 6.0Hz, J_{BX} = 8.9 Hz, 2H), 3.64-3.72 (m, 1H), 7.41-7.43 (m, 4H);

ACKNOWLEDGEMENTS: We wish to thank. Dr. Adrian Pohlit for the kind revision of this manuscript. We also would like to thank Profs. Carlos R.D.Correia, Ronaldo A. Pilli, Albert J. Kascheres and Paulo Imamura for some reagents. The authors thank the Brazilian Council for Science Development (CNPq) and FAPESP for financial support.

REFERENCES AND NOTES

1. a) Bowery, N.G., Hudson, A.L. and Price, G.W. *Neuroscience*, **1987**, *20*, 365; b) Nicoll, R.A. *Science*, **1988**, *241*, 545; c) Hill, D.R. and Bowery, N.G. *Nature*, (London), **1981**, *290*, 149.

2. Mann, A., Boulanger, T., Brandau, B., Durant, F., Evrard, G.,

Downloaded by [University of Arizona] at 03:30 06 May 2013

Heaulme, M., Desaules, E. and Wermuth, C.-G. *J. Med. Chem.*, **1991**, *34*, 1307.

3. Bowery, N.G.and Williams, L.G. *Br. J. Pharmacol.*, **1986**, *87*, 37P.

4. Bowery, N.G. *Trends Pharmacol. Sci.*, **1982**, 400.

5. Bowery, N.G., Pratt, G.D. and Knott, C. "$GABA_B$ Receptors in Mammalian Function," Bowery, N.G.; Bittiger, H.; Olpe, H.-R. Eds.; John Wiley and Sons, Chichester, **1990**, p.3.

6. Johnston, G.A.R. Benzodiazepine/GABA receptors and chloride channels. "*Receptor Biochemistry and Methodology*;" Olsen, R.W.; Veuter, J.C. Eds., A.R. Liss, Inc., New York, **1986**, Vol. 5, pp 57-71.

7. a) Kerr, D.I.B. and Ong, J. *Med. Res. Revs.*, **1992**, *12*, 593; b) Berthelot, P., Vaccher, C., Flouquet, N., Debaert, M., Luyckx, M., Brunet, C. *J. Med. Chem.*, **1991**, *34*, 2557; c) Kerr, D.I.B., Ong, J., Doolette, D.J., Abbenante, J. and Prager, R.H. *Eur. J. Pharmacol.*, **1989**, *96*, 239; d) Olpe, H.-R., Demieville, H., Baltzer, V., Bencze, W.L., Koella, W.P., Wolf, P.and Haas, H.L. *Eur. J. Pharmacol.*, **1978**, *52*, 133.

8. For some examples of racemic synthesis of Baclofen and derivatives see: a) Kerberle, H., Faigle, J.W. and Wilhelm, M. Swiss Patent, 499,046, (*Chemical Abstracts*, **1968**, *69*, 106273f); b) Ibuka, T., Schoenfelder, A., Bildstein, P.and Mann, A. *Synth. Commun.*, **1995**, *25*,

Downloaded by [University of Arizona] at 03:30 06 May 2013

1777; c) Pifferi, G., Nizzola, R. and Cristoni, A. *Il Farmaco*, **1994**, *49*, 453 (*Chemical Abstracts*, **1995**, *122*, 204918c); d) Wall, G.M. and Baker, J.K. *J. Med. Chem.*, **1989**, *32*, 1340.

9. For some examples of asymmetric synthesis of (-)-Baclofen and derivatives see: a) Chênevert, R. and Desjardins, M. *Tetrahedron. Lett.*, **1991**, *32*, 4249; Chênevert, R. and Desjardins, M., *Can. J. Chem.*, **1994**, *72*, 2312; b)Herdeis, C. and Hubmann, H.P. *Tetrahedron Asymmetry*, **1992**, *3*, 1213; c) Schoenfelder, A., Mann, A. and Le Coz, S. *Synlett*, **1993**, 63; d) Prager, R.H., Schafer, K., Hamon, D.P.C. and Massy-Westropp, R.A. *Tetrahedron*, **1995**, *51*,11465; e) Yoshifuji, S., Kaname, M., *Chem. Pharm. Bull.*, **1995**, *43*, 1302.

10. Tidwell, T.T., *Ketenes*; Wiley-Insterscience, New York, 1995.

11. For a recent discussion about the mechanism of [2+2] cycloaddition of dichloroketenes see: a) Hyatt, J.A. and Raynolds, P.W. *Org. React.* **1994**, *45*, 159-646; b) Valenti, E., Pericàs, M.A. and Moyano, A. *J. Org. Chem.*, **1990**, *55*, 3582; c). Wang, X. and Houk, K.N. *J. Am. Chem. Soc.*, **1990**, *112*, 1754.

12. a) Olah, G.A. and Fung, A.P. *Synthesis*, **1979**, 537; b) Laurent, A., Jacquault, P., Di Martino, J.-L. and Hamelin, J. *J. Chem Soc. Chem. Commun.*, **1995**, 1101.

13. Brooks, L.A. *J. Am. Chem. Soc.*, **1944**, *66*, 1295.

Downloaded by [University of Arizona] at 03:30 06 May 2013

14. Borka, L. *Acta Pharm. Suec.*, **1979**, *16*, 345 (*Chemical Abstracts*, **1980**, *92*, 82536r)

15. a) Staudinger, H. *Chem. Ber.*, **1905**, *38*, 1735; b) Smith, C.W., Norton, D.G. *Organic-Synthesis, Coll. Vol. IV*, **1963**, 348; c) McCaney, C.C., Ward, R.S. *J. Chem. Soc. Perkin Trans I*, **1975**, 1600; d) For the activation of zinc see: Tsuda, K.; Ohki, E.; Nozoe, S. *J Org. Chem.*, **1963**, *28*, 783; e) For the preparation of the couple Zn-Cu see: Brady, W.T.; Liddell, H.G.; Vaughan, W.L. *J. Org. Chem.*, **1966**, *31*, 626.

(Received in the USA 06 February 1997)

Downloaded by [University of Arizona] at 03:30 06 May 2013