



A rigid GABA analog from a [4+3]-cycloaddition

Paitoon Rashatasakhon, Michael Harmata*

Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA

ARTICLE INFO

Article history:

Received 8 February 2009

Revised 17 February 2009

Accepted 17 February 2009

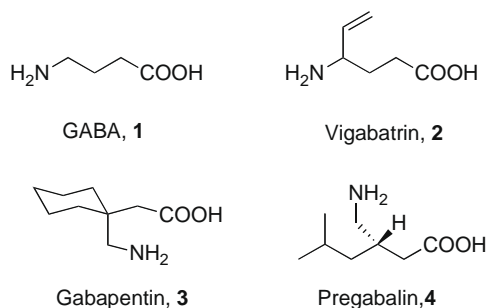
Available online 21 February 2009

ABSTRACT

A rigid GABA analog has been prepared from the adduct obtained from the [4+3]-cycloaddition of pentachloroacetone and a 2-substituted furan.

© 2009 Elsevier Ltd. All rights reserved.

As an extremely important inhibitory neurotransmitter in mammalian central nervous system, *gamma*-aminobutyric acid or GABA (**1**) has captured much attention in pharmacological research.¹ One of the most effective ways to prevent epilepsy is to use GABA analogs to deactivate enzyme that degrades GABA. Several synthetic compounds such as vigabatrin² (**2**), gabapentin³ (**3**), and pregabalin⁴ (**4**) have been used as anticonvulsant drugs. Among the synthetic GABA analogs in the literature, compounds with a restricted conformation are very desirable since the orientation of the two functional groups in three-dimensions is known. They can provide substantial information on active conformations of the neurotransmitter that participate in various processes such as receptor activation, cellular uptake, or enzymatic transamination.⁵ Even with many advances, the design and development of new structurally rigid GABA analogs are still very important.



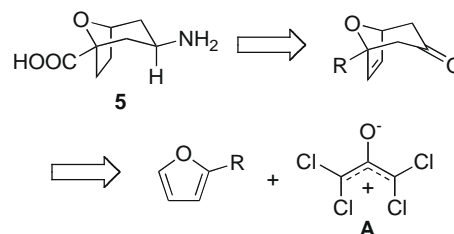
The [4+3] cycloaddition reaction has long been known as a convenient method for the construction of compounds with a seven-membered ring,⁶ especially those with rigid bicyclic frameworks. As part of our continuous research program in the [4+3]-cycloaddi-

tion,⁷ we now wish to demonstrate the utility of this methodology by reporting the synthesis of a new GABA analog (**5**) from an advanced intermediate generated from this reaction.

Our retrosynthetic analysis involved a series of functional group transformations of oxabicyclic ketones derived from cycloaddition between oxyallyl zwitterions **A** and a functionalized furan (Scheme 1).

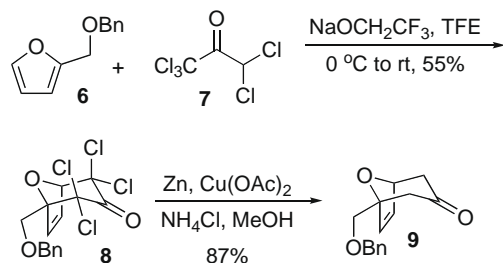
We began the synthesis by treatment of pentachloroacetone (**7**) with 2-substituted furans (Scheme 2) under the conditions developed by Föhlich.⁸ The intermediate oxyallyl zwitterion **A** reacted with electron-rich furans to afford cycloadducts with an oxabicyclic framework in moderate yields. In order to simplify the following protection–deprotection strategies, we decided to pursue the synthesis with 2-(benzyloxymethyl)furan⁹ even though the reaction of 2-(dimethoxymethyl)furan¹⁰ was quite effective. It is worth-mentioning that this reaction with furans bearing an electron-withdrawing group, such as methyl or benzyl furan-2-carboxylate, resulted only in recovery of the starting diene and decomposition of the pentachloroacetone. The reductive dehalogenation of the relatively unstable tetrachloroketone **8** took place smoothly using zinc powder and copper(I) acetate in saturated methanolic ammonium chloride solution, affording **9** in 87% yield.¹¹

With the intermediate **9** in hand, we carried out the functional group manipulation outlined in Scheme 3. A highly stereoselective reduction of ketone **9** was achieved using a bulky borane such as L-

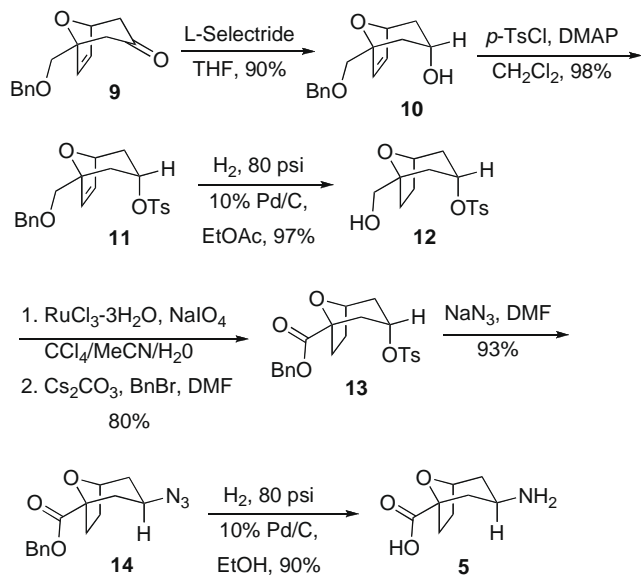


Scheme 1. Retrosynthesis of **5**.

* Corresponding author. Tel.: +1 573 882 1097; fax: +1 573 882 2754.
E-mail address: harmatam@missouri.edu (M. Harmata).



Scheme 2. Synthesis of key [4+3]-cycloadduct.



Scheme 3. Synthesis of 5.

Selectride®. The analysis of the ^1H NMR spectrum of a crude product revealed that a single diastereomer was produced.¹² The hydroxyl group in **10** was subsequently transformed into a *p*-toluenesulfonate ester. A facile removal of the benzyl group and a hydrogenation/hydrogenolysis afforded alcohol **12** in one simple operation.

After extensive screening, it was found that many oxidizing conditions, especially the acidic ones, tended to give low yields in the attempted oxidation of the primary alcohol **12** to the corresponding carboxylic acid. We suspected that protonation of the oxabridge leading to decomposition was responsible for the inefficient reaction. To our delight, we found that the alcohol **12** could be oxidized to a corresponding carboxylic acid in nearly quantitative yield using NaO_4 and RuCl_3 .¹³ The crude product was very clean as characterized by both ^1H and ^{13}C NMR. Transformation of this carboxylic acid into benzyl ester **13** was accomplished by treatment with Cs_2CO_3 and benzyl bromide. Upon heating this with NaN_3 in DMF, the *p*-toluenesulfonate group in **13** was converted into an azide group with inversion of configuration. Finally, hydrogenolysis of the benzyl ester and reduction of the azide were carried out in one-pot to afford γ -amino butyric acid **5** in good yield.¹⁴

In conclusion, we have successfully synthesized a new analog of GABA from a [4+3]-cycloaddition product. This compound has a rigid skeleton with a restricted conformation about the amino and carboxylic acid functional groups. The synthesis should serve as a paradigm for future work, since the asymmetric [4+3]-cycloaddi-

tion is known¹⁵ and a wide variety of structural possibilities exist for the cycloaddition. Moreover, the [4+3]-cycloadducts can possess a variety of functional groups that are subject to elaboration. All of these factors point to an opportunity to make diverse libraries of GABA analogs using this approach. Further results will be reported in due course.

Acknowledgment

This work was supported by the National Science Foundation to which we are grateful.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.113.

References and notes

- (a) Dutar, P.; Nicoll, R. A. *Nature* **1988**, 332, 156; (b) Krogsgaard-Larsen, P. *J. Med. Chem.* **1981**, 24, 1377; (c) Bowery, N. G.; Collins, J. F.; Hudson, A. L.; Neal, M. J. *Cell. Mol. Life Sci.* **1978**, 34, 1193; (d) Krnjevic, K. *Physiol. Rev.* **1974**, 54, 418.
- Lippert, B.; Metcalf, B. W.; Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, 74, 441.
- Gee, N. S.; Brown, J. P.; Dissanayake, V. U. K.; Offord, J.; Thurlow, R.; Woodruff, G. N. *J. Biol. Chem.* **1996**, 271, 5768.
- Miller, R.; Frame, B.; Corrigan, B.; Burger, P.; Bockbrader, H.; Garofalo, E.; Lalonde, R. *Clin. Pharmacol. Ther.* **2003**, 73, 491.
- (a) Krogsgaard-Larsen, P.; Falch, E. *Mol. Cell. Biochem.* **1981**, 38, 129; (b) Wang, Z.; Yuan, H.; Silverman, R. B. *Biochemistry* **2006**, 45, 14513; (c) Lu, H.; Silverman, R. B. *J. Med. Chem.* **2006**, 49, 7404; (d) Yuan, H.; Silverman, R. B. *Bioorg. Med. Chem. Lett.* **2007**, 17, 1651; (e) Wanka, L.; Cabrele, C.; Vanejews, M.; Schreiner, P. R. *Eur. J. Org. Chem.* **2007**, 1474.
- (a) Rigby, J. H.; Pigge, F. C. *Org. React. (N.Y.)* **1997**, 51, 351; (b) Cha, J. K.; Oh, J. *Curr. Org. Chem.* **1998**, 2, 217; (c) Mann, J. *Tetrahedron* **1986**, 42, 4611.
- (a) Harmata, M.; Brackley, J. A., III; Barnes, C. L. *Tetrahedron Lett.* **2006**, 47, 8151; (b) Harmata, M.; Rashatasakhon, P.; Barnes, C. L. *Can. J. Chem.* **2006**, 84, 145; (c) Harmata, M.; Wacharasindhu, S. *Org. Lett.* **2005**, 8, 2563; (d) Harmata, M.; Bohnert, G. L. *Org. Lett.* **2003**, 5, 59; (e) Harmata, M.; Rashatasakhon, P. *Tetrahedron Lett.* **2001**, 42, 5593; (f) Harmata, M.; Rashatasakhon, P. *Synlett* **2000**, 1419; (g) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, 2, 2913.
- (a) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Henle, G. H.; Korfant, H.; Reiner, S.; Föhlich, B. *J. Org. Chem.* **1999**, 64, 3398–3408; (b) *Synthesis of 8*: To a 50 mL round-bottomed flask were placed 6.20 g (26.9 mmol) of pentachloroacetone and 4.61 g (24.5 mmol) of 2-(benzyloxymethyl)furan. The mixture was cooled in an ice bath for 5 min. A 2 M solution of sodium trifluoroethoxide in trifluoroethanol (17 mL) was added via syringe over a period of 30 min and the ice bath was removed. The reaction was stirred at room temperature for 2 h and 40 mL of water was added in order to quench the reaction. The mixture was allowed to settle and the aqueous layer was separated and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using 10:1 hexanes/EtOAc as the eluent. Compound **8** was obtained as white solid in 55% yield. ^1H NMR (250 MHz, CDCl_3) δ 7.38–7.26 (m, 5H), 6.52 (d, $J = 6.0$ Hz, 1H), 6.47 (dd, $J = 6.0, 1.6$ Hz, 1H), 5.24 (d, $J = 1.6$ Hz, 1H), 4.69 (d, $J = 12.0$ Hz, 1H), 4.57 (d, $J = 12.0$ Hz, 1H), 4.26 (d, $J = 12.0$ Hz, 1H), 4.09 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 184.5, 137.2, 135.9, 133.1, 128.4, 127.9, 127.6, 94.2, 87.4, 85.0, 82.1, 73.9, 67.5; IR (KBr) 3108, 3031, 2919, 2874, 1764, 1603, 1491, 1453, 1367, 1095, 928, 874 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{Cl}_5\text{O}_3$: C, 47.15; H, 3.17. Found: C, 47.20; H, 3.23.
- Arjona, O.; Iradier, F.; Manas, R. M.; Plumet, J.; Grabuleda, X.; Jaime, C. *Tetrahedron* **1998**, 54, 9095.
- Gopinath, R.; Jialu Haque, S.; Bhisma, K. P. *J. Org. Chem.* **2002**, 67, 5842.
- Wege, D. *J. Org. Chem.* **1990**, 55, 1667.
- In the reduction using NaBH_4 or LiEt_3H , there were two sets of signals in the ^1H NMR spectra of the crude product which indicated two isomers (*exo* and *endo*). For the carbinol proton, the chemical shift of the *exo* isomer should be more downfield since it is shielded by the olefinic π -system. When L-Selectride ($\text{LiB(s-Bu)}_3\text{H}$) was used, the more downfield carbinol signal completely disappeared.
- Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, 46, 3936.
- Characterization of **5**: ^1H NMR (250 MHz, D_2O) δ 4.51–4.45 (m, 1H), 3.70–3.55 (m, 1H), 2.32 (dd, $J = 12.7, 5.6$ Hz, 1H), 2.20–1.50 (m, 7H); ^{13}C NMR (62.5 MHz, D_2O) δ 179.3, 83.4, 74.4, 43.2, 37.5, 34.4, 31.9, 27.9.
- Harmata, M. *Adv. Synth. Catal.* **2006**, 348, 2297.