Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8905–8907
Tetrahedron Letters

Synthesis of new triazole substituted pyroaminoadipic and pipecolic acid derivatives

Fatimazohra Lenda,[a] Farhate Guenoun,[a] Bouchra Tazi,[b] Najib Ben larbi,[c] Jean Martinez[d] and Frédéric Lamaty[d,*]

[a]*Faculté des Sciences B.P 4010, Beni M'hamed, Meknès, Morocco*
[b]*Ecole Nationale d'Agriculture, Département des Sciences de Base, Meknès, Morocco*
[c]*Faculté des Sciences Dhar El Mehraz, Fès, Morocco*
[d]*Laboratoire des Aminoacides, Peptides et Protéines (LAPP), UMR 5810—CNRS—Universités Montpellier 1 et 2, Place Eugène Bataillon, 34095 Montpellier Cedex 5, France*

Received 28 May 2004; revised 24 September 2004; accepted 28 September 2004

Abstract—Racemic 5-(4,5-substituted-1*H*-1,2,3-triazol-1yl)-pyroaminoadipic and pipecolic acid derivatives were synthesized from *meso* dimethyl-α,α′-dibromoadipate **1** in good yields using mild reaction conditions. The key step of this reaction sequence was the 1,3-dipolar cycloaddition of an acetylenic compound on α-azido-α′-bromoadipate **2**. A reactive α-(substituted-1*H*-1,2,3-triazol-1-yl)-α′- bromoadipate derivative **3a**–**d** was generated and reacted with sodium azide followed by Pd/C-catalyzed hydrogenation to provide lactams **5a**–**d**. The chemoselective reduction of the amide carbonyl group of **5a**–**d** with BH_3 followed by acid hydrolysis provided 5-(4,5-substituted-1*H*-1,2,3-triazol-1-yl) pipecolic acids in racemic form.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

α-Amino acids with heterocyclic side chains have a particular importance in various fields, especially in biochemistry, enzymology and pharmacology.[1–3] Among the heterocyclic substituents which are currently being studied, the 1*H*-1,2,3-triazole heterocyclic entity is an interesting moiety in terms of biological activity. It is found in bioactive compounds such as anti-HIV[4,5] and anti-microbial[6] agents as well as β_3 selective adrenergic receptor agonist.[7] Indeed, the 1,2,3-triazole moiety is present in a number of drugs such as the β lactam antibiotic Tazobactam or the cephalosporine Cefatrizine. Furthermore, only tetrazole substituted pipecolic acids such as LY 233053 (Fig. 1), known for their selective and potent antagonist activity at the NMDA receptor have been prepared.[8] To our knowledge, triazole substituted pipecolic acid derivatives have not been synthesized so far. Few examples in the literature describe 1*H*-1,2,3-triazole-α-amino acids. Also, since the selective discovery of D,L-α-aminoadipic acid as an antagonist of the NMDA receptor,[8] several modified structures were prepared in order to study the structure–activity relationships.[2,9–11]

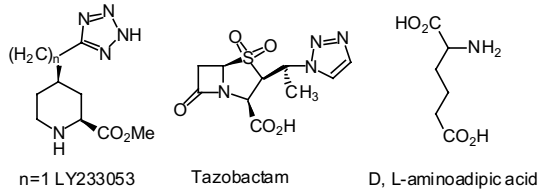
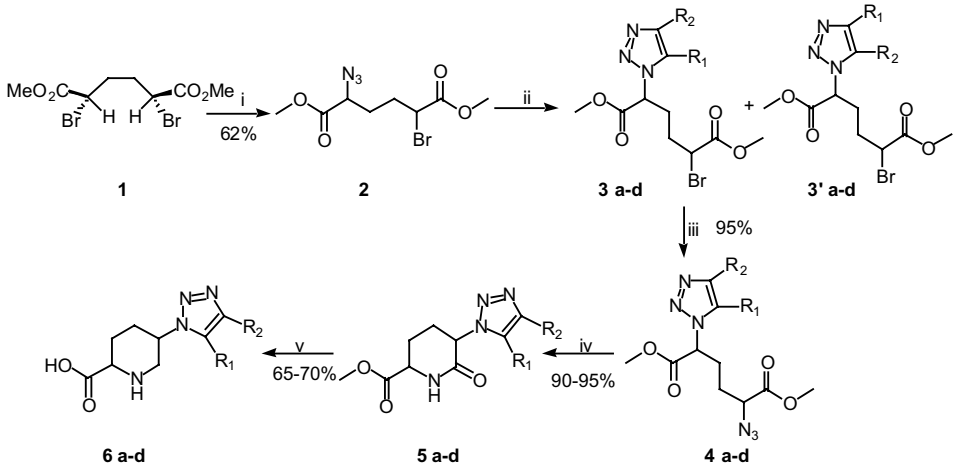


Figure 1.

In order to study the effects of the substituents on α-aminoadipic acid in the neuroexcitatory activity of the acid, we decided to prepare different pyroaminoadipates **5a**–**d**, precursors of δ-substituted aminoadipic acids and also the 5-substituted derivatives of pipecolic acid **6a**–**d**. The substituents we considered were 4,5-substituted-1*H*-1,2,3-triazoles. The synthetic strategy relied on the double substitution of *meso* dimethyl-α,α′-dibromoadipate **1** successively by sodium azide (followed by a 1,3-dipolar cycloaddition with an acetylenic compound) and again by sodium azide (Scheme 1).

* Corresponding author. Tel.: +33 04 67 14 38 47; fax: +33 04 67 14 48 66; e-mail: frederic@univ-montp2.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.166



Scheme 1. Reagents: (i) NaN_3, acetone, RT; (ii) acetylene (see Table 1); (iii) NaN_3, acetone, RT; (iv) 5% Pd/C, MeOH, H_2 (1 atm), RT; (v) (a) $BH_3 \cdot THF$, THF, −10 °C, (b) 6 N HCl, propylene oxide, CH_2Cl_2.

Table 1.

Products **3**, **3′**	R_1	R_2	Reaction time (h)/Temperature	Isolated yield of **3** + **3′** (%)	Ratio of **3**/**3′**
a	CO_2Me	CO_2Me	24/RT[a]	100	–
b	H	CO_2Et	48/RT[a]	90	90/10
c	H	Ph	48/80 °C[b]	80	70/30
d	H	$(CH)OHCH_3$	48/80 °C[b]	90	85/15

[a] The reaction was carried out in the absence of solvent.
[b] Benzene used as solvent.

2. Results and discussion

According to the synthetic approach described in Scheme 1, we initially studied the reaction of an equimolar quantity of sodium azide with *meso* dimethyl-α,α′-dibromoadipate, easily obtained from adipic acid.[12]

This reaction, carried out in acetone in the presence of 1.1 equiv of sodium azide, led mainly to the product of monosubstitution. Formation of the products of disubstitution was also observed, and experimental results showed that the ratio between mono- and di-substituted products depended on the number of equivalents of sodium azide. While successive substitutions of **1** with one nucleophile to make cyclic compounds have been reported,[13–20] we present herein the first examples, to our knowledge, of two successive intermolecular substitutions.

As it was reported by Huisgen et al.[21] the 1,3-dipolar cycloaddition reaction is a well-established and general method for the construction of five-membered ring heterocycles.[22] Particularly, addition of azides to acetylenes has been a method of choice for the synthesis of 1,2,3-triazoles.[23–25] The triazole ring is a system of the aza-pyrrole type and two regioisomers can form at the cycloaddition step. In all cases, we obtained both N-regioisomers, as detected by ^1H NMR spectroscopy. The experimental results showed that the ratio between the 1,4-regioisomer and the 1,5-regioisomer depended upon the acetylene derivative. Table 1 summarizes these results.

The 1,4- and 1,5-regioisomers of α-(4,5-substituted-1*H*-1,2,3-triazol-1-yl)-α′-bromoadipate derivatives **3b–d** and **3′b–d** were separated by column chromatography and were isolated in good yields. When benzene was replaced by toluene as the reaction solvent, the acetylenic reactant was inert towards the α-azido-α′-bromoadipate derivative.

The triazole derivatives **3a–d** were then substituted by reaction of three equivalents of sodium azide in acetone.[26] **4a–d** were obtained in high yields (90–95%). Reduction of **4a–d** by catalytic hydrogenation over Pd/C in methanol,[26] led quantitatively to the corresponding substituted pyroaminoadipic acids **5a–d** via an intramolecular aminolysis. Lactams **5a–d** were selectively reduced with BH_3 in THF at −10 °C[27] and acid hydrolysis (6 N HCl, 60 °C, 12 h) followed by neutralization with propylene oxide yielded the fully deprotected (±)-5(4,5-substituted-1*H*-1,2,3-triazol-1-yl) pipecolic acid derivatives. ^1H NMR showed that in all cases a 1/1 mixture of the two possible diastereoisomers was obtained.

3. Conclusion

The present study describes an efficient synthesis of racemic 5-(4,5-substituted-1*H*-1,2,3-triazol-1-yl) pipecolic acids starting from *meso* dimethyl-α,α′-dibromoadipate. The 4,5-substituted-1*H*-1,2,3-triazol-1-yl were selectively synthesized in position 5 of the piperidine ring by 1,3-dipolar cycloaddition of acetylenic compounds on dimethyl-α-azido-α′-bromoadipate followed by

hydride reduction. Further investigation on the successive substitutions of *meso* dimethyl-α,α′-dibromoadipate **1** to prepare biologically active compounds is currently under investigation in our laboratory.

References and notes

1. (a) Döbler, C.; Kreuzfeld, H. J.; Michalik, M.; Krause, H. W. *Tetrahedron: Asymmetry* **1996**, *7*, 117–125; (b) Schmidt, U.; Weinbrenner, S. *Synthesis* **1996**, *1*, 28–30; (c) Balsamini, C.; Diamantini, G.; Duranti, A.; Spadoni, G.; Tontini, A. *Synthesis* **1995**, *4*, 370–372; (d) Ley, J. P.; Peter, M. G. *Synthesis* **1994**, *1*, 28–30; (e) Guibourdenche, C.; Roumestant, M. L.; Viallefont, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2041–2046; (f) Dua, R. K.; Phillips, R. S. *Tetrahedron Lett.* **1992**, *33*, 29–32; (g) Guillerm, D.; Guillerm, G. *Tetrahedron Lett.* **1992**, *33*, 5047–5050; (h) Lunn, W. H. W.; Schoepp, D. D.; Calligaro, D. O.; Vasilef, R. T.; Heinz, L. J.; Salhoff, C. R.; O'Malley, P. J. *J. Med. Chem.* **1992**, *35*, 4608–4612; (i) Aldington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J.; Tang, L. T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 303–305; (j) Aldington, R. M.; Baldwin, J. E.; Catterick, D.; Pritchard, G. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 299–302; (k) Farthing, C. N.; Baldwin, J. E.; Russell, A. T.; Schofield, C. J.; Spivey, A. C. *Tetrahedron Lett.* **1996**, *37*, 5225–5226; (l) Falorni, M.; Giacomelli, G.; Spanedda, A. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3039–3046; (m) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 309–311; (n) Luca, L. D.; Giacomelli, G.; Porcheddu, A.; Spanedda, A. M.; Falorni, M. *Synthesis* **2000**, *9*, 1295–1298; (o) Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1999**, *40*, 4099–4102.
2. Orstein, P. L.; Schoepp, D. D.; Arnold, M. B.; Leander, J. D.; Lodge, D.; Paschal, J. W.; Elzey, T. *J. Med. Chem.* **1991**, *34*, 90–97.
3. Monn, J. A.; Valli, M. J.; True, R. A.; Schoepp, D. D.; Leander, J. D.; Lodge, D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 95–98.
4. Alvarez, R.; Velazquez, S.; San, F.; Aquaro, S.; De Clercq, C.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194.
5. Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De Clercq, C.; Balzarini, J.; Camarasa, M. *J. Antivir. Chem. Chemother.* **1998**, *9*, 481–489.
6. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970.
7. Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111–2114.
8. Evans, R. H.; Francis, A. A.; Watkins, J. C. *Brain Res.* **1978**, *148*, 536–542.
9. Evans, R. H.; Francis, A. A.; Hunt, K.; Oakes, D. J.; Watkins, J. C. *Br. J. Pharmacol.* **1979**, *67*, 591–603.
10. (a) Orstein, P. L.; Schaus, J. M.; Chambers, J. W.; Huser, D. L.; Leander, J. D.; Wong, D. T.; Paschal, J. W.; Jones, N. D.; Deeter, J. B. *J. Med. Chem.* **1989**, *32*, 827–833; (b) Aebischer, B.; Frey, P.; Haerter, H. P.; Herrling, P. L.; Mueller, W.; Olverman, H. J.; Watkins, J. C. *Helv. Chim. Acta* **1989**, *72*, 1043–1051.
11. (a) Fagg, G. E.; Olpe, H. R.; Pozza, M. F.; Faud, J.; Steinmann, M.; Schmutz, M.; Portet, C.; Baumann, P.; Thedinga, K.; Bittiger, H.; Allgeier, H.; Heckendorn, R.; Angst, C.; Brundish, D.; Dingwall, J. G. *Br. J. Pharmacol.* **1990**, *99*, 603–791; (b) Whitten, J. P.; Baron, B. M.; Muench, D.; Miller, F.; White, H. S.; McDonald, I. A. *J. Med. Chem.* **1990**, *33*, 2961–2963.
12. Guha, P. C.; Sankaran, D. K. *Org. Syn. Coll. III* **1955**, 623–625.
13. Cignarella, G.; Nathansohn, G. *J. Org. Chem.* **1961**, *26*, 1500–1504.
14. Lowe, G.; Redley, D. D. *J. Chem. Soc., Perkin. Trans 1* **1973**, 2024–2029.
15. Watson, H. A.; O'Neil, B. T. *J. Org. Chem.* **1990**, *55*, 2950–2952.
16. Sturn, P. A.; Henry, D. W.; Thompson, P. E.; Zeigler, J. B.; Mc Call, J. W. *J. Med. Chem.* **1974**, *17*, 481–487.
17. Guenoun, F.; Zair, T.; Lamaty, F.; Pierrot, M.; Lazaro, R.; Viallefont, P. *Tetrahedron Lett.* **1997**, *38*, 1563–1566.
18. Daly, A. M.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 127–137.
19. Aggarwal, V. K.; Sandrinelli, F.; Charmant, J. P. H. *Tetrahedron: Asymmetry* **2002**, *13*, 87–93.
20. Fliri, A. F. J.; Gallaschun, R. J. *Eur. Pat. App*. **2002** EP 1178047 A1 20020206 CAN: 136:151188.
21. Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014–4021.
22. Lwowsky, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons: NY, 1984; Vol. 1, pp 621–627, Chapter 4.
23. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons: NY, 1984.
24. L'abbé, G. *Chem. Rev.* **1969**, *69*, 345–363.
25. For most recent work see: (a) Suarez, P. L.; Gándara, Z.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2004**, *45*, 4619–4621; (b) Suh, B.-C.; Jeon, H. B.; Posner, G. H.; Silverman, S. M. *Tetrahedron Lett.* **2004**, *45*, 4623–4625, and references cited therein.
26. Oppolzer, W.; Pedrosa, R.; Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831–834.
27. Agami, C.; Kadouri-Puchot, C.; Le Guen, V.; Vaissermann, J. *Tetrahedron Lett.* **1995**, *10*, 1657–1660.