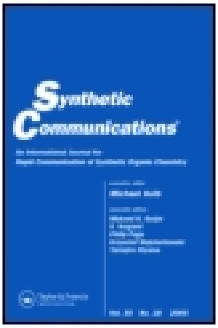

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SYNTHESIS OF AROMATIC AMINO ACID AMIDES

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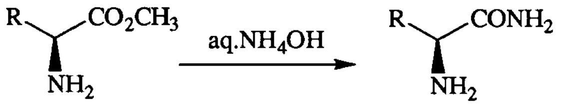
ABSTRACT: Aromatic amino esters, in toluene or water, react with aqueous ammonium hydroxide to give moderate to high yields of the corresponding amides.

Amino acid amides are important precursors in the synthesis of cholecystokinin analogs,[1] gastrin analogs,[2] cacitonin gene related peptides (CGRP),[3] renin inhibitors,[4] antibacterial and antiviral agents,[5] metalloproteinase inhibitors,[6] anticonvulsants,[7] sweeteners[8] and agrochemical fungicides.[9] General methods for the preparation of the amino acid amides involves either amination of the activated carboxylic acid of *N*-protected amino acids[10] or amino ester hydrochlorides with methanolic ammonia.[11] The former method involves several steps and is time consuming, whereas in the latter case, the reaction is slow and takes several days. They are also prepared by the DCC coupling of the *N*-protected amino acids with protected amines,[12] or by the hydrolysis of amino nitriles.[13] There is also a report for the synthesis of L-phenylalanine amide from L-phenylalanine using resin and either aqueous ammonia or ammonia gas.[14] This reaction in our hands gave only the ammonium salt of L-phenylalanine. There are no efficient methods high yielding methods for the preparation of aromatic amino acids amides and our interest in aromatic amino acids amides prompted us to look for the efficient, simple and high yield methods and now we wish to report that. The procedure described herein is also applicable to amino acids with alkyl side chains.[15]

Treatment of the methyl esters of L-phenylalanine and L-phenylglycine in toluene with aqueous ammonium hydroxide gave high yields of corresponding amino acid amides. A small amount of the amino acids was formed due to the hydrolysis of amino acid esters. In case of L-tyrosine, the reaction was carried out in water.



1 2

R=Ph, $PhCH_2$, p-$HOC_6H_4CH_2$

The procedure is straightforward and does not require the usage of "exotic" reagents.

EXPERIMENTAL SECTION

The melting points are uncorrected. ^1H NMR spectra were recorded on a GE 300 spectrometer in D_2O/NaOD using TMS as internal standard. Mass spectra were recorded on Finnigan SSQ 70. The optical purity was checked by chiral hplc.

L-Phenylalaninamide:

To a solution of phenylalanine methyl ester in toluene (100 mL, 12% wt/wt%, 0.067 mol) was added ammonium hydroxide (25 mL, 28%) and the mixture was stirred at room temperature for 16 hours. The completion of the reaction was checked by tlc. The mixture was evaporated to dryness. The residual solid was heated with ethyl acetate (185 mL) and filtered. The ethyl acetate layer was evaporated to dryness to give 7.8 g (71%) of white solid, mp 92-93°C [lit.[10] mp 90-91°].[17]

L-Phenylglycinamide:

This reaction was carried out as above: yield, 79% ; white solid, mp 137-138°C [lit.[16] mp 134-135°].[17]

L-Tyrosinamide:

To a slurry of L-tyrosine methyl ester (1.95 g, 0. 01mol) in water was added ammonium hydroxide (25 mL, 28%) and the mixture was stirred at room temperature for 16 hours. A clear solution was obtained. The completion of the reaction was checked by tlc. The mixture was evaporated to dryness to give 1.7 g (94%) of white solid, mp 153-155 °C [lit.[11] mp 154 °].[17]

References and notes:

1. Waleed, D. ; Tilley, J. W.; Triscari, J. and Wagner, R. Eur. Pat EP 89-107396 890424 , 1989; *Chem. Abstr.* **1990**, 112, 235846; Horwell, D. C. and Richardson, R. S. PCT Int. Appl. WO 9219253, 1992; *Chem. Abstr.* **1993**, 119, 73117.
2. Chen, J.; Zhang, C.; Luo, X.; Wang, X. and Hu S. *Shengwu Huaxue Zazhi* **1989**, 5, 107; *Chem. Abstr.* **1989**, 111, 50527.
3. Kempe, T. G. US Pat. US 85-812893 851223, 1985; *Chem. Abstr.* **1987**, 107, 237303.
4. Allen, M. C.; Fuhrer, W.; Tuck, B.;Wade, R. and Wood, J. M. *J. Med.Chem.* **1989**, 32, 1652.
5. Antoine, M.; Barreau, M.; Desconclois, J. F.; Girard, P. and Picaut, G. Eur. Pat. Appl. EP 431991, 1991; *Chem. Abstr.* **1992**, 116, 6538.
6. Beckett, R. P.; Whittaker, M.; Miller, A. and Martin, F. M. PCT Int. WO 9519956, 1995; *Chem. Abstr.* **1996**, 124, 56708.

7. Bailer, M.; Haded, S.; Herzig, J.; Sterling, J.; Lerner, D. and Shirvan, M. PCT Int. WO 9501956, 1995; *Chem. Abstr.* **1996**, 123, 199402.
8. Sweeny, J. G.; D'Angelo, L.L.; Edith, A. and Iacobucci, G. A. *J. Agric Food.Chem.* **1995**, 43, 1969.
9. Vermehren, J.; Braun, P. and Sachse, B. Ger. Offen. DE 93-4321897, 1993; *Chem. Abstr.* **1994**, 123, 133844.
10. Ramage, R.; Hopton, D.; Parrott, M. J.; Richardson, R. S. *J. Chem. Soc. Perkin Trans I* **1985**, 461; Lee, J. C.; Cho, Y. H.; Lee, H. K.; Cho, S. H. *Synth. Commun.* **1995**, 25, 2877; Fujii, N.; Shimokura, M.; Akaji, K.; Kiyama, S. and Yajima, H. *Chem. Pharm. Bull.* **1984**, 32, 510.
11. Meares, C. F.; Yeh, S. M. and Sherman, D. G. Can. Pat. 841204, 1984; *Chem. Abstr.* **1985**, 103,71701; Schnell, K. *Helv. Chim. Acta* **1955**, 38, 2036; Gani, D.; Young, D. W.; Carr, D. M.; Poyser, J. P. and Sadler, I. H. *J. Chem. Soc. Perkin Trans.* 1 **1983**, 11, 2811; Kato, Y.; Asano, Y.; Nakazawa, A. and Kondo, K. *Tetrahedron* **1989**, 45, 5743; Sowa, T.; Tsunoda, K.; Akimoto, N. and Osawa, H. Jpn. Pat. JP 70-119958, 1973; *Chem. Abstr.* **1973**, 79, 5603.
12. Rzeszotarska, B.; Makowski, M. and Kubica, Z. *Pol. J. Chem.* **1984**, 58, 293.
13. Lee, Y. B.; Goo, Y. M.; Lee, Y. Y. and Lee, J. K. *Tetrahedron Lett.* **1990**, 31, 1169.
14. Roteman, R. US pat. 558,581, 1975; *Chem. Abstr.* **1977**, 87, 39842.
15. Erickson, R.; Bray, R.; Johnson, M.; Loriane, K. and Seagle, D. A. US Pat. US 92-988052 921209, 1994; *Chem. Abstr.* **1994**, 121, 681222; Banko, G. and Haenggi, U. Ger. Pat. DE 91-4133688 911011, 1993; *Chem. Abstr.* **1993**, 119, 496173; Hosten, N. and Antenuis, M. J. O. *Bull Soc. Chim. Belg.* **1988**, 97, 48.
16. Neilson, D. G. and Ewing, D. F. *J. Chem. Soc.* **1966**, 393.
17. These compounds had satisfactory nmr and mass spectra, and elemental analysis.

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