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Synthesis of a Serinamide by Aminolysis of an N-Unsubstituted α-Amino Ester

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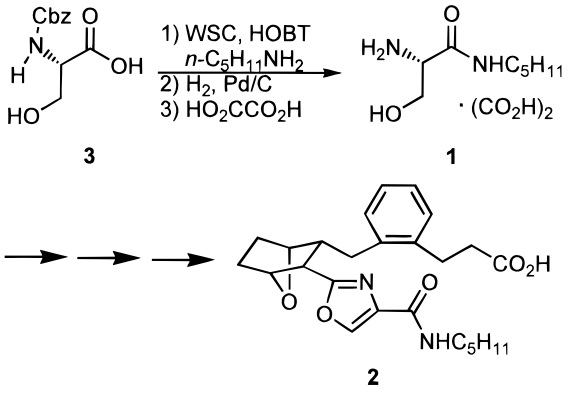
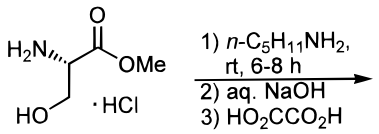
Abstract:
L-2-Amino-3-hydroxy-*N*-pentylpropanamide (1) was readily prepared and isolated as its oxalate salt in 81% yield and >99% ee through a "one-pot" process from L-serine methyl ester (4).

L-2-Amino-3-hydroxy-*N*-pentylpropanamide (*N*-pentyl-L-serinamide, **1**) is an intermediate in the synthesis of the long-acting thromboxane receptor antagonist BMS 180291 (**2**).[1,2] Its preparation has previously been described in two steps from Cbz-L-serine (**3**) by coupling with *n*-pentylamine followed by Cbz removal in 59% overall yield.[1] We have recently discovered a more direct and cost-effective procedure for the preparation of this intermediate which relies on the aminolysis of the methyl ester of L-serine (**4**).



3 **1** **2**

Aminolysis of carboxylic esters with amines or ammonia is a well-known and valuable transformation in organic synthesis.[3] The rate of reaction is sensitive to the nature of the esters and amines being used, and this has led to the development of a variety of procedures.[4−10] Aminolysis of α-amino esters has received only little attention, and those cases that have been reported[7,9b] were carried out on substrates with substituted amino groups. The aminolysis of N-unsubstituted α-amino esters has not been reported, probably due to concerns about self-condensation of the starting material. We envisioned that a combination of the lower reactivity of the α-amino ester and the use of excess alkylamine might minimize self-condensation and lead to a practical procedure.



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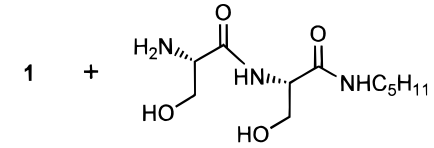

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Heating L-serine methyl ester (**4**) in *n*-pentylamine at reflux (103−104 °C) for 4 h resulted in the formation of the desired amino amide (**1**). After workup and crystallization as its oxalate salt, a 75% yield was achieved, but analysis by chiral HPLC[11] indicated that the product was partially racemized (72% ee). Lowering the reaction temperature to 15−25 °C and carefully controlling the pH and temperature during the workup allowed the preparation of essentially enantiomerically pure (99.9% ee) amide **1** in 81% yield. Analysis of the reaction mixture indicated that self-condensation product **5** is formed in only 5−10% yield. Unlike racemization, the level of this impurity was not influenced to any significant degree by changes in reaction conditions. Its level in the isolated salt, however, was strongly influenced

(1) Misra, R. J.; Brown, B. R.; Sher, P. M.; Patel, M. M.; Hall, S. E.; Han, W.-C.; Barrish, J. C.; Floyd, D. M.; Sprague, P. W.; Morrison, R. A.; Ridgewell, R. E.; DiDonato, G. C.; Harris, D. N.; Hedberg, A.; Schumacher, W. A.; Webb, M. L.; Ogletree, M. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 73.
(2) Das, J.; Reid, J. A.; Kronenthal, D. R.; Singh, J.; Pansegrau, P. D.; Mueller, R. H. *Tetrahedron Lett.* **1992**, *33*, 7835.
(3) Beckwith, A. L. J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Wiley-Interscience: New York, 1970; pp 96−109.
(4) For direct aminolysis, see: Bell, K. H. *Tetrahedron Lett.* **1986**, *27*, 263. Allen, C. F. H.; Humphlett, W. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 80. Kibler, C. J.; Weissberger, A. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 108. Allen, C. F. H.; VanAllan, J. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 764. Roe, E. T.; Scanlan, J. T.; Swern, D. *J. Am. Chem. Soc.* **1949**, *71*, 2215.
(5) For base-promoted aminolysis, see: Huebner, C. F.; Lucas, R.; MacPhillamy, H. B.; Troxell, H. A. *J. Am. Chem. Soc.* **1955**, *77*, 469. Singh, B. *Tetrahedron Lett.* **1971**, 321. De Fevand, R. J.; Strickler, P. D. *J. Org. Chem.* **1963**, *28*, 2915. Bassett, H. L.; Thomas, C. R. *J. Chem. Soc.* **1954**, 1188. Yang, K.-W.; Cannon, J. G.; Rose, J. G. *Tetrahedron Lett.* **1970**, 1791.
(6) For tin(II) amide mediated aminolysis, see: Wang, W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101.
(7) For cyanide-catalyzed aminolysis, see: Hogberg, T.; Strom, P.; Ebner, M.; Ramsby, S. *J. Org. Chem.* **1987**, *52*, 2033.
(8) For electrochemical aminolysis, see: Arai, K.; Shaw, C. H.; Nazawa, K.; Kawai, K. I.; Nakajima, S. *Tetrahedron Lett.* **1987**, *28*, 441.
(9) For enzymatic aminolysis, see: (a) Zaks, A.; Klibanov, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 3192. (b) West, J. B.; Wong, C.-H. *Tetrahedron Lett.* **1987**, *28*, 1629.
(10) For other miscellaneous aminolyses, see: Openshaw, H. T.; Whittakar, N. J. *J. Chem. Soc. C* **1969**, 89. Nakamizo, N. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1071.
(11) The optical purity of **1** could be determined by HPLC using a CrownPak CR(+) column (from Diacel, Inc.).

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by the crystallization solvent composition and temperature, ranging from 7% (solvent = butyl acetate) to 0.2% (solvent = ethanol).

The following procedure is illustrative: *n*-Pentylamine (50 mL, 0.432 mol) was charged to a three-neck 250-mL flask and cooled to 15 °C. L-Serine methyl ester hydrochloride (**4**, 20.0 g, 0.129 mol) was added over 30 min while the temperature was maintained at 15−25 °C. Over the following 30−60 min the solids were dissolved to form a clear solution. The reaction mixture was then stirred under nitrogen at 25 °C for 5−7 h. Water (10 mL) and concentrated sodium hydroxide (prepared by dissolving 5.25 g of sodium hydroxide in 5.5 mL of water) were added sequentially, followed immediately by the formation of a white precipitate. *n*-Butanol (350 mL) was added, and the excess *n*-pentylamine, water, and methanol were removed via vacuum distillation (bath temperature, 55 °C; final volume, ∼130 mL). After cooling to 25 °C, the slurry was filtered to remove sodium chloride and the cake was washed with *n*-butanol (20 mL).

The volume of the filtrate was then reduced to ∼45 mL via vacuum distillation (bath temperature, 55 °C), and then ethanol (140 mL) and water (30 mL) were added. After heating to 70−72 °C, a solution of oxalic acid (12.6 g, 0.140 mol) in ethanol (80 mL) was added slowly over 10−15 min, the temperature being kept in the range of 68−72 °C. Following the addition, the resulting slurry was cooled to 20−25 °C and filtered. After the product was washed with ethanol (2 × 75 mL), it was dried under vacuum at 50 °C. Yield = 27.4 g (81%).

Five runs of this procedure were made in a pilot plant on a 25 kg (input) scale. Yields ranged from 62.7 to 80.3%. Four of the lots were very high quality (>98% purity, <0.5% **5**, <0.1% D-enantiomer), but one was lower quality and needed to be reworked (96% purity, <0.1% **5**, 1.1% D-enantiomer). A straightforward recrystallization from aqueous ethanol gave high-quality product (100% purity, <0.1% **5**, <0.1% D-enantiomer). A subsequent investigation of the cause of the low quality of this batch was inconclusive.

In summary, a highly efficient process for the synthesis of amide **1** has been developed and demonstrated on a pilot plant scale. The simplicity of this new procedure may be useful for the preparation of other N-unsubstituted α-amino amides.

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