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A Straightforward Synthesis of N-Tert-butoxycarbonyl Serinate Acetonide Methyl Ester

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A STRAIGHTFORWARD SYNTHESIS OF N-TERT-BUTOXYCARBONYL SERINATE ACETONIDE METHYL ESTER

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Abstract: N-tert-Butoxycarbonyl serinate acetonide methyl ester, an important intermediate in organic synthesis, can be obtained in large quantity according to the procedure described herein.

The synthesis of N-tert-butoxycarbonyl serinate acetonide methyl ester has already been described by Garner and al. (1). Their method suffers from a dramatic limitation due to the use of diazomethane in the esterification step of Boc-serine. We demonstrate herein, that use of the Mitsunobu reaction (2,3) can overcome this difficulty as the esterification of Boc-L-serine proceeds in almost 100% yield on large scale (up to 100g). This molecule is the precursor of the title molecule, which is an important starting material for asymmetric synthesis as it can easily be reduced into N-Boc-serinal acetonide (Dibal, -75°C, toluene) (3), which possesses enormous potential in stereoselective synthesis of aminoacids (4-7), dipeptide isosteres (8), monocyclic β-lactams (9), α-aminodeoxypuronic acids (10,11) and other molecules of important therapeutic value (unpublished data from our laboratory). It can also be reduced into the corresponding alcohol for which a wide variety of applications can be expected.

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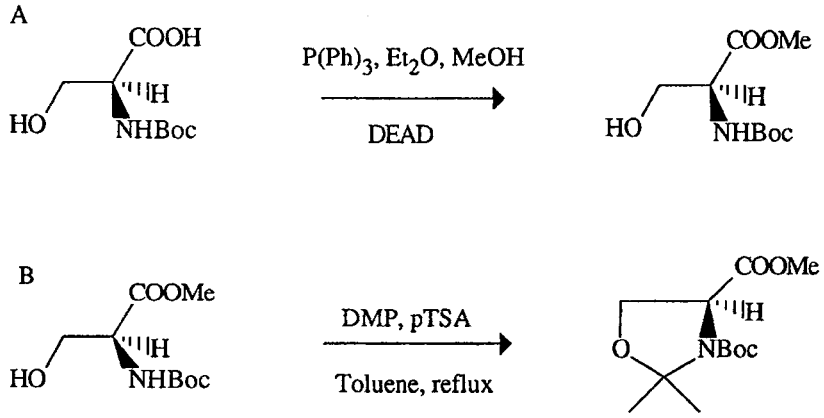

EXPERIMENTAL SECTION:

A. N-tert-butoxycarbonyl-L-serine methyl ester. Into a three-necked 1L flask fitted with a stirrer, a reflux condenser, a pressure equalized dropping funnel to which is attached a drying tube containing calcium chloride, are placed 50g (0.24 mole) of Boc-L-serine (note 1), 10.5mL (0.26 mole) of dry methanol, and 68.2g (0.26 mole) of triphenylphosphine (note 1) dissolved in 600 mL of dry diethyl ether, and the mixture is stirred for five minutes. To the stirred mixture is added from the dropping funnel over 25 minutes 50.9 mL (0.26 mole) of diethyl azodicarboxylate (note 1). The temperature in the reactor must be maintained below 45°C (note 2). After the end of the addition, stirring is continued for 30 minutes at room temperature. The diethyl hydrazinodicarboxylate thus formed as a precipitate is filtered off and washed with 2 X 50 mL of cold diethyl ether. The filtrate and washing solutions are combined and concentrated to 500 mL under vacuum, then placed for one hour at -20°C (note 3) to allow triphenylphosphine oxide to crystallize. It is filtered off and washed with 2 X 50 mL of diethyl ether. The filtrate and washing solutions are combined and diethyl ether is removed by vacuum distillation leaving 55 g of a yellow oily residue (note 4).

B. N-tert-butoxycarbonyl serinate acetonide methyl ester. In a one necked, 1L round-bottomed flask fitted with a reflux condenser are placed 55g of the oil from part A, 600 mL of toluene, 59.8 mL (0.49 mole) of 2,2-dimethoxypropane and 0.65g (0.003 mole) of p-toluenesulfonic acid monohydrate.The solution is refluxed for 30 minutes, then 200 mL of a mixture of

methanol-toluene is distilled off. To the residue are added 15.3 mL (0.125 mole) of 2,2-dimethoxypropane which is again refluxed for 30 minutes. Then 150 mL of a mixture of methanol, toluene and 2,2-dimethoxypropane are distilled off and the course of the reaction is checked by TLC (note 6). The cooled solution is poured into 100 mL of a satured aqueous sodium hydrogenocarbonate solution, the organic layer is separated and the aqueous layer extracted with 2 X 100 mL of diethyl ether. The organic layers are combined, washed with brine (150 mL) and dried over magnesium sulfate. The solvent is removed by vacuum distillation leaving a crude amber oil. It is distilled under reduced pressure (note 7) to separate 44g (70% yield) of N-tert-butoxycarbonyl serinate acetonide methyl ester as a pale yellow liquid (bp $_{(0,05mm\ Hg)}$ = 85 - 90°C. $[\alpha]_D^{20}$ = - 56° (C = 0.95, chloroform) (note 8).

NOTE:

1. Commercially available compound or easily prepared from L-serine and di-tert-butyl dicarbonate (12,13). All the other products are commercially available.
2. There is some risk of violent decomposition if diethyl azodicarboxylate is heated above 100°C (safety, 2, 1197 A).
3. The crystallization of triphenylphosphine oxide can be induced by adding a few crystals of the compound to the medium.
4. Analysis of the crude product reveals that it is pure enough to perform the subsequent reaction and the esterification reaction proceeds with a yield better than 98% : TLC analysis is performed with precoated silica gel 60F254 plates. Elution is done with a mixture of pentane/ethyl acetate (6/4). Visualisation is obtained by treating the plate with fumes of trifluoracetic acid followed by spraying an alcoholic ninhydrin solution, Rf = 0.33.
5. The solution becomes amber.
6. TLC conditions : silica gel 60F254 plates; elution pentane/ethyl acetate (8/2); visualisation: like in note 4, Rf = 0.55.
7. Hahn double jacket column of 12 cm.
8. Perkin-Elmer polarimeter 241, Sodium Lamp 589 nm, $[\alpha]_D^{20}$ = -57° (3) has been reported after distillation and flash chromatography. The other analyses are in agreement with the literature (3).

References

1) Garner, P. and Min Park, J. *J. Org. Chem.*, **1987**, *52*, 2361
2) Mitsunobu, O. *Synthesis*, **1981**, 1
3) Varasi, M.; Walker, K. A. M. and Maddox, M. *J. Org. Chem.*, **1987**, *52*, 4235
4) Beaulieu, L. P. and Schiller, P. W. *Tetrahedron Lett.*, **1988**, *29*, 2019
5) Garner, P. and Min Park, J. *J. Org. Chem.*, **1988**, *53*, 2979
6) Jako, I.; Uiber, P.; Mann, A.; Wermuth, C-G.; Boulanger, T.; Norberg, T.; Evrard, G. and Durant, F. *J. Org. Chem.*, **1991**, *56*, 5729
7) Beaulieu, P. L.; Duceppe, J-S. and Johnson, C. *J. Org. Chem.*, **1991**, *56*, 4196
8) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.and Yamamoto, Y. *J. Org. Chem.*, **1991**, *56*, 4370
9) Palomo, C.; Cossio, F. P. and Cuevas, C. *Tetrahedron Lett.*, **1991**, *32*, 3109
10) Casiraghi, G.; Colombo, L.; Rassu, G. and Spanu, P. *J. Org. Chem.*, **1991**,*56*, 6523
11) Casiraghi, G.; Colombo, L.; Rassu, G. and Spanu, P. *J. Chem. Soc., Chem.Comm.*, **1991**, 603
12) Bodansky, M.; Bodansky, A. "The Practice of Peptide Synthesis", Springer-Verlag, Berlin Heidelberg New-York Tokyo, 1984
13) Keller, O.; Keller, W. E.; Van Look, G. and Wersin, G. O.S., Vol 63, 160

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