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THE PREPARATION OF 2-HYDRAZINYL ESTERS IN HIGH OPTICAL PURITY FROM 2-SULFONYLOXY ESTERS

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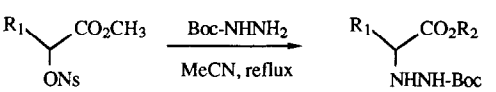
Chiral 2-triflyloxy esters, prepared from chiral 2-hydroxy esters, react enantiospecifically with $BocNHNH_2$ to produce optically pure 2-hydrazinyl ester derivatives in high yields. The reaction of 2-nosyloxy esters with $BocNHNH_2$ gives 2-(Boc-hydrazinyl) esters, thus providing an efficient (albeit slow) method for the conversion of esters to 2-hydrazinyl ester derivatives.

The synthesis of unnatural amino acids has recently become an area of intense interest because of their biological activity and because of varied effects which result from their inclusion in physiologically active peptides. Methods for the preparation of α-alkylated-α-amino acids[1], N-alkylated-α-amino acids[2], and N-hydroxy-α-amino acids[3], have all been recently reported. Another group of uncommon amino acids is the N-amino-α-amino acids (2-hydrazinyl acids) which display a variety of biological activities.[4] In particular, antibiotic activity is found for several 2-hydrazinyl acids[5], and for compounds such as L-156,602[6] and epinegamycin[7], which contain 2-hydrazinyl acid units as structural components. A variety of methods have been used to prepare 2-hydrazinyl acids starting from either amino acids or 2-halo carboxylic acids.[8] These earlier procedures suffer from low yields and/or experimental complexity. Recently several groups have utilized the amination of ester enolates with azodicarboxylic esters to produce 2-hydrazinyl esters in good yields and high enantiomeric excess.[9]

We recently reported that 2-(((4-nitrobenzene)sulfonyl)oxy) (2-nosyloxy) esters are easily prepared from esters.[10] Our previous work on 2-nosyloxy ketones[11] suggested that the reaction of a hydrazine equivalent nucleophile with 2-nosyloxy esters might give a simple synthesis of 2-hydrazinyl esters. We wish to report that such is, indeed, the case and, that the use of chiral 2-trifyloxy esters yields 2-hydrazinyl esters of high enantiomeric excesses.

The 2-nosyloxy esters 1a-c were refluxed with t-butylcarbazate ($BocNHNH_2$, Boc-hydrazide) in acetonitrile. Boc-hydrazide is a protected, monodentate hydrazine nucleophile which is easily deprotected. Monitoring the reaction mixture with tlc showed a slow disappearance of the starting 2-nosyloxy ester. After five days, the reaction was worked up

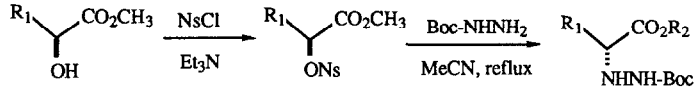


(1)

1a, R_1=CH_3 — 2a, 80%
1b R_1= CH_2CO_2Me — 2b, 82%
1c, R_1= CH_2Ph — 2c, 62%

to give the corresponding 2-(Boc-hydrazinyl) esters 2a-c in good yield (Eqn. 1).[12] Although sluggish, this procedure gives racemic 2-hydrazinyl esters from esters in two steps in good overall yields.

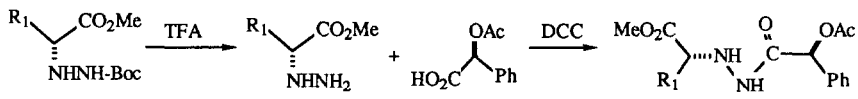
In order to produce chiral 2-hydrazinyl esters, enantiomerically pure methyl (2S)-2-nosyloxy esters 1a-c were synthesized from the corresponding hydroxy esters 3a-c .[13] Reaction with Boc-hydrazide gave 2-(Boc-hydrazinyl) esters 2a-c in the same yields as the racemic materials (Eqn. 2).



(2)

3a, R_1=CH_3 — 1a, 100% — 2a, 72%ee
3b, R_1= CH_2CO_2Me — 1b, 80% — 2b, >95%ee
3c, R_1= CH_2Ph — 1c, 97% — 2c, 83%ee

The optical purity of 2c was determined by hydrolysis to the 2-(Boc-hydrazinyl) carboxylic acid with 1N sodium hydroxide (25°, 20hr) and comparison of the optical rotation with the literature value.[8c] The configuration was inverted (R) as expected for an Sn2 displacement mechanism. The optical purity of 2a,b was determined by cleavage of the Boc group with TFA, formation of the methyl (2R)-(((S)-O-acetylmandelic)hydrazinyl) ester, 4, by condensation with (S)-O-acetylmandelic acid in the presence of DCC, and determination of the diastereomeric ratios by pmr (Eqn. 3).[15] Based on the results for 2c, the configurations of 2a,b were assumed to be inverted (R) also. Authentic diastereomeric mixtures from racemic 2a,b were used for comparison.[12]

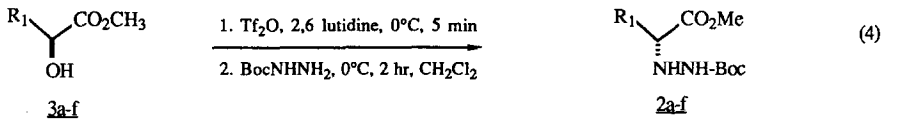


(3)

4

While the displacement of nosylate by Boc-hydrazide exhibits fair enantioselectivity, evidently the long reaction time leads to racemization in either the 2-nosyloxy ester starting material or the 2-(Boc-hydrazinyl) ester product. Loss of optical purity might be due to ionization of the nosylate group. Internal return in the ion pair before substitution or substitution by an Sn1 process could both result from ionization and account for racemization. In any event the leaving ability of the nosylate group is not well-matched with the nucleophilicity of Boc-hydrazide to provide an enantiospecific substitution.

During the course of this study, a report appeared in which O-benzylhydroxylamine was found to react with 2-trifyloxy esters with clean inversion of configuration.[3d] Since the nucleophilicity of Boc-hydrazide is comparable to that of O-benzylhydroxylamine, it appeared that the enhanced leaving ability of triflate would provide a better match with the nucleophilicity of Boc-hydrazide to increase enantiospecific substitution. Accordingly a series of methyl (2S)-2-hydroxy esters, 3a-f,[13] in dichloromethane (0°C) was treated with triflic anhydride and lutidine. After 5 minutes, $BocNHNH_2$ (2 equiv.) was added and the mixture was stirred for 2 hrs at 0°C. Evaporation of the solvent and purification of the reaction mixture by radial chromatography gave methyl 2-(Boc-hydrazinyl) esters, 2a-f (Eqn. 4), whose yields, optical rotations $[\alpha]_D^{25}$, and optical purities are shown in Table 1.



(4)

Optical purities were determined as described in above (Eqn. 3) and were found to be very high as only one 2-((O-acetylmandelic)hydrazinyl) ester diastereomer could be detected by pmr. Authentic diastereomeric mixtures were used for comparison.[12] Thus within the limits of detection (>95%) substitution occurred with complete inversion of configuration. As a check on the method, the optical purity of 3c was determined both by optical rotation and by preparation of the 2-((O-acetyl mandelic)hydrazinyl) ester, and the results were the same within experimental uncertainty. Compound 2e gave reduced enantioselectivity as has been noted for triflate substitution by O-benzylhydroxylamine in this substrate.[3d] Best results for 2e (71% ee) were obtained using hexane: methylene chloride (1: 1) from -78° to room temperature. If the reaction was carried out in methylene chloride at 0°C, the usual conditions, only 28% ee was achieved. This solvent effect was noted previously for hydroxylamine substitution in this substrate and apparently is due to decreased ionization in the less polar solvent.[3d]

Table 1. The Conversion of (2S)-2-Hydroxy Esters (R_1-CH(OH)CO_2Me), 3a-f, to (2R)-2-(Boc-hydrazinyl) Esters, 2a-f

Entry	Hydroxy Ester	Yield of 2 (%)	$[\alpha]_D^{25}(CHCl_3)$	ee(%)
1.	3a, R_1=Me	82	+53.4	>95
2.	3b, R_1= CH_2CO_2Me	91	+6.2	>95
3.	3c, R_1= CH_2Ph	81	+12.0	>95
4.	3d, R_1= $CH_2CH(CH_3)_2$	100	+41.2	>95
5.	3e, R_1= Ph	98	-71.4	71[a]
6.	3f, R_1= H	100	-	-

a. This reaction was carried out in hexane: methylene chloride (1: 1) from -78° to room temperature.

These results demonstrate that the substitution reaction between 2-triflyloxy esters and Boc-hydrazide provides a simple and efficient way to prepare 2-hydrazinyl carboxylic acid derivatives of high optical purity. As such it provides an attractive alternative to enolate aminations that are currently used for the preparation of 2-hydrazinyl ester derivatives.

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12. All new compounds were fully characterized by spectroscopy and elemental analysis.

13. Compounds 3a , 3e, and 3f were purchased (Aldrich). Compound 3b was made by Fischer esterification of (S)-2-hydroxysuccinic acid (Aldrich) according to the procedure of Mori, K, *Tetrahedron*, **1976**, *32*, 1101. Compounds 3c and 3d were prepared from phenylalanine and leucine, respectively, by diazotization to the hydroxy acid according to Cook, A. N.; Cox, S. F.; Farmer, T. H. *J. Chem. Soc.* **1949**, 1022, followed by esterification with potassium carbonate, methyl iodide as described by Moore, G. G.; Foglia, T. A., McGahan, T. J., *J. Org. Chem.*, **1979**, *44*, 2425.

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