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PREPARATION OF OPTICALLY ACTIVE 2-AMINOALKYLPHOSPHINIC AND PHOSPHONIC ACIDS

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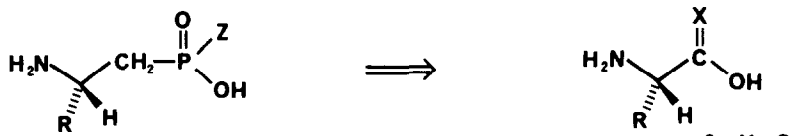
ABSTRACT: The reaction of sodium alkylphosphinates or sodium dialkylphosphonates with tosylamino tosylates of amino alcohols derived from 1-aminoalkylcarboxylic acids gives high yields of optically active 2-tosylaminoalkylphosphinic or phosphonic esters.

Since the discovery of β-ethylaminophosphonic acid in various organisms,[1] the aminophosphonic acids have attracted considerable interest as replacements for the natural amino acids in various peptides[2a-d] and in peptide-based enzyme inhibitors.[2e-g] Although several general methods for the preparation of 1-aminoalkylphosphonic acids have been reported,[3] relatively few reports have involved the synthesis of 2-aminoalkylphosphonic acids.[4] To our knowledge, 2-aminoalkylphosphonic acids have never been prepared in optically active form.

We wish to report an efficient synthesis of optically active 2-aminoalkylphosphinic 1 and phosphonic 2 acids from 2-aminoalcohols 4 prepared by reduction[5] of the readily available optically active amino acids 3.

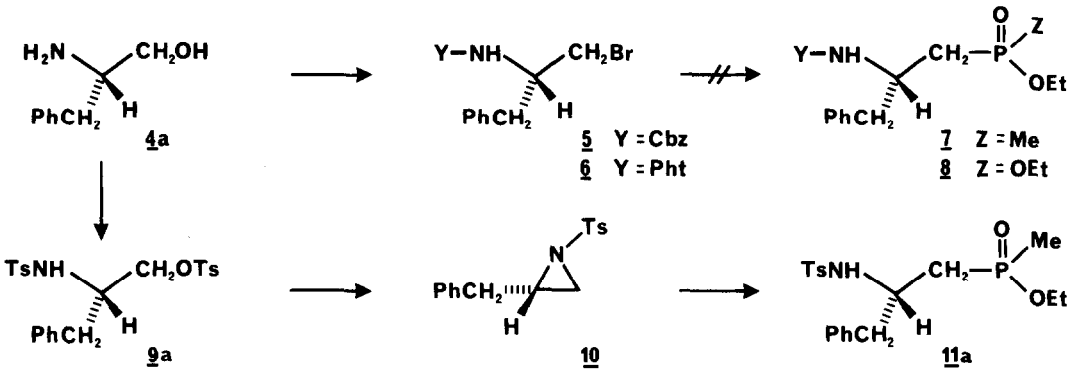


1 Z = Me
2 Z = OH

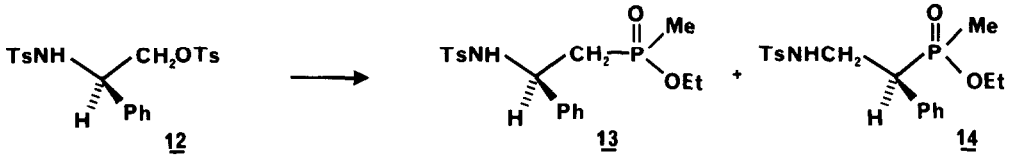
3 X = O
4 X = H2

Attempted Arbuzov [$CH_3P(OEt)_2$ or $(EtO)_3P$, 150-160°] or Michaelis-Becker reaction [$NaPO(OEt)CH_3$ or $NaPO(OEt)_2$, THF, reflux] of protected amino halides 5 or 6, prepared from L-phenylalaninol (4a), failed to give the desired aminophosphinates 7 or aminophosphonates 8. However, when N-tosylamino tosylate 9a was treated with excess sodium ethyl methylphosphinate in THF at room temperature, the desired N-tosylaminophosphinate 11a was isolated in 90% yield. The facile conversion of N-tosylaziridine 10 (mp 90-91°C), prepared by treatment of 9a with triethylamine in DMF (96% yield) to 11a under similar conditions suggests that the product is formed by nucleophilic attack on the cyclic intermediate.

Scheme 1



Further evidence for a N-tosylaziridine intermediate came from the observation that treatment of the N-tosylamino tosylate 12 (from D-phenylglycinol) with sodium ethyl methylphosphinate gave a 2:1 mixture of regioisomers 13 and 14 resulting from competing attack at the least hindered vs. the most electrophilic center of the intermediate aziridine.



We have prepared a number of 2-aminoalkylphosphinates 11a-f by this method. In general, aminoalcohols 4a-f, obtained commercially or by sodium borohydride reduction of the corresponding aminoester hydrochlorides,[5] were converted to N-tosylamino tosylates 9a-f (p-toluenesulfonyl chloride, pyridine, 0°C) and treated with 3 equivalents of sodium ethyl methylphosphinate[7] in THF at room temperature for 3-5 hrs. This method has also proven useful for the preparation of 2-aminoalkylphosphonates 15a-f by substituting sodium diethyl phosphonate for sodium ethyl methylphosphinate and carrying out the reaction at reflux (3 hrs.). In each case the products 11a-f and 15a-f were obtained as crystalline compounds in the yields shown in Table 1. The protecting groups were conveniently removed by hydrolysis with 48% hydrobromic acid-phenol[8] (reflux, 3-5 hrs.) and the resulting aminoalkylphosphinic 1a-f and phosphonic acids 2a-f isolated by ion exchange chromatography [AG50W-X2 (H^+ form), $H_2O \rightarrow$ 5% pyridine/H_2O].

With the exception of tosylate 12 noted above, opening of the intermediate aziridine (e.g. 10) was completely regiospecific giving only products resulting from attack at the least substituted carbon. Phosphinates 11a,c-f were also produced with high diastereoselectivity with respect to the phosphorus chiral center; only phosphinate 11b was produced as a diastereomeric mixture. The optical purity of 2a was established to be greater than 99% by comparison of the ^{1}H-NMR and ^{19}F-NMR spectra of the (+) α-methoxyl-α-trifluoromethylphenylacetic acid (MTPA) derivative[9] of S-2a, diethylester[10] with that of R,S-2a, diethyl ester prepared from d,ℓ-phenylalaninol.[11]

Scheme 2

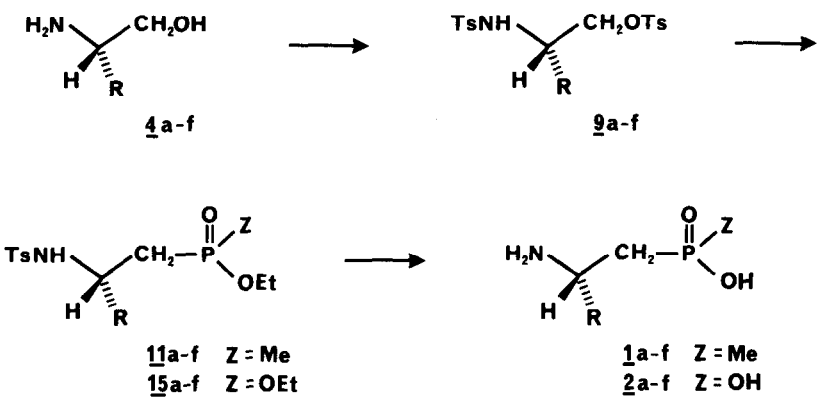


Table 1

Key: a. R=CH_2Ph d. R=H
b. R=$CH_2CH(CH_3)_2$ e. R=$CH(CH_3)_2$
c. R=$(CH_2)_2Ph$ f. R=CH_3

No.	Yield[a]	$[\alpha]_D^b$	mp[c]
11a	90%	-62.4°	121-122°
11b	96%	-39.3°	99-101°
11c	95%	*	108-109°
11d	84%	-	126-127°
11e	83%	- 3.8°	124-125°
11f	88%	-33.2°	103-104°
15a	82%	-43.0°	69-71°
15b	89%	-35.7°	81-82°
15c	91%	*	86-87°
15d	84%	-	67-69°
15e	87%	+10.4°	99-100°
15f	98%	-31.2°	45-46°

No.	Yield[a]	$[\alpha]_D^b$	mp[c]
9a	66%	-57.4°	97-98°
9b	79%	-53.2°	99-101°
9c	78%	*	95-97°
9d	86%	-	89-90°
9e	81%	-35.3°	109-110°
9f	80%	-50.4°	104-105°
1a	81%	- 9.5°	300-302°
1b	88%	- 2.4°†	283-284°
1c	66%	*	244-245°
1d	83%	-	259-260°
1e	71%	+28.8°	226-229°
1f	89%	+ 5.8°	243-245°
2a	69%	-15.6°	305-308°
2b	63%	- 3.4°†	270-275°
2c	63%	*	300-305°
2d	80%	-	277-280°
2e	72%	+24.1°	269-270°
2f	84%	+ 0.6°	301-302°

All compounds gave satisfactory microanalysis (C,H,N,S,P).

[a]Isolated yields of analytically pure product. [b]$[\alpha]_D$ for 9a-f, 11a-f and 15a-f in MeOH (c=1.0); for 1a-f and 2a-f in 1N HCl (c=1.0). [c]m.p. are uncorrected in degrees centigrade.

*Prepared from d,ℓ-homophenylalanine.

†Rotation measured at 365 nM.

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6. Prepared by treatment of the N-Cbz or N-Pht phenylalaninol with CBr_4/PPh_3 in THF.
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10. Prepared by successive treatment of 2a with [1] BSTFA/CH_3CN; [2] the acid chloride derived from (+) MTPA; [3] $CsCO_3$, EtI, DMF (50% overall yield).
11. The (+) MTPA derivative of R,S-2a, diethyl ester: ^{1}H-NMR ($CDCl_3$) δ 3.34 and 3.28 ppm (CH_3O); ^{19}F-NMR ($CDCl_3$, $CFCl_3$ reference = 0.00 ppm) -65.30 and -65.40 ppm (CF_3). The (+) MTPA derivative of S-2a, diethyl ester: ^{1}H-NMR ($CDCl_3$) δ 3.34 (CH_3OH); ^{19}F-NMR ($CDCl_3$, $CFCl_3$ reference = 0.00 ppm) -65.30 (CF_3).

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