

PREPARATION OF OPTICALLY ACTIVE 2-AMINOALKYLPHOSPHINIC AND PHOSPHONIC ACIDS

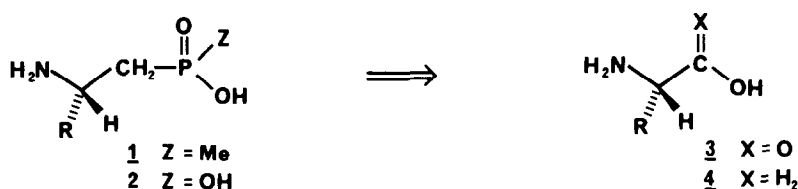
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ABSTRACT: The reaction of sodium alkylphosphinates or sodium dialkylphosphonates with tosyl-amino tosylates of amino alcohols derived from 1-aminoalkylcarboxylic acids gives high yields of optically active 2-tosylaminoalkylphosphinic or phosphonic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

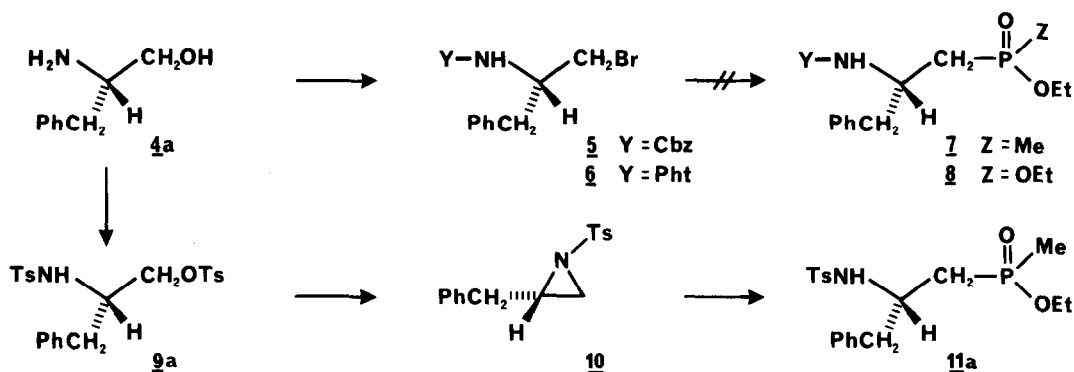
Since the discovery of β -ethylaminophosphonic acid in various organisms,¹ the amino-phosphonic acids have attracted considerable interest as replacements for the natural amino acids in various peptides^{2a-d} and in peptide-based enzyme inhibitors.^{2e-g} Although several general methods for the preparation 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 reduction⁵ of the readily available optically active amino acids 3.

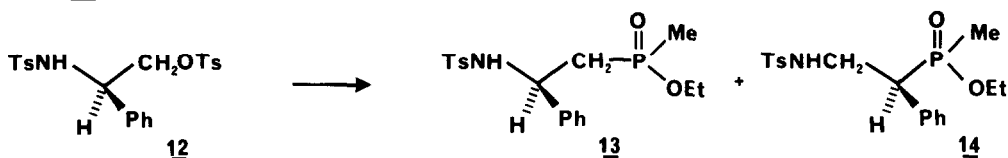


Attempted Arbuzov [$\text{CH}_3\text{P}(\text{OEt})_2$ or $(\text{EtO})_3\text{P}$, 150-160°] or Michaelis-Becker reaction [$\text{NaPO}(\text{OEt})\text{CH}_3$ or $\text{NaPO}(\text{OEt})_2$, THF, reflux] of protected amino halides 5 or 6, prepared from L-phenylalaninol (4a), failed to give the desired 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 methylphosphinate⁷ 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-phenol⁸ (reflux, 3-5 hrs.) and the resulting aminoalkylphosphinic **1a-f** and phosphonic acids **2a-f** isolated by ion exchange chromatography [AG50W-X2 (H^+ form), $\text{H}_2\text{O} \rightarrow 5\%$ 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 ^1H -NMR and ^{19}F -NMR spectra of the (+) α -methoxyl- α -trifluoromethylphenylacetic acid (MTPA) derivative⁹ of S-**2a**, diethylester¹⁰ with that of R,S-**2a**, diethyl ester prepared from d,l-phenylalaninol.¹¹

Scheme 2

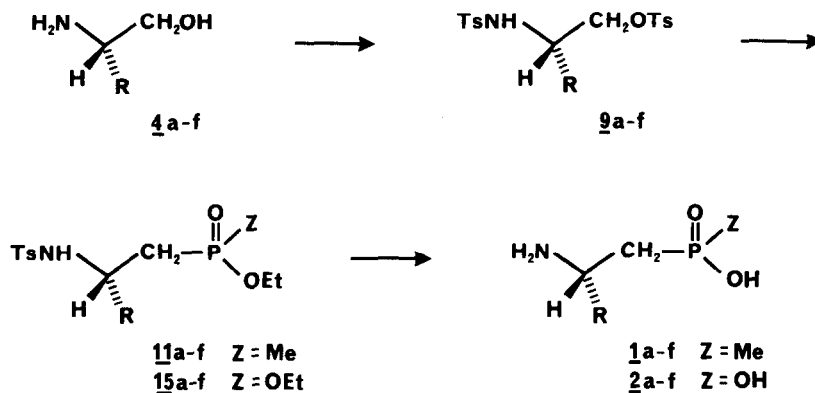


Table 1

				No.	Yield ^a	$[\alpha]_D^b$	mp ^c
Key: a. R=CH ₂ Ph d. R=H b. R=CH ₂ CH(CH ₃) ₂ e. R=CH(CH ₃) ₂ c. R=(CH ₂) ₂ Ph f. R=CH ₃				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°
No.	Yield ^a	$[\alpha]_D^b$	mp ^c				
11a	90%	-62.4°	121-122°	1a	81%	-9.5°	300-302°
11b	96%	-39.3°	99-101°	1b	88%	-2.4° [†]	283-284°
11c	95%	*	108-109°	1c	66%	*	244-245°
11d	84%	-	126-127°	1d	83%	-	259-260°
11e	83%	-3.8°	124-125°	1e	71%	+28.8°	226-229°
11f	88%	-33.2°	103-104°	1f	89%	+5.8°	243-245°
15a	82%	-43.0°	69-71°	2a	69%	-15.6°	305-308°
15b	89%	-35.7°	81-82°	2b	63%	-3.4° [†]	270-275°
15c	91%	*	86-87°	2c	63%	*	300-305°
15d	84%	-	67-69°	2d	80%	-	277-280°
15e	87%	+10.4°	99-100°	2e	72%	+24.1°	269-270°
15f	98%	-31.2°	45-46°	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 $\text{CBr}_4/\text{PPh}_3$ in THF.
7. Prepared by treatment of ethyl methylphosphinate with 1 equiv. NaH in THF at reflux.
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10. Prepared by successive treatment of λ 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: $^1\text{H-NMR}$ (CDCl_3) δ 3.34 and 3.28 ppm (CH_3O); $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3 reference = 0.00 ppm) -65.30 and -65.40 ppm (CF_3). The (+) MTPA derivative of S-2a, diethyl ester: $^1\text{H-NMR}$ (CDCl_3) δ 3.34 (CH_3OH); $^{19}\text{F-NMR}$ (CDCl_3 , CFCl_3 reference = 0.00 ppm) -65.30 (CF_3).

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