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Direct Preparation of N-Diphenylphosphinoyl Aziridines from 1,2-Aminoalcohols Utilizing Nucleofugacity of Diphenylphosphinates

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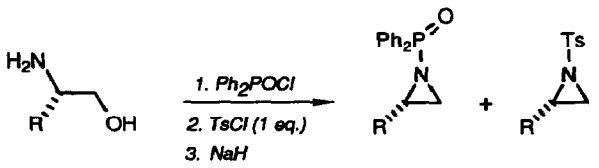
Abstract: *The improved preparation of N-diphenylphosphinoylaziridines is facilitated by the leaving group ability of the diphenylphosphinate anion*

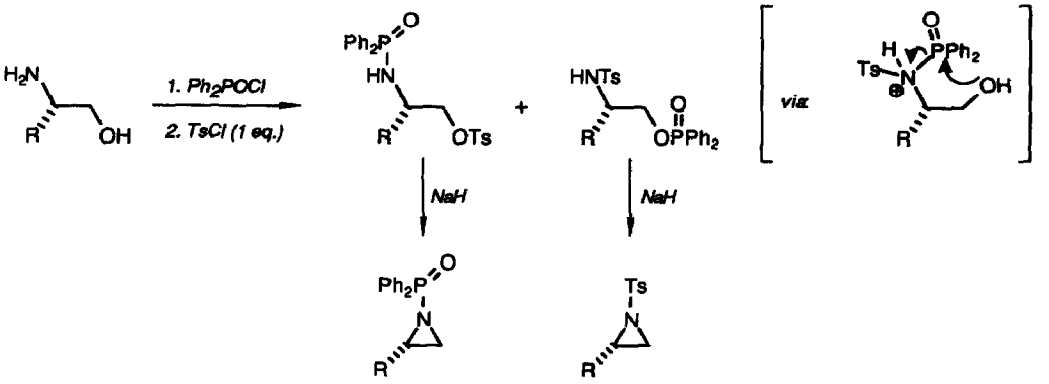
We recently reported the first preparation of N-phosphinylated aziridines and described the preliminary results of our investigations into ring-opening reactions of these heterocycles.[1] *N*-Diphenylphosphinylaziridines may be efficiently prepared from 1,2-hydroxyamines *via* a three-step process (scheme 1). Thus, reaction of 1,2-amino alcohols with diphenylphosphinic chloride delivers in excellent yield the corresponding N-phosphinylated compounds which are then reacted (without



SCHEME 1

need for purification) with *para*-toluenesulphonyl chloride to give N-diphenylphosphinyl-O-tosylates in good yield. The reaction of chromatographically-purified N-phosphinyl-O-tosyl compounds with base then furnishes the desired phosphinoylated aziridines in good yield. This reaction sequence proceeds in reasonable overall yield from the aminoalcohol starting materials but the products resulting are invariably accompanied by a small amount of N-tosylaziridine. This product could arise from an incomplete phosphinoylation reaction, thereby leading to N,O-ditosylated compounds which upon treatment with base would give the observed aziridine but we thought that another, more interesting, possibility was migration of the phosphinoyl group from nitrogen to oxygen during the subsequent tosylation reaction. This would

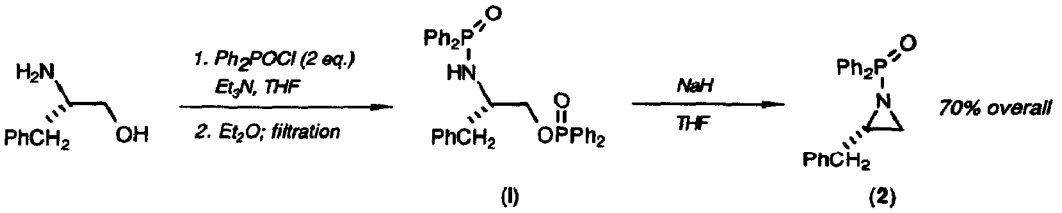
then produce the structurally isomeric N-tosyl-O-diphenylphosphinoylated compound (scheme 2) which, upon treatment with base, would cyclize to the tosyl aziridine because of the well-known (but little



SCHEME 2

exploited) excellent nucleofugacity[2] of the diphenylphosphinic acid group. If this process were operating, we reasoned it should be, in principal, possible to effect an efficient phosphinoylation-aziridination reaction sequence by a vastly simplified procedure; treatment of aminoalcohols with TWO equivalents of diphenylphosphinic chloride would lead to the N,O-bisdiphenylphosphinoylated compounds, which would readily cyclize on treatment with base. This process would offer obvious and substantial advantages over our existing procedure.

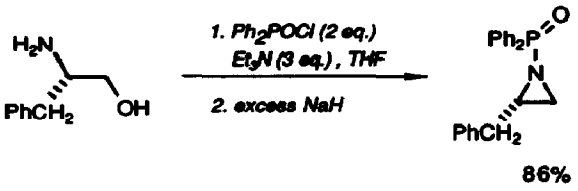
It was pleasing to witness our predictions being vindicated by experiment (scheme 3). Reaction of (2S)-2-amino-3-phenylpropanol with two equivalents of diphenylphosphinic chloride in THF



SCHEME 3

containing Et_3N yielded the N,O-diphenylphosphinoylated amino alcohol (**1**) in essentially quantitative yield; concentration of the reaction medium *in vacuo*, followed by removal of the hydrochloride by-product *via* precipitation with ether delivered this compound in crude form. Exposure of this crude product to sodium hydride in THF at room temperature then produced (2S)-N-diphenylphosphinoyl-2-phenylmethylaziridine (**2**) in good yield. This crude product of this much simplified, essentially "one-pot" reaction sequence was >90% pure[3] and was fit to be reacted in ring-opening processes such as those we have described.

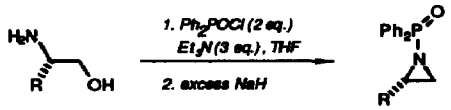
Even greater simplification of the reaction procedure is possible, since subsequent optimizations demonstrated clearly that removal of the amine hydrochloride by-product is unecessary: addition of excess sodium hydride to the phosphinoylation reaction mixture is sufficient both to neutralize the latent acid present and effect cyclization (scheme 4). Under these truly "one-pot" conditions, analytically pure aziridine

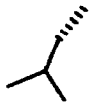


SCHEME 4

(2) was produced directly in 86% yield.[4] The reaction conditions are generally applicable to preparation of a wide range of homochiral aziridines and are high-yielding (table); using a variety of 2-amino acid-derived 1,2-aminoalcohols, N-diphenylphosphinoylated aziridines are accessible in excellent overall yield.

Table - Preparation of N-Diphenylphosphinoylaziridines from aminoalcohols



R	Yield of aziridine
	78%
	67%
	86%
Ph	52%
Me	51%
	79%
	87%

In summary, we have developed a new and extremely efficient method to prepare N-phosphinoylated aziridines using a one flask process by exploiting the nucleofugacity of diphenylphosphinate anions. We are currently examining the range of reactions which this nucleofugacity will benefit.

Acknowledgement

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Representative procedure for preparation of N-diphenylphosphinoyl aziridines:

To a solution of (2S)-2-amino-3-phenyl-propanol (200 mg) in THF (20ml), under argon at 0ßC, 2 equivalents of diphenylphosphinic chloride (510 µl), and 3 equivalents of triethylamine (550 µl), was added. A white precipitate of triethylammonium hydrochloride was immediately formed. The resulting suspension was stirred for 20 hours, after which excess sodium hydride, (400 mg, >5 equivalents), was added. The resulting suspension was stirred at room temperature overnight. After this time, water (one equivalent, based on NaH) was added and the resulting suspension filtered through anhydrous magnesium sulphate, and the filter cake washed with 100ml of diethyl ether. The solvent was then removed *in vacuo* to leave a white solid. Filtration through silica gel using ethylacetate (100ml), gave analytically pure (2S)-N-diphenylphosphinoyl-2-phenylmethylaziridine (379 mg, 86%) as a white crystalline solid.

References

1. Howson, W.; Osborn, H.M.I.; Sweeney, J.B.; *SynLett*, **1993**, in press.
2. Boche, G.; Bernheim, M; Schrott, W.; *Tetrahedron Letters*, **1982**, *23*, 5399; Kl tzer, W.; Baldinger, H; Karpitschka, E-M; Knopflach, J.; *Synthesis*, **1982**, 592
3. Tlc , high field ^{1}H and ^{13}C nmr spectra indicated only one compound present.
4. All compounds yielded satisfactory analytical data.

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