Direct Conversion of Activated Alcohols to Azides Using Diphenyl Phosphorazidate. A Practical Alternative to Mitsunobu Conditions

Andrew S. Thompson,* Guy R. Humphrey, Anthony M. DeMarco, David J. Mathre, and Edward J. J. Grabowski

Merck Research Laboratories, Department of Process Research, Rahway, New Jersey 07065-0900

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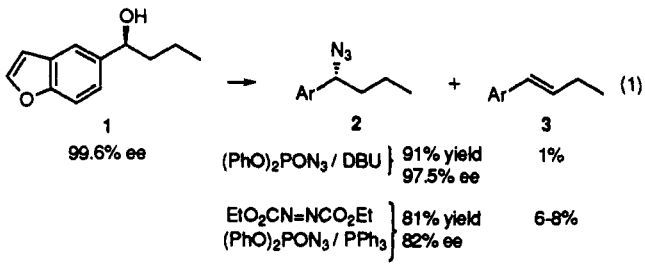
Summary: Fourteen alcohols were converted to their corresponding azides with inversion of configuration using diphenyl phosphorazidate and DBU.

While evaluating a new route to a potential elastase inhibitor,[1] we required the conversion of optically active alcohol 1 into azide 2. Since the starting alcohol was enantiomerically pure,[2] introduction of the azide would have to proceed with clean S_N2 inversion. Our initial efforts using a sulfonate derivative were abandoned when it became obvious that the activated alcohol was decomposing before the azide displacement step could occur (decomposition was observed at 0 °C).

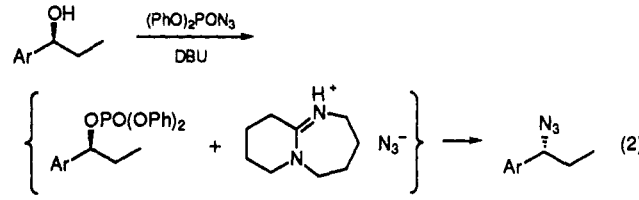
An examination of the literature provided few methods for alcohol to azide conversions which maintain optical activity with electron-rich benzylic alcohols. Use of the Mitsunobu displacement[3] with an azide nucleophile appeared to have the best precedent. Azide was first introduced under Mitsunobu conditions using hydrazoic acid as the azide source,[4] and this method was recently extended to chiral α-arylethylamines.[5] Alternatives to hydrazoic acid include diphenyl phosphorazidate[6] (DPPA) and zinc azide/bis-pyridine complex.[7] In this paper we briefly report our results using Mitsunobu conditions and describe a simple alternative which allows electron-rich benzylic alcohols to be converted into optically active azides.



Using modified Bose conditions,[6] the alcohol 1 and triphenylphosphine were added sequentially to a THF solution of diethyl azodicarboxylate and DPPA at 0 °C. After 30 min the product was isolated using an aqueous workup. Since the azide was contaminated with six times its weight in Mitsunobu byproducts, two chromatographies and a distillation were required to obtain pure product. The azide 2 was isolated in 81% yield with an enantiomeric purity of 82% ee. The reaction also produced 6-8% of the olefin 3. Erosion of enantiomeric purity as well as olefin formation were attributed to highly reactive intermediates which can partition between ionization and displacement chemistry (S_N1 vs S_N2).

We now report that the Mitsunobu conditions can be avoided altogether, and that the use of a base in the presence of DPPA suppresses S_N1 chemistry resulting in nearly complete stereocontrol for the overall conversion. The reaction was carried out by dissolving alcohol 1 and DPPA (1.2 equiv) in toluene such that the final concentration of alcohol was ca. 0.5–1 M. To the mixture was added a slight excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After 12 h at 23 °C the azide 2 was isolated in 91% yield using an aqueous workup and filtration through silica gel. The enantiomeric excess of the azide was 97% ee, and there was less than 1% of the elimination product 3.

Mechanistically, the reaction takes place in two discrete steps, the first of which is phosphate formation followed by azide displacement (eq 2). For substrates that are



relatively electron deficient the intermediate phosphate has a finite lifetime and has been observed by NMR. The benzylic proton was coupled to phosphorus and resonates as an apparent quartet at δ = 5.5 ppm for entries 3 and 4 in Table I. A balanced equation requires the formation of the DBU salt of hydrazoic acid in addition to the phosphate. The azide salt is similar to a quarternary ammonium azide which has some solubility in organic solvents. This combination of events in which a sufficiently reactive leaving group was formed in the presence of an organic-soluble form of azide leads to displacement at ambient temperatures. The *in situ* generated azide will completely displace the phosphate without the need for any additional azide source.[8] Once the azide displacement was complete (benzylic methine at δ = 4.3 ppm in entries 3 and 4), the reaction byproduct was the DBU salt of diphenyl phosphate. This salt is water soluble and was removed with an aqueous wash. Any excess DBU can be removed with an acid wash, and one is left with a reaction

• Abstract published in *Advance ACS Abstracts*, October 1, 1993.

(1) Knight, W. B.; Green, B. G.; Chabin, R. M.; Gale, P.; Maycock, A. L.; Weston, H.; Kuo, D. W.; Westler, W. M.; Dorn, C. P.; Finke, P. E.; Hagmann, W. K.; Hale, J. J.; Liesch, J.; MacCoss, M.; Navia, M. A.; Shah, S. K.; Underwood, D.; Doherty, J. B. *Biochemistry* **1992**, *31*, 8160.

(2) The alcohol was prepared via the enantioselective addition of di-*n*-propylzinc to 5-formylbenzo[*b*]furan using the conditions from ref 15.

(3) (a) The first example in which an amine equivalent was installed under Mitsunobu conditions used phthalimide as the nucleophile. Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (b) The Mitsunobu displacement has been extensively reviewed by Hughes. References to the variation in which a C–N bond is formed can be found in this review; see: Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(4) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1977**, *60*, 417.

(5) Chen, C.-P.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **1991**, *32*, 7175.

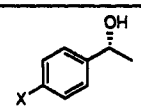
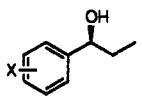
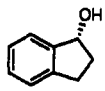
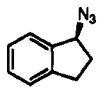
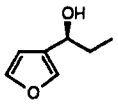
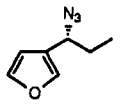
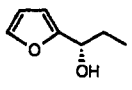
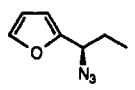
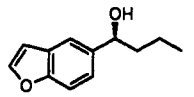
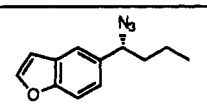
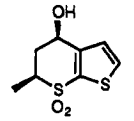
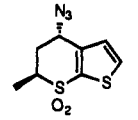
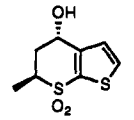
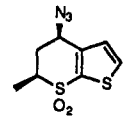
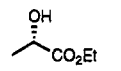
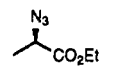
(6) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977. Using the conditions in which the alcohol and the DEAD/TPP complex are mixed *prior* to DPPA addition resulted in racemization and olefin formation.

(7) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.

(8) A similar observation was made in the β-lactam area; see: Gasparski, C. M.; Teng, M.; Miller, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 2741.

0022-3263/93/1958-5886$04.00/0

Table I. Alcohol to Azide Conversion

entry	alcohol	ee[a]	azide[b]	yield
1	 X = CF_3[c]	95.2% ee	94.3% ee	94%
2	X = H[d]	99.0% ee	98.7% ee	93%
3	 X = m-OCH_3[e]	97.5% ee	96.0% ee	89%
4	X = p-Me[e]	97% ee	95% ee	91%
5	X = p-OMe[e]	99.4% ee[f]	87.6% ee	80%
6				95%
	99.5% ee[c]		94.1% ee	
7				82%
	97.4% ee[e]		96.9% ee	
8				86%
	92.5% ee[e]		71.3% ee	
9				90%
	99.6% ee[e,g]		97.5% ee[b]	
10				92%
	95:5[h] cis:trans		5:95[h,i] cis:trans	
11				92%
	2:98[h] cis:trans		97:3[h,i] cis:trans	
12				87%
	99% ee[j]		98% ee[i,k]	
13	n-decanol		n-decyl azide	88%
14	cholesterol		cholesteryl azide	20%

[a] The enantiomeric purity was determined by gas chromatography using a Cyclodex-B column (J&W Scientific). [b] The ratio of enantiomers was determined by reversed-phase HPLC after reducing the azide to the amine with $LiAlH_4$ and converting the amine to the menthyl carbamate ((−)-menthyl chloroformate, triethylamine). All examples were compared to independently prepared racemic samples. [c] The alcohol was prepared via an enantioselective ketone reduction, ref 14. [d] The alcohol was purchased from Aldrich. [e] The alcohol was prepared via an asymmetric dialkylzinc addition according to the procedure outlined in ref 15. [f] The optical purity was determined using a chiralcel OD column. [g] The optical purity was determined using a chiralcel OB column (Diacel Chemical Industries). [h] The alcohol ratio was determined by reversed-phase HPLC, and the azide ratio was determined by ^1H NMR. [i] The azidation was run in THF. [j] The optical purity was taken as the chemical purity from Aldrich. [k] The ratio of enantiomers was determined using a chiralcel crownpak (CR+) column (Diacel Chemical Industries) after reducing the azide with triphenylphosphine.

product which contains only the slight excess of DPPA initially used. Analytically pure samples of alkyl azide were then obtained by distillation, silica gel chromatography, or crystallization. In addition to the operational simplicity of this reaction, there are fewer byproducts to contend with than the Mitsunobu reaction, the yield was improved, and the integrity of the desired S_N2 displacement was enhanced.

We have extended this reaction to a variety of structurally diverse alcohols as shown in Table I. The examples shown in entries 1–5 span a range from electron-deficient (*p*-CF_3) to electron-rich benzylic alcohols (*p*-OMe). A benzylic alcohol attached to a *m*-methoxy-substituted phenyl group (entry 3) was recently used in conjunction with the Mitsunobu displacement to demonstrate a chiral amine synthesis.[5] However, the *m*-methoxy substituent is in fact electron withdrawing (positive Hammett σ value) and less prone to racemization than is an unsubstituted phenyl.[9] We have demonstrated the method using a more general class of benzylic alcohols. It is clear that the substrates need not be electron rich for a successful conversion. However, variations in the electronic nature of substituents on the aryl ring affect the rate of the displacement step. In most cases the phosphate was formed within 1 h; however, entry 1 (*p*-CF_3) required warming to 40 °C to complete the displacement, while entry 5 (*p*-OMe) was complete in several hours at 0 °C. Entries 7–9 show the extension to electron rich heterocycles. Racemization was typically less than 2% for all examples except for the *p*-methoxyphenyl (entry 5) and the 2-substituted furan (entry 8). In these two examples there was 5% and 10% of the opposite enantiomer produced, respectively. Entries 10 and 11 demonstrate the method using intermediates from our carbonic anhydrase inhibitor program.[10] The C-4 *cis* and *trans* alcohols undergo complete inversion. That both diastereomers invert rules out the possibility of an α-face selective attack of azide.[10] Currently, this is the highest level of stereocontrol reported for introducing the C-4 amine into our carbonic anhydrase inhibitors. The method was extended to afford a protected amino acid (entry 12). This example demonstrates that an ester sufficiently activates the hydroxyl for displacement without an adjacent phenyl ring.[11,12] Since azido esters are prone to epimerization,[11b] a slight undercharge of base was used (0.98 equiv). This example also demonstrated that our method proceeds with inversion of configuration since our product had a rotation of +17.5° while the azido ester derived from natural L-alanine has a rotation of −16.4°.[12]

(9) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper and Row: New York, 1981; p 134.

(10) Blacklock, T. J.; Sohar, S.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 1672.

The primary alcohol in entry 13 formed an azide very slowly in toluene or THF at ambient temperature (5% conversion after 24 h). Use of conditions more favorable for an S_N2 displacement led to complete azide formation (DMF at 65 °C for 3 h).[13] A secondary alcohol formed an azide in low yield even under forcing conditions (entry 14; DMF at 125 °C for 18 h). However, this substrate forms an azide in 60% yield using the Mitsunobu conditions.[6] This observation allows for a ranking of the relative reactivities using Mitsunobu conditions compared with our method. In the Mitsunobu reaction, the reactive intermediate is proposed to be an alkoxyphosphonium species.[3b] This highly reactive intermediate readily allows unactivated secondary alcohols to be displaced. Such highly reactive intermediates can be undesirable when an optically active electron-rich benzylic alcohol is the substrate. In this case, the phosphate has the appropriate balance of reactivity such that racemization is suppressed, yet the displacement with azide is facile at temperatures between 0–25 °C.

In conclusion, we have developed a new method for the direct conversion of activated alcohols to azides. The method is operationally simple, and the yields are excellent. In the cases where maintaining optical activity is a concern, we have not found a superior method.

Acknowledgment. We would like to thank Professor D. Evans and Dr. Paul J. Reider for enlightening discussions throughout this work.

Supplementary Material Available: Experimental procedures and spectral data for the azides prepared in Table I (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) For examples displacing an α-hydroxy ester with an amine equivalent see the following references. (a) Displacement of a trifluoromethanesulfonate: Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 65. (b) For an example using the Mitsunobu displacement with HN_3 see: Fabiano, E.; Golding, B. T.; Sadeghi, M. M. *Synthesis* **1987**, 190. (c) For an example using a protected hydroxylamine under Mitsunobu conditions see: Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978. (d) Displacement of a *p*-nitrobenzenesulfonate: Hoffman, R. V.; Kim, H.-O. *Tetrahedron* **1992**, *48*, 3007.

(12) For the preparation of azido derivatives of amino acids by diazo transfer, see: Zaloom, J.; Roberts, D. C. *J. Org. Chem.* **1981**, *46*, 5173.

(13) We have observed gas evolution (N_2?) when DPPA and DBU were mixed in polar solvents such as CH_3CN or DMF *without* the alcohol present. The base should always be the last reagent charged.

(14) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.

(15) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657. Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Ibid.* **1989**, *30*, 7095.

(16) The boiling points (melting point) and rotations for the azides in Table I are as follows (entry, bp, rotation): 1, 65 °C/0.5 mm, $[\alpha]^{25}_D$ = −69.4° (*c* = 1.02, hexane); 2, 105–110 °C/15 mm, $[\alpha]^{25}_D$ = −115.1° (*c* = 1.02, hexane); 3, 95 °C/1 mm, $[\alpha]^{25}_D$ = +155.5° (*c* = 1.0, hexane); 4, $[\alpha]^{25}_D$ = +170.5° (*c* = 1.0, hexane); 5, 110 °C/0.6 mm, $[\alpha]^{22}_D$ = +141.2° (*c* = 0.99, hexane); 6, 140 °C/15 mm; $[\alpha]^{23}_D$ = −25.3° (*c* = 1.1, hexane); 7, 100 °C/30 mm, $[\alpha]^{25}_D$ = +99.2° (*c* = 1.0, hexane); 8, 105 °C/35 mm, $[\alpha]^{25}_D$ = +96.7° (*c* = 1.0, hexane); 9, $[\alpha]^{25}_D$ = +135.6° (*c* = 1.02, hexane); 10, mp = 118–119 °C, $[\alpha]^{25}_D$ = −232° (*c* = 1.13, MeOH); 11, mp = 99–101 °C, $[\alpha]^{25}_D$ = −53.9° (*c* = 1.02, MeOH); 12, 105–110 °C/100 mm, $[\alpha]^{25}_D$ = +17.5° (*c* = 1.03, hexane).

(17) **Experimental Procedures.** A mixture of alcohol 1 (2.0 g, 10.5 mmol) and diphenyl phosphorazidate (3.5 g, 12.7 mmol) was dissolved in dry toluene (18 mL). The mixture was cooled to 0 °C under N_2, and neat DBU (1.9 mL, 12.7 mmol) was added. The reaction was stirred for 2 h at 0 °C and then at 20 °C for 16 h. The resulting two-phase mixture was washed with H_2O (2 × 10 mL) and 5% HCl (10 mL). The organic layer was concentrated *in vacuo* and purified by silica gel chromatography using 95:5 hexane/ethyl acetate to afford 2.07 g (91%) of a clear, colorless oil: $[\alpha]^{25}_D$ = +135.6° (*c* = 1.02, hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.2 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.25 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H), 6.78 (dd, *J* = 2.2 Hz, 1H), 4.53 (t, *J* = 7.3 Hz, 1H), 2.0–1.7 (m, 2H), 1.52–1.25 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.73, 145.75, 134.63, 127.75, 123.31, 119.74, 111.71, 106.73, 66.42, 38.66, 19.64, 13.76; IR (thin film) 2090. The enantiomeric purity was determined after reducing a 50-mg sample with $LiAlH_4$ (25 mg) in THF (1-2 mL). The reduction was quenched with H_2O (25 μL), 15% NaOH (50 μL), and H_2O (75 μL), and the amine was then derivatized by adding triethylamine (150 μL) and (−)-menthyl chloroformate (100 μL). The ratio of enantiomers was determined by reversed-phase HPLC [Rx C-18, CH_3CN/H_2O gradient elution from 50:50 to 90:10 over 30 min, flow = 1.5 mL/min, UV detection at 238 nm]: t_R minor = 26.2 min (1.3%) and t_R major = 26.8 min (98%).