Efficient method for the one-pot azidation of alcohols using bis(*p*-nitrophenyl) phosphorazidate

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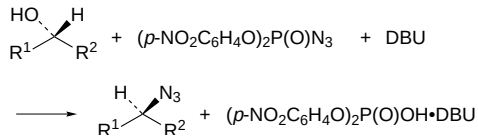
The direct stereoselective conversion of various alcohols and hexopyranoses into the corresponding alkyl azides and glycosyl azides, respectively, is efficiently accomplished by using bis(*p*-nitrophenyl) phosphorazidate and DBU.

Azides have been used extensively in organic synthesis, especially for the introduction of primary amino groups and the construction of heterocyclic structures.[1] In most cases, aliphatic azides are prepared by nucleophilic substitution of the corresponding halides or sulfonates by the azide anion.[2] The only known methods for the direct conversion of alcohols into azides are the Mitsunobu reaction,[3] in which removal of the by-products is troublesome, and the diphenyl phosphorazidate (DPPA)–DBU method[4] which is effective only for activated alcohols. In the course of our investigation on the reactivity of some analogs of DPPA, we have discovered that bis(*p*-nitrophenyl) phosphorazidate (*p*-NO_2DPPA), prepared easily by nitration of DPPA,[5] in combination with DBU is quite useful and efficient for the direct conversion of alcohols into azides, as shown in Scheme 1.



Scheme 1

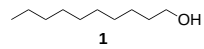
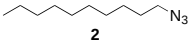
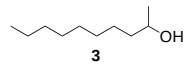
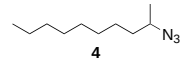
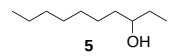
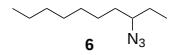
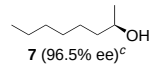
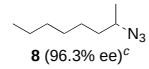
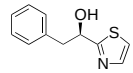
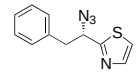
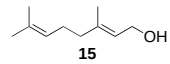
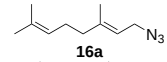
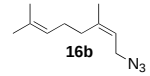
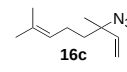
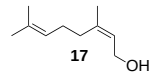
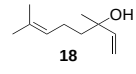
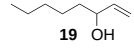
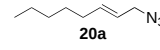
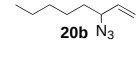
Treatment of decan-1-ol **1** or decan-2-ol **3** with *p*-NO_2DPPA (1.2 equiv.) and DBU (1.2 equiv.) in toluene (1 mol l^{-1}) smoothly afforded the corresponding azides **2** and **4** in good yield. Superior features of this method are that the reactions proceed with considerably faster rates than when DPPA–DBU is used (5 and 3% yields, respectively), and there are fewer byproducts to struggle with than in the Mitsunobu reaction. In the azidation of decan-2-ol **3**, DBU (81% yield) was much superior to triethylamine (28%), triethylamine with 0.1 part of DMAP (44%) and diisopropylethylamine (32%) under analogous reaction conditions. Toluene was the solvent of choice though THF and DMF can also be used.

Various azides prepared from alcohols according to this method are listed in Table 1. High stereoselectivity was observed in the reaction of optically active alcohols; for instance, (*R*)-(−)-octan-2-ol **7** and (*R*)-(+)-1-phenylethanol **9** afforded (*S*)-(+)-2-azidooctane **8** and (*S*)-(−)-1-phenylethyl azide **10**, respectively, in good yield with inversion of configuration without loss of stereochemical integrity. (*R*)-(+)-2-Phenyl-1-(thiazol-2-yl)ethanol **11** was also conveniently converted to the (*S*)-azide **12**, which was an intermediate for the synthesis of dolaphenine [(*S*)-(−)-2-phenyl-1-(thiazol-2-yl)ethylamine],[6] the C-terminal unit of dolastatin 10 having strong anticancer activity. Allylic alcohols gave a mixture of the isomeric azides (entries 8–11 and 13) due to rapid 1,3-rearrangement of the allylic azides.[7] However, the azidation of alicyclic alcohols such as cyclohexanol **31** and (−)-menthol **32** were unsuccessful under the same reaction conditions.

This method was extended to the preparation of glycosyl azides, key intermediates in the synthesis of glycosyl amino acids.[8] The results summarized in Table 2 demonstrate that this method selectively gives 1,2-*trans*-glycosyl azides. The stereochemical outcome of these direct azidations may be rationalized on grounds similar to those proposed by Sabesan and Neira[9] for the preparation of anomerically enriched glycosyl phosphates from hexopyranoses, *i.e.* probably the azidation occurs *via* initial formation of the thermodynamically stable 1,2-*cis*-glycosyl phosphate which subsequently undergoes the azide displacement with inversion of configuration.

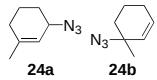
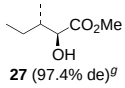
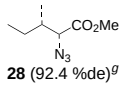
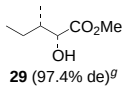
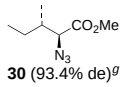
In summary, compared to other methods[2–4] that have been reported, this present method for the stereoselective synthesis of

Table 1 Azidation of alcohols[a]

Entry	Alcohol	Solvent	*t*/h	Azide	Yield (%)
1	 **1**	toluene	16	 **2**	76
2[b]	 **3**	toluene	6	 **4**	81
3[b]	 **5**	toluene	6	 **6**	87
4[b]	 **7** (96.5% ee)[c]	toluene	6	 **8** (96.3% ee)[c]	90
5	 **9** (100% ee)[d]	THF	1	 **10** (100% ee)[d]	94
6	 **11** (95.9% ee)[e]	THF	3	 **12** (95.6% ee)[e]	91
7	 **13** (100% ee)[c]	THF	2	 **14** (81.3% ee)[f]	82
8	 **15**	toluene	2	 **16a**  **16b**  **16c**	94 (9 : 5 : 2)[g]
9	 **17**	toluene	0.5	**16a** + **16b** + **16c**	95 (3 : 4 : 1)[g]
10	 **18**	toluene	2	**16a** + **16b** + **16c**	30 (7 : 10 : 3)[g] Sm 61[h]
11	 **19**	toluene	2	 **20a**  **20b**	82 (1 : 1)[g]

continued

Table 1 *continued*

Entry	Alcohol	Solvent	*t*/h	Azide	Yield (%)
12	 **21**	THF	2	 **22**	74
13	 **23**	THF	1	 **24a** **24b**	77 (8 : 1)[g]
14	 **25**	THF	2	 **26**	74 (*E* : *Z* 97 : 3)[g]
15[b]	 **27** (97.4% de)[g]	toluene	6	 **28** (92.4 %de)[g]	71
16[b]	 **29** (97.4% de)[g]	toluene	6	 **30** (93.4% de)[g]	68
17[b]	 **31**	toluene	24	none	
18[b]	 **32**	toluene	24	none	

[a] The reaction was carried out at room temp. unless stated otherwise. The absolute configuration of the chiral products was assigned by comparison of the sign of specific rotation with the literature value. [b] At 50 °C. [c] Determined by GC analysis using a Chiraldex G-TA capillary column. [d] Determined by GC analysis using a Chiraldex B-PM capillary column. [e] Determined by HPLC analysis using a Chiralpak AS chiral column. [f] Determined by GC analysis using a Chiraldex B-DA capillary column. [g] Determined by ^{1}H NMR analysis. [h] Sm = starting material.

azides has the advantages of simple procedure, mild reaction conditions and easy isolation of products.

This paper is dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

Footnote and References

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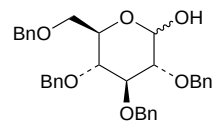
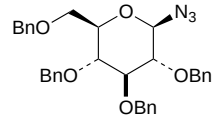
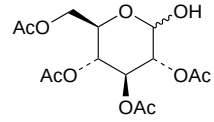
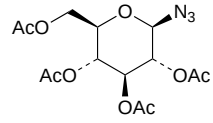
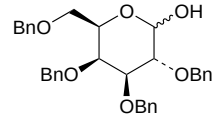
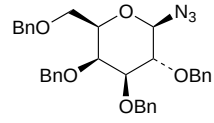
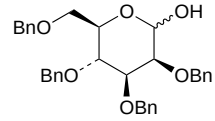
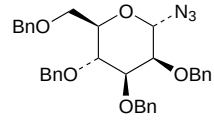
1 T. Sheradsky, in *The Chemistry of the Azido Group*, ed. S. Patai, Interscience, New York, 1971, p. 331.

Table 2 Azidation of hexopyranoses[a]

Entry	Hexopyranose	Azide	Yield (%)[b]
1	 **33**	 **34**	76 Sm 18
2	 **35**	 **36**	34 Sm 56
3	 **37**	 **38**	85[c] α 9
4	 **39**	 **40**	75 β 13

[a] Reaction in DMF for 2 h at room temp. [b] Sm = starting material. [c] Determined by ^{1}H NMR analysis.

2 (*a*) M. E. C. Biffin, J. Miller and D. B. Paul, in *The Chemistry of the Azido Group*, ed. S. Patai, Interscience, New York, 1971, p. 57; (*b*) S. G. Alvarez and M. T. Alvalez, *Synthesis*, 1997, 413.
3 (*a*) D. L. Hughes, *Org. Prep. Proced. Int.*, 1996, **28**, 127; (*b*) A. Saito, K. Saito, A. Tanaka and T. Oritani, *Tetrahedron Lett.*, 1997, **38**, 3955.
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Received in Cambridge, UK, 7th August 1997; 7/05768G