Zinc Azide Mediated Mitsunobu Substitution. An Expedient Method for the One-Pot Azidation of Alcohols

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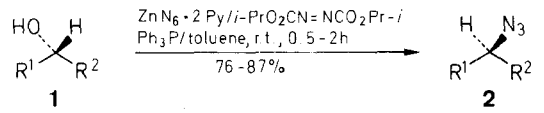
In the presence of the diisopropyl azodicarboxylate/triphenylphosphine couple, alcohols react with zinc azide/bis-pyridine complex to give various azides via a Mitsunobu-type substitution.

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 displacement of the corresponding halides or sulfonates by azide anion;[2] diverse modifications have been proposed in view of improving the yields and reducing the hazards.[3] Several methods have been reported that involve an oxy-phosphonium-type activation,[4,5] including Mitsunobu reaction[6] with diphenylphosphoryl azide[7] or inconvenient hydrazoic acid[8,9] as the nucleophilic partner.

In the course of our investigation on the reactivity of zinc salts in the Mitsunobu reaction,[10,11] we now report on the use of zinc azide, in the form of its more stable bis-pyridine complex,[12] for the one-pot conversion of alcohols into azides.

Treatment of primary and secondary alcohols **1a–l** with zinc azide/bis-pyridine complex (1.5 equiv), triphenylphosphine (2 equiv) and diisopropyl azodicarboxylate (2 equiv) in toluene smoothly afforded the corresponding azides **2a–l** in good yields. Allylic-type structures **1c**, **1k** and **1l** did not rearrange through a S_N2' pathway.



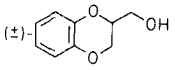
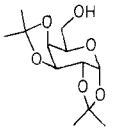
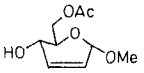
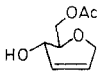
Substrate		Product
1a	2-phenyl ethanol	**2a**
1b	(±)-1-phenyl ethanol	**2b**
1c	(*E*)-cinnamyl alcohol	**2c**
1d	(*S*)-(−)-ethyl lactate	**2d**
1e	(−)-menthol	**2e**
1f	β-cholestanol	**2f**
1g	β-cholesterol	**2g**
1h		**2h**
1i	(±)-*trans*-1-hydroxymethyl-2-phenyloxirane	**2i**
1j		**2j**
1k[13]		**2k**
1l[14]		**2l**

Table. Azides **2** Prepared, Selected Data

Product	Yield (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	Molecular Formula[a] or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[b] δ, *J*(Hz)
2a	83	–	–[19]	2.89 (t, 2H, *J* = 7.3), 3.50 (t, 2H, *J* = 7.3)
2b	81	–	–[20,21]	1.53 (d, 3H, *J* = 7.0), 4.61 (q, 1H, *J* = 7.0)
2c	85	–	–[21]	3.94 (d, 2H, *J* = 6.6), 6.24 (dt, 1H, *J* = 6.6, 16.0), 6.65 (d, 1H, *J* = 16.0)
2d	83	+ 15° (1.0)	–[22,b]	1.29 (t, 3H, *J* = 7.3), 1.45 (d, 3H, *J* = 7.1), 3.91 (q, 1H, *J* = 7.1), 4.23 (q, 2H, *J* = 7.3)
2e	76	+108° (2.5)	–[10]	3.97 (br s, 1H, H-3eq)
2f	82	+ 19° (0.7)	+18.2°[8] (0.9)	3.88 (m, 1H, H-3eq)
2g	80	− 6° (0.8)	− 4.7°[8] (1.38)	3.88 (m, 1H, H-3eq), 5.39 (m, 1H, H-6)
2h	87	–	–[23]	3.50 (dd, 1H, *J* = 5.1, 13.4, H-α), 3.58 (dd, 1H, *J* = 6.1, 13.4, H-α'), 4.08 (dd, 1H, *J* = 6.4, 11.4, H-3), 4.26 (dd, 1H, *J* = 2.1, 11.4, H-3'), 4.35 (m, 1H, H-2)
2i	78	–	$C_9H_9N_3O$ (175.2)	3.22 (m, 1H, H-2), 3.44 (dd, 1H, *J* = 5.0, 13.4, H-1), 3.64 (dd, 1H, *J* = 3.3, 13.4, H-1'), 3.85 (d, 1H, *J* = 1.6, H-3)
2j	82	− 94° (1.0)	$[\alpha]_D^{20}$ + 96.9°[24] (*c*, 1.1, $CHCl_3$)	1.33 (s, 6H), 1.44 (s, 3H), 1.53 (s, 3H), 3.34 (dd, 1H, *J* = 5.3, 12.4, H-6), 3.48 (dd, 1H, *J* = 7.7, 12.4, H-6'), 3.90 (ddd, 1H, *J* = 5.3, 7.7, H-5), 4.17 (dd, 1H, J_{43} = 8.2, H-4), 4.32 (dd, 1H, *J* = 2.2, 5.0, H-2), 4.61 (dd, 1H, *J* = 2.2, 8.2, H-3), 5.52 (d, 1H, *J* = 5.0, H-1)
2k	85	−547° (1.2)	$C_9H_{13}N_3O_4$ (227.2)	2.09 (s, 3H, $COCH_3$), 3.36 (m, 1H, H-4), 3.45 (s, 3H, OMe), 4.42 (m, 1H, H-5), 4.96 (d, 1H, *J* = 2.4, H-1), 6.08 (dd, 1H, *J* = 5.0, 10.0, H-3), 6.16 (dd, 1H, *J* = 3.0, 10.0, H-2)
2	80	−452° (2.5)	$C_8H_{11}N_3O_3$ (197.2)	2.10 (s, 3H, $COCH_3$), 3.41 (m, 1H, H-4), 3.84 (dd, 1H, $J_{1,4}$ = 2.4, $J_{1,1'}$ = 12.3, H-1), 4.13 (dd, 1H, *J* = 6.3, 12.0, H-6), 4.18 (dd, 1H, $J_{1',4}$ = 1.6, $J_{1',1}$ = 12.3, H-1'), 4.26 (dd, 1H, *J* = 3.9, 12.0, H-6'), 6.03 (m, 1H, H-2), 6.08 (dd, 1H, $J_{2,3}$ = 10.6, H-3)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.16, N ±0.30.
[b] Optical rotation of the *S* enantiomer $[\alpha]_D^{20}$ − 16.4° (neat).
[c] Only relevant NMR data are given and interpreted where necessary.

Chiral secondary alcohols **1d–g**, **1k** and **1l** underwent complete configuration inversion as evidenced by ^{1}H-NMR data and optical rotations. This was particularly striking in the conversion of α-D-*erythro* compound **1k**[13] into methyl 6-*O*-acetyl-4-azido-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranoside **(2k)**, which showed typical ^{1}H-NMR features (strong downfield shift for H-5, enhanced values of the H-1, H-2 and H-4, H-5 coupling constants),[15,16] and was strongly laevorotatory as expected.[17] Similar observations were made for 6-*O*-acetyl-1,5-anhydro-4-azido-2,3,4-trideoxy-D-*threo*-hex-2-enitol **(2l)** obtained from the corresponding epimeric alcohol **1l**.[14]

Thus, the present method offers an easy novel access to azides, including labile compounds such as **2d**, **2i**, **2k** and **2l**, and was successfully applied to aminosaccharide syntheses.[18] The use of other covalent salts as nucleophile-carrier in the Mitsunobu reaction is presently being investigated in our laboratory.

IR spectra were recorded on a Perkin Elmer 297 spectrophotometer: all compounds **2a–l** displayed the azido absorption band around ν = 2100 cm^{-1}. Observed rotations at the Na-D line were measured at 25°C using a Perkin Elmer Model 141 polarimeter. ^{1}H-NMR spectra (300 MHz) were recorded on a Bruker AM 300 WB instrument. The procedure of Agrell[12] for the preparation of $ZnN_6 \cdot 2Py$ was modified as described below.

$ZnN_6 \cdot 2Py$:
To a stirred 2M aq. solution of $Zn(NO_3)_2$ (60 mL, 120 mmol) is added dropwise a 2 M aqueous solution of NaN_3 (120 mL, 240 mmol). The white suspension is brought to ca. 50°C, then a slight excess of pyridine (20 mL, 247 mmol) is added dropwise forming a dense white precipitate. Stirring is continued while the mixture is slowly cooled to r.t. The salt is filtered, washed with ice-cold water and dried *in vacuo* to give a white crystalline powder; yield 30 g (81%).

Conversion of Alcohols 1 into Azides 2; General Procedure:
$ZnN_6 \cdot 2Py$ (0.46 g, 1.5 mmol) is suspended in a solution of the alcohol **1** (2 mmol) and Ph_3P (1.05 g, 4 mmol) in anhydrous toluene (10 mL). To this stirred mixture at r.t., diisopropyl azodicarboxylate (0.8 mL, 4 mmol) is added dropwise, causing a slightly exothermal reaction. Stirring is continued until complete consumption (TLC monitoring) of **1** ($\leq$ 2 h) is observed. The heterogeneous mixture is filtered over a Celite pad, concentrated *in vacuo* and purified by column chromatography over 70–230 mesh silica gel (eluents: hexane/EtOAc, 9:1 or 4:1) to afford the pure azides (Table).

The authors wish to thank Prof. G. Guillaumet for multiform support.

Received: 13 April 1989; revised: 2 August 1989

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