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Ring opening reaction of epoxides with diphenyl phosphorazidate

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Abstract

Diphenyl phosphorazidate with 4-dimethylaminopyridine and lithium perchlorate opens epoxides regio- and stereoselectively to give *O*-diphenylphosphoryl vicinal azidohydrins. For the α,β-epoxy ketones and esters, only the corresponding α-azidovinyl ketones and esters were directly obtained, respectively. © 1999 Elsevier Science Ltd. All rights reserved.

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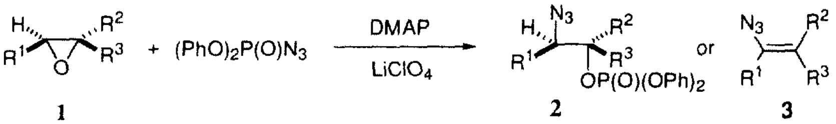
Vicinal azidohydrins, potential precursors for β-amino alcohols and aziridines, are compounds of undoubted interest in organic synthesis.[1] The most common synthetic route to vicinal azidohydrins is the ring opening reaction of epoxides with azide compounds such as trimethylsilyl azide or sodium azide promoted by Lewis acids or transition-metal complexes.[2] Our continued interest in the use of diphenyl phosphorazidate [DPPA, $(PhO)_2P(O)N_3$][3] as an azidation reagent prompts us to report a novel procedure for the direct transformation of epoxides **1** to *O*-diphenylphosphoryl vicinal azidohydrins **2**. We have now found that DPPA reacts regio- and stereoselectively with epoxides **1** in the presence of 4-dimethylaminopyridine (DMAP) and lithium perchlorate to give *O*-diphenylphosphoryl vicinal azidohydrins **2**, as shown in Scheme 1. For the α,β-epoxy ketones **1** (R^1=RCO-) and esters **1** (R^1=ROCO-), the corresponding α-azidovinyl ketones and esters **3** are respectively obtained.



Scheme 1.

The treatment of glycidyl phenyl ether **1d** with DPPA (1.2 equiv.) in the presence of DMAP (1.2 equiv.) and lithium perchlorate (0.1 equiv.) in DMF (1 mol/L) at 50°C for 10 h afforded the corresponding *O*-diphenylphosphoryl vicinal azidohydrin **2d** resulting from opening on the less hindered side in 86%

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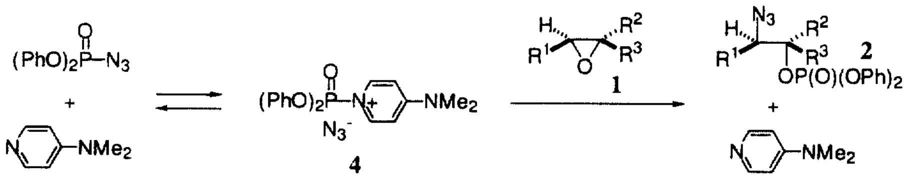
yield.[4] DMAP turned out to be the most effective base in this reaction, leading to a higher yield than triethylamine (46%), while the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to a complex reaction mixture not containing the desired product. Although a full equivalent of the base was not required for the complete reaction, no reaction occurred in the absence of the base. When this reaction was carried out without lithium perchlorate, the time needed for the completion of this reaction was extremely prolonged (36 h). DMF was the solvent of choice though acetonitrile and THF can also be used.

A possible mechanism for this novel ring opening reaction is shown in Scheme 2. At first, DMAP reacts with DPPA to form 1-(diphenylphosphoryl)-4-(dimethylamino)pyridinium azide **4**, which then cleaves the epoxy ring to give the desired *O*-diphenylphosphoryl vicinal azidohydrin **2** and the regenerated DMAP. To confirm this assumption, a 1:1 mixture of DPPA and DMAP was heated at 50°C and analyzed by IR spectroscopy. The mixture immediately showed a new azide absorption peak at 2041 cm^{-1} in addition to the parent DPPA peak at 2170 cm^{-1}. These results indicated that 1-(diphenylphosphoryl)-4-(dimethylamino)pyridinium azide **4** is the real reactive species of this ring opening reaction. Lithium perchlorate would activate the epoxide **1** to facilitate its ring opening in an S_N2 reaction manner.

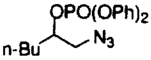
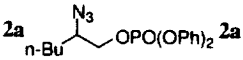
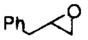
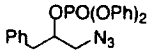
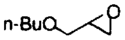
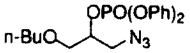
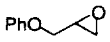
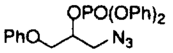
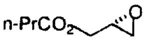
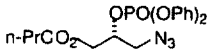
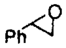
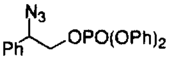
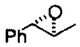
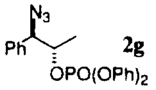
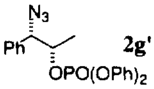
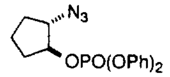
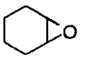
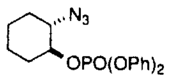
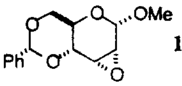
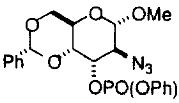
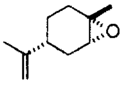
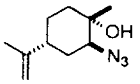
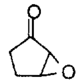
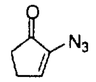
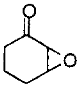
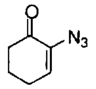
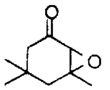
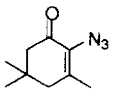
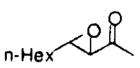
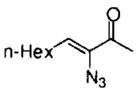
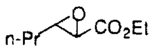
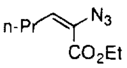


Scheme 2.

The representative results of this reaction are summarized in Table 1. Although the trisubstituted epoxide **1k** gave only the *O*-deprotected vicinal azidohydrin **5k**, the monosubstituted **1a–1f** and disubstituted epoxides **1g–1j** underwent this ring opening reaction to give the corresponding *O*-diphenylphosphoryl vicinal azidohydrins **2a–2j** in moderate to good yields. The rate of the reactions turned out to depend on the structure of the employed epoxides. As a general trend, the reaction of the epoxides **1c–1e** with a neighboring alkoxy or carboalkoxy group, which forms the five-membered chelate including the epoxide oxygen and alkoxy or carboalkoxy oxygen with lithium ion, proceeded much faster than that of the isolated epoxides **1a**, **1b** and **1f**. In the case of a sterically hindered epoxide such as 2,3-anhydro-allopyranoside **1j**, the reaction sluggishly progressed even if a stoichiometric amount of lithium perchlorate was used. The reactions carried out with our new methodology are completely *anti* stereoselective, as shown by the exclusive presence of the *anti* adduct in the reactions of the cyclic epoxides **1h–1j**. As for the regiochemistry of the ring cleavage for unsymmetrical epoxides **1a–1g** and **1j**, the reactions are highly regioselective with the attack of the azide on the less hindered carbon of the epoxide, except for the phenyl-substituted epoxides **1f** and **1g**, in which the azide exclusively attacks the benzylic carbon of the epoxide.

However, when this method was applied to the α,β-epoxy ketones **1l–1o** and ester **1p**, only the corresponding α-azidovinyl ketones **3l–3o** and ester **3p** were regioselectively obtained, respectively, instead of resulting in the usual *O*-diphenylphosphorylative cleavage. Obviously, the initial product is the *O*-diphenylphosphoryl vicinal azidohydrin **2** in which the hydrogen atom at the α-position is relatively acidic and **2** easily undergoes the dephosphorylation by the action of DMAP to give the α-azidovinyl ketones and esters **3**, respectively. For the acyclic α,β-epoxy ketone **1o** and ester **1p**, the reactions sluggishly proceeded to give the corresponding α-azidovinyl ketone **3o** and ester **3p** as a single geometrical isomer in moderate yields (27% and 23%, respectively), and the unchanged epoxides **1o** (51%) and **1p** (58%) were recovered even after 96 h. The use of a stoichiometric amount of lithium

Table 1
Azidolysis of epoxides with DPPA in the presence of DMAP and $LiClO_4$

Entry	Epoxide		Method[a]	Time (h)	Product[b]		Yield (%)[c]
1		**1a**	A	72	 **2a** 	**2a'**	43 (94:6)[d]
2		**1b**	A	48		**2b**	64
3		**1c**	A	18		**2c**	71
4		**1d**	A	10		**2d**	86
5		**1e**	A	7		**2e**	70
6		**1f**	A	60		**2f**	29
7		**1g**	A	96	 **2g** 	**2g'**	67 (96:4)[d]
8		**1h**	A	72		**2h**	60
9		**1i**	A	84		**2i**	73
10		**1j**	B B (80°C)	96 24		**2j**	36 (sm 37) 48
11		**1k**	B	84		**5k**	52
12		**1l**	A	3		**3l**	88
13		**1m**	A	12		**3m**	68
14		**1n**	A	96		**3n**	70
15		**1o**	A	96		**3o**	27 (sm 51)
16		**1p**	A	96		**3p**	23 (sm 58)

a) Method A: DPPA (1.2 eq), DMAP (1.2 eq), $LiClO_4$ (0.1 eq), DMF, 50 °C; Method B: DPPA (1.5 eq), DMAP (1.5 eq), $LiClO_4$ (1.5 eq), CH_3CN, 50 °C. b) All products were fully characterized by ^1H and ^{13}C NMR, IR, and HRMS. c) Isolated yield after chromatographic purification. sm: recovered starting material. d) Determined by ^1H NMR analysis.

perchlorate or elevated temperature (80°C) for the reaction of acyclic epoxides **1o** and **1p** did not have the intended effect but rather increased the amount of impurities. The stereochemistry of the products **3o** and **3p** could be assigned using a ^{1}H NMR analysis of the corresponding iminophosphoranes[5] obtained by treatment with triphenylphosphine. The olefinic protons of the iminophosphoranes derived from **3o** and **3p** were observed as H–P coupling constants of 6.8 Hz and 2.8 Hz, respectively, which suggested that the stereochemistry of the α-azidovinyl ketone **3o** is the *Z* configuration, while that of the α-azidovinyl ester **3p** is the *E* configuration on the basis of data of the analogs reported in the literature,[6] although the mechanism for the remarkable change in the stereoselectivity is unclear. It should be noted that a representative method for the azidolysis of epoxides using sodium azide in the presence of ammonium chloride or lithium perchlorate,[7] when applied to the α,β-epoxy ketone **1m**, gave a very complex reaction mixture because this method is susceptible to causing other reactions such as isomerization and addition to the carbonyl group. Accordingly, our procedure might provide a new and convenient method for the synthesis of α-azidovinyl ketones and esters.

In conclusion, this new procedure, which is the first example of the use of DPPA as a source of azide for the azidolysis of epoxides, provides a regioselective transformation of epoxides to *O*-diphenylphosphoryl vicinal azidohydrins, except for the α,β-epoxy ketones and esters, which directly afford the corresponding α-azidovinyl ketones and esters, respectively. An investigation of the synthetic utility of *O*-diphenylphosphoryl vicinal azidohydrins as well as more favorable conditions for the azidolysis of epoxides is in progress.

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4. A typical experimental procedure is as follows: A mixture of glycidyl phenyl ether **1d** (95%, 430 μL, 3.0 mmol) and LiClO$_4$ (32 mg, 0.3 mmol) was dissolved in dry DMF (3 mL). To the resulting solution was added DPPA (96%, 810 μL, 3.6 mmol) followed by DMAP (440 mg, 3.6 mmol) with stirring. After being stirred at 50°C for 10 h, the mixture was diluted with EtOAc (30 mL) and washed with 0.5N HCl (15 mL) and then water (15 mL). Drying over MgSO$_4$, evaporation of the solvents, followed by purification by silica gel column chromatography with acetone:toluene (1:200) as eluant afforded *O*-diphenylphosphoryl vicinal azidohydrin **2d** (1.10 g, 86%) as a colorless oil: IR (neat) 3064, 2106, 1589, 1489, 1289, 1189, 1024, 958 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.59 (1H, dd, *J*=13.2, 5.6 Hz), 3.64 (1H, ddd, *J*=13.2, 4.4, 0.8 Hz), 4.08 (1H, dd, *J*=10.4, 5.2 Hz), 4.10 (1H, dd, *J*=10.4, 5.2 Hz), 4.91–4.99 (1H, m), 6.81 (2H, d, *J*=8.4 Hz), 6.95 (1H, t, *J*=7.2 Hz), 7.11–7.34 (12H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 51.5, 66.4, 76.2, 114.4, 119.9, 121.4, 125.4, 129.4, 129.7, 150.2, 157.7; HRMS (FAB) calcd for $C_{21}H_{21}N_3O_5P$ [(M+H)$^+$] 426.1219, found 426.1229.
5. Data for the iminophosphorane derived from **5o**: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.88 (3H, t, *J*=6.8 Hz), 1.28–1.43 (6H, m), 1.51 (2H, tt, *J*=7.2, 6.8 Hz), 2.16 (3H, s), 2.59 (2H, dt, *J*=7.2, 7.2 Hz), 5.90 (1H, td, *J*=7.2, 6.8 Hz), 7.34–7.43 (9H, m), 7.70–7.75 (6H, m). Data for the iminophosphorane derived from **5p**: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.90 (3H, t, *J*=7.2 Hz), 0.98 (3H, t, *J*=7.2 Hz), 1.42 (2H, tq, *J*=7.6, 7.2 Hz), 2.37 (2H, tdd, *J*=7.6, 6.8, 2.8 Hz), 3.84 (2H, q, *J*=7.2 Hz), 6.01 (1H, td, *J*=6.8, 2.8 Hz), 7.37–7.47 (9H, m), 7.68–7.74 (6H, m).
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