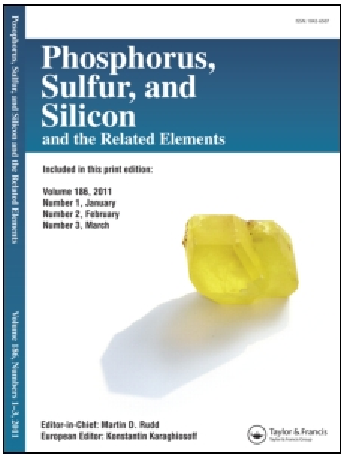

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SILICA GEL PROMOTED HIGHLY REGIOSELECTIVE RING OPENING OF EPOXIDES USING NaN_3 UNDER SOLVENT FREE CONDITIONS

Ali Reza Kiasat and Foad Kazemi
Shahid Chamran University, Ahvaz, Iran

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A convenient and efficient synthesis of vicinal azidohydrin has been achieved by ring opening of epoxides using SiO_2/NaN_3 *under solvent free conditions. The reaction is highly regioselective and afforded the corresponding products in good to excellent yields under mild and neutral reaction conditions.*

Keywords: Azidohydrine; azidolysis; epoxide; ring opening; silica gel; solid state; solvent free

Oxiranes are well known electrophiles capable of reacting with a wide variety of nucleophiles to generate ring-opened products.[1] Among the various nucleophiles employed in epoxide opening reactions the azidolysis of epoxides enjoys a prominent position because the vicinal azidohydrins obtained upon ring opening can be easily reduced to 1,2 aminoalcohols,[2] which have been extensively used in pharmaceuticals,[3] carbohydrates,[2] and in carboxylic nucleosides.[4]

Azidation of epoxides as the most recognized method to 1,2-aminoalcohols are often performed in aqueous solution under alkaline or acidic conditions.[5] Even though the classical protocol uses sodium azide and ammonium chloride, the azidolysis reaction requires a long reaction (12–48 h) and the azidohydrin is often accompanied by isomerization, epimerization, and rearrangement of products.[6] A great variety of reagents or catalysts have emerged as a result of sustained efforts by chemists to discover new and mild methods to effect azidolysis of epoxides under non aqueous conditions.[7] Onaka et al.[8] reported that sodium azide supported on three types of porous solid acids (zeolite, alumina, and silica gel) can be used as reagents for azidolysis of epoxides. They showed that the activities of the supported reagents are greatly

Address correspondence to Foad Kazemi, Chemistry Department, College of Sciences, Shahid Chamran University, Ahvaz, Iran.

influenced by loading amounts of NaN_3, amounts of adsorbed water in the reagents, acidic properties of the solid acids, and reaction solvents. The reactions of tributyltin and dibutyltinazide[9] or LiN_3[10] with epoxides and the reaction of epoxide with NaN_3 in the presence of catalytic amount of $LiClO_4$,[11] CAN,[12] $CeCl_3$,[6] or $LiBF_4$,[7] trimethylsilylazide in the presence of catalytic amount of Lewis acids[13] or tetrabutylammonium salt[14] in nonaqueous solvents have been reported. Unfortunately, some of these methods are not always fully satisfactory and suffer from disadvantages such as acidity, relative long reaction times, low regioselectivity, or need of application of wet solvent. Consequently, it seems that there is still a need for development of newer methods that proceed under mild and economically appropriate conditions.

Keeping in mind these facts as well as reports about advantages of reaction under dry conditions in the presence of inorganic solids, we describe our successful result that led to an efficient and simple method for the transformation of epoxides into the corresponding azidohydrins using NaN_3/SiO_2 in solvent free process in excellent isolated yields.

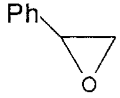
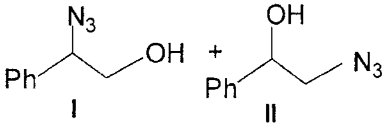
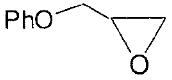
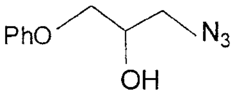
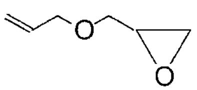
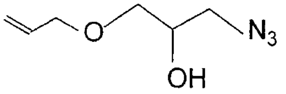
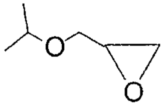
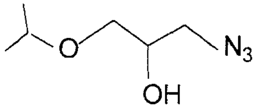
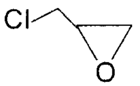
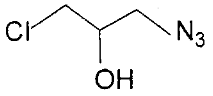
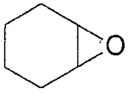
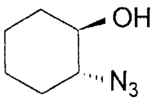
RESULTS AND DISCUSSION

Several ring-opening reactions of styrene oxide were performed at various temperatures and with different amounts of inorganic solid and sodium azide in order to find the most adequate conditions for this reaction under solvent-free conditions. In a preliminary study, the effect of alumina and silica gel as inorganic solids on the yield of azidohydrin was investigated with the reaction of styrene oxide as a model reaction. The obtained results, clearly indicated, silica gel is the best solid support for this reaction. The required mole ratio 2:1 of NaN_3 and substrate, respectively, silica gel 0.5 g, and the maximum oil bath temperature of 80°C were found to be optimal conditions.

The procedure involves a simple mixing of neat epoxides with NaN_3/silica gel and heating the mixtures in an oil bath for the time being specified in Table I. Different types of oxiranes carrying activated and deactivated groups were cleanly, easily, and efficiently converted to the corresponding azidohydrins as exclusive and virtually pure products according to TLC and ^{1}HNMR, in considerably short times and in excellent yields. The scope and generality of this process is illustrated with several examples and the results are summarized in Table I. The structure of all the products were settled from their analytical and spectral (IR, ^{1}H NMR) data and by direct comparison with authentic samples.

The promoting effect of silica gel was definitely confirmed by reaction of styrene oxide with sodium azide under similar conditions, without

TABLE I Regioselective Ring Opening of Epoxides to the Corresponding Azidohydrines with NaN_3/SiO_2 at 80°C Under Solvent-Free Conditions

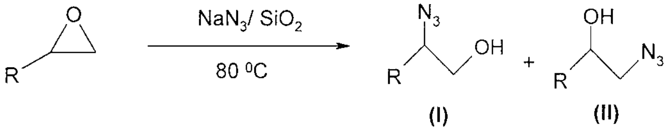
Entry	Epoxide	Azido alcohol[a]	Time (min)	Yield[b] (%)
1			15	94 (I: 90%) (II: 10%)
2			25	94
3			25	92
4			25	92
5			15	88
6			30	86

[a] Products were identified by compersion of their physical and spectral data with those of authentic samples.

[b] Isolated yield.

adding silica gel, the reaction time period was longer and the yield was found to be considerably lower.

The regioselectivity of the ring opening of epoxides is thoroughly dependent on the mechanism of the reaction and particularly on steric and electronic factors. The reaction of styrene oxide with sodium azide supported on silica gel was completed under solvent free condition in 80°C after 15 min and produced 94% of 1,2-azidoalcohol as a mixture of two isomers. The ratio of α-attack (2-azido-2-phenylalcohol) **I** to β-attack (2-azido-1-phenylalcohol) **II** was found to be 90:10. Epoxides carrying electron-withdrawing groups reacted under similar reaction conditions and their corresponding 1,2-azidoalcohols were produced in excellent yields and regioselectivity. In these cases, with the attack of the azide ion on the less substituted oxirane carbon, the regioselectivity is reversed and the 1,2-azidoalcohol **II** is obtained. It is shown that, for epoxides carrying electron-donating groups, the electronic factor predominates and the nucleophilic attack of azide ion is strongly favored on the more substituted carbon atom of epoxides. In contrary, epoxides carrying electron-withdrawing groups, it is the steric factor which predominates and the nucleophilic attack of azide ion is strongly favored on the less substituted carbon atom of epoxides (Scheme 1).



SCHEME 1

The advantage of using NaN_3/SiO_2 as reagent for the azidation of epoxides is shown by comparing our results with those previously reported in the literature (Table II).

Compared to some previously reported methods with major or minor drawbacks, several noteworthy features of this reagent are apparent. These are the easy work-up procedure, availability of the reagent, operational simplicities, and use of inexpensive reagent.

CONCLUSION

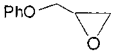
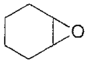
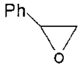
We believe that the present procedure for azidation of epoxides provides an easy, mild, efficient, versatile, and general methodology for the preparation of azidohydrins from different classes of epoxides, and we feel that it may be a suitable addition to methodologies already present in the literature.

EXPERIMENTAL

General

IR spectra were recorded on a Shimadzo 450 spectrophotometer; and ^{1}HNMR spectra in $CDCI_3$ on a Bruker Avance DPX instrument (250 MHz). Required epoxides were purchased from Fluka and Merck. Products were characterized by comparison of their physical data, IR, and ^{1}H NMR spectra with authentic samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates.

TABLE II Comparison of Azidolysis of Some Epoxides with Different Methods

Entry	Epoxide	Reagent and Reaction Conditions	Time (h)	α-Attack	β-Attack	Yield (%)
1		LiCIO$_2$/NaN$_3$/CH$_3$CN/reflux[11]	5	<1	>99	97
		Mg(CIO$_4$)$_2$/NaN$_3$/CH$_3$CN/reflux[11]	2	<1	>99	96
		LiOTf/NaN$_3$/CH$_3$CN/reflux[11]	5	<1	>99	92
		LiN$_3$/CH$_3$CN/reflux[11]	5	<1	>99	97
		NaN$_3$/CH$_3$CN/reflux[11]	24	—	—	NR
		NH$_4$CI/NaN$_3$/MeOH/H$_2$O/reflux[15]	12	<1	>99	95
		KCIO$_4$/NaN$_3$/CH$_3$CN/reflux[11]	24	—	—	NR
		NaCIO$_4$/NaN$_3$/CH$_3$CN/reflux[11]	24	—	—	NR
		Zn(OTf)$_2$/NaN$_3$/CH$_3$CN/rt[11]	2	<1	>99	88
		CAN/NaN$_3$/t-BuOH/reflux[12]	0.5	<1	>99	85
		LiBF$_4$/NaN$_3$/wet t-BuOH/reflux[7]	1.16	<1	>99	95
		CeCI$_3$·7H$_2$O/NaN$_3$/CH$_3$CN/reflux[6]	3	—	—	99
		SiO$_2$/NaN$_3$/Solvent free/80°C	0.42	—	—	92
2		LiCIO$_4$/NaN$_3$/CH$_3$CN/reflux[11]	36	—	—	95
		Mg(CIO$_4$)$_2$/NaN$_3$/CH$_3$CN/reflux[11]	24	—	—	94
		NH$_4$CI/NaN$_3$/MeOH/H$_2$O/reflux[15]	36	—	—	92
		Zr(OTf)$_2$/TMGA/CH$_3$CN/rt[16]	42	—	—	84
		CAN/NaN$_3$/t-BuOH/reflux[12]	5	—	—	91
		LiBF$_4$/NaN$_3$/wet t-BuOH/reflux[7]	0.4	—	—	96
		R$_4$NCI/Me$_3$SiN$_3$/solvent free/r[14]	24	—	—	89
		CeCI$_3$·7H$_2$O/NaN$_3$/CH$_3$CN/reflux[6]	3	—	—	98
		SiO$_2$/NaN$_3$/Solvent free/80°C	0.5	—	—	86
3		LiCIO$_4$/NaN$_3$/CH$_3$CN/reflux[11]	5	82	18	92
		Mg(CIO$_4$)$_2$/NaN$_3$/CH$_3$CN/reflux[11]	2	83	17	78
		LiN$_3$/CH$_3$CN/reflux[11]	5	81	19	90
		NH$_4$CI/NaN$_3$/MeOH/H$_2$O/reflux[15]	20	79	21	94
		Zr(OTf)$_2$/TMGA/CH$_3$CN/rt[16]	42	74	26	67
		CAN/NaN$_3$/t-BuOH/reflux[12]	0.25	90	10	98
		LiBF$_4$/NaN$_3$/wet t-BuOH/reflux[7]	0.16	90	10	96
		R$_4$NCI/Me$_3$SiN$_3$/solvent free/rt[14]	24	76	8	84
		CeCI$_3$·7H$_2$O/NaN$_3$/CH$_3$CN/reflux[6]	3	86	10	96
		SiO$_2$/NaN$_3$/Solvent free/80°C[a]	0.25	90	10	94

[a] Present method.

GENERAL PROCEDURE FOR THE AZIDOLYSIS OF EPOXIDES

Fine powdered sodium azide (2 mmol, 0.13 g) was mixed with 0.5 g of silica gel in a 25 ml round bottomed flask. To the resulting powder, epoxide (1 mmol) was added and stirred at 80°C for 15–30 min. The progress of the reaction was followed by TLC until no starting material could be detected. The mixture was shaken with CH$_2$CI$_2$ (5 ml) and filtered.

The residue was thoroughly stirred and washed with CH_2Cl_2 and the solvent evaporated under reduced pressure to afford crude products. Further purification was achieved by preparative TLC or by silica gel column chromatography to give pure azidohydrin in 86–94% isolated yields.

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