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Nasser Iranpoor^a; Habib Firouzabadi^a; Arezu Jamalian^a

^a Department of Chemistry, Shiraz University, Shiraz, Iran

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Silphos [$\text{PCl}_{3-n}(\text{SiO}_2)_n$]: A Heterogeneous Phosphine Reagent for the Regioselective Synthesis of *vic*-Haloalcohols

Nasser Iranpoor
Habib Firouzabadi
Arezu Jamalian

Department of Chemistry, Shiraz University, Shiraz, Iran

*Silphos as a silica-based phosphine [$\text{PCl}_{3-n}(\text{SiO}_2)_n$] provides a practical method for the conversion of epoxides to *vic*-haloalcohols in the presence of molecular bromine, iodine, or *N*-halosuccinimides (NXS, X = Cl, Br, I) in CH_3CN or under solvent-free conditions at r.t. The simple filtration of heterogeneous Silphos oxide from the reaction mixture affords the pure *vic*-haloalcohols with excellent yields.*

Keywords Epoxide; heterogeneous phosphine; molecular halogens; *N*-halosuccinimide; Silphos; *vic*-haloalcohol

INTRODUCTION

Supported reagents have continuously received attention from the synthetic points of view for their high efficiency, environmentally benign conditions, and convenient work-up procedures.^{1,2} Silica gel has been presented to be one of the most useful inorganic solid supports for functional group transformations.^{1,3–4} One of the major advantages of using silica gel as a supporting reagent is its weak acidic character (pH 5.5–7.5).^{1g} On the other hand, *vic*-haloalcohol formation from epoxides has been achieved in the presence of various catalysts and reagents.⁵ Furthermore, phosphine-containing reagents have also been applied for this transformation.⁶ However, the use of these phosphine reagents is not always fully satisfactory and suffers from disadvantages such as the need for time-consuming chromatographic separation of the produced phosphine-oxide,^{6a,d,f} the use of toxic⁷ dimethyl aminopyridine along

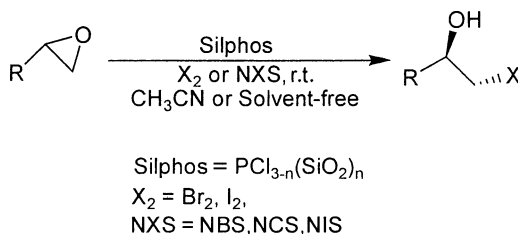
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Address correspondence to Nasser Iranpoor, Shiraz University, Department of Chemistry, College of Sciences, Shiraz 71454, Iran. E-mail: iranpoor@chem.susc.ac.ir

with the phosphine reagent,^{6e} and the use of expensive polymeric phosphine reagents.^{6b}

In connection with our interest in using heterogeneous phosphines, we now report that Silphos [$\text{PCl}_{3-n}(\text{SiO}_2)_n$] as a novel and easily prepared heterogeneous silica-based phosphine reagent converts epoxides to *vic*-haloalcohols conveniently with the ease of removal of the produced Silphos oxide by a simple filtration (Scheme 1). In this article, the results that successfully led to presenting a versatile procedure for the epoxide-haloalcohol transformation are described.



SCHEME 1

RESULTS AND DISCUSSION

For preliminary studies, we reacted 2,3-epoxypropylphenyl ether with different amounts of Silphos (0.6–1.0 g) and N-bromosuccinimide (NBS) (1.0–1.2 mmol) to optimize the reaction condition. As it is represented in Table I, in both cases, the reaction in CH_3CN or under solvent-free condition's with the molar ratio of epoxide to NBS (1:1.2) and

TABLE I The Optimization of the Reaction Conditions for the *vic*-Haloalcohol Formation From 2,3-Epoxypropylphenyl Ether in the Presence of Silphos and Different Brominating Agents at R.T.

Entry	mmol (Brominating Agent)	g of Silphos	Solvent	Time (h)	Conversion (%) ^a
1	1.0 (NBS)	0.6	CH_3CN	24	30
2	1.0 (NBS)	0.8	CH_3CN	24	55
3	1.0 (NBS)	1.0	CH_3CN	24	70
4	1.1 (NBS)	1.0	CH_3CN	8	90
5	1.2 (NBS)	1.0	CH_3CN	1	100
6	1.2 (NBS)	1.0	—	15 min	100
7	1.2 (Br_2)	1.0	CH_3CN	1	100
8	1.2 (CBr_4)	1.0	CH_3CN	8	100

^aConversion was determined by GC analysis using *n*-octane as an internal standard.

1.0 g of Silphos [$\text{PCl}_{3-n}(\text{SiO}_2)_n$] led to the 100% conversion of 2,3-epoxypropylphenyl ether to its corresponding *vic*-bromoalcohol (Table 1, entries 5 and 6). The similar ratio was applied for Br_2 and CBr_4 as the brominating agents, which needed 1 and 8 h, respectively, for the quantitative conversion of 2,3-epoxypropylphenyl ether to its corresponding *vic*-haloalcohol (Table 1, entries 7 and 8).

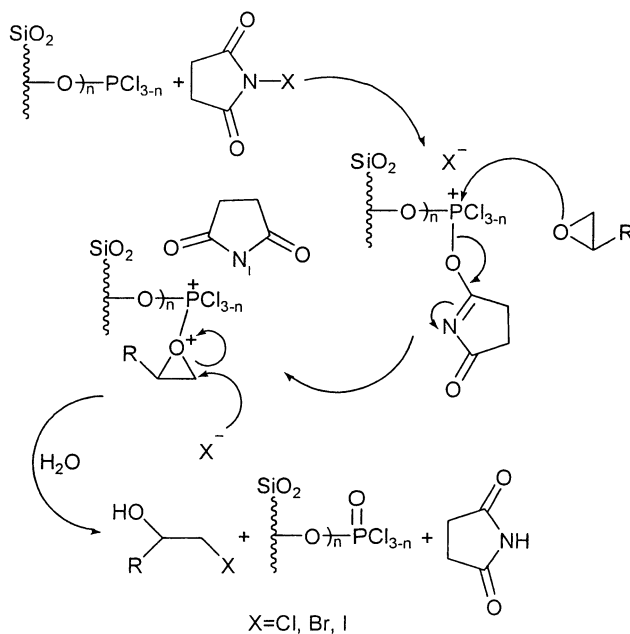
We applied the optimized conditions both in CH_3CN and under solvent-free conditions for the ring opening of structurally different epoxides to their corresponding *vic*-haloalcohols with molecular bromine and iodine, and also *N*-halosuccinimides (NXS, Cl, Br, I) as halogenating agents. The obtained results are summarized in Table II.

Under the optimized reaction conditions, the carbon–carbon double bond, ester group, ethereal bonds, and aromatic ring remained unchanged. The attack of the halide ion on the epoxides ring was influenced by both the electronic and steric factors. In the case of styrene oxide, the nucleophilic attack of the halide ion was oriented by the electronic factors to the more substituted carbon atom. On the other hand, the major product produced from the epoxides containing alkyl or electron-withdrawing substituents occurred from an attack to the less-hindered carbon atom.

Utilizing the optically active epoxide, (*R*)-(+)-styrene oxide as the substrate, the epoxide ring cleavage appeared to be stereospecific, producing the product with the inversion of the configuration. The specific rotation observed for (*S*)-2-bromo-2-phenylethanol was found to be $[\alpha]_{\text{D}} = +99.3$ ($c = 1$, CHCl_3 , Lit. $[\alpha]_{\text{D}} = +102.1$ ($c = 1$, CHCl_3)).^{1g}

The exact mechanism of the method is not clear; however, the proposed mechanism for this conversion with Silphos in the presence of NXS (Cl, Br, I) and molecular bromine or iodine could be the same. Similar to PPh_3 , Silphos can readily react with both molecular halogens or NXS to produce partially ionic adducts, which increase the electrophilic nature of the phosphorus atom.^{6a,8} However, there are some reports that *N*-halosuccinimide (NXS) has acted as the source of the halide ion and not the activating group for the phosphorus atom of the phosphine reagents.⁹ We observed that Silphos reacts with molecular bromine or NXS before the addition of epoxide to produce the positively charged phosphorus intermediate, which is already reported in the literature.^{8,9} It was therefore concluded that the phosphorylation of the oxygen atom of the epoxide by the positively charged phosphorus atom of Silphos followed by the nucleophilic attack of the halide ion can lead to the desired product (Scheme 2).

In conclusion, Silphos [$\text{PCl}_{3-n}(\text{SiO}_2)_n$] appears to be a very efficient reagent for the conversion of epoxides to *vic*-haloalcohols with molecular bromine or iodine, or *N*-halosuccinimides both in CH_3CN or under



SCHEME 2

solvent-free conditions. The advantages of this *regio*- and *stereoselective* method are high to quantitative yield of the product, easy removal of the Silphos oxide byproduct, and the simple the preparation of Silphos as a cheap and heterogeneous reagent.

EXPERIMENTAL

All the reagents and solvents were purchased from Fluka or Merck Chemical Companies. FTIR spectra were recorded on a Shimadzu DR-8001 spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument. Silphos was prepared according to the literature.^{4a}

The Typical Procedure for the Conversion of 2,3-Epoxypropylphenyl Ether to 1-Bromo-3-Phenoxy-Propan-2-ol by Silphos/NBS in CH_3CN

To a heterogeneous mixture of 1.0 g of Silphos and 1.2 mmol (0.21 g) of NBS in 5 mL of CH_3CN , 2,3-epoxypropylphenyl ether (1.0 mmol, 0.15 g) was added. The reaction mixture was stirred at r.t. and

TABLE II The Conversion of 1.0 mmol of Epoxide to *vic*-Haloalcohol in the Presence of 1.0 g of Silphos [$PCl_{3-n}(SiO_2)_n$] and 1.2 mmol of Molecular Bromine, Iodine, or N-Halosuccinimides in CH_3CN or Under Solvent-Free Conditions

Entry	Substrate	Product	Reagent	in CH_3CN		Solvent-Free	
				Time (min)	Yield (%) ^a	Time (min)	Yield (%) ^a
1			Br_2	40	85	10	90
			I_2	25	87	5	94
			NBS	50	91	15	95
			NCS	40	88	10	91
			NIS	35	89	10	95
2			Br_2	50	90	10	93
			I_2	30	92	10	94
			NBS	60	88	15	94
			NCS	55	90	10	95
			NIS	45	91	10	95
3			Br_2	40	75 (15)	15	77 (18)
			I_2	30	74 (15)	10	80 (15)
			NBS	60	70 (20)	10	75 (17)
			NCS	20	72 (20)	5	81 (13)
			NIS	20	73 (17)	5	85 (10)
4			Br_2	60	88	15	95
			I_2	60	92	10	97
			NBS	60	91	15	94
			NCS	50	89	20	92
			NIS	40	94	20	94
5			Br_2	55	87	15	93
			I_2	25	93	15	96
			NBS	30	90	10	95
			NCS	10	86	5	94
			NIS	10	90	5	95
6			Br_2	45	84 (10)	20	82 (15)
			I_2	30	86 (10)	20	87 (10)
			NBS	60	84 (12)	15	88 (10)
			NCS	40	80 (11)	10	84 (11)
			NIS	50	83 (15)	10	85 (10)
7			Br_2	30	94	10	94
			I_2	20	92	10	95
			NBS	10	95	5	95
			NCS	25	92	5	90
			NIS	20	94	5	92

^aAll products are known compounds and are identified by their physical or spectral data^{6c}; Yield (%) in parenthesis shows the formation of the other regio-isomer which is measured by GC and NMR.

monitored by TLC and GC analysis. The reaction was completed after 60 min. After evaporation of the solvent, the residue was washed with 2×15 mL of ethyl acetate. The organic layers were combined, washed with 20 mL of sodium thiosulfate (10%) and 20 mL of water, and dried over anhydrous Na_2SO_4 . Evaporation of the solvent produced pure 1-bromo-3-phenoxy-propan-2-ol in a 91% yield. ^1H -NMR(CDCl_3 , 250 MHz): δ 2.85 (s, 1H, $-\text{OH}$), 3.52–3.76 (m, 2H, $-\text{CH}_2\text{Br}$), 4.01–4.08 (m, 2H, $-\text{CH}_2\text{OPh}$), 4.15–4.23 (m, 1H, $-\text{CHOH}$), 6.75–7.65 (m, 5H, $-\text{Ph}$) ppm; ^{13}C -NMR (CDCl_3 , 62.9 MHz): δ 35.07 ($-\text{CH}_2\text{Br}$), 68.60 ($-\text{CHOH}$), 69.60 ($-\text{CH}_2\text{OPh}$), [115.08, 121.50, 129.23, 158.23 ($-\text{Ph}$)], ppm.

The Typical Procedure for the Conversion of 2,3-Epoxypropylphenyl Ether to 1-Iodo-3-Phenoxy-Propan-2-ol by Silphos/ I_2 Under Solvent-Free Conditions

2,3-Epoxypropylphenyl ether (1.0 mmol, 0.15 g) was added to a solvent-free mixture of 1.0 g of Silphos and 1.2 mmol (0.3 g) of molecular iodine. The reaction mixture was stirred at r.t. TLC monitoring and GC analysis showed the completion of the reaction after 15 min. The mixture was washed with 2×15 mL of ethyl acetate. Then the combined organic layers were washed with 20 mL of sodium thiosulfate (10%) and 20 mL of water, respectively. Drying of the organic layer over anhydrous Na_2SO_4 and evaporation of the solvent afforded 1-iodo-3-phenoxy-propan-2-ol in 97% yield. ^1H -NMR (CDCl_3 , 250 MHz): δ 2.65 (s, 1H, $-\text{OH}$), 3.37–3.43 (m, 2H, $-\text{CH}_2\text{I}$), 4.0–4.18 (m, 2H, $-\text{CH}_2\text{OPh}$), 4.18–4.22 (m, 1H, $-\text{CHOH}$), 6.96–7.56 (m, 5H, $-\text{Ph}$) ppm; ^{13}C -NMR (CDCl_3 , 62.9 MHz): δ 9.03 ($-\text{CH}_2\text{I}$), 69.3 ($-\text{CHOH}$), 70.53 ($-\text{CH}_2\text{OPh}$), [(115.63, 118.2, 137.11, 139.72, $-\text{Ph}$)] ppm.

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