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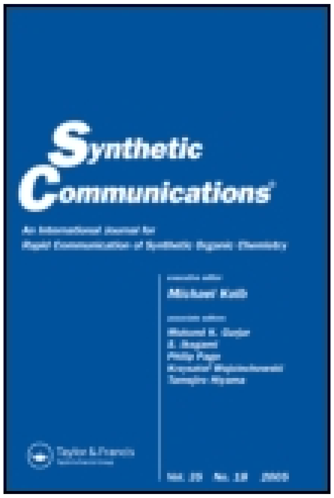

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tris(2-Carboxyethyl)phosphine (TCEP) for the Reduction of Sulfoxides, Sulfonylchlorides, N-Oxides, and Azides

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tris(2-Carboxyethyl)phosphine (TCEP) for the Reduction of Sulfoxides, Sulfonylchlorides, *N*-Oxides, and Azides

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Boehringer Ingelheim (Canada) Ltd.,
Research and Development,
Laval (Québec), Canada

INTRODUCTION

tris(2-Carboxyethyl)phosphine (TCEP), commercially available as a hydrochloride complex, is an efficient reducing agent most commonly used to reduce disulfide bonds. It is a good substitute for dithiothreitol (DTT) to prevent the formation of intramolecular disulfide bridges in protein, thus preserving their bioactive secondary structure.[1–3] Other uses of TCEP seem to be limited to an analytical tool used for the quantification of sulfides, disulfides, hypochlorous acid, hypochlorite ions, iodine, and iodate ions.[4] In this article, we wish to report how TCEP can be used as a convenient reducing agent in synthesis for the reduction of several functional groups.

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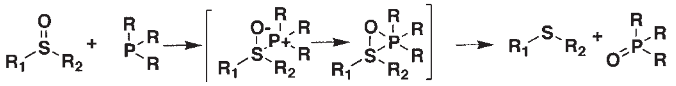
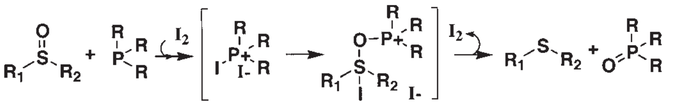
There are several methods available for the reduction (de-oxygenation) of sulfur- and nitrogen-containing molecules.[5–13] For sulfur-containing molecules, one of the mildest reduction methods involves the transfer of oxygen to a trivalent phosphorous atom. However, many phosphorous reagents, and their corresponding oxides, present handling challenges. When HMPT[8] is used for reduction, it produces HMPA which is toxic. Trialkylphosphines are often flammable and have unpleasant odors. As well, when trialkylphosphines are used as reducing agents, a chromatographic separation is required to remove phosphine oxide by-products from the desired material.[5,6,9,10] TCEP is an air stable, odorless, crystalline phosphine. The three carboxyl groups embedded in the structure contribute to the aqueous solubility of TCEP and its corresponding oxide. These features give TCEP an advantage over other phosphines in preparative reactions.

There are many reaction conditions described in the Lit.[5,6,8–10] for the de-oxygenation of sulfur-containing molecules with trivalent phosphorous compounds. When the trivalent phosphorous compound is a trialkylphosphine, it can be used alone or in the presence of a co-reactant such as iodine, CCl_4, acylating agents, etc. When used alone, the accepted reaction mechanism involves a nucleophilic attack by phosphorous according to Eq. (1). For less reactive sulfoxides, it may be advantageous or even necessary to perform the reaction in the presence of a co-reactant such as iodine. In this case, an iodophosphonium iodide complex becomes the reactive species and the accepted reaction mechanism is shown in Eq. (2).


(1)



(2)

RESULTS AND DISCUSSION

Sulfur-containing compounds with a high oxidation state were selected to react with TCEP alone or in the presence of iodine. Dibenzylsulfoxide was treated with TCEP (1.1 equiv.) in a mixture of dioxane and water under reflux. The sulfoxide was converted to the corresponding thioether in 18.5 h (Entry 1). Completion of the reaction was achieved more rapidly (2.5 h) when the concentration of the reaction mixture was increased (Entry 2). Several experiments were performed to determine if water as co-solvent and/or the molecule of hydrogen chloride associated with commercially available TCEP had a role in the reduction reaction. The reaction was conducted in the absence of water (Entry 3) and resulted in a rapid consumption of dibenzylsulfoxide but the reaction mixture contained only 40% of desired thioether and two by-products. The product distribution did not change with prolonged heating (17 h). These observations indicate that the appearance of thioether reduction product is more rapid in absence of water, but also suggest that the starting sulfoxide undergoes side reactions, possibly through reaction with ‘‘naked’’ chloride ions. The reaction was then performed in the presence of molecular sieve to trap moisture and HCl (Entry 4). Under these conditions, the reaction was inhibited. The addition of an equimolar amount of sodium hydroxide to the reaction mixture to neutralize HCl while maintaining water present (Entry 5) also had an inhibitory effect. When solid TCEP was preheated (in a different attempt to remove HCl from the reaction mixture, Entry 6) the reaction proceeded to completion but had a slower rate. Therefore, it was concluded that the presence of HCl in the commercially available TCEP is beneficial to the reduction reaction and that water may decrease the reaction rate but also prevents side reactions. Adding a sub-stoichiometric amount of iodine to the reaction mixture, but omitting water to preserve the iodophosphonium iodide formed (Eq. (2)), improved the reaction rate (compare Entries 1 and 7). The reaction did not require sodium iodide which is the case with other trivalent phosphorous reagent.[8,9] A TCEP-iodine mixture was the condition of choice for less reactive sulfoxides or sulfoxide bearing a reactive functional group that did not withstand prolonged heating. The reduction of benzylphenylsulfoxide with TCEP was too sluggish to be useful (Entry 8), but with the addition of iodine, the conversion to benzylphenylthioether was complete within 1 h (Entry 9). As well, the reduction of methyl phenylsulfoxide with TCEP alone to its corresponding thioether took 42 h (Entry 10), but only 1 h in the presence of iodine (Entry 11). The reduction of methyl (phenylsulfinyl)-acetate with TCEP did not give the desired product (Entry 12), but when iodine was added, the desired thioether was obtained in 1 h (Entry 13). Diphenylsulfoxide was completely converted in 2 h to the desired thioether in the presence of iodine (Entry 14). Sulfones were inert to the reaction conditions that involved the use of water or iodine in presence of two equivalents of TCEP (Entries 15 to 18). *p*-Toluenesulfonic acid and pyridinium *p*-toluenesulfonate were also inert to the reaction conditions with and without iodine (Entries 19 to 21). These later results contrast with what has been reported for other trialkylphosphines.[10a] However, an alternative to the generation of thiols from sulfonates involved the use of sulfonyl chlorides which were rapidly and cleanly converted to the corresponding thiols (Entries 22 and 23) using four equivalents of TCEP in a refluxing dioxane-water mixture.

The de-oxygenation procedures could also be applied to *N*-oxides. 4-Phenylpyridine-*N*-oxide was deoxygenated using TCEP (1.1 equiv.) in dioxane at reflux in 25 h (Entry 24). The use of water or iodine had no apparent effect on the reaction rate (Entries 24 and 25). TCEP also deoxygenated collidine-*N*-oxide with no significant difference in reaction rate compared to 4-phenylpyridine-*N*-oxide (Entries 26 and 27). Competition experiments involving equimolar amounts of TCEP, collidine-*N*-oxide, and 4-phenylpyridine-*N*-oxide, with water or with iodine, produced collidine and phenylpyridine as a 1:1.2 mixture. Nicotine-*N*-oxide and *N,N*-dimethylbenzylamine-*N*-oxide were completely reduced by TCEP within 1 h in a refluxing mixture of dioxane and water (Entries 28 and 29).

Azides are known to react with tertiary phosphines to produce phosphinimines.[14] The phosphinimines are then converted to their corresponding primary amines and phosphine oxides in the presence of water.[15] *P*-Azidobenzoic acid in the presence of TCEP and water was converted to *p*-aminobenzoic acid within 15 min at ambient temperature with a slight exotherm (Entry 30). The reaction was complete when gas evolution had ceased. Thus, the transformation of azides to primary amines is rapid, clean, and efficient with TCEP.

EXPERIMENTAL

All substrates used in this study and their respective reaction products are known and most are commercially available. The reaction products were characterized by ^{1}H NMR, HPLC, and MS and the collected data was compared with that of the literature. Commercially available solvents and reagents, including TCEP (Sigma), were used as received without purification. The reactions were monitored by reverse phase HPLC (water-acetonitrile, 0.1% trifluoroacetic acid) on an YMC Combiscreen ODS-AQ column. NMR spectra were acquired on a Brucker 400 MHz spectrometer using DMSO-d_6 and MS spectra were obtained from a Micromass LCZ instrument in electrospray mode. We also performed LCMS analyses on a Waters-Micromas ZQ platform in electrospray mode.

General Procedure for the Reduction of Sulfoxides, Sulfonyl Chlorides, and *N*-Oxides with TCEP and Water

To a solution of substrate in a mixture of dioxane and water was added TCEP (see "Table of Results" for amounts). The resulting solution was heated to reflux under an atmosphere of nitrogen and the reaction was monitored by HPLC. Upon completion, the reaction mixture was diluted with water (1N NaOH when an amine was the reaction product) and extracted with dichloromethane. The resulting organic solution was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure affording in most cases a crude isolate with greater than 90% homogeneity (HPLC) which could be purified further by flash chromatography on a short column of silica using mixtures of hexane and ethyl acetate as eluent.

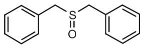
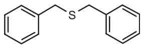
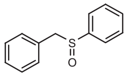
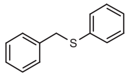
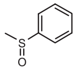
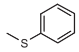
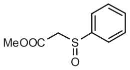
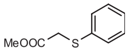
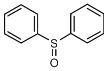
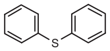
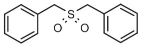
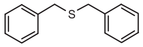
General Procedure for the Reduction of Sulfoxides, Sulfonyl Chlorides, and *N*-Oxides with TCEP and Iodine

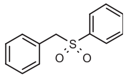
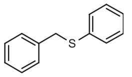
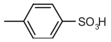
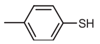
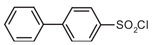
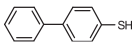
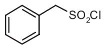
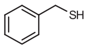
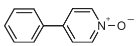
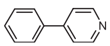
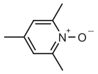
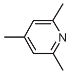
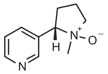
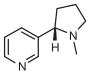
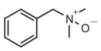
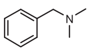
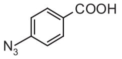
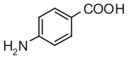
Same as above but water was omitted and iodine was added. Upon completion, the crude reaction mixture was diluted with dichloromethane and washed with aqueous 30% $NaHSO_3$ and water, then treated with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a crude isolate with greater than 90% homogeneity (HPLC).

General Procedure for the Reduction of *p*-Azidobenzoic Acid with TCEP and Water

Same as above for sulfoxides, sulfonyl chlorides, and *N*-oxides except that the reaction was performed at ambient temperature. Upon completion, the reaction mixture was diluted with 1N NaH_2PO_4 (pH 4.5) and extracted with ethyl acetate. The organic phase was then treated with anhydrous $MgSO_4$ and concentrated under reduced pressure to afford a crude isolate with greater than 99% homogeneity (HPLC).

Table 1. Table of results.

			Conditions						
Entry	Substrate	Amount (mmol)	TCEP (equiv.)	I_2 (equiv.)	Dioxane (mL)	Water (mL)	Product	Time (h)	% Conversion (yield)
1		0.43	1.1	0	1.5	0.35		18.5	>99%
2		0.86	1.1	0	1.5	0.35		2.5	>99% (93%)
3		0.43	1.1	0	1.5	0		1	>98% (40% + side products)
4		0.43	1.1	0	1.5	0^a		17	2%
5		0.43	1.1	0	1.5	0.5^b		23	2%
6		0.43	1.1	0	1.5	0.35^c		27	>99%
7		0.87	1.1	0.5	3	0		1	>99% (98%)
8		0.46	1.1	0	1.5	0.35		17	3%
9		0.46	1.1	0.55	1.5	0		1	>98% (97%)
10		0.82	1.1	0	2.6	0.6		42	>99% (67%, volatile)
11		0.94	1.1	0.55	3	0		1	>99% (78%, volatile)
12		0.57	1.1	0	1.9	0.44		24	>99% (0%, degradation)
13		0.57	1.1	0.55	1.9	0		1	>99% (96%)
14		0.49	1.1	0.55	1.7	0		2	97% (86% purified)
15		0.81	2	0	1.4	0.33		23	0%
16		0.41	2	0.5	0.7	0		17	0%

17		0.86	2	0	1.5	0.35		22	0%
18		0.44	2	0.5	0.7	0		17	0%
19		0.36	4	0	1.5	0.35		24	0%
20		0.53	4	0.5	1.7	0		22	0%
21	(Pyridinium salt)	0.4	5	0.5	1.3	0		21	0%
22		0.79	4	0	1.5	0.35		6	>99% (96%)
23		1.05	4	0	2	0.47		4.5	72% (64% purified) side product with longer rx time
24		1.17	1.5	0	1.5	0.35		25	96% (84%, purified)
25		1.17	1.5	0.2	1.5	0		27	>90% (85%, purified)
26		1.27	1.5	0	1.6	0.39		24 42	84% 85% (91% conversion by NMR)
27		1.2	1.5	0.2	1.5	0		24 42	96% >96% (38%, water solubility)
28		0.06	1.5	0	0.38	0.04		1	>99%
29		0.66	1.5	0	0.83	0.12		1	>99%
30		1.2	1.5	0	1.6	0.36 (r.t.)		0.25	>99% (98%)

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[a] Powdered molecular sieve (4A, 200 mg) was added to the reaction mixture.
[b] NaOH 1.1 equiv. was added to the reaction mixture.
[c] TCEP was heated at 112°C under N_2 for 2.5 h prior to conducting the reaction.

CONCLUSION

tris(2-carboxyethyl)phosphine (TCEP) has been shown to efficiently reduce sulfoxides, sulfonylchlorides, *N*-oxides, and azides with significant practical value. TCEP is particularly attractive compared to other trialkylphosphines because it is an air stable and odorless solid. Also, this phosphine and its corresponding oxide are water soluble thus facilitating a clean isolation of the desired end-product using simple aqueous/organic extraction procedures.

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