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Rhenium Catalyzed Sulfoxide Reduction

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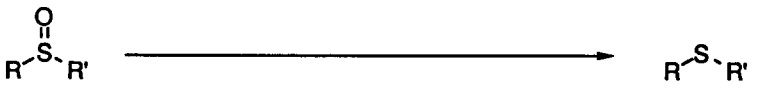
Abstract: A mild, efficient method for the catalytic reduction of sulfoxides to sulfides with triphenylphosphine and the catalyst $ReOCl_3(PPh_3)_2$ (I) is reported. Aryl sulfoxides are reduced faster than alkyl, and the reaction is successful for sterically hindered sulfoxides and those with common organic functional groups.

The reduction of sulfoxides to sulfides is an important transformation in organic synthesis.[1] Sulfoxide reduction is frequently employed in natural product syntheses, which require mild conditions, selectivity, and functional group tolerance. The desire for convenient, inexpensive reagents continues to stimulate the development of new methods for sulfoxide reduction. Although the reaction between methyl sulfoxide (Me_2SO) and triphenylphosphine (PPh_3) to produce methyl sulfide (Me_2S) and triphenylphosphine oxide ($OPPh_3$) is enthalpically favorable with ΔH_g = -46.7 kcal mol^{-1}, this reaction proceeds only with elevated temperatures and extended reaction times,[2] or with the addition of halogen derivatives[3] or acid catalysts.[4] Transition metals are also capable of catalyzing this reaction, and other oxo transfer processes.[5] Molybdenum catalysts are both biologically[6] and synthetically relevant for sulfoxide reduction, but are sensitive to air and moisture.[7] Several rhenium-oxo complexes react with trivalent phosphorus compounds,[5] and the catalytic oxidations of PPh_3 by Me_2SO[8] or H_2O_2[9] have been observed. We recently reported the mild, rhenium-catalyzed oxidation of sulfides with phenyl sulfoxide (Ph_2SO) as the oxidant.[10] During the initiation of this reaction the triphenylphosphine ligands of the catalyst precursor complex [$ReOCl_3(PPh_3)_2$] (I) were rapidly oxidized by Ph_2SO at ambient temperature, producing phenyl sulfide (Ph_2S), $OPPh_3$ and the active oxidation catalyst. The mild conditions under which the phenyl sulfoxide was reduced in this rhenium catalyzed process, along with the stability, and availability of complex (I)[11] led us to investigate the Re-catalyzed reduction of sulfoxides with triphenylphosphine. We report the results of this investigation here, and provide a convenient synthetic procedure that is suitable for reducing a wide range of sulfoxides using inexpensive, readily available reagents.

Our experiments were carried out using a variety of aryl and alkyl sulfoxides, and the results are shown in Table 1. In a typical experiment[12] a catalytic amount of (I) was added to a solution of the sulfoxide and

triphenylphosphine in dichloromethane. The progress of the reaction was followed by thin layer chromatography and / or ^{1}H-NMR. The reactions were performed in air, and were unaffected by adventitious water in the solvent. Control experiments demonstrated no sulfoxide reduction in the absence of the catalyst under the reaction conditions used.

Table 1. Rhenium Catalyzed Reduction of Sulfoxides with Triphenylphosphine



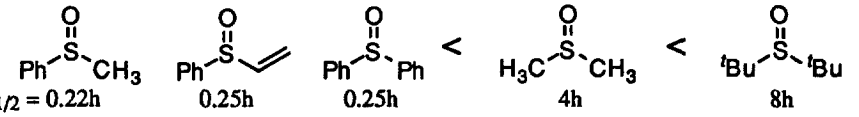
entry	substrate	reaction conditions[a]	time (h)	yield[b] (%)
1	R = -Ph R' = -CH_3	c	1	92
2	R = -Ph R' = -CH=CH_2	c	1	96
3	R, R' = -Ph	c	1	95
4	R, R' = -CH_3	c	22	95[d]
5	R, R' = -$C(CH_3)_3$	e	5	92[f], 80
		e	1	46[f]
		e,g	1	24[f]
		e,h	1	78[f]
6	R = -CH_2CH_3 R' = -CH_2CH_2OH	e	5	84
7	R = -CH_3 R' = -$CH_2CH_2CH(NHCOCH_3)CO_2Et$	e	5	96[i]

[a]Molar ratio of substrate : triphenylphosphine : complex (I) = 1.0 : 0.9 : 0.05 unless noted otherwise.
[b]All yields are based on isolated sulfide purified by vacuum distillation (bulb-to-bulb) or silica gel chromatography using CH_2Cl_2 eluent.
[c]Reaction at ambient temperature.
[d]Isolated as the mercury (II) complex $[(CH_3)_2S]_2$-$3HgCl_2$.[4]
[e]Reaction heated to reflux.
[f]Percent conversion determined by ^{1}H NMR integration of the [-$C(CH_3)_3$] singlets.
[g]Molar ratio of substrate : triphenylphosphine : complex (I) = 1.0 : 1.9 : 0.05
[h]Slow addition of a 0.12 M triphenylphosphine solution in CH_2Cl_2.
[i]Isolated as the carboxylic acid after saponification, aqueous extraction, and neutralization with 2 M HCl.

The isolated yields of sulfide products using this method were very good (80-96%). The rates of the rhenium catalyzed reductions of the dialkyl sulfoxides were significantly slower than those of the mono- or diaryl sulfoxides, and entries 5-7 were heated to reflux for the preparative reactions. The optimum reaction conditions employed a stoichiometric ratio of triphenylphosphine to sulfoxide. The effect of increased phosphine concentration was investigated for entry 5, where it was found that doubling the triphenylphosphine concentration reduced the percent conversion of the reaction after one hour reflux by a factor of two. However, the percent conversion was increased by slowly adding a solution of PPh_3 to the

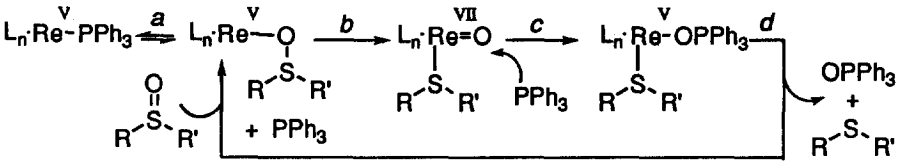
refluxing reaction mixture of the sulfoxide and rhenium catalyst. The functional group tolerance of this method is evident from entries 2, 6, and 7 which show that vinyl groups, primary alcohols, esters, and amides are unaffected by the reaction conditions. The facile reduction of the methionine-S-oxide derivative in entry 7 demonstrates the potential of this method for accomplishing this important deprotection step in peptide synthesis.[13] The half-lives for entries 1-5 at room temperature were measured by NMR in CD_2Cl_2 and found to follow the order of reducibility shown below (1).[14]

(1)



This order of reactivity is opposite that observed for the high temperature reduction of sulfoxides with PPh_3,[2] or when activated by other reagent combinations.[3b] The faster reduction of aryl sulfoxides by the Re-catalyzed system does not follow the relative S-O bond strengths, where aryl sulfoxides typically possess stronger S-O bonds than alkyl sulfoxides by 1-3 kcal mol^{-1}.[15] Steric effects on the rhenium catalyzed reduction of alkyl sulfoxides were also evidenced by the slower reduction of *t*-butyl sulfoxide compared to methyl sulfoxide. However, there were no significant differences in reactivity between sterically different aryl sulfoxides such as methyl phenyl, phenyl vinyl, and diphenyl sulfoxide.

The mechanism proposed for the acid catalyzed reduction of sulfoxides with PPh_3 involves nucleophilic attack of the phosphine on the protonated sulfoxide oxygen. The rate of this reaction depends on the basicity of the sulfoxide, and is faster with the more basic alkyl sulfoxides.[4] Sulfoxide basicity and steric factors have also been observed to affect the rate of the acid-catalyzed reduction by iodide ion and thiols.[16] The preferential reduction of aryl sulfoxides has been observed in the reaction of aryl methyl sulfoxides with dialkyl sulfides in aqueous methanol acidified with HCl, where S-O bond cleavage leading to the formation of a chlorosulfonium ion intermediate $[ArSMeCl]^+$ was identified as rate determining.[17,18] The similar reactivity of aryl sulfoxides in the mild, rhenium-catalyzed system and under these strongly acidic conditions is mechanistically intriguing. A catalytic cycle for the rhenium catalyzed reduction that is consistent with our results is proposed in Scheme 1.



Scheme 1. Possible Oxidative-Addition Mechanistic Pathway

The observed inhibition of the rate by excess PPh_3 (entry 5) would be expected for a pre-equilibrium step (*a*) involving substitution of a triphenylphosphine ligand with sulfoxide to form an *O*-bound Re(V) sulfoxide complex. The faster reduction of aryl sulfoxides in this system could be the result of an oxidative-addition step (*b*) in which the S-O bond breaking is stabilized by phenyl substitution, forming an electrophilic Re(VII) oxo sulfide complex. Phosphine reduction of the oxo ligand (*c*) would form a phosphine oxide complex and return the metal to its reduced state, where ligand substitution by sulfoxide (*d*) would release

the product sulfide and phosphine oxide, allowing the catalytic cycle to resume. The proposed formation of a colorless d^0 Re(VII) intermediate in step (*b*) is consistent with the observed decolorization of solutions containing (I) by sulfoxides in the absence of PPh_3. The characteristic green color of Re(V) species returns to these solutions following the addition of PPh_3.

Synthetic applications and further mechanistic studies of this mild, efficient, catalytic reduction, and the development of related oxygen transfer reactions from sulfoxides to other organic substrates are currently being investigated.

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11. (I) Trichlorooxobis(triphenylphosphine)rhenium, $ReOCl_3(PPh_3)_2$, is commercially available from the Aldrich Chemical Co., or can be easily prepared using the procedure of Johnson, N. P.; Lock, C. J. L.; Wilkinson, G. *Inorg. Synth.* **1967**, *9*, 145-148.
12. **General Procedure**: The catalyst $ReOCl_3(PPh_3)_2$ (I) (.05 molar equivalents) was added to a 0.125 M solution of the sulfoxide (1 equivalent) and triphenylphosphine (0.9 equivalents) in CH_2Cl_2. Aryl sulfoxides were stirred at ambient temperature for 1 hour, alkyl sulfoxides were refluxed for 5 hours. The sulfide products were isolated by vacuum distillation (bulb-to-bulb) or silica gel chromatography using CH_2Cl_2 eluent.
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