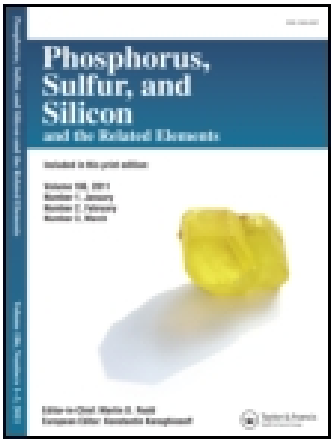

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Applications of the $(PhO)_3PCl_2$ Reagent: A New Protocol for Mild Cleavage of Sulfinamides and Sulfonamides

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The triphenyl phosphite-chlorine reagent, freshly in situ *prepared by the action of chlorine on a solution of triphenyl phosphite in dichloromethane, is successfully used in the cleavage of both sulfinamides and sulfonamides under extremely mild conditions (−15°C to r.t.). Final amines are easily recovered by a simple acid / base extraction, and no further purification is required.*

Keywords Amines; chlorine; cleavage; sulfinamides; sulfonamides; triphenyl phosphite

INTRODUCTION

Sulfinamides and sulfonamides represent two classes of highly versatile intermediates in chemical synthesis.[1–3] Along with their usefulness, however, they are strictly endowed with a remarkably strong chemical stability, which makes them either resistant and, conversely, quite difficult to cleave off,[4] thus often discouraging their application as protective groups. In the course of our recent investigations into the chemistry of the triphenyl phosphite-chlorine reagent,[5,6] we had already faced *N*-monosubstituted amides and had reported a highly efficient, and so far the mildest, method for the deacylation of such compounds.[5] Thus, spurred by the gratifying success obtained in those circumstances and encouraged by the intrinsic structural resemblance, we decided to make a preliminary study aimed at exploring whether

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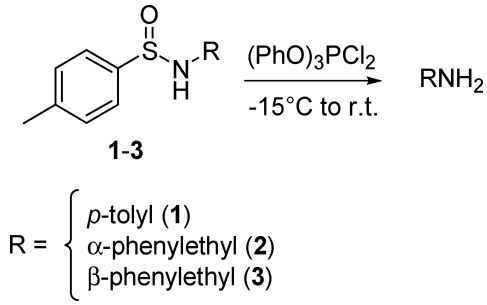
the same reagent could be conveniently employed also in the cleavage of more resistant sulfinamides.

Available methods described in the literature for carrying out the removal of the sulfur-containing fragment in sulfinamides often deal with severe reaction conditions, like acidic[7,8] or basic[9] hydrolysis. Acid-catalyzed alcoholysis to sulfinates[10] and, more recently, the use of a periodinane reagent reported by Davis et al.[11] as well as the reaction with thiols associated to Lewis' acid settled by Li et al.[1] represent the only attempts to provide milder methods for cleavage. Also, sulfonamides usually require severe conditions to be cleaved, such as, for instance, the action of organolithium reagents,[12] alkali metals,[13] arene radical anions,[14] and hydrobromic acid.[15] Thus, the quest for a general cleavage protocol under mild conditions would be a desirable issue in organic sulfur chemistry, and this communication therefore aims to propose a novel route that can possibly be applied to all kinds of amides by simply exploiting the high versatility of the same phosphorus-based halogenating reagent.

RESULTS AND DISCUSSION

In this context, we describe here our preliminary results when sulfinamides **1–3** were treated with $(PhO)_3PCl_2$ in dry dichloromethane, according to the reaction pathway, as depicted in Scheme 1.



SCHEME 1

The reagent was prepared in situ, by bubbling chlorine in a solution of triphenyl phosphite in anhydrous dichloromethane at -15°C. A substrate was added, quickly followed by triethylamine, and the reaction mixture was left to stir at this temperature over a three-hour period.[16] A large excess of ethylene glycol was then added, and the mixture was stirred for an additional twelve-hour period. Dichloromethane was then removed under reduced pressure and replaced by water. Vigorous

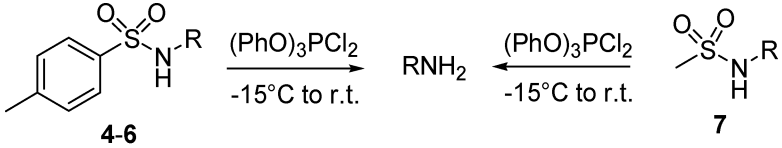
TABLE I $(PhO)_3PCl_2$-Promoted Cleavage Results on Sulfur-Containing Amides

Entry	R	Yield (%)
1	*p*-tolyl	41
2	$CH(CH_3)Ph$ (α-phenylethyl)	50
3	CH_2CH_2Ph (β-phenylethyl)	52
4	*p*-tolyl	61
5	$CH(CH_3)Ph$ (α-phenylethyl)	47
6	CH_2CH_2Ph (β-phenylethyl)	50
7	*p*-tolyl	40

stirring was continued for two hours and a final acid/base extraction with dichloromethane yielded the expected amines in 41–52%, as reported in Table I (entries 1–3).

According to the same procedure, we also tried to assess the feasibility of this protocol when applied to sulfonamides (Scheme 2), yet another valuable class of compounds largely used in organic synthesis.

Again, when substrates **4–6** were first exposed to the $(PhO)_3PCl_2$ reagent at $-15^\circ C$ in dry dichloromethane in the presence of triethylamine and then treated with an excess of ethylene glycol, the corresponding amines were easily recovered in a 47–61% yield (Table I, entries 4–6), thus demonstrating that the oxophilic phosphorus reagent can exert its action independently in the presence of more than one oxygen atom, and, consequently, by the oxidation state of the sulfur atom as well.

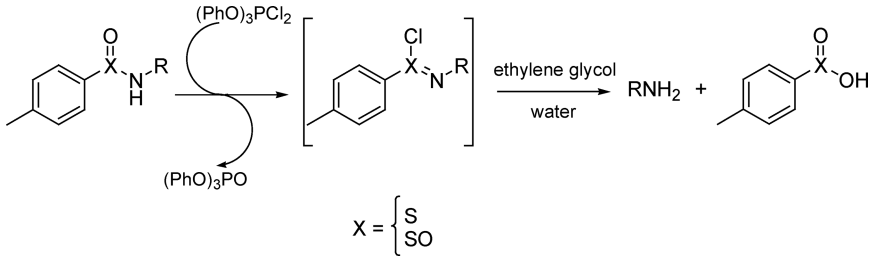


SCHEME 2

By close analogy to tosylamides, mesylamides also, as in the case of *p*-tolylmesylamide **7**, proved to be sensitive when exposed to the same reaction conditions.

As far as the mechanistic insights are concerned, these preliminary results would suggest that, similar to carboxyamides, sulfonamides and

sulfinamides also proceed to amines through an iminosulfinyl- or iminosulfonyl chloride analogue (Scheme 3).



SCHEME 3

This initial transformation is achieved by a means of the halogenating action of the oxophilic phosphorus reagent $(PhO)_3PCl_2$ which, in turn, is converted to triphenyl phosphate, according to its already explored reactivity.[5] A final alcoholysis of the iminochloride with ethylene glycol and water finally reveals the expected amine, along with either *p*-toluenesulfonyl or *p*-toluenesulfinyl acid, which remains, as sodium salt, in the aqueous layer at the end of the extraction.[17] To the best of our knowledge, although this method does not represent the most efficient protocol for the cleavage of sulfur-based amides, and despite its limitation to the *N*-monosubstituted amides, it involves, however, the mildest reaction conditions, avoiding both harsh reagents and high temperatures, thus becoming a potentially intriguing choice for performing these deprotections when sensitive functionalities are present everywhere in the substrates. This circumstance seriously blocks the route of the most common (and severe) procedures of cleavage. We are at present undertaking further investigations into this reaction, as well as into mechanistic studies, and will report fully in due course.

EXPERIMENTAL

General

All glassware used in the reaction was oven dried and argon flushed. Dichloromethane was dried according to the standard procedure. Triphenyl phosphite was purchased from Aldrich and used without further purification. Chlorine used in the synthesis of the $(PhO)_3PCl_2$ was checked, and it had a 99.8% title. Triethylamine was purchased from Acros Organics and distilled and stored over KOH before using. Sulfonamides and sulfinamides **1–7** were prepared according to standard procedures.

General Procedure for the Cleavage of Sulfinamides and Sulfonamides

In a two-necked 50 mL round-bottom flask, anhydrous dichloromethane (15 mL) was cooled to -15°C under an argon atmosphere, and triphenyl phosphite (1100 μL, 4.2 mmol) was added. Chlorine was then bubbled in until the solution became intensely yellow. The color was discharged by the addition of a few drops of triphenyl phosphite, and sulfonamide **4** (1000 mg, 3.8 mmol) was added, quickly followed by triethylamine (610 μL, 4.4 mmol). The reaction was stirred at this temperature over a two-hour period, and then the cold bath was removed, and the mixture was slowly warmed to r.t. After two hours, ethylene glycol (4000 μL, 49 mmol) was added, and the stirring continued overnight. Dichloromethane was removed under reduced pressure and replaced by water (10 mL). After two hours, the mixture was acidified to pH of about 4 by 10% HCl, and the aqueous phase was then basified to pH 11 by 20% NaOH. A final extraction with dichloromethane yielded the expected *p*-toluidine in 61%.

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[17] A GC-MS analysis of the crude reaction mixture in the course of desulfonylation of amide **4** revealed the presence of *p*-toluenesulfonyl chloride.