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Low-Temperature Deacylation of N-Monosubstituted Amides

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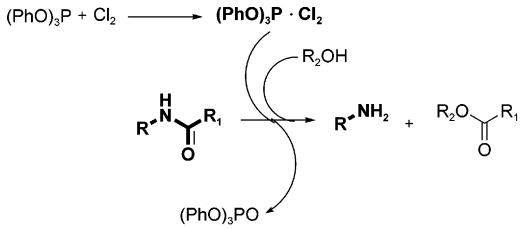
ABSTRACT



The $(PhO)_3P{\cdot}Cl_2$ reagent, prepared in situ by titrating a solution of triphenyl phosphite with chlorine, is used to convert N-monosubstituted amides into their corresponding amines. The reaction, if compared to other traditional methods, shows the advantage of very mild conditions and low temperature (−30 °C→rt).

Functional group interconversion is one of the most important processes in organic synthesis. Transformation of amides into their corresponding amines is a crucial example among such interconversions due to the widespread use of amides as amine protecting groups. The most common methods described in the literature often involve harsh conditions such as acid or base exposure at high temperature, involve multistep procedures,[1] or deal with cumbersome reagent combinations.[2,3] Hence, the need for milder, more selective methods is clearly evident, especially when the substrates are highly functionalized molecules that do not tolerate high temperatures or harsh reagents. Here we describe a convenient and general method for deacylation of N-monosubstituted amides under extremely mild conditions by means of triphenyl phosphite−chlorine complex ($TPP{\cdot}Cl_2$).

The first investigations into the chemistry of triphenyl phosphite chlorine complex described its use for conversion of simple alcohols to the corresponding alkyl chlorides.[4] A more complete study to better understand the nature of this reaction focused specifically on applications in the field of β-lactam antibiotics.[5] In fact, when a solution of $(PhO)_3P$ in dichloromethane is titrated with chlorine gas at −30 °C, a distinctly new reagent is formed. The complex is stable enough at this temperature to allow convenient and general application in organic synthesis. However, despite several efforts aiming to clarify the nature of these dihalotriphenoxyphosphoranes,[6] the exact nature of such compounds remains, at present, uncertain.[7] As part of our ongoing

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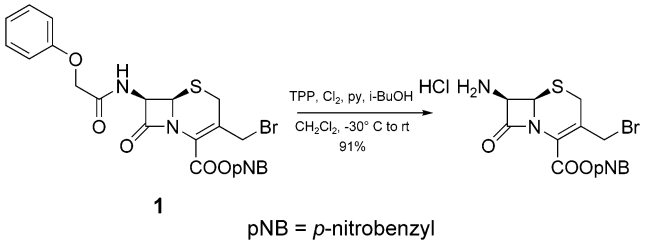
Scheme 1. Deacylation of a Cephalosporin V Derivative



1

pNB = *p*-nitrobenzyl

research on the synthesis of new dual-action cephalosporins as β-lactamase inhibitors, we applied the new reagent to a phenoxyacetamido cephalosporin (cephalosporin V) derivative as shown in Scheme 1.

A similar method using PCl_5 as the oxophilic phosphorus reagent has found application in medicinal chemistry, mainly to remove the amide side chain in cephalosporins. However, the hygroscopic PCl_5 is more cumbersome in practice and side products are formed in the dark reaction mixture.[8] Using the TPP·Cl_2 instead, we performed the same reaction on a cephalosporin V derivative, obtaining, in a one-pot synthesis, the 7-amino derivative (as an easily filterable hydrochloride) in 91% yield.

Encouraged by the ease and convenience of this method, which chemoselectively cleaves the amide side chain of the sensitive cephalosporin without affecting the disubstituted amide of the β-lactam ring, we sought to explore the application of such a reaction as a general method for the deacylation of N-monosubstituted amides. To assess the generality of this deacylation method, we explored the same reaction on a wide set of N-monosubstituted amides. By varying either the acyl moieties (**2**−**8**) or the amine residue (**9**−**15**), we explored aromatic, aliphatic, and aryl-aliphatic amides, as well as a urethane (**7**) and an amino acid (**15**), as reported in Figure 1.

A general procedure follows. The TPP·Cl_2 reagent is generated in situ by bubbling chlorine gas into an anhydrous solution of triphenyl phosphite at −30 °C. Dichloromethane

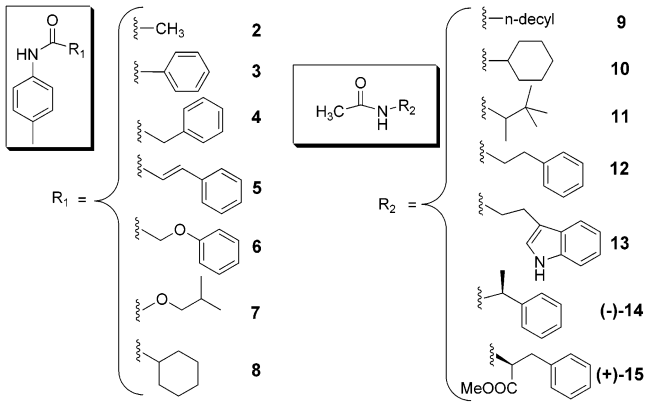


Figure 1. Examples of amides cleaved to their corresponding amines by means of TPP·Cl_2 reagent.

and THF are the preferred solvents. To this clear and almost colorless solution is then added the substrate followed by dropwise addition of an appropriate base (usually anhydrous triethylamine or pyridine). The tertiary amine is used to stabilize the kinetic intermediate;[7] adventitious HCl accelerates conversion to the thermodynamic form. The reaction is left to stir at this temperature for 2 h. After the cold bath is removed, a large excess of alcohol is added (usually methanol, ethylene glycol, or isobutyl alcohol) to convert the iminochloride intermediate into the corresponding iminoester derivative, which, in turn, undergoes hydrolytic cleavage when treated with a mixture alcohol/water. In the cases where the newly formed amine gave a sufficiently insoluble hydrochloride, that product precipitates after the first excess of alcohol was added. In the case of **1**, in fact, a conspicuous precipitation occurred after about 1 h from the addition of isobutanol. In many other cases, however, when the amine hydrochloride did not precipitate spontaneously, an extraction step was required. The final product was recovered as a free base instead of a hydrochloride salt.[9] In all cases, however, the final amine was recovered free of all byproducts (triphenyl phosphate and the residual ester), and the final amine did not require any further purification. The results, summarized in Table 1, show that in all the examined

(7) We found that this kind of $(PhO)_3P$·Cl_2 reagent is substantially different from that described in the prior art, to which previous literature is referred.[4] ^{31}P NMR spectroscopy experiments were carried out by some authors to observe the different chemical behavior of phosphorus, as well as to monitor its change during the course of the reaction.[6f] Similar experiments performed in our laboratory showed interesting results. In fact, when the reagent was prepared by the action of chlorine gas in a solution of $(PhO)_3P$ at −30 °C and the reaction was followed in an NMR tube, we observed the disappearance of the $(PhO)_3P$ signal at 128.1 ppm, while new signals at 7.4 ppm (intense) and −22.5 ppm (weak) appeared, as, however, Tseng[6f] already reported in his work. These two signals ought to be referred to as two distinct forms of the reagent; more precisely, the active form seems to correspond to that resonating at 7.4 ppm (kinetic intermediate), which, when the temperature is increased, slowly converts to the other form, corresponding to the peak at −22.5 (thermodynamic product, not active). The half-life of the kinetic form has been estimated to be about 8 h at room temperature.

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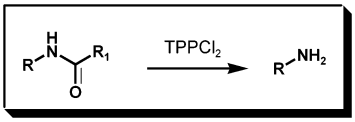
(9) **Typical Experimental Procedure.** In a 50 mL, three-necked, round-bottom flask was dissolved 1.8 mL (6.7 mmol) of triphenyl phosphite in 15 mL of dry dichloromethane. The system was kept under argon and magnetic stirring at −30 °C, and chlorine gas was then bubbled via a glass septum, until the solution became bright yellow. The color was discharged by adding a few drops of triphenyl phosphite, until the solution turned pale yellow to almost colorless. The amide **12** (1000 mg, 6.1 mmol), dissolved in 5 mL of dry dichloromethane, was added, and 960 μL (7.0 mmol) of dry triethylamine was dropped in. The system was maintained at these conditions for 2 h, and then the cold bath was removed and 1.6 mL (39.6 mmol) of dry methanol was added. After 5 h, the solvent was removed in vacuo and replaced by 20 mL of a mixture methanol/water (1/1) and the reaction was stirred for an additional 12 h period. The phase at the bottom of the flask (triphenyl phosphate) was removed, and the remaining homogeneous solution was acidified to pH about 3 by 10% HCl and extracted with diethyl ether (2 × 20 mL). The aqueous phase was then basified to about pH 11 with 10% NaOH and finally extracted with diethyl ether (2 × 20 mL). The organic phases were pooled and dried over $MgSO_4$, filtered, and evaporated under reduced pressure, affording 652 mg of the expected amine in 90% yield.

Table 1. Results and Conditions for Deacylation of Amides into Amines by Means of $(PhO)_3P{\cdot}Cl_2$ Reagent



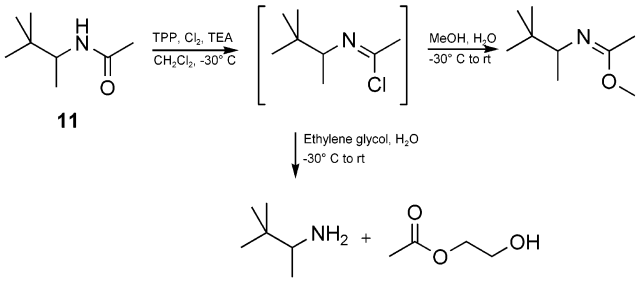
amide	conditions*	yield (%)
1	*c*	91 (as HCl salt)
2	*a*	90
3	*b*	80
4	*b*	70
5	*b*	72
6	*b*	74
7	*d*	87
8	*d*	96
9	*b*	72
10	*d*	76
11	*d*	73
12	*b*	90
13	*d*	81
(−)-14	*d*	70
(+)-15	*e*	95 (as HCl salt)

* Solvent, base, alcohol: (a) THF, triethylamine, methanol; (b) CH_2Cl_2, triethylamine, methanol; (c) CH_2Cl_2, pyridine, isobutanol; (d) CH_2Cl_2, triethylamine, ethylene glycol; (e) THF, triethylamine, isobutanol.

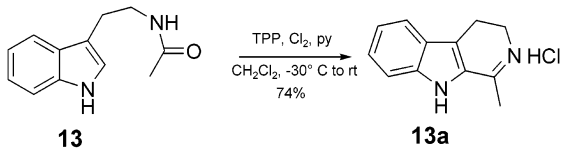
cases the amine was recovered in good to excellent yield, thus indicating that this method can be usefully applied to deacylate different kinds of variously substituted amides, as well as to cleave urethanes (Table 1, compound **7**). Importantly, no racemization occurred in deacylation of either (*S*)-(−)-**14** or (*S*)-(+)-**15**, which afforded the expected amines in unchanged enantiomeric composition (ee > 98%).

The most significant variable in the reaction conditions is represented by the alcohol used to convert the iminochloride into iminoester. We observed that methanol is the alcohol of choice for general application, whereas isobutanol seems to give better results when the product is highly insoluble, as in cephalosporin **1**. Ethylene glycol was particularly efficient in the deacylation of amides **10** and **11** (Scheme 2). When methanol was applied to these cases, the corresponding iminoesters were recovered in high yield, with no evidence of the expected amines (Scheme 2). Once formed,

Scheme 2. Iminoester Formation



Scheme 3. Mild Conditions of Bischler−Napieralski-Type Cyclization



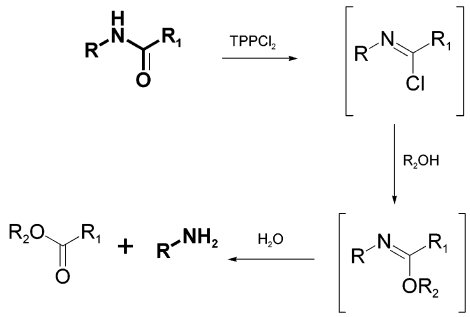
these methyliminoesters proved to be extremely stable in the reaction conditions and even under prolonged hydrolysis did not convert into the expected amines.

Interestingly, when the same reaction was performed on tryptamine acetamide (**13**), a dual behavior was observed. In fact, we found that this substrate afforded the expected amine (*deacylation pathway*) when sequentially treated with $TPP{\cdot}Cl_2$ and ethylene glycol (Table 1, compound **13**) but could also follow a different route (*cyclization pathway*) when no alcohol was added. In the latter case, a ring was formed leading to a β-carboline derivative, namely *harmalane* (Scheme 3, **13a**),[10] indicating that a Bischler−Napieralski-type cyclization occurred on this electron-rich β-arylethylamine.

Since this classically important reaction is usually performed under severe conditions,[11] needed for the formation of the iminochloride as the key intermediate,[12] we think that a new method to carry out such a cyclization under very mild conditions could be an attractive tool for synthesis of heterocycles.

These experimental observations allow us to infer a possible general mechanism for the process as depicted in Scheme 4.

Scheme 4. General Deacylation Mechanism



Preliminary results would suggest that bromine can be used instead of chlorine during the preparation of the key reagent

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(11) See for some examples: (a) Itoh, N.; Sugasawa, S. *Tetrahedron* **1957**, *1*, 45. (b) Kanaoka, Y.; Sato, E.; Yonemitsu, O.; Ban, Y. *Tetrahedron Lett.* **1964**, *35*, 2419. (c) Bosch, J.; Domingo, A.; Linares, A. *J. Org. Chem.* **1983**, *48*, 1075. (d) Rao, A. V. R.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5071. (e) Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Hino, T. *Tetrahedron Lett.* **1989**, *30*, 6549. (f) Sanchez-Sancho, F.; Mann, E.; Herradon, B. *Synlett* **2000**, *4*, 509. For a review on these cyclization methods, see also: Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1.

with triphenyl phosphite. In this view, in fact, a few tests performed on selected substrates gave encouraging results, even if yields appear slightly lower with respect to those obtained using the original chlorine-based reagent.

To summarize, TPP·Cl_2 chemistry can be successfully applied to a wide range of amides, affording corresponding amines in good to excellent yield. This represents an interesting and new method for deacylating amides under extremely mild conditions. Further extensions of this chemistry are currently under study in our laboratories.

(12) For syntheses of iminochlorides, see also: Kantlehner, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 485−599.

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