Diethyl Chlorophosphite: A Mild Reagent for Efficient Reduction of Nitro Compounds to Amines

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Phosphorus reagents are well established as deoxygenating agents in various important reactions such as Wittig,[1] Mitsunobu,[2] Arbuzov,[3] etc. The driving force in all these reactions is the high energy, ranging from 120 to 150 kcal/mol, released upon formation of phosphine oxide or phosphate products.[4]

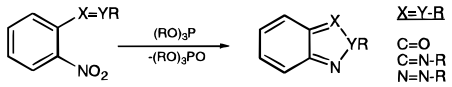
Cadogan and others reported the abstraction of oxygen from aromatic nitro and nitroso compounds by triethyl phosphites and related reagents to form various heterocyclic compounds (Scheme 1).[5] The mechanism of these reactions probably involves a nucleophilic attack of the phosphorus atom on the nitro oxygen with the formation of a nitrene intermediate that, if generated in proximity to a suitable side chain, gives a nitrogen-containing heterocycle.[5b] Alternatively, the nitrene intermediate can undergo reaction with electronegative atoms.[5a] This provides a general route to a wide variety of heterocyclic compounds including carbazoles, indoles, 3*H*-azepines, benzoxazoles, etc., described in numerous reports by Cadogan and others.[5]

We have exploited the highly efficient driving force of phosphate formation from the corresponding phosphite derivative, to devise a quantitative reduction of various nitro compounds to amines in a one-pot synthesis under mild conditions.

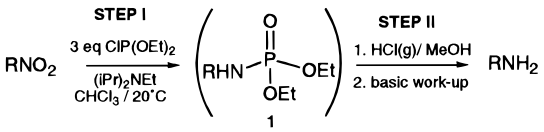
In a typical experiment, 3 equiv of diethyl chlorophosphite and 3 equiv of a tertiary amine are added (no reaction takes place in the absence of a tertiary amine, and lower yields are obtained when only 2 equiv of diethyl chlorophosphite are used) to 1 equiv of the nitro compound in $CHCl_3$ under a nitrogen atmosphere. After 0.5−5 h at room temperature, excess HCl(g) in MeOH is added and the mixture is stirred at 50 °C for 6−10 h. Workup with 10% NaOH affords the free amine, usually in a quantitative yield (Scheme 2).

In the course of this process, substituents such as chloro, nitrile, aldehyde, or ketone are not affected. The procedure is applicable to the reduction of nitroso compounds as well, but not to compounds containing hydroxyl or primary and secondary amine functions, which under these conditions are converted into phosphite derivatives.

Scheme 1



Scheme 2



The scope of the reaction is illustrated in Table 1. Whereas nitroalkanes are known not to react with $P(OEt)_3$[6] and in general their reduction is difficult (e.g., it can give rise to the corresponding oxime), 1-nitrohexane was converted smoothly and quantitatively to hexylamine by the above procedure.

Moreover, the scope of most of the common nitro reduction methodologies is rather limited; various functional groups or substituents do not survive the reaction conditions. For example, hydride or hydrazine reductions are not applicable to carbonyl-containing nitro compounds.[7] Even under the mild conditions of catalytic hydrogenation, halogenated aromatic nitro compounds often suffer dehalogenation.[7]

In this new procedure, groups commonly sensitive to reduction such as aldehyde or ketone not only survived but even promoted the reaction, when present at the para position; thus, *p*-nitrobenzaldehyde and *p*-nitroacetophenone (entries 3 and 7) were reduced completely. The former reacted after 0.5 h even at −10 °C. Nitrosobenzene was reduced efficiently at room temperature. A *m*-chloro substitution (entry 4) did not lower the yield; however, a *p*-cyano group (entry 5), or a *p*-methoxy group (entry 8) decreased the yield to 20%.

In addition to diethyl chlorophosphite, we evaluated the efficiency of other tervalent phosphorus compounds in this respect. Thus, when trimethyl phosphite, $P(OMe)_3$, was added under the above reaction conditions, at room temperature, no product formation was observed. Likewise, no reaction took place with either PCl_3 or bis(diisopropylamino) chlorophosphite.

Diethyl chlorophosphite is responsible for the high efficiency of this reaction as reflected in reaction rate, mild temperature (e.g., room-temperature instead of ca. 150 °C in $P(OR)_3$-induced reductive cyclizations,[5] Scheme 1), and quantitative yields. By comparison, reaction of *p*-nitrotoluene with an excess of $P(OEt)_3$ at 156 °C was reported to produce a mixture of four products, which were isolated in low yields and were identified as diethyl toluene-*p*-phosphonate (5%), diethyl 4-methyl-3*H*-azepine-7-phosphonate (6%), diethyl *N*-ethyl-*N*-*p*-tolylphosphoramidate (24%), and diethyl *N*-*p*-tolylphosphoramidate (26%).[8,9] Under our conditions, the reductive step (step

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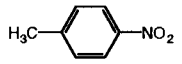
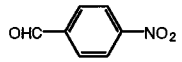
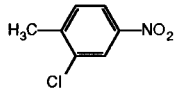
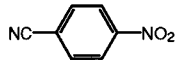
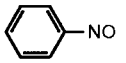
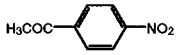
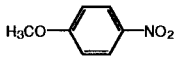
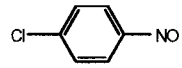
Table 1. Reduction of Nitro Compounds to Corresponding Amines

Entry	Reactant	T/°C	Time/h	Yield % [a]
1	$CH_3(CH_2)_5NO_2$	20 [b], 50 [c]	4 [b], 10 [c]	>95
2		20, 50	4, 6	>95
3		-10, 50	0.5, 10	>95
4		20, 50	24, 10	>95
5		20, 50	4 d, 10	ca. 20 [d]
6		20, 50	4, 12	>95
7		20, 50	5, 6	>95
8		20, 50	8, 10	ca. 20 [d]
9		20, 50	0.7, 10	92

a Yield based on ^{1}H NMR; *b* Step I (scheme 2); *c* Step II (scheme 2); *d* Rest is starting material.

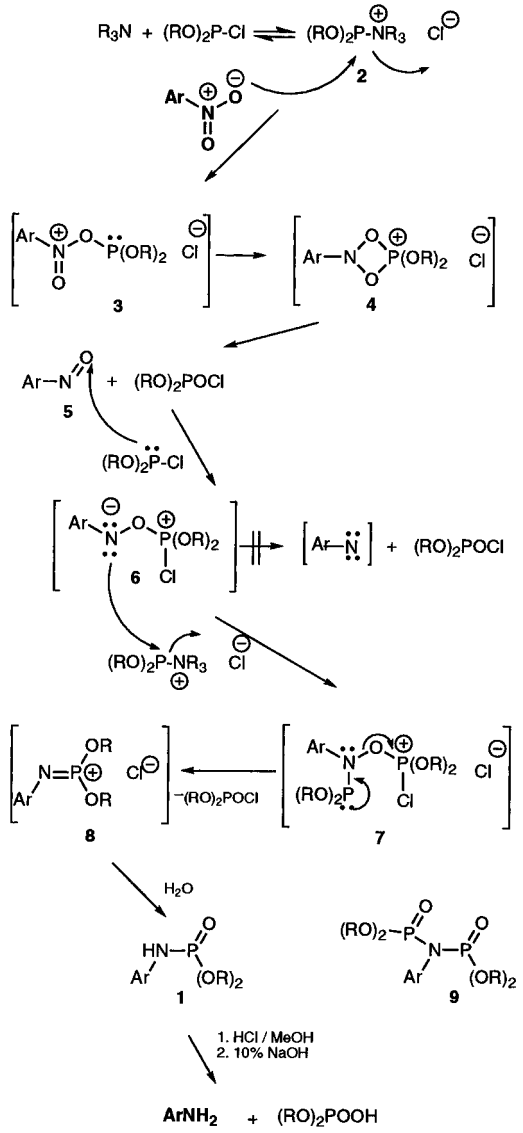
I, Scheme 2) of *p*-nitrotoluene took place at 20 °C within 4 h to afford a quantitative yield of the reduced product, diethyl *N*-*p*-tolylphosphoramidate, **1**.

To characterize the special role of $ClP(OEt)_2$ here, we need to compare it with literature reports illustrating the nucleophilic character of $P(OEt)_3$ and the electrophilic nature of PCl_3, used for deoxygenation of nitro- (nitroso) and *N*-oxide functions, respectively. The fact that reductive cyclizations of aromatic nitro compounds require trialkyl phosphite or triphenylphosphine, whereas PCl_3 does not react at all under these conditions, suggests a nucleophilic attack of triethyl phosphite on the nitro (or nitroso) oxygen.[5c] It is known, however, that pyridine *N*-oxide and related compounds undergo rapid reduction with PCl_3 which is accelerated in the presence of 2,6-lutidine.[8] In this case, the qualitative evidence is in agreement with PCl_3 acting as an electrophile, which is attacked by the *N*-oxide oxygen atom. This is further supported by the observation that with 4-nitropyridine *N*-oxide, the reaction rate is markedly decreased.[8] In contrast, in nitroso reductions induced by trialkyl phosphite, electron-donating groups at the para position of a nitrosoarene increase the electron density on the nitroso oxygen and make reduction to *N*-arylphosphorimidate much slower.[5c]

Diethyl chlorophosphite represents a "biphilic" reagent, a hybrid of triethyl phosphite and phosphorus trichloride, which could play both an electrophilic and a nucleophilic role. This is illustrated in the suggested mechanism shown in Scheme 3.

Since a tertiary amine is essential for the reaction, we suggest that the reactive species at the first deoxygenation step is $[R_3N{-}P(OEt)_2]^+\ Cl^-$, **2**, formed from the amine and diethyl chlorophosphite as evidenced by ^{1}H NMR.[10] In the first deoxygenating step, reactive species **2** acts as an *electrophile* to reduce the nitro to a nitroso compound, possibly via the intermediacy of a four-membered ring **4**, common in phosphorus chemistry. One equivalent of diethyl chlorophosphate is released in this step. A supporting evidence for the intermediacy of a nitroso compound was suggested by reacting nitrosobenzene (entry 6) under the same reaction conditions to give a phosphoramidate **1**, in a quantitative yield.

Scheme 3. Suggested Mechanism of the Title Reaction



The second deoxygenating step requires a *nucleophilic* tervalent phosphorus reagent, which attacks at the nitroso oxygen with the probable formation of intermediate **6**. Supporting evidence for this mechanistic step is the fact that an electron-poor nitroso (*p*-chloronitrosoben-

(10) Diethyl chlorophosphite was mixed with an equimolar amount of diisopropylethylamine in $CDCl_3$. After 10 min at rt, the ^{1}H NMR spectrum showed a new set of signals which are downfield shifted, relative to those of the phosphite and the amine. The downfield shift, as well as the more complex splitting pattern, indicates the formation of a quaternary ammonium as described for reactive species **2**. On the basis of the ^{1}H NMR spectrum taken after 10 min at 25 °C, a 40% conversion to species **2** had taken place. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.95 (m, 4H), 3.67 (septet d, J = 5, 3 Hz, 2H), 3.09 (dqd, J = 15, 5, 3 Hz, 2H), 1.33 (td, J = 5, 0.3 Hz, 6H), 0.96 (t, J = 5 Hz, 3H), 0.95 (d, J = 5 Hz, 12H).

zene, entry 9) reacted rapidly (within 40 min) under the reaction conditions to form phosphoramidate **1** in high yield. Moreover, as expected, *p*-cyanonitrobenzene (entry 5) reacted sluggishly, probably due to the rate-limiting step, which is the reaction of the electron poor nitro compound with the electrophilic reagent **2**. The possibility of intermediate **6** decomposing to produce a nitrene is unlikely, since we observed no reductive cyclization products, e.g. diethyl-4-methyl-3*H*-azepine-7-phosphonate,[9] due to nitrene insertion and ring expansion. By comparison, a reaction of nitrobenzene with diethyl methylphosphonite in a large excess of diethylamine at 55 °C for 5 days was reported to give 2-diethylamino-3*H*-azepine (83%).[11]

Intermediate **6** probably reacts subsequently with an additional molecule of reagent **2**, acting as an *electrophile*, leading to **7**. The isolated product **1**, characterized by ^{31}P NMR,[12] is most probably obtained by hydrolysis of intermediate **8**. A release of a second phosphate ester is concomitant. When the reaction was run with 4 equiv of $ClP(OEt)_2$, product **9** was isolated in trace amounts and was characterized by MS, ^{1}H and ^{31}P NMR.[13] The low yields of reduction products obtained with strong electron-donating (entry 8) or -withdrawing (entry 5) substituents further support the biphilic nature of the reagent.

In step II (Scheme 2), the phosphoramidate moiety is cleaved by treatment with HCl(g)/MeOH[14] to yield a quaternary ammonium product (from which the free amine is liberated by neutralization with 10% NaOH) and a third equivalent of phosphate ester.

The new methodology for reduction of nitro compounds into amines is a versatile procedure enabling a one-pot quantitative transformation, under mild conditions, of aliphatic and aromatic nitro compounds to the corresponding amines. The "biphilic" character of the reagent, diethyl chlorophosphite, is responsible for the high efficiency of the reaction. Further applications of this reagent for deoxygenating various functions is currently under investigation.

Experimental Section

General. ^{1}H NMR and ^{31}P NMR spectra were recorded at 300 and 200 MHz, respectively, in $CDCl_3$. Mass spectra were recorded on AutoSpec-E-Fision VG high-resolution mass spectrometer. Moisture sensitive reactions were carried out in two-necked flasks, flame-dried under nitrogen. Chloroform was distilled from CaH_2. Commercial nitro compounds were recrystallized. Nitroso compounds were prepared according to literature.[15] Diethyl chlorophosphite was used as received without additional purification.

Reduction of Nitro Compounds to Amines. Typical Procedure. To a solution of *p*-nitrotoluene (0.25 g, 1.82 mmol) in dry $CHCl_3$ (10 mL) under a nitrogen atmosphere were added diisopropylethylamine (0.95 mL, 5.47 mmol) and diethyl chlorophosphite (0.79 mL, 5.47 mmol). The solution was stirred at room temperature for 4 h. MeOH (7.4 mL, 100 equiv) was added until complete dissolution. The flask was immersed in an ice bath, and acetyl chloride (6.5 mL, 50 equiv) was added dropwise. The reaction mixture was then stirred at 50 °C for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$, washed with 10% NaOH (3 × 25 mL), dried over $MgSO_4$, and evaporated. Traces of diisopropylethylamine and phosphate ester were removed by chromatography (silica gel, $CHCl_3$:MeOH 10:1) to give the free amine (*p*-toluidine) in quantitative yield; spectroscopic data (^{1}H NMR and MS) were consistent with the given structure.

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(12) Compound **1**: ^{31}P NMR (200 MHz, $CDCl_3$) δ 2.70 (d, J = 10 Hz). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (d, J = 7.5 Hz, 2H), 6.88 (d, J = 7.5 Hz, 2H), 5.15 (d, J = 10 Hz, 1H), 4.2 (m, 4H), 2.30 (s, 3H), 1.31 (td, J = 6, 0.5 Hz, 6H). MS (CI/NH_3): 243 (M^+), 244 ($M + H^+$).

(13) Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (ABq, 4H), 4.2 (m, 4H), 2.28 (s, 3H), 1.31 (td, J = 6, 0.5 Hz, 6H). ^{31}P NMR (200 MHz, $CDCl_3$): 2.68 (s). MS (CI/NH_3): 380 ($M + H^+$).

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