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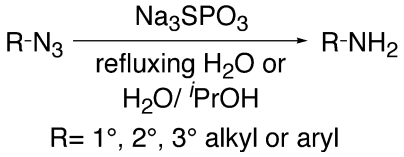

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Reduction of alkyl and aryl azides with sodium thiophosphate in aqueous solutions

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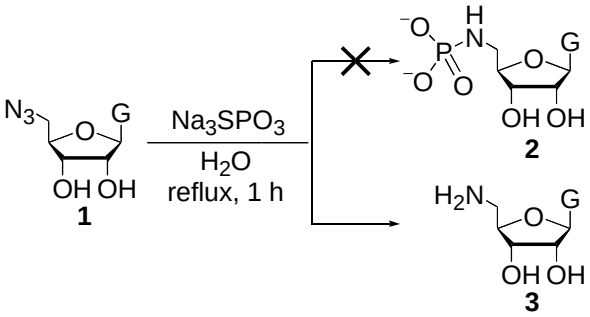
ABSTRACT

A simple aqueous method for the conversion of alkyl and aryl azides into the corresponding amines using trisodium thiophosphate is presented. Thiophosphate is converted into phosphate ions during these formal reduction processes.

The formation of primary amines is a cornerstone of organic synthesis. Classical methods for the preparation of these systems from alkyl halides revolve primarily around the use of phthalimide (Gabriel) followed by deprotection, or the displacement of halide ions with azide followed by reduction of the resulting organic azide. The reduction of azides is commonly achieved through metal-based hydrogenations, hydride-based reductions or the Staudinger procedure using PPh_3. Less common methods include the use of H_2S and hydrogen transfer methods from hydrazine. In addition, reductions that proceed in aqueous solvent systems have been developed, where transition metal catalysts in combination with hydride reagents[1] or transition metal based single electron transfer reducing agents[2] are employed. While these methods are reliable, they each present their own limitations in terms of cost, convenience and disposal of effluents.

Recently, in an attempt to form an *N*-phosphorylated 5'-amino-5'-deoxy-nucleoside **2**[3,4] from the azidonucleoside **1**, we investigated the use of thiophosphate ions (Scheme 1). Our procedure was based on precedents set with reactions between thiocarboxylate systems and organic azides for the formation of carboxylic amides and *N*-acyl sulfonamides.[5-8] However, we found that reaction mixtures containing thiophosphate ions effected a formal reduction of the azide **1** to amine **3** rather than the formation of the desired phosphoramidate **2**.[9]

With this transformation in mind, we now present details of the use of thiophosphate as a general reagent for the reduction of organic azides to their corresponding amines.



Scheme 1. Reaction of 5'-amino-5'-deoxyguanosine with thiophosphate ion.

We began our investigations using benzyl azide (**4a**)[10] as a convenient model. As the quality of commercially available sodium thiophosphate was found to be variable, a quantity was synthesised according to a literature procedure.[11] The product was found to be free of phosphate and anhydrous, according to ^{31}P NMR and thermogravimetric analyses. Initially, we explored the use of a fully aqueous solvent system where we employed one equivalent of thiophosphate ion (Table 1, entry 1). The azide **4a** was refluxed with the thiophosphate for 3 hours before being subjected to standard work-up. Unfortunately, only 77% reduction to the amine was observed, which we attributed to the limited solubility of the azide substrate. To overcome the poor solubility, we adopted a mixed water/*iso*-propanol solvent system and repeated the procedure using one equivalent of thiophosphate ion. After work-up, reduction had improved to 93% (entry 2), however, complete conversion of the thiophosphate into phosphate was observed by ^{31}P NMR spectroscopy. We surmised

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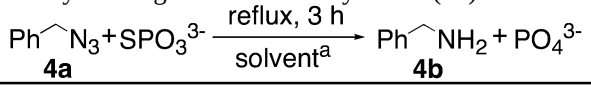
that the thiophosphate ion underwent a desulfurization process leading to the production of thiolate ions. Thiolate ions may also act as a reducing agent, but can be lost from the reaction in the form of H_2S. To overcome this, we increased the number of equivalents of thiophosphate ion being employed and repeated the procedure, whereupon benzyl azide (**4a**) was cleanly converted into benzyl amine (**4b**) (entry 3). ^{31}P NMR spectroscopy performed on the crude reaction mixture after reflux showed that more than one equivalent of thiophosphate was consumed. To confirm that thiophosphate was the source of the reduction process, benzyl azide (**4a**) was heated in the solvent mixture without thiophosphate, and unreacted azide was recovered from the reaction mixture (entry 4). In addition, thiophosphate was heated in the absence of benzyl azide (**4a**), and decomposition to phosphate was still observed (entry 5).

Table 1
Preliminary investigations with benzyl azide (**4a**)



Entry	Solvent[a]	SPO_3^{3-} equiv	Conversion of **4a** into **4b** (%)[b]	Conversion of SPO_3^{3-} into PO_4^{3-} (%)[c]
1	H_2O	1	77	100
2	H_2O/^{i}PrOH	1	93	100
3	H_2O/^{i}PrOH	3	100	80
4[d]	H_2O/^{i}PrOH	0	0	-
5[e]	H_2O/^{i}PrOH	3	-	100

[a] H_2O/^{i}PrOH was used in 2:1 ratio.

[b] Determined by ^1H NMR spectroscopy of the crude product mixture after work-up.

[c] Determined by ^{31}P NMR spectroscopy of the crude reaction mixture before work-up.

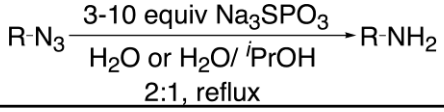
[d] Reaction performed under the same conditions as entries 1-3, but without Na_3SPO_3.

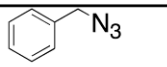
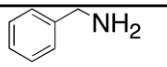
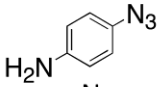
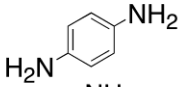
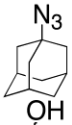
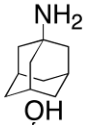
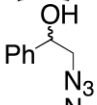
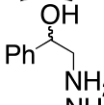
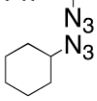
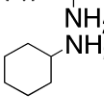
[e] Reaction performed at 95 °C in an NMR tube under the same concentration conditions as entry 3, but without benzyl azide (**4a**).

With an appreciation of the desulfurization process in hand, and having achieved clean conversion of benzyl azide (**4a**) into **4b**, we explored the scope of the SPO_3^{3-}-based reduction with a range of azide substrates. The azide substrates were prepared using established aqueous (Table 2, entries 3 and 6),[12,13] DMSO-based procedures (entries 1, 2, 7 and 8),[10,14] or obtained commercially (entries 4 and 5). Reductions were carried out with 3 equivalents of SPO_3^{3-}, unless stated otherwise.

In all cases the azide functionality was reduced to the amine. With simple 1°- and 2°-alkyl systems (entries 1, 2, 6 and 7), the products were isolated from reaction mixture using standard work-up procedures. For α-azidoethyl acetate (entry 3), complete hydrolysis of the methyl ester was also observed, which likely arises because of the basic nature of trisodium thiophosphate solution in combination with the prolonged reflux. The glycine product was not isolated, but its identity was confirmed by 'spiking' the crude D_2O-based reaction mixture with authentic glycine. The aromatic system, *p*-amino-azidobenzene (entry 4), showed complete reduction in trial ^1H NMR experiments in D_2O, and, thus, we attribute the relatively low isolated yield to poor extraction of the diamino product on work-up. The 3°-azido adamantyl system showed conversion into the amine (entry 5), however, the process occured very slowly even in the presence of elevated concentrations of SPO_3^{3-} and extended reflux. In the presence of 5 equivalents after 24 hours of reflux, complete consumption of thiophosphate was observed, however, only partial reduction of the azide was observed. An additional 5 equivalents of SPO_3^{3} were added and the mixture was refluxed for an additional 24 hours resulting in complete reduction of the azide and an isolated yield of 43% of 1-aminoadamantane. 2-Azido-1-phenylethanol (entry 6) was reduced to the corresponding amine in a yield of 72%. Cyclohexyl azide (entry 7) showed clean conversion to cyclohexyl amine, and was isolated in good yield via standard work-up. After 3 hours of heating, 1-azido-3-cyanopropane (entry 8) was reduced to a mixture of γ-aminobutyric acid (GABA) and 2-pyrrolidone. Addition of sodium deuteroxide and a further 16 hours of heating afforded GABA as the sole product, as confirmed by spiking with authentic GABA.

Table 2
Preparation of amines from azides



Entry	Substrate	Product	t (h)	Yield (%)[a]
1			3	93
2	n-C_8H_{17}-N_3	n-C_8H_{17}-NH_2	16	54
3	$MeO_2CCH_2N_3$	$^-O_2CCH_2NH_2$	1	-[b]
4[c]			3	56
5[d]			48	43
6			3	72
7			16	87
8	$NC(CH_2)_3$-N_3	$^-O_2C(CH_2)_3$-NH_2	3	-[e]

[a] Yields were determined after work-up without further purification.

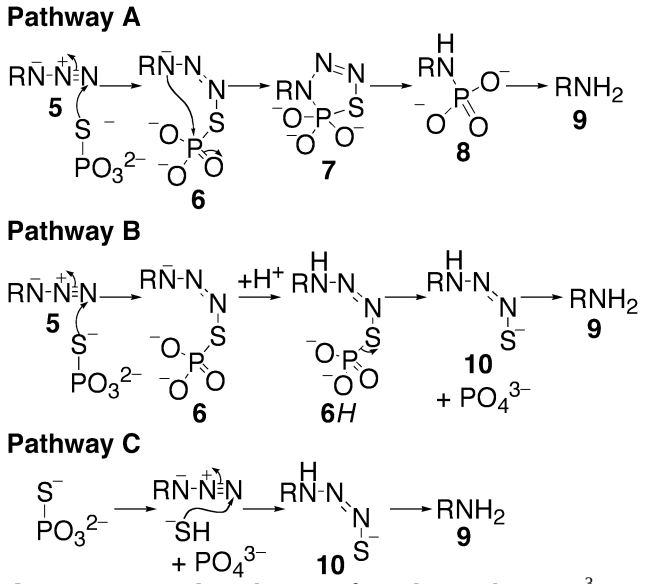
[b] Reaction was performed in D_2O at 95 °C in an NMR tube. Glycine was not isolated from the reaction mixture, but its identity was confirmed by ^1H and ^{13}C NMR spectroscopy.

[c] The HCl salt of the substrate was used with 1 equiv of NaOH added to the reaction mixture.

[d] 10 equiv of SPO_3^{3-} were used, added over two portions, one at the outset of the reaction, and one after 24 h reflux.

[e] Reaction was performed in D_2O at 90 °C in an NMR tube, producing a mixture of γ-aminobutyric acid (GABA) and 2-pyrrolidone. This mixture was then hydrolysed by the addition of NaOD. GABA was not isolated from the reaction mixture, but its identity was confirmed by ^1H and ^{13}C NMR spectroscopy.

Mechanistically, we can consider three possible pathways for the formal reduction process (Scheme 2). Initially, in our work with nucleoside substrate **1**, we aimed to form phosphoramidate **2**, via a stepwise, or concerted route, analogous to pathway **A**. Kinetic studies on phosphoramidates **8**,[4,15] suggest they would be short-lived under the reflux conditions, and their breakdown would result in the formation of amines **9** and phosphate ions.



Scheme 2. Potential mechanisms for reduction by SPO_3^{3-}.

While we cannot exclude pathway **A** conclusively, the intramolecular capture of the nitrogen anion by the phosphoryl dianions **6**, or a concerted addition of the sulfur anion of SPO_3^{3-} to azides **5** to give cyclic intermediates **7**, seems improbable on the basis of charge repulsion. This contrasts with the formation of iminophosphorane intermediates during Staudinger reductions where a nitrogen anion is captured by a cationic phosphorus centre, and the formation of cyclic intermediates between azides and thiocarboxylic acids *en route* to amides. However, protonation of one of the phosphoryl oxygen anions could occur in the aqueous solvent, reducing the intramolecular repulsion. Pathway **B** would also give rise to a thiophosphoryl-azide adduct **6**, which, on *N*-protonation, could decompose via loss of the phosphoryl group, followed by formal loss of N_2S, to give amine **9**. Pathway **C** would also produce thiolate intermediate **10** through direct addition of SH^- formed from desulfurization of SPO_3^{3-} and would likely proceed via the same mechanism as H_2S-based reductions of azides. In order to gain some understanding of the potential mechanism, we performed ^1H and ^{31}P NMR kinetic studies on the reduction of 4-azido-aniline (Figure 1).

The desulfurization of SPO_3^{3-} to afford phosphate ions and thiolate appears to exhibit zero-order kinetics. This is likely attributable to the pH dependence of desulfurization, where lower pH leads to a greater rate of desulfurization. Measurements of the pH of a solution of SPO_3^{3-} confirm that the pH decreases from ~11 to ~9 over the course of 3 hours. The appearance of *p*-diaminobenzene displays a lag period that suggests a requirement for the build-up of an intermediate that acts as the reducing agent. This is consistent with pathway **C**, where the build-up of thiolate ions as the reducing agent is required. In addition, the ^1H spectra contained signals correponding to 4-azido-aniline and *p*-diaminobenzene alone, with no evidence of the formation of intermediates. This is reinforced by the fact that ^{31}P spectra show clean conversion of SPO_3^{3-} into phosphate ions. With these observations in mind, we tentatively put forward a mechanistic proposal in line with pathway **C** with a rate-limiting attack of thiolate ion followed by fast decomposition of the resulting adduct. On this basis, SPO_3^{3-} represents a convenient, "caged" form of thiolate ions which are a known reducing agent for organic azides.

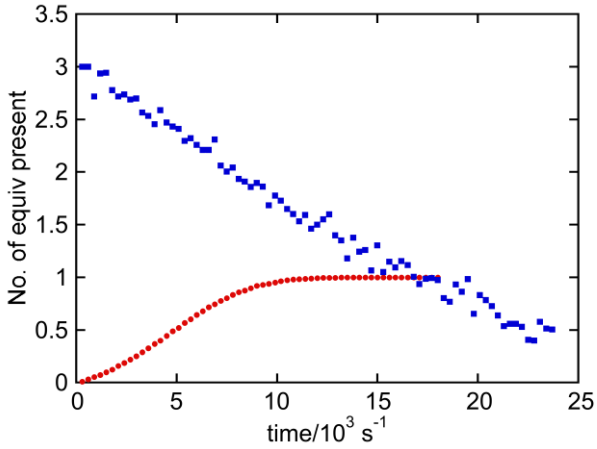


Figure 1. ^1H and ^{31}P NMR kinetic experiments on the reduction of 4-azido-aniline to *p*-diaminobenzene by SPO_3^{3-} at 70 °C in D_2O. Blue squares represent the remaining number of equivalents of SPO_3^{3-} determined by ^{31}P NMR. Red circles represent the number of equivalents of *p*-diaminobenzene determined by ^1H NMR.

In summary, we have developed a convenient, aqueous method for the reduction of organic azides to amines. The by-product from the reduction process is inorganic phosphate ions, which apart from being easy to remove on work-up, represents an inoccuous effluent. Future studies will centre on the mechanism of the reduction process and exploring the reactions of esters of thiophosphoric acid with azides.

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References and notes

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at