Graphical Abstract

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ABSTRACT

Phosphonohydrazines were prepared in good yield from corresponding arylamines by a one-pot reaction through diazotization with an organic nitrite and treatment with a trialkyl phosphite. The trialkyl phosphite is postulated to function as a nucleophile as well as a reducing agent.

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1. Introduction

Arylamines react readily with inorganic nitrite in acid to form diazonium compounds, which can be transformed to halides and other derivatives through the Sandmeyer reaction.¹ The reaction of aryl amines with organic nitrite is reported to form a series of diazo compounds as shown in Scheme 1. The formation and reaction of diazoamino compound **1** have been established and carefully investigated; whereas the formation of diazo intermediates **2** and **3** has not been fully established.²⁻⁹ The formation of aryl radical intermediates from the decomposition of these diazo intermediates has been utilized in aryl-aryl coupling reactions.⁵⁻⁹ The aryl radical intermediates were also implicated in the conversion of aryl amines to aryl halides in the presence of organic nitrite as an alternative method to the Sandmeyer reaction.^{4,10,11} In Meerwein and related reactions, cupric chloride was proposed to catalyze the direct decomposition of aryl diazonium to form aryl radicals in the arylation of α,β -unsaturated carbonyl compounds.^{12,13}

Scheme 1

2. Results and Discussion

We are interested in the synthesis of arylphosphonate esters. Dialkylphosphite has been reported to react with alkenes to form phosphonate and phosphite radical from the homo-cleavage of the P-H bond was proposed as the reactive intermediate.¹⁴ We thus sought to prepare aryl phosphonate esters through radical coupling of the phosphite radical and aryl radicals derived from arylamines as depicted in Scheme 1. However, aryl-phosphorus coupling did not occur when arylamine was treated with alkyl nitrite in the presence of dialkyl or trialkyl phosphite. When trialkyl phosphite was used, phosphonohydrazines **4** were formed in good yield instead (Scheme 2). In this Letter, we report the one-pot reaction of arylamines with isoamyl nitrite in the presence of triisopropyl phosphite to form phosphonohydrazines in good yield.

Scheme 2

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Phosphonohydrazines have been proposed as potential candidates for novel insecticides.¹⁵ Simple phosphonohydrazines (without aryl groups) were synthesized by the reaction of monochlorophosphonate and hydrazine.¹⁶⁻¹⁸ In a special case, 2,4-dinitrophenylated phosphonohydrazine has been isolated as a rearranged product from the reaction of bis(2,4-dinitrophenyl) phosphate with hydrazine.¹⁹ This reaction therefore presented a convenient method for the preparation of phosphoryl derivatives of aromatic hydrazines.

The reaction was conveniently carried out in one pot and works with mild electron-donating and electron-withdrawing

substituting groups on the aromatic ring as shown in Table 1.²⁰ Arylamines with strong electron-withdrawing or electron-donating groups such as nitro and methoxy groups, respectively, did not react very well. It may be difficult to form intermediates such as **3** from arylamines with strong electron-withdrawing groups. On the other hand, the reaction of diazo intermediates with phosphite (first step in the proposed mechanism shown in Scheme 3) may not proceed well when strong electron-donating group is present.

Table 1. Transformation of arylamines to phosphonohydrazines

4a-4j

Entries	Product #	Y=	Time	Yield (isolated, %)
1	4a	4-bromo	3 hr	52
2	4b	4-chloro	3 hr	44
4	4c	3-chloro	3 hr	84
5	4d	4-methyl	3 hr	49
6	4e	3,4-dimethyl	3 hr	46
7	4f	4-cyano	overnight	27 (79) ^a
8	4g	4-methoxy	3 hr-overnight	Not isolated ^b
9	4h	3-methoxy	3 hr-overnight	Not isolated ^b
11	4i	4-nitro	overnight	No reaction ^c
12	4j	2,4-dinitro	overnight	No reaction ^c

^aThe reaction only proceeded to 34% of initial reactant consumed and unreacted reactant was recovered. The number in parentheses refers to yield calculated based on amount of reactant consumed.

^bReaction produced multiple products or intermediates and pure product was not isolated.

^cNo reaction was observed even at elevated temperatures (up to 80 °C).

The reaction progress was monitored by thin-layer chromatography (TLC). In most cases, the reaction was completed in three hours. However, reactions run overnight did not seem to decrease the yield. The products were characterized using NMR and HRMS and the yields were found to be generally moderate to very good (Table 1).²⁰

The mechanism of the reaction is still under investigation. However, it is conceivable that the reaction involves nucleophilic attack by phosphite on intermediate such as **3** to form phosphonium intermediate **5** as shown in Scheme 3. Elimination of the isopropyl group leads to the formation of the phosphorus-oxygen double bond in phosphonodiaz intermediate **6**. Subsequent reduction of the diazo moiety in **6** by phosphite generates the final product **4**. Phosphites are known to be excellent reducing agents and the reduction of N–N bonds in diaziridinones and N–O bonds in nitro compounds has been reported.²¹⁻²³ Further mechanistic investigation is currently under way and focuses on the characterization of reaction intermediates.

Scheme 3

3. Conclusion

In summary, arylamines can be converted to aromatic phosphonohydrazines in good yield by reacting with organic nitrite in the presence of trialkyl phosphite. The reaction is likely to involve diazo intermediates formed by the reaction of arylamines and alkyl nitrite. Trialkyl phosphite is postulated to be the nucleophile as well as reducing agent. Considering the convenient and efficient one-pot nature of the reaction, this mechanistically interesting transformation represents an excellent

method for the preparation of some aromatic phosphonohydrazines.

23. Reactions between diazonium salts and trivalent phosphorus did not produce phosphonohydrazines as product. Reduction of diazoniums to arenes were observed instead, see: Yasui, S.; Fujii, M.; Kawano, C.; Nishimura, Y.; Shioji, K.; Ohno, A. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 177-183.

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- Experimental details*: All reagents were obtained from commercial sources and used without further purification. Typical experimental procedures are described below using the 4-bromophenyl derivative (**4a**) as an example.
Isopentyl nitrite (292 mg, 2.5 mmol) was added to a solution of 4-bromoaniline (172 mg, 1.0 mmol) in triisopropyl phosphite (1 mL). The solution was stirred for three hours (monitored by TLC). The excess triisopropyl phosphite was removed by vacuum and the residue was purified by column chromatography using 50:50 hexanes/methylene chloride as eluents. The product **4a** was obtained as an off-white solid (182 mg, 52%). ¹H NMR (ppm, CDCl₃) 7.32 (2H, d, aromatic, J = 9.0); 6.82 (2H, d, aromatic, J = 9.0); 5.39 (1H, s, NH-Ar); 4.74-4.66 (3H, m, NH-P, 2 x CH); 1.34 (6H, d, 2 x CH₃, J = 6.0); 1.27 (6H, d, 2 x CH₃, J = 6.0). ¹³C NMR (ppm, DMSO-d₆) 7.32 (1H, s, NH-Ar); 7.26 (2H, d, aromatic, J = 8.5); 6.93 (1H, d, NH-P, J = 33.9); 6.80 (2H, d, aromatic, J = 8.5); 4.50 (2 H, m, 2 x CH); 1.23 (6H, d, 2 x CH₃, J = 6.0); 1.19 (6H, d, 2 x CH₃, J = 6.0). HRMS (Electrospray, negative mode) m/z calculated for C₁₂H₁₉BrN₂O₃P (M-H) 349.0317, found 349.0323.
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