

Synthesis of phosphorothioates using thiophosphate salts

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Published: 16 March 2006

Received: 10 December 2005

Beilstein Journal of Organic Chemistry 2006, 2:4 doi:10.1186/1860-5397-2-4

Accepted: 16 March 2006

This article is available from: <http://bjoc.beilstein-journals.org/content/2/1/4>

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This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Abstract**

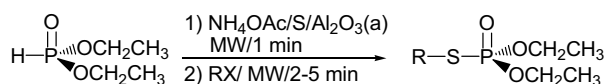
Reactions of *O,O'*-dialkyl thiophosphoric acids with alkyl halides, in the presence of a base, provide a direct synthetic route to phosphorothioates via *O,O'*-dialkyl thiophosphate anion formation. Studies on the reaction of ambident nucleophile ammonium *O,O'*-diethyl thiophosphate with benzyl halides and tosylate in different solvents show that only *S*-alkylation is obtained. Reaction of this ambident nucleophile with benzoyl chloride (a hard electrophile), gave the *O*-acylation product. A simple, efficient, and general method has been developed for the synthesis of phosphorothioates through a one-pot reaction of alkyl halides with the mixture of diethyl phosphite in the presence of triethylamine/sulfur/and acidic alumina under solvent-free conditions using microwave irradiation.

Introduction

Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates. [1] The synthesis of phosphate esters is an important objective in organic synthesis, since they have found use in the preparation of biologically active molecules, and also versatile intermediate in synthesis of amides and esters. [2-4] Among the phosphate esters, phosphorothioate derivatives are of interest as effective pesticides. [5-8] In recent years a number of phosphorothioates have been introduced as potential chemotherapeutic agent. [9-12] Despite their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of phosphorothioates has received little attention. The following methods, not generally applicable, have been reported in the literature: (i) reaction of dialkyl phosphites with sulfonyl chlorides, [13] sulfonyl cyanides, [14] thiosulfonates, [15,16] disulfides, [17] and sulfur, [18-21] (ii) condensation of

phosphorochloridate with thiols [22-26] and (iii) redox-type reactions of phosphorus triesters with thiols in the presence of tellurium (IV) chloride. [27,28] However, all of these methods have problems, including drastic reaction conditions and also some severe side reactions. Surface-mediated solid phase reactions are of growing interest [29-35] because of their ease of set-up, work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts. The application of microwave energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques. [36] Synthesis of molecules that normally require long reaction times, can be achieved conveniently and very rapidly in a microwave oven. As a part of our efforts to explore the utility of surface-mediated reactions for the synthesis of organophosphorus compounds, [37-48] we report a new method for the preparation of phosphorothioates by reaction of diethyl phosphite with alkyl halides in the presence of a mixture of ammonium acetate/sulfur/alumina

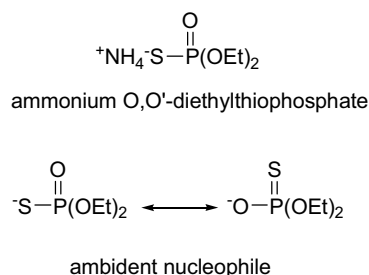
under solvent-free conditions using microwave irradiation which produces high yields of phosphorothioates (Scheme 1).



Scheme 1: Synthesis of phosphorothioates using microwave irradiation

Results and Discussion

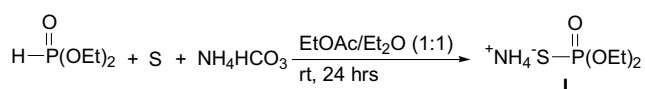
Recently we have found that ammonium *O,O'*-diethyl thiophosphate can be obtained by reaction of diethylphosphite in the presence of a mixture of ammonium acetate/sulfur/acidic alumina under solvent-free conditions using microwave irradiation. [49] This reagent can be used as an efficient reagent for the conversion of epoxides to thiranes. This ambident nucleophile has two potentially attacking atoms (S or O) and can attack with either of them, depending on conditions, and mixtures are often obtained in the reaction with electrophilic centers (Scheme 2). [50]



Scheme 2: Ambident nucleophile ammonium *O,O'*-diethylthiophosphate

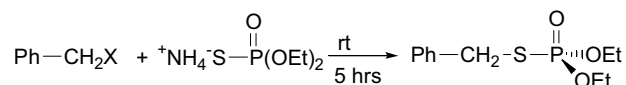
We have found that the reaction of diethyl phosphite with alkyl halides in the presence of a mixture of ammonium acetate/sulfur/alumina under solvent-free conditions using microwave irradiation produces high yields of phosphorothioates (*S*-alkylation, Scheme 1). [44] We decided to investigate the reaction of this ambident nucleophile under different conditions (different leaving groups and solvents).

Firstly, we introduce a novel method for large-scale synthesis of ammonium *O,O'*-diethyl thiophosphate. The reaction of sulfur with diethylphosphite in the presence of ammonium hydrogen carbonate under reflux condition in a solvent mixture of ethyl acetate and diethyl ether (1:1) gave ammonium *O,O'*-diethyl thiophosphate in quantitative yield (Scheme 3).



Scheme 3: Synthesis of ammonium *O,O'*-diethyl thiophosphate

The results of the reaction of this reagent with benzyl bromide, chloride and tosylate in different aprotic and protic solvents show that *S*-benzyl *O,O'*-diethyl phosphorothioate (*S*-alkylation) was formed as sole product (Scheme 4).



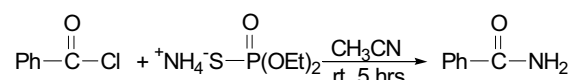
X=Br-, Cl-, and TsO-

Solvent: DMF, DMSO, Acetonitrile, EtOH, and MeOH

Scheme 4: Solvent and leaving group effects on the synthesis phosphorothioates

We conclude here that changing of leaving group and use of different media gives no *O*-alkylation product (i.e. changing from soft to hard leaving group and aprotic to protic solvent). Although ammonium *O,O'*-diethyl thiophosphate is a potential ambident nucleophile, only its soft center is reactive in this case.

Recently the synthesis of *S*-thioacyl dithiophosphates has been reported as an efficient and chemoselective thioacylating agent using the reaction of acyl chlorides with dithiophosphoric acid in the presence of pyridine or triethylamine. [51-53] In another study we decided to investigate the reaction of the ambident nucleophile ammonium *O,O'*-diethyl thiophosphate salt with acyl chlorides. Reaction of ammonium *O,O'*-diethyl thiophosphate with benzoyl chloride, as a model compound, in acetonitrile gave benzamide as the major product (Scheme 5).



Scheme 5: Reaction of ammonium *O,O'*-diethyl thiophosphate with benzoyl chloride

Benzoyl chloride reacts with ammonia (from ammonium *O,O'*-diethyl thiophosphate) faster than anion *O,O'*-diethyl thiophosphate to give benzamide. All efforts for solving this problem failed and in all cases benzamide was obtained as the major product.

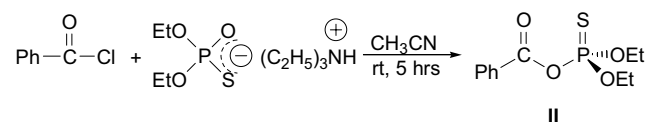
We decided to replace this ammonium ion with a triethyl ammonium ion and then to study the reaction of new salt with benzoyl chloride. Triethylammonium *O,O'*-diethyl thiophosphate was obtained by reaction of diethylphosphite, sulfur and triethyl amine. [54-57] We found that reaction of triethylammonium *O,O'*-diethyl thiophosphate with benzoyl chloride gave benzoyl *O,O'*-diethyl phosphorothioate with *O*-acylation product (Scheme 6).

Table 1: Reaction of alkyl halides and tosylates in the presence of a mixture of triethylamine/sulfur/alumina with diethylphosphite under solvent-free conditions

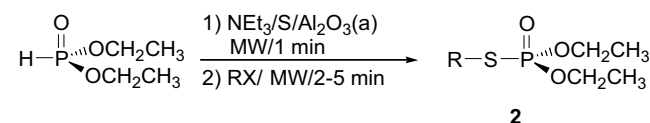
| 2 | R | X | Reaction Time (min) | Yield % ^a |
|---|---|-----|---------------------|----------------------|
| a | PhCH ₂ | Br | 3 | 62 |
| a | PhCH ₂ | OTs | 3 | 67 |
| b | PhCH ₂ CH ₂ | Br | 2 | 72 |
| c | <i>p</i> -NO ₂ C ₆ H ₄ CH ₂ | Br | 4 | 70 |
| c | <i>p</i> -NO ₂ C ₆ H ₄ CH ₂ | OTs | 5 | 83 |
| d | <i>o</i> -MeC ₆ H ₄ CH ₂ | Br | 3 | 65 |
| d | <i>o</i> -MeC ₆ H ₄ CH ₂ | Cl | 3 | 65 |
| e | <i>p</i> -ClC ₆ H ₄ CH ₂ | OTs | 2 | 67 |
| f | <i>m</i> -ClC ₆ H ₄ CH ₂ | OTs | 2 | 55 |
| g | <i>p</i> -MeC ₆ H ₄ CH ₂ | Br | 4 | 62 |
| h | <i>i</i> -Butyl | Br | 2 | 76 |
| i | <i>i</i> -Hexyl | Cl | 5 | 75 |

a: Isolated Yields

We conclude that replacement of benzyl with benzoyl group (hard electrophilic center) gives the *O*-acylation product.

**Scheme 6: Reaction of triethylammonium O,O'-diethyl thiophosphate with benzoyl chloride**

As a part of our efforts to explore the utility of surface-mediated reactions for the synthesis of organophosphorus compounds, [16-18] herein we report a new method for the preparation of phosphorothioates by reaction of diethyl phosphite with alkyl halides in the presence of a mixture of triethylamine/sulfur/alumina under solvent-free conditions using microwave irradiation. We found that a mixture of alumina, sulfur, diethylphosphite and triethylamine under microwave irradiation gave triethylammonium *O,O'*-diethyl thiophosphate that can be used for the synthesis of phosphorothioates under solvent free conditions (Scheme 7, Table 1). As shown in Table 1, a wide range of alkyl halides in the presence triethylamine/sulfur/alumina reacted with diethyl phosphite, giving the required products 2 in moderate to good yields.

**Scheme 7: Synthesis of phosphorothioates using triethylammonium O,O'-diethyl thiophosphate using microwave irradiation.**

In summary, a simple work-up, low consumption of solvent, fast reaction rates, mild reaction conditions, good to excellent yields, relatively clean reactions with no tar formation make these methods an attractive and a useful contribution to present methods for the preparation of phosphorothioates. Studies on the reaction of ambident nucleophile ammonium *O,O'*-diethyl thiophosphate with benzyl halides and tosylate in different solvents show that only *S*-alkylation will be obtained as sole product. Reaction of this ambident nucleophile with benzoyl chloride (hard electrophilic center), gave the *O*-acylation product.

Additional material

Additional File 1

The additional file contains full experimental details

Click here for file

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Acknowledgements

The Institute for Advanced Studies in Basic Sciences (ASBS) is thanked for supporting this work.

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