Synthesis of phosphorothioates using thiophosphate salts

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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 phosphate 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 sulfenyl chlorides,[13] sulfenyl 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](image)

**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 thiiranes. 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](image)

**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 produces high yields of ammonium \(O,O'\)-diethyl thiophosphate (Scheme 3).

![Scheme 3](image)

**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).

![Scheme 4](image)

**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](image)

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

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 phosphate 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 triethylamine/sulfur/alumina under solvent-free conditions using microwave irradiation gave triethyl phosphate, giving the product. Reaction of this ambident nucleophile with benzoyl chloride (hard electrophilic center), gave the O-acylation product.

**Additional material**

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

| R       | X     | Reaction Time (min) | Yield % |
|---------|-------|---------------------|---------|
| PhCH₂   | Br    | 3                   | 62      |
| PhCH₂   | OTs   | 3                   | 67      |
| PhCH₂CH₂| Br    | 2                   | 72      |
| p-NO₂C₆H₄CH₂| Br  | 4                   | 70      |
| p-NO₂C₆H₄CH₂| OTs| 5                   | 83      |
| o-MeC₆H₄CH₂| Br  | 3                   | 65      |
| o-MeC₆H₄CH₂| Cl   | 3                   | 65      |
| p-ClC₆H₄CH₂| OTs | 2                   | 67      |
| m-ClC₆H₄CH₂| OTs | 2                   | 55      |
| p-MeC₆H₄CH₂| Br  | 4                   | 62      |
| I-Butyl | Br    | 2                   | 76      |
| I-Hexyl | Cl    | 5                   | 75      |

a: Isolated Yields

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.

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