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A simple and new method for the synthesis of thiophosphates

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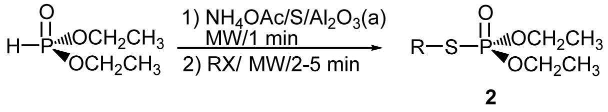
Abstract—A simple, efficient, and general method has been developed for the synthesis of thiophosphates through a one-pot reaction of alkyl halides with the mixture of diethyl phosphite in the presence of ammonium acetate/sulfur and acidic alumina under solvent-free conditions using microwave irradiation. © 2002 Elsevier Science Ltd. All rights reserved.

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.[2,3] Among the phosphate esters, thiophosphate derivatives are of interest as effective pesticides.[4] In recent years a number of thiophosphates have been introduced as potential chemotherapeutic agent.[5,6] Despite their wide range of pharmacological activity, industrial and synthetic applications, the synthesis of thiophosphates has received little attention. The following methods, not generally applicable, have been reported in the literature: (i) reaction of dialkyl phosphites with sulfenyl chlorides,[7] sulfenyl cyanides,[8] thiosulfonates,[9] disulfides,[10] and sulfur,[11] (ii) condensation of phosphorchloridate with thiols.[12] However, all of these methods have problems, include drastic reaction conditions and also some severe side reactions. Surface-mediated solid phase reactions are of growing interest[13] because of their ease of set up and 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.[14] Synthesis of molecules which normally require large periods, 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,[15–18] we report here a new method for the preparation of thiophosphates 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 produces high yields of thiophospates (Scheme 1, Table 1).

As shown in Table 1, a wide range of alkyl halides in the presence ammonium acetate/sulfur/alumina were reacted with diethyl phosphite, giving the required



Scheme 1.

Table 1. Reaction of diethyl phosphite with alkyl halides in the presence mixture of ammonium acetate/sulfur/alumina under solvent-free conditions using microwave irradiation

2	R	X	Reaction time (min)	Yield (%)[a]
a	PhCH$_2$-	Br	2	76
a	PhCH$_2$-	Cl	2	82
b	Ph$_2$CH-	Br	3	88
c	PhCH$_2$CH$_2$-	Br	2	75
d	p-NO$_2$C$_6$H$_4$CH$_2$-	Br	2	90
e	p-MeC$_6$H$_4$CH$_2$-	Cl	2	88
f	o-MeC$_6$H$_4$CH$_2$-	Cl	5	76
g	m-MeC$_6$H4CH$_2$-	Cl	3	85
h	1-C$_{10}$H$_7$CH$_2$-	Cl	2	87
i	PhCH$_2$CH$_2$CH$_2$-	Cl	2	80

[a] Isolated yields.

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products **2** in excellent yields. The reactions were clean with no tar formation. Ammonium formate (NH_4O_2CH) is not as effective as ammonium acetate and gave low yields of required product. Other ammonium salts (NH_4Cl, NH_4Br, NH_4PF_6) are not effective and didn't give any product.

This solvent-free reaction method is operationally simple. 10 mmol of the reagent was prepared by the combination of ammonium acetate (10 mmol, finely ground), sulfur (10 mmol) and alumina (Al_2O_3, acidic, 2.5 g) in a mortar and pestle by grinding them together until a fine, homogeneous, powder was obtained (5–10 min). Diethyl phosphite (10 mmol) was added to this mixture and the mixture was irradiated by microwave for 1 min using 720 W. The alkyl halide (9 mmol) was added to this reagent (solid alkyl halides need to be grinded) and was irradiated by microwave for 2-5 min using 720 W (A kitchen-type microwave was used in all experiments). Chromatography through a plug of silica gel with EtOAc/*n*-hexane (1:9–5:5) and evaporation of the solvent under reduced pressure gave the pure products as oils in 75–90% yields.[19]

In summary, a simple work-up, low consumption of solvent, fast reaction rates, mild reaction condition, good yields, relatively clean with no tar formation the reaction make this method an attractive and a useful contribution to present methodologies. Indeed, a wide range of alkyl halides was converted to corresponding thiophosphates using this method.

Acknowledgements

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19. All products gave satisfactory spectral data in accord with the assigned structures. For **2a** (*S*-benzyl *O*,*O*-diethyl phosphorothioate) as an example ^1H NMR ($CDCl_3$/TMS-500 MHz): 1.31 (6H, t, $J=7.1$ Hz), 4.01–4.25 (6H, m), 7.27–7.29 (5H, m); ^{31}P NMR ($CDCl_3$/H_3PO_4-85%): 27.05 ppm; ^{13}C NMR: 16.39, 35.4, 63.9, 128.0, 129.1, 137.9; IR (neat): 1260 (P=O), 1162(P–O–Et) cm^{-1}.