Indian Journal of Chemistry
Vol. 48B, April 2009, pp. 602-605

## Note

# A facile and efficient microwave-mediated *S*-alkylation of thiophosphates

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*Received 24 September 2008; accepted (revised) 12 January 2009*

A convenient, highly efficient, safe microwave-mediated *S*-alkylation of *O,O'*-dialkyl thiophosphate has been reported. Clean and rapid *S*-alkylation of thiophosphates can be achieved by irradiating a mixture of dialkylthiophosphate salt and alkyl halide under microwave for a brief period. Alkylation occurs exclusively at sulfur to provide *S*-alkylated products. Through a simple workup, pure compounds have been obtained easily in good yields.

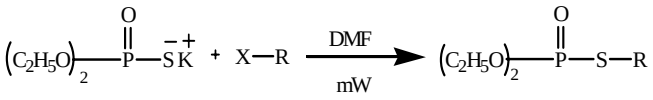
**Keywords**: Microwave, *S*-alkylated thiophosphate, alkyl halides, *O, O'*-dialkyl thiophosphates.

Organophosphorous compounds are important due to their diverse chemical and biological properties[1]. Major interest associated with these stems from their extensive application as synthetic reagents[2], intermediates[1b,3], pharmaceuticals[3b,4], and agrochemicals[5]. Phosphorous-sulfur compounds, often thiol ester of phosphoric acid derivative, exhibits biological activities and many *S*-substituted thiophosphates are among the most promising chemotherapeutic[6,7] and radio protective agents[8]. In view of their synthetic importance, many routes have been developed to gain access to *S*-substituted thiophosphates from various sources such as dialkyl and trialkyl phosphites[9], phosphorochloridates[10], tertiary phosphorothionates[11], etc. and accordingly, several methods are reported for their preparation[12], Though the reported procedures are useful, but often limited by drawbacks such as harsh reaction conditions, formation of undesired side products, use of corrosive and malodorous compounds, incompatibility with a multi-component system and complex experimental procedure which makes isolation of the desired product tedious. Hence, the development of novel synthetic strategies for synthesis of title compounds, which have advantage with respect to clean reaction, short reaction time, mild reaction condition, safe handling and easy isolation of the product are highly desired.

Alkylation of sulfur atom of thiophosphate is a viable synthesis of *S*-alkylated thiophosphates[12]. This relatively straightforward reaction is particularly useful in terms of simplicity, employment of non–corrosive or non-malodorous reactants and their ease of availability/preparation. However, the reported classical procedures involving solvent and heating conditions were not satisfactory. We required a simple procedure for the synthesis of *S*-alkylated thiophosphates which is convenient, expeditious and environmentally benign. The application of microwaves in organic synthesis is a widely accepted tool to achieve clean reaction condition in context of green and sustainable alternative methods[13,14]. Hence, we reasoned that the impediments of reported conventional procedure may be circumvented with a microwave mediated approach and we set to explore this reaction under microwave. Herein, we present a microwave assisted procedure for the synthesis of *S*-alkylated thiophosphates which is very simple, convenient, rapid and non hazardous. With this reported procedure formation of the target compounds can be achieved very easily by irradiating a mixture of dialkylthiophosphate salt and alkyl halide under microwave for a brief period (**Scheme I**). Through a simple workup pure compounds were obtained easily in good yields.

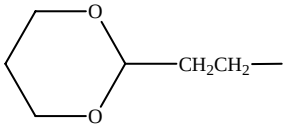
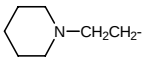
## Results and Discussion

Initially an investigation with the condensation of hexyl bromide and potassium *O,O'*-diethyl thiophosphate as model reaction was carried out. Both the substrates were commercially available. The studies were then directed towards exploring the feasibility of this reaction under microwave. First, various solvent were examined to carry out the reaction. Of the several solvents tested, DMF was found to be the solvent of choice, whereas other polar aprotic solvent such as DMSO and $CH_3CN$ were less suitable. Next, reaction was studied for optimum mol. ratio of the substrates and time required for completion of the reaction. 1:1 mol. Ratio of the substrates was found optimum. An equimolar amount



**Scheme I**

**Table I —** *S*-Alkylation of *O, O'*-diethyl thiophosphate

| Compd | R | X | Time[a] (min.) | Conversion[b] | Yield[c] (%) |
|---|---|---|---|---|---|
| **2a** | *n*-$C_6H_{13}$- | Cl | 8 × 1 | 98 | 87 |
| **2a** | *n*-$C_6H_{13}$- | Br | 5 × 1 | 99 | 88 |
| **2a** | *n*-$C_6H_{13}$- | I | 4 × 1 | 99 | 87 |
| **2a**[d] | *n*-$C_6H_{13}$- | Br | 4 hrs | 89[e] | - |
| **2b** | $C_6H_5CH_2CH_2$- | Br | 5 × 1 | 99 | 82 |
| **2c** |  | Br | 5 × 1 | 94 | - |
| **2d** | $(C_6H_5)_2CH$- | Br | 4 × 2 | 97 | 87 |
| **2e** | $CH_3$ $CH_2COOCH_2CH_2CH_2$- | Br | 5 × 1 | 96 | 82 |
| **2f** | $CH_2$=$CHCH_2CH_2$- | Br | 4 × 1 | 99 | - |
| **2g** | *p*-$ClC_6H_4CH_2$- | Br | 3 × 2 | 96 | 78 |
| **2h** | *o*-$ClC_6H_4CH_2$- | Br | 3 × 2 | 96 | 81 |
| **2i** | $HOCH_2CH_2$- | Br | 4 × 1 | 97 | 72 |
| **2j** |  | Br | 3 × 2 | 96 | - |
| **2k** |  | Br | 6 × 1 | 98 | 87 |
| **2l** | $NCCH_2CH_2$- | Br | 5 × 1 | 96 | 83 |
| **2m** | *n*-$C_{14}H_{29}$- | Br | 4 × 2 | 98 | 85 |
| **2n** | $C_6H_5$- | Br | 5 × 2 | 0 | - |

[a] Number of irradiation for a given time; 4 × 1 indicates 4 irradiations of 1 min duration each at 450 W.
[b] GC conversion and identification by their MS data.
[c] Isolated Yield.
[d] Reaction with conventional heating at 80°C,
[e] 9% Side products were formed.

of dialkylthiophosphate and alkyl halide was taken in minimum amount of DMF and irradiated with microwave. Rapid reaction occurs, which is indicated by the precipitation of potassium halide and reaction is completed within minutes. Contents were dissolved in appropriate solvent and filtered. Removal of the solvent afforded pure compound.

The generality of this new methodology was determined by examining a variety of substrates, with the above established microwave assisted method for *S*-alkylation of thiophosphates. The results of the formation of several *S*-alkylated thiophosphates are summarized in **Table I**. This protocol has excellent functional group compatibility and applicable to a great array of substrates.

Comparison among the three halides **2a** showed that with all the three halides viz. Iodide, bromide, chloride, reaction took place readily, though with chloride rate was slightly slow but parallel yields were obtained. The influence of steric hindrances was also studied. Various primary aliphatic halides reacted promptly while reaction of secondary halides required longer reaction times for the desired transformation. A sterically more demanding secondary halide, Diphenyl methyl halide offered similar result **2d**.

As expected aryl halide were found resistant **2n**. Reaction in aqueous medium was also found to occur but a few phosphorothioates tend to hydrolyze in water. Though thiophosphates salts have two potential attacking sites (S and O) alkylation took place

exclusively at sulfur, no evidence of formation of *O*-alkylated product was obtained. Furthermore, since the reaction is very clean and isolation of the pure product (94-97% purity) can be achieved through a simple and brief workup without involving distillation or tedious chromatographic separation, it is particularly useful for preparation of phosphorothioates which are not amenable to purification through distillation. In addition, the procedure does not involve acidic or basic conditions; it is suitable for acid/base sensitive compounds **(2c, 2e** and **2l)**.

## Experimental Section

In a typical experimental procedure, Potassium *O, O′*-diethyl thiophosphate 0.21 g (1 mmole) was taken in a test tube. To this alkyl bromide 2 mmoles and DMF (0.1-0.3 mL) was added, mixed thoroughly and microwaved at 450 W (Sam-sung CE2977N operating at 2450 MHz) for 2 min, whereupon dissolution of the contents in DMF takes place. 0.21 g (1 mmole) of thiophosphate salt was added again and the contents were irradiated further. Rapid reaction occurs, which is indicated by the precipitation of potassium bromide. Microwave exposures were intermittent with 15 sec. break **(Table I)**. Content were mixed gently with the help of a glass thermometer which also indicated the temperature of the reaction mixture. Depending on the substrate, temperature of the reaction mixture was found to vary from 75-85°C. Progress of the reaction was monitored by GC. On completion of the reaction, DMF was removed by distillation under vacuum from the reaction mixture. Residue obtained was dissolved in hexane/DCM and filtered. Removal of the solvent under reduced pressure gave the product as colourless oil (purity 94-97%). This is sufficient for most of the purposes and if required, compounds can be purified further by distillation or by crystallisation.

Selective spectral analysis of some representative compounds:

**2a**: Colourless oil; $^1$H NMR ($CDCl_3$/TMS-400 MHz): δ 0.91(3H, t, 6.8 Hz), 1.30-1.43 (12H, m), 1.69 (2H, qui, 7.5 Hz), 2.81-2.88 (2H, m), 4.13-4.22 (4H, m); $^{31}$P NMR ($CDCl_3$/$H_3PO_4$-161.9 MHz): δ 28.40 ppm; $^{13}$C NMR ($CDCl_3$/TMS-100.6 MHz): δ 14.10 (d, $J_{PC}$ = 6.0 Hz), 16.15 (d, $J_{PC}$ = 7.0 Hz), 22.56, 28.31, 30.83 (d, $J_{PC}$ = 5.8 Hz), 31.01 (d, 4.1 Hz), 31.28, 63.49 (d, 5.6 Hz); EIMS: *m/z* 254[$M^+$], 191, 158, 148, 133, 114, 101, 86, 63, 52; IR (neat): 1257 (P=O), 1120-960 (P-O-Et) cm$^{-1}$; Anal. Cacld for $C_{10}H_{24}PSO_3$. C, 47.06; H, 9.41. Found: C, 46.93; H, 9.45.

**2g**: Colourless oil; $^1$H NMR ($CDCl_3$/TMS-400 MHz): δ 0.99 (6H, t, $J$ = 7.0 Hz), 3.60-3.95 (6H, m), 6.90-7.18 (4H, m); $^{31}$P NMR ($CDCl_3$/$H_3PO_4$-161.9 MHz): δ 26.27 ppm; $^{13}$C NMR ($CDCl_3$/TMS-100.6 MHz): δ 15.7 (d, $J_{PC}$ = 7.9 Hz), 33.9 (d, $J_{PC}$ = 3.3 Hz), 63.3 (d, $J_{PC}$ = 5.8Hz), 128.5, 130.1, 133.1, 136.1 (d, $J_{PC}$ = 4.7 Hz); EIMS: *m/z* 294[$M^+$], 265, 157, 141, 125, 109, 89, 63; IR (neat): 1235 (P=O), 1133-952 (P-O-Et) cm$^{-1}$; Anal. Calcd for $C_{11}H_{16}ClPSO_3$. C, 44.82; H, 5.43. Found: C, 45.01; H, 5.33.

**2m**: Colourless oil; $^1$H NMR ($CDCl_3$/TMS-400MHz): δ 0.877(3H, t, $J$ = 6.8 Hz), 1.25-1.38 (m, 28 H), 1.67 (2H, qui, $J$ = 7.6 Hz), 2.78-2.85 (2H, qui, $J$ = 7.2 Hz), 4.12-4.19 (4H, m); $^{31}$P NMR ($CDCl_3$/$H_3PO_4$-161.9 MHz): δ 28.60 ppm; $^{13}$C NMR ($CDCl_3$/TMS-100.6 MHz): δ 16.21, 22.80, 28.66, 29.13, 29.46, 29.56, 29.66, 29.74 (d, $J_{PC}$ = 1.9 Hz), 29.76, 29.79, 30.86, 30.92, 31.01, 31.05, 32.03, 63.52 (d, $J_{PC}$ = 5.8 Hz) EIMS: *m/z* 366[$M^+$], 229, 197, 170, 143, 115, 81, 55; IR (neat): 1257 (P=O), 1123-962 (P-O-Et) cm$^{-1}$; Anal. Cacld for $C_{18}H_{39}PSO_3$. C, 59.02; H, 10.66. Found: C, 59.04; H, 10.64.

## Conclusion

In summary, a very simple and rapid microwave assisted procedure for *S*-alkylation of thiophosphate has been established. The advantages and highlights of the present microwave protocol includes, convenience of the method and ease of isolation of the product, compatibility with various functional groups and use of non corrosive and non-malodorous substances. The advantages associated with this method may lead to its wider application. Further application of this synthetic methodology is being investigated in our laboratory.

## Acknowledgement

The authors are thankful to A. Narasimha Rao for recording the mass spectra. Authors also thank Dr. R. Vijayaraghavan Director, DRDE for his keen interest and encouragement.

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