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Thionation of phosphoramidodichloridates and phosphoramidate diesters using phosphorus pentasulfide and hexamethyldisiloxane under microwave irradiation. Part 1

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Abstract—A new, mild, efficient, and solvent-free microwave promoted synthesis of thiophosphoramidodichloridates and thiophosphoramidate diesters is described. The thionation reaction was accelerated with microwave irradiation using the combination of P_4S_{10} and HMDO. The conversion of P=O to P=S by this method gave the desired product in higher yields and shorter reaction times as compared to conventional methods.

Thiophosphoramidodichloridates are important intermediates for the synthesis of various biologically active organophosphorus compounds. Many of the syntheses of phosphoramidates and their thio analogues depend upon the availability of such compounds as the phosphorus chlorine bond is easily replaced with dialkyl or diarylamino groups. For this reason, about ninety percent of the commercially known pesticides make use of this synthetic strategy in their manufacturing processes.[1] Thiophosphoramidate diesters are also reported to have activity at the commercial level in the major pesticide areas, and are currently most prominent as insecticides,[2] fungicides,[3] and herbicides.[4] They play a very important role in various biological processes,[1,5] and are also used as chiral phosphorus auxiliaries in the asymmetric synthesis of various organic compounds.[6]

An unusual fish toxin isolated from the red tide dinoflagellate *Ptychodiscus brevis* was also found to have a phosphoramidate as an active moiety in its structure.[7]

Several methods have been reported in the literature,[8–12] which make use of various thionating agents (either alone or in combination) such as elemental sulfur,[11] phosphorus pentasulfide,[10] and Lawesson's reagent[12] (LR), but only two deserve mention here as convenient laboratory methods.[10,12] The most commonly used method for the direct conversion of P=O to P=S is the high temperature reaction (100–150 °C) of phosphorus pentasulfide with phosphoramidates, which invariably results in contamination by the starting material and also in the formation of several by-products. The second route not only makes use of high temperatures but also a less easily workable and costly reagent,[12] which in turn results in lower yields of the desired products. Recently Curphey,[13–15] has shown that a combination of P_4S_{10} and HMDO as a thionating agent efficiently converts esters, lactones, amides, and ketones into their thio derivatives. Although the reported method is good in terms of selectivity under standard conditions (dry toluene/xylene, thermal heating), the use of P_4S_{10} and HMDO under microwave conditions has provided an increase in the selectivity and yields of the organophosphorus compounds. Lizzani-Cuvelier and co-workers[16] have also reported the synthesis of thio γ-lactones by making use of a new combination of Lawesson's reagent and hexamethyldisiloxane (HMDO) in solvent-free conditions under microwave irradiation. Nevertheless there are, to our knowledge no reports dealing with the synthesis of thio-analogues of organophosphorus compounds under microwave irradiation. We were interested in a procedure, which would allow us easily to prepare the thiophosphoramidodichloridates and thiophosphoramidate diesters, since such compounds are

Keywords: Phosphoramidodichloridates; Phosphoramidate diesters; Solvent-free; Phosphorus pentasulfide; HMDO; Microwave irradiation.
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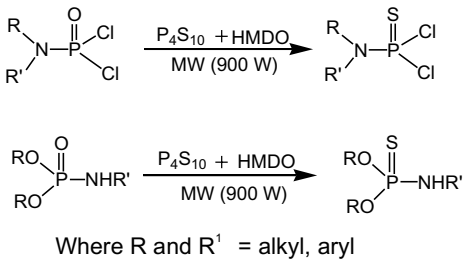
intermediates in synthetic routes to various biologically active compounds.



Microwave activation as a nonconventional energy source has been an increasingly popular method that can be used to carry out a variety of reactions within short reaction times and with high yields and selectivity.[17,18] Microwave irradiation increases the dipole–dipole interactions with the polar molecules and can reduce the activation energy.[17] This method also reduces thermal degradation by-products and takes place in the absence of solvent.[19–22]

Various phosphoramidodichloridates and phosphoramidate diesters were treated with different mole ratios of P_4S_{10}, hexamethyldisiloxane (HMDO) at different microwave powers. We found that phosphoramidodichloridates/phosphoramidate diesters, P_4S_{10}, and HMDO in a mmol ratio of 1:0.8:1.5 at 900 W are the appropriate mole ratios to obtain maximum yields of the desired products. For these studies a microwave oven (Samsung CE 2977N operating at 2450 MHz with an oven cavity of $336 \times 241 \times 349$ mm and 28 L volume) at a power level of 900 W, equipped with inverter technology that provide better control of the MW power was used. The mixture of phosphoramidodichloridates and phosphoramidate diesters, P_4S_{10}, and HMDO was exposed to microwave irradiation with intermittent heating and mixing, to obtain better yields and cleaner products. Intermittent heating reduces the formation of hot spots. It was observed that, at elevated power levels, partial decomposition or charring of the reaction mixtures occurred possibly due to localized overheating. At the end of the reaction, the internal temperature reached 110 °C. Under the above conditions various phosphoramidodichloridates and phosphoramidate diesters were examined and the results are shown in Table 1.

Table 1. Thionation of phosphoramidodichloridates and phosphoramidate diesters with P_4S_{10} and HMDO under microwave irradiation at 900 W using the optimized conditions

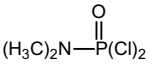
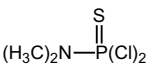
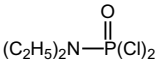
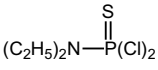
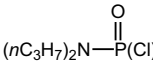
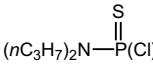
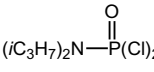
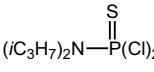
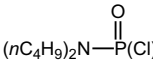
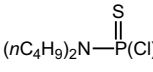
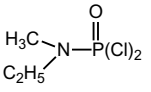
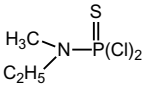
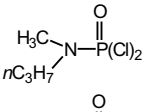
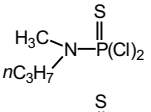
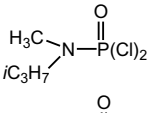
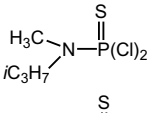
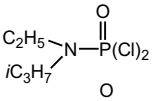
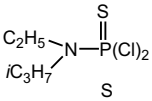
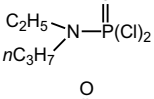
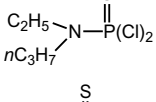
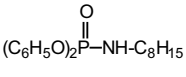
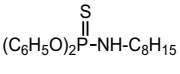
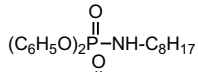
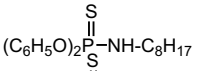
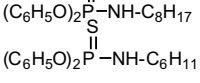
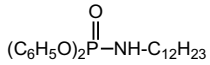
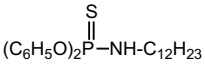
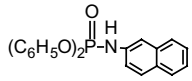
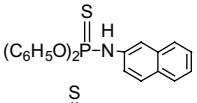
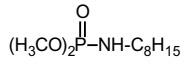
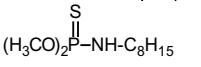
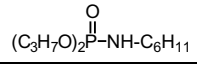
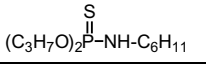
Entry	Substrate	MW heating time (s)[a]	Product	Yield (%)[b]
1		8×30		89
2		8×30		90
3		8×30		92
4		8×30		90
5		8×30		92
6		8×30		88
7		8×30		90
8		8×30		92
9		8×30		90
10		8×30		90
11		16×30		90

Table 1 (*continued*)

Entry	Substrate	MW heating time (s)[a]	Product	Yield (%)[b]
12		16 × 30		86
13		16 × 30		85
14		16 × 30		82
15		20 × 30		84
16		20 × 30		87
17		12 × 30		89

All compounds demonstrated satisfactory IR, NMR (^{1}H and ^{31}P), and MS data and were compared with literature values as well as with authentic samples.

[a] Number of irradiations for a given time; 8 × 30 indicates eight irradiations of 30 s each.

[b] Isolated yield.

In order to confirm the microwave effect on the reaction, comparative studies were carried out by examining one representative example each of phosphoramidodichloridates and phosphoramidate diesters (entries 1 and 13) under microwave as well as under conventional heating using the same mole ratios of the reactants. Under microwave irradiation, the reactions were complete in 4 and 8 min as compared to 3 and 5 h, with conventional heating, respectively. With conventional heating the conversion of phosphoramidodichloridate (entry 1) in 4 min was only 12% complete as compared with 89% under microwave irradiation. Similarly the conversion of the phosphoramidate diester (entry 13) under conventional heating in 8 min was only 14% complete as compared to 90% under microwave irradiation. Thus, it was confirmed that microwave heating has advantages in terms of reaction times and product yield over the conventional heating method. Using the conventional method, the transformation is effected at higher temperatures (100–150 °C), for long periods of time (4–10 h). The conventional method also involves a tedious work up giving poor to moderate yields.

In order to evaluate the influence of HMDO, reactions (entries 1 and 13) were also carried out in the absence of HMDO under the same conditions. We found that the reaction time increased from 4 to 25 and from 8 to 30 min, respectively. The yields of the products also decreased by 10–12 percent. This clearly shows that HMDO plays an important role. Many factors such as a change in the alkyl group of the phosphoramidate diesters, microwave power, and reaction time also have profound effects on the progress of the reaction. The reactivity of phosphoramidate diesters (entries 11–15) is less comparatively than that of *N*,*N*-dialkylphosphoramidodichloridates. This may be due to the greater lyophobic character of the phenyl and β-naphthyl groups, which reduce dipole–dipole interactions.[17] Microwave power was also varied and reactions were conducted at 100, 180, 300, 450, 600, and 900 W using the substrates from entries 1 and 13. We observed that at 900 W, the time taken for complete conversion was less and yields were also very high. Furthermore, if the reaction time was increased, then decomposition took place. This resulted in reduced yields of the desired products and work up also became tedious.

In conclusion, we have developed a new and useful procedure, which is very effective for the synthesis of various organophosphorus compounds and which can be easily scaled up to large quantities. Further synthetic utility of this thionating procedure with other organic substrates is currently under investigation.

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Typical procedure: Phosphoramidodichloridates and phosphoramidate diesters[7] (1.0 mmol), P_4S_{10} (0.8 mmol), and HMDO (1.5 mmol) were taken in a 250 mL conical flask and mixed thoroughly on a cyclomixer. After initial exposure for 30 s in a MW oven at a power level of 900 W, the flask was taken out, shaken for 10 s and then exposed to the same MW power for further periods of time as indicated in Table 1 until the formation of the thio compounds was virtually complete. The recorded internal temperature of the reaction mixture was 110 °C. The progress of the reaction was monitored by TLC (silica plates, 10% acetone in toluene) and GC. After the completion of reaction, the reaction mixture was dissolved in dichloromethane, filtered, concentrated, and purified by column chromatography (silica 60–120 mesh), using toluene as the eluent.