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PREPARATION OF S,S-DIALKYL(DIARYL) PHOSPHORODITHIOATES BY MEANS OF TRIMETHYLSILYL PHOSPHORODICHLORIDATE

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Trimethylsilyl phosphorodichloridate prepared by the reaction of methyl phosphorodichloridate with trimethylsilyl bromide was found to be a useful phosphorylating agent for the synthesis of S,S-dialkyl phosphorodithioates.

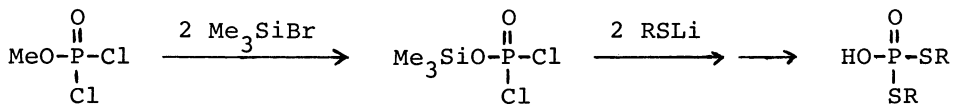
S,S-Dialkyl(diaryl) phosphorodithioates (1) are promised as useful phosphorylating agents in the synthesis of oligonucleotides bearing 5'-phosphate end group *via* phosphotriester approach.[1] We have reported[2] the preparation of S,S-diaryl phosphorodithioates by using N-methylpyridinium dichlorophosphate. However, this agent is unsatisfactory for the preparation of S,S-dialkyl phosphorodithioates.

We now wish to report the preparation of S,S-dialkyl phosphorodithioates by using trimethylsilyl phosphorodichloridate (2) which is more widely applicable than N-methylpyridinium dichlorophosphate to the synthesis of the phosphorodithioates.

Compound 2 was first prepared by Schmidt et al.[3] from hexamethyldisiloxane and tetrachloropyrophosphate. Beyond our expectation, 2 is stable and can be purified by distillation under reduced pressure. In order to avoid the use of tetrachloropyrophosphate, we tried the reaction of methyl phosphorodichloridate with trimethylsilyl bromide by a modification of the procedure of McKenna et al.[4]

To a solution of methyl phosphorodichloridate (3.5 ml, 35 mmole) in dry ether (60 ml) at room temperature was added dropwise trimethylsilyl bromide (12.6 g, 80.5 mmole). The mixture was refluxed for 2 h and it was concentrated under reduced pressure. Compound 2 (bp 85-87°C/29 mmHg) was obtained (6.7 g,91%).

This agent (2) was successfully applied to the selective synthesis of 1 without accompaning S,S,S-trialkyl(triaryl) phosphorotrithioates.



(2) (1)

To a solution of lithium ethanethiolate (1.08 g, 16 mmole) in dry ether (60 ml) was added 2 (1.55 g, 7.5 mmole) dropwise at -78°C. The mixture was further stirred at room temperature for 4 h and it was poured into water (30 ml).

The solution was extracted with three 35 ml portions of a mixture of chloroform and 1-butanol (8:2 v/v) and the organic layer was dried over sodium sulfate. After removal of sodium sulfate, the solution was concentrated to dryness and the residue was further dissolved in chloroform (20 ml). It was treated with cyclohexylamine (0.75 g, 7.5 mmole) and the chloroform was removed. Then a mixture of ether and n-hexane (1:1 v/v) was added with continuous stirring for 15 min, until precipitates appeared. Precipitates were collected by filtration and washed with a mixture of ether and n-hexane (1:1 v/v). Monocyclohexylammonium salt of S,S-diethyl phosphorodithioate (mp. 133-135°C) was obtained (1.37 g, 64%).

In a similar manner, several S,S-dialkyl(aryl) phosphorodithioates (1) were obtained as shown in Table 1. Structures of the compounds were confirmed by their NMR and IR spectra and also by their elemental analyses.

Table 1. Preparation of S,S-dialkyl(aryl) phosphorodithioates

R	pKa value of RSH	time (h)	Product yield(%)	mp.(°C)*
C_2H_5	10.6	3.5	64	133-135
i-C_3H_7	10.9	4.0	61	202-203
n-C_4H_9	10.7	4.0	66	151-152
i-C_4H_9	10.9	3.5	61	185-187
C_6H_5	7.8	4.0	44	178-179

* Monocyclohexylammonium salt

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