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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS XLVII⁺
PREPARATION OF THIATED SYNTHONS OF AMIDES, LACTAMS AND IMIDES BY USE OF SOME NEW P,S-CONTAINING REAGENTS

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Abstract - The thionation properties of 2,4-bismethylthio-1,3,2,4-dithiadiphosphetane 2,4-disulfide, 1, 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, 2, 2,4-bis(4-phenylthiophenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, 3, and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide (LR), 4, have been investigated on a series of amides, lactams and imides. The most remarkable feature is that 2, 3 and 4 thionate most amides and lactams in THF at room temperature (reaction time 5 min) to give the corresponding thionated compounds. Imides are easily thionated by 2, 3 and 4 in DME at 60 °C. The reactions of 1 with amides, imides and most lactams are run at 60 °C to give good yields of the corresponding thionated compounds.

INTRODUCTION

In the last few years we have studied 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide, LR, as a thionation reagent.[1] Based on these studies and the general interest of thiocarbonyl containing compounds,[2] we have, in our search for milder and more effective methods to transform carbonyls into the corresponding thiocarbonyls, studied P,S-containing reagents 1-4 (Fig. 1), and have found[3,4] that 1 thionates at lower temperature than earlier used procedures with LR.[1] The reagent 1 has also been shown to be quite useful for the preparation of dithioesters and for the same purpose 2 and 3 (in DME) have been used. Another ether solvent, THF, also seems to have a pronounced effect on certain thionation reactions[5] in peptide chemistry. This paper reports on thionation of amides by reagents 1-4 using THF and DME as solvents.

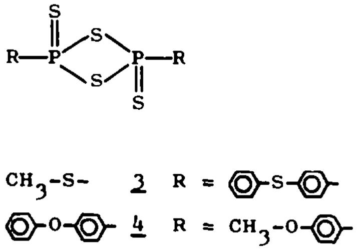

Fig. 1

[+] Part XLVI, see ref. 3.

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RESULTS AND DISCUSSIONS

Starting Materials

The reagent 1 is prepared from O,O-dimethyl dithiophosphoric acid and P_4S_{10}[4] and crystallographic investigations show it to exist in the E-configuration.[6] The reagents 2 and 3 are prepared in refluxing o-dichlorobenzene from P_4S_{10} and diphenyl ether or diphenyl sulfide, respectively.[4] Mass spectra show them to be dithiadiphosphetanes (like 1 and 4), and it is assumed that they exist in E-forms. The reagent 4 is commercially available and can be prepared from anisole and P_4S_{10}.[1]

Reactions of 1

A series of lactams and primary, secondary and tertiary amides are reacted with 1 in DME (comparison between DME and benzene as solvent has been made: DME gives slightly higher yields) to give the thionated compounds in good yields (entries 1-11 Table). After reaction for 15 min at room temperature, the starting materials are consumed (TLC), and higher yields are obtained if the reaction mixtures then are kept at 60 °C for 15 min. Reaction of N,N-dimethyl acetamide and benzamide with 1 in THF gives low yields of the corresponding thionated products.

Attempts to thionate N-benzoylglycine, 2-pyridone, 4-pyridone, salicylamide, salicylanilide and different enaminones do not meet with success. Common for these substrates is that they contain nucleophilic sites which can attack phosphorus of the reagent and result in side products.

Reactions of 2, 3 and 4

Some amides (entries 1-9 Table) and the 5- and 7-membered lactams (entries 10,11 Table) react with 2, 3 or 4 in THF at room temperature to give the corresponding thionated compound in high yields. With a few exceptions (see the Table) the reactions are finished within a few minutes.

Finally it should be mentioned that in this investigation the mole ratio between the reagent[1-3] and the substrate in all cases has been chosen to be 1:2 for monothionation. Preliminary studies of the thionation of N,N-dimethyl acetamide by 2 in THF at room temperature gave 98%, 89% and 78% yields of the N,N-dimethylthioacetamide, when the mole ratio was 1:2, 1:3 and 1:4, respectively. These results show that more than two sulfur atoms per mole of 2 (probably also 3 and 4) can be used for thionation.

CONCLUSION

It has been found that reagents 2-4 thionate amides and most lactams at room temperature in THF to give the corresponding thionated compounds in high yields after short reaction time (minutes). The reaction of amides and lactams with 1 (in DME) also gives good yields, but requires longer reaction time (15 min at room temperature + 15 min at 60 °C). The reagents 2, 3 and 4 have quite similar thionation properties, whereas the reagent 1 seems to have a more limited scope, besides which it has a very bad odour.

Table

$$>=O \xrightarrow{1,2,3 \text{ or } 4} >=S$$

Experimental and physical data for thionation reactions with 1, 2, 3 and 4. Reactions with 1 are run in DME, reactions with 2, 3 and 4 are run in THF (except for entries 12, 14 and 15 which are run in DME).

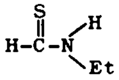
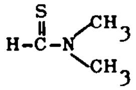
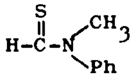
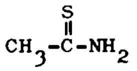
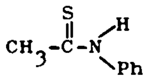
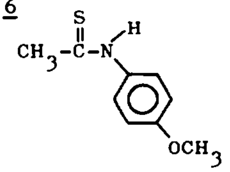
Product	Thionation reagent	Molar ratio of substrate and reagent	Reaction temp. (℃)	Reaction time (min)	M.p.(℃) Found (Reported)	Yield (%)
1 	1	2:1,12	20^{d} 60	15 15	oil $(oil)^{7}$	73
	2	2:1	20	2		72
	3	2:1	20	5		60
	4	2:1	20	5		88
2 	1	2:1,12	20^{d} 60	15 15	oil $(oil)^{8}$	74
	2	2:1	20	5		89
	3	2:1	20	5		79
	4	2:1	20	5		96
3 	1	2:1,12	20^{d} 60	15 15	oil $(oil)^{8}$	75
	2	2:1	20	5		93
	3	2:1	20	5		91
	4	2:1	20	5		94
4  $CH_3-\overset{\overset{S}{\parallel}}{C}-NH_2$	1	2:1,12	20^{d} 60	15 15	110 $(111)^{8}$	65
	2	2:1	20	5		83
	3	2:1	20	5		61
	4	2:1	20	10		87
5 	1	2:1,12	20^{d} 60	15 15	76 $(76)^{8}$	91
	2	2:1	20	45		88
	3	2:1	20	30		78
	4	2:1	20	ON		89
6 	1	2:1,12	20^{d} 60	15 15	115 $(116)^{8}$	88
	2	2:1,12	20	30		87
	3	2:1	20	30		81
	4	2:1	20	ON		99

Table (cont.)

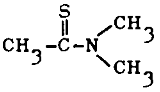
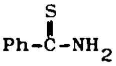
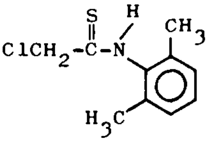
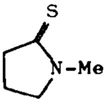
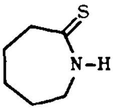
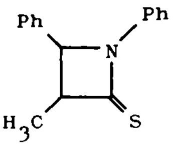
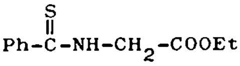
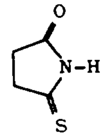
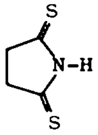
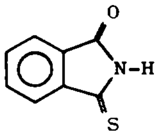
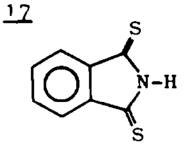
Product	Thionation reagent	Molar ratio of substrate and reagent	Reaction temp. (°C)	Reaction time (min)	M.p. (°C) Found (Reported)	Yield (%)
7  $CH_3-C(=S)-N(CH_3)_2$	1	2:1,12	20[d] 60	15 15	73 (73-74)[9]	85
	2	2:1	20	5		89
	3	2:1	20	5		66
	4	2:1	20	5		77
8  $Ph-C(=S)-NH_2$	1	2:1,12	20[d] 60	15 15	118 (118)[8]	67
	2	2:1	20	5		67
	3	2:1	20	10		64
	4	2:1	20	90		74
9 	1	2:1,12	20[d]	20	110[a] (-)	86
	2	2:1	20	30		74
	3	2:1	20	30		71
	4	2:1	20	ON		47
10 	1	2:1,12	20[d] 80	15 2	oil (oil)[2]	88
	2	2:1	20	5		91
	3	2:1	20	10		77
	4	2:1	20	5		95
11 	1	2:1,12	20[d] 80	15 2	106 (106)[8]	85
	2	2:1	20	5		98
	3	2:1	20	5		79
	4	2:1	20	5		98
12 	1	1,25:1,05	20[d] 60	15 45	118 (118-119)[10]	97
	2	1,25:0,625	60	180		99
	3	1,25:0,625	60	60		99
	4	1,25:0,625	60	300		99
13  $Ph-C(=S)-NH-CH_2-COOEt$	1	2:1,2	20[d] 60	30 5	51 (51-52)[11]	87
	2	2:1	20	240		71
	3	2:1	20	60		97
	4	2:1	20	ON		75

Table (cont.)

Product	Thionation reagent	Molar ratio of substrate and reagent	Reaction temp. (℃)	Reaction time (min)	M.p.(℃) Found (Reported)	Yield (%)
14 	1	2:1,12	20[d] 60	60 30	102 (100-104)[12]	65[b] traces[c]
	2	2:1	60	90		64[b] 33[c]
	3	2:1	60	90		47[b] 46[c]
	4	2:1	60	90		60[b] 10[c]
15 	1	1:1,2	20[d] 60	60 30	85 (84-87)[12]	29[b] 41[c]
	2	1:1	60	120		26[b] 72[c]
	3	1:1	60	120		18[b] 69[c]
	4	1:1	60	120		74[b] 21[c]
16 	2	2:1	60	120	176 (176)[10]	33[b] 16[c]
	3	2:1	60	180		32[b] 34[c]
	4	2:1	60	180		22[b] 0.6[c]
17 	2	1:1	60	300	194 (180)[10]	40[b] 50[c]
	3	1:1	60	300		15[b] 48[c]
	4	1:1	60	300		67[b] 7[c]

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[a] Anal.Found (%): C, 56.17; H, 5.74; N, 6.34; S, 14.70; Cl, 16.39.
Calc. (%): C, 56.22; H, 5.62; N, 6.56; S, 14.99; Cl, 16.61.

^{1}H NMR ($CDCl_3$): 2.1 (6H,s), 4.6 (2H,s), 7.0 (3H,s), 9.0-9.3 (H,b).

^{13}C NMR ($CDCl_3$): 17.7 ($-CH_3$), 49.8 ($-CH_2Cl$), 128.3 (Ph carbon no. 3-5), 128.5 (Ph carbon no. 2,6), 135.06 (Ph carbon no. 1), 193 ($>$=S).

UV (EtOH) 210 nm, 276 nm log ϵ = 4.31.

MS: M+1 (215,213), M^+-Cl (178,180), M^+-H_2S (181, 179), 165, 163, 121, 119, 106, 104.

[b] Monothionated analogue.

[c] Dithionated analogue.

[d] To be read as the reaction run at 20℃ followed by 60℃.

EXPERIMENTAL

The starting reagents and substrates are purchased or prepared by standard methods. The final products are identified by physical data (m.p.), ^{1}H NMR, and MS and are in all cases identical with authentic samples.

^{1}H NMR spectra are recorded at 60 MHz on a Varian A-60 spectrometer in $CDCl_3$ int.ref. TMS. IR spectra are recorded on a Beckmann IR-18 spectrometer, and mass spectra were recorded on a Micromass 7070F spectrometer operating at 70 eV using direct inlet. Micro analyses are carried out by Løvens Kemiske Fabrik, DK-2750 Ballerup (Microanalytical Laboratory).

General procedure for the preparation of thioamides and 5- and 7-membered thiolactams by use of 1. The substrate (0.01 mole) and 1.60 g of 1 (0.0056 mole) in 10 ml anhydrous dimethoxyethane are stirred for 15 min. at room temperature and then heated on an oil bath (see Table). The amide 1,3-dimethyl-chlorobenzamide is not heated, but reacts at room temperature for 20 min. The reaction mixture is evaporated on silica gel and separated on a silica gel column.

General procedure for the preparation of thioamides and 5- and 7-membered thiolactams by use of 2, 3 or 4. The substrate (0.001 mole) and 0.0005 mole of 2, 3, or 4 in 10 ml anhydrous THF are stirred at room temperature for the time given in the Table. The reaction mixture is evaporated on silica gel and separated on a silica gel column.

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