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Studies on Organophosphorus Compounds. XIII.* About Conversion of Carboxylic Esters into *N,N*-Dimethylthiocarboxamides. Synthesis of 2-Phenylbenzothiazole

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In a one pot reaction esters of carboxylic acids, RCOOR′, are converted directly into the corresponding *N,N*-dimethylthiocarboxamides, $RCSNMe_2$, by heating with sulfur in HMPA. The benzylic part of esters $RCOOCH_2Ph$ is oxidized to *N,N*-dimethylthiobenzamide. Methyl and allyl benzoates produce *N,N*-dimethylbenzamide. The methyl group of methyl benzoate is oxidized to carbon disulfide with dimethylpolysulfides as probable intermediates. 2-Phenylbenzothiazole is formed in the reaction of benzyl benzoate with sulfur and aniline in HMPA at 185 °C. Also benzaldehyde, benzyl alcohol, and thiobenzanilide produce 2-phenylbenzothiazole in high yields under similar reaction conditions.

Recently it was shown that sulfur in hexamethylphosphoric triamide (HMPA) is a very convenient thiation agent at elevated temperatures.[1] Thus different benzylic derivatives, $PhCH_2X$, alkyl aryl ketones, benzaldehydes, and α- and γ-picolines were smoothly converted into the corresponding aromatic *N,N*-dimethylthiocarboxamides. Reducing properties of S_8 in HMPA have also been established.[2] In a reaction of ethyl phenylacetate [1] both *N,N*-dimethylthiobenzamide, I, and phenyl-*N,N*-dimethylthioacetamide, II, were isolated:

$$PhCH_2COOEt \xrightarrow[\Delta]{S_8,\ HMPA} PhCSNMe_2 + PhCH_2CSNMe_2$$

I II

This means that a carboxylic ester directly had been converted into the corresponding *N,N*-dimethylthiocarboxamide. This prompted us to investigate the scope of the reaction, and a series of benzoates, methyl nicotinate and some aliphatic esters were reacted with sulfur in HMPA at elevated temperatures.

RESULTS AND DISCUSSION

Many functional groups have been converted into thiocarboxamides by heating with sulfur and amines,[3] but as far as we know direct conversion of an ester into a thiocarboxamide has not been reported. In fact many reactions with sulfur at high temperatures have been performed, where the ester group has remained unchanged.[4,5] In most of our reactions the esters were smoothly converted into the corresponding *N,N*-dimethylthiocarboxamides as indicated in Table 1. In the reactions of benzyl benzoate and benzyl butyrate the benzylic part of the esters was oxidized to *N,N*-dimethylthiobenzamide, I.

$$RCOOCH_2Ph \xrightarrow[\Delta]{S_8,\ HMPA} RCSNMe_2 + PhCSNMe_2$$

IV I

It appears that esters containing ethyl or longer primary or secondary alkyl groups as the alcoholic parts are quite difficult to react. In these reactions starting material was inevitably

* Part XII, see Ref. 2.

Table 1.[a]

$$\underset{\text{III}}{\text{RCOOR}'} \xrightarrow[\Delta]{S_8,\ \text{HMPA}} \underset{\text{IV}}{\text{RCSNMe}_2}$$

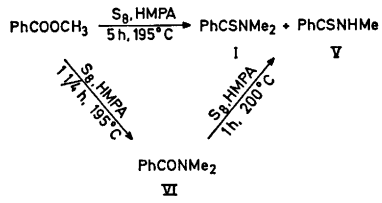
R	R′	React.time (h)	React.temp. (°C)	Yield of IV (%)	Yield of PhCSNHMe (%)	Other products
Ph	Ph	1	207	89	<5	
Ph	$PhCH_2$	1.5	205	91	<5	
Ph	Me	5	195	86	6	[b] CS_2, $CH_3S_xCH_3$, CH_3SH, $PhCONMe_2$
Ph	Et	2	210	53	10	23 % of III recovered
Ph	i-Pr	3.5	205	27	11	58 % of III recovered
Ph	cyclohexyl	2	210	18	9	67 % of III recovered
Ph	*t*-Bu	1.75	200	80	19	
Ph	allyl	0.1	180 – 230	52	5	$PhCONMe_2$ (12 %)
C_5H_4N	Me	4	185	87		
Me	Ph	1.25	185	59		
i-Pr	Ph	1.75	205	71		
Pr	$PhCH_2$	1	210	40		30 % of III recovered, $PhCSNMe_2$ (40 %)
hexyl	Et	5	reflux			III recovered

[a] 0.1 mol of substrate, 0.6 mol of S_8 and 50 ml of HMPA were used in all reactions. [b] Isolated in separate reactions.

recovered (Table 1). In the reactions of the benzoates oxidative demethylation of *N,N*-dimethylthiobenzamide, I, produced *N*-methylthiobenzamide, V, in minor amounts. From NMR-spectra of the reaction mixtures the yields of V were estimated (Table 1). This demethylation has also been observed earlier where *N,N*-dimethylthiobenzamide has been produced at high temperatures in HMPA in the presence of S_8.[1,2]

Detailed mechanistic considerations have to await further investigations of HMPA + S_8 as a thiation agent, but a few observations should be noted. *N,N*-Dimethylbenzamide, VI, was found in the reactions of methyl and allyl benzoates with S_8 in HMPA. Methyl benzoate yielded 61 % of VI after a reaction time of about one hour, but further reaction produced I and V exclusively. Reaction of VI with sulfur in HMPA also gave I and V.[6]

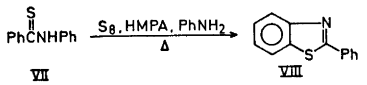
In the reaction of methyl benzoate a low-boiling fraction distilled from the reaction vessel and addition of dimethylamine to it produced,



dimethylammonium dimethyldithiocarbamate which shows the formation of CS_2. Further proof was obtained by a mass spectrum. Small amounts of methylmercaptan were also detected by spectroscopic methods (NMR, MS). In a reaction, run under less severe reaction conditions, dimethyltrisulfide was isolated in 24 % yield, and only very small amounts of CS_2 were isolated. Also other dimethylpolysulfides were probably present, as the fraction from which the trisulfide was isolated gave a distillation residue with the approximate composition of $C_2H_6S_5$. Three singlet peaks in an NMR-spectrum at δ 2.6 further indicate the

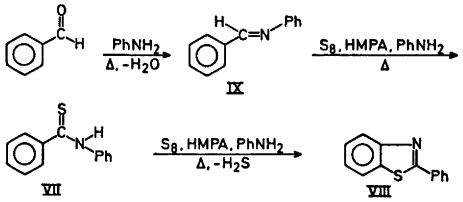
presence of the tetra-, penta-, and hexasulfides. For the formation of these polysulfides it is tentatively suggested that *S*-methyl groups are cleaved from an intermediate in the reaction, and CS_2 is formed by further oxidation of these.

In an attempt to prepare thiobenzanilide, VII, the reaction of benzyl benzoate with S_8 in HMPA was run with aniline present. However, VII was only isolated in minor amounts and the main products were 2-phenylbenzothiazole, VIII, and benzanilide. Apparently VII has reacted further to give VIII. In a separate experiment this was proved, as VII was oxidized to VIII with sulfur in HMPA with aniline present:



VII VIII

These findings made us investigate reactions with other substrates than esters. From benzyl alcohol and benzaldehyde high yields of VIII were obtained. Benzaldehyde first reacts with aniline to give *N*-benzylidene aniline, IX, which was isolated in 85 % yield when the reaction was run at 130 – 140 °C. IX reacts further with sulfur in HMPA in the presence of aniline to give thiobenzanilide, VII. This was confirmed in a separate experiment, when IX was heated with sulfur in HMPA in the presence of aniline at 170 °C for 40 min to give 42 % of VII. Finally oxidative ring-closure of VII produces VIII in an over-all yield of 80 %.



VII VIII

VIII has earlier been prepared in 64 % yield by fusing *N*-benzylidene aniline with S_8 at 250 – 60 °C.[7] Also other reactions are known, when S_8 and aniline are heated with different substrates to give benzothiazoles. Recently it has been reported that formaldehyde, when heated with S_8 and aniline in a sealed tube above 200 °C, produces 2-mercaptobenzothiazole.[8] It has also been shown that α- and γ-picolines produce the corresponding benzothiazoles when reacted with S_8 in the presence of aniline.[9,10]

EXPERIMENTAL

NMR-spectra were recorded at 60 Mc/s on a Varian A-60 spectrometer. TMS was used as internal reference standard. The chemical shifts are expressed in δ-values (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). IR-spectra were recorded on a Beckmann IR-18 spectrophotometer. Mass-spectra were recorded on a CEC 21-104 operating at 70 eV, using direct inlet. Ion source temperature 250 °C. Column chromatography was carried out with Silica gel 60 (Merck). Commercial HMPA dried over molecular sieves (3A) was used. Elemental analysis were performed by Novo Industry A/S, Copenhagen. M.p's and b.p's are uncorrected.

General procedure for the reactions of the esters

0.1 mol of ester was heated under stirring with 0.6 mol of S_8 in 50 ml of HMPA until the ester or all S_8 was consumed, (for reaction conditions, see Table 1.) After cooling to room temperature 300 ml of H_2O and 100 ml of ether were added, and non-reacted S_8 was filtered off. After ether extraction (3 × 100 ml) and washing with 2 × 50 ml of H_2O the combined ether phases where dried ($MgSO_4$), and the ether evaporated. In the reactions of the benzoates the yields of *N*-methylthiobenzamide were estimated from NMR-spectra of these worked-up mixtures. Distillation twice afforded the *N*,*N*-dimethylthiocarboxamides (Table 1). Exceptions to this general procedure and psysical properties of the isolated thiocarboxamides are given below.

All the benzoates were reacted and worked up according to the procedure above to give N,N-*dimethylthiobenzamide*, m.p. 67 °C (EtOH) (lit.[1] m.p. 67 °C), except for *allyl benzoate*, which reacted exothermically. Column chromatography (elution with ether) of the worked-up reaction mixture yielded 8.6 g (52 %) of N,N-*dimethylthiobenzamide* and 1.8 g (12 %) of N,N-*dimethylbenzamide*, which had physical properties in accordance with an authentic sample.[1]

The reaction of methyl benzoate was repeated, and interruption after 1.25 h at 195 °C gave a reaction mixture, which after the working-up procedure above, followed by column chromatography (elution with mixtures of ether/light petroleum) yielded: I. 3.2 g of a mixture of products. Distillation (52 – 58 °C/14 mmHg) gave 1.5 g (24 %) of *dimethyltrisulfide*. (Found: C 19.03; H 4.71; S 76.41. $C_2H_6S_3$ requires: C 19.05; H 4.76; S 76.19).

NMR ($CDCl_3$): 2.5(s). An NMR-spectrum ($CDCl_3$) of the distillation residue showed three singlets at $\delta \sim 2.6$. (Found: C 12.15; H 2.90; S 84.75 which gives $C_6H_{5.8}S_{5.2}$). II. 2.3 g (14 %) of N,N-*dimethylthiobenzamide* and III. 9.1 g (61 %) of N,N-*dimethylbenzamide*. In a third reaction of methyl benzoate at 205 °C for 1.5 h, 6.9 g of a low-boiling liquid were trapped in a cool-bath, b.p. 43–47 °C. NMR (without solvent): 1.2 (q, 1 H), 2.1 (d, 3 H), which was identical with an NMR-spectrum of authentic CH_3SH in CS_2. MS: *m/e* 76(CS_2^+, 100 %), 48(CH_3SH^+, 10 %). 2 g of the liquid were dissolved in 25 ml of CH_2Cl_2 and $NHMe_2$ was slowly bubbled through for 15 min. Evaporation of CH_2Cl_2 and washing with ether yielded 3.1 g of *dimethylammonium dimethyldithiocarbamate*, m.p. 129–130 °C (lit.[11] m.p. 130–132 °C). Methyl nicotinate (0.1 mol) was heated with S_8 (0.6 mol) in HMPA (50 ml) for 4 h at 185 °C. After cooling to room temperature the reaction mixture was poured into 300 ml of H_2O and 100 ml of benzene. Excess S_8 was filtered off. After benzene extraction (4 × 100 ml), drying ($MgSO_4$) and evaporation of benzene the remaining mixture was distilled twice to give 14.5 g (87 %) of N,N-*dimethylthionicotinamide*, b.p. 151–154 °C/0.7 mmHg, $n_D^{20} = 1.6347$. (Found: C 57.59; H 6.16; N 16.98; S 19.51. $C_8H_{10}N_2S$ requires: C 57.83; H 6.02; N 16.87; S 19.28). NMR ($CDCl_3$): 3.2 (s, 3 H); 3.6 (s, 3 H); 7.5 (m, 2 H); 8.6 (m, 2 H).

The reaction mixture from the reaction of phenyl acetate was directly filtered through a column (elution with ether). Column chromatography (elution with ether/light petroleum) yielded 6.1 g of N,N-*dimethylthioacetamide*. Physical properties were in accordance with an authentic sample.[1]

Column chromatography (elution with ether/light petroleum) of the worked-up reaction mixture from the reaction of phenyl isobutyrate yielded 9.3 g (71 %) of *2-methyl*-N,N-*dimethylthiopropionamide*, b.p. 69–71 °C/0.3 mmHg, $n_D^{20} = 1.5393$. NMR($CDCl_3$): 1.2 (d, 6 H); 3.3 (m, 1 H); 3.4 (s, 3 H); 3.5 (s, 3 H).

Column chromatography (elution with ether/light petroleum) of the worked-up reaction mixture from the reaction of benzyl butyrate yielded 5.3 g (30 %) of starting material and 11.8 g of an approximately 1:1 mixture of N,N-*dimethylthiobutyramide* and N,N-*dimethylthiobenzamide*. Distillation twice yielded pure *N,N*-dimethylthiobutyramide, b.p. 119–120 °C/10 mmHg, $n_D^{20} = 1.5412$. (Found: C 55.11; H 9.92; N 10.62; S 24.34. $C_6H_{13}NS$ requires: C 54.96; H 9.92; N 10.69; S 24.43). NMR($CDCl_3$): 1.0 (t, 3 H); 1.8 (m, 2 H); 2.8 (t, 2 H); 3.3 (s, 3 H); 3.5 (s, 3 H).

Preparation of 2-phenylbenzothiazole

Benzyl benzoate (0.1 mol) was heated with S_8 (0.6 mol) in HMPA (15 ml) and aniline (30 ml) at 185 °C for 6 h. After cooling to room temperature the reaction mixture was poured into 300 ml of 2 M HCl and extracted with ether (4 × 100 ml). The combined ether phases were washed with 50 ml of 2 M HCl and further extracted with 1 M NaOH (4 × 50 ml). After drying ($MgSO_4$) and evaporation of the ether column chromatography (elution with ether/light petroleum) yielded 20.2 g (48 %) of *2-phenylbenzothiazole*, m.p. 113 °C (lit.[7] m.p. 114 °C). NMR ($CDCl_3$): 7.2–8.2 (m). IR (CCl_4): 960, 1120, 1315, 1485, 1515, 3030 and 3070 cm^{-1}. Finally 7.1 g (36 %) of *benzanilide* was eluted, m.p. 162 °C (lit.[12] m.p. 160–161 °C). IR (KBr): 1500, 1540, 1590, 1610 and 1670 cm^{-1}. The NaOH-fraction was acidified with 150 ml of 2 M HCl. After ether extraction (3 × 100 ml), drying ($MgSO_4$) and evaporation of the ether, column chromatography (elution with ether/light petroleum) yielded 1.1 g (3 %) of thiobenzanilide, m.p. 99–100 °C (lit.[13] m.p. 99 °C) NMR (CS_2): 7.0–7.8 (m, 10 H); 9.2 (m, 1 H). IR (KBr): 980, 1360, 1430, 1480, 1520, 1580 and 3100 cm^{-1}.

Thiobenzanilide (6.3 g) was heated with S_8 (0.3 mol) in HMPA (7.5 ml) and aniline (15 ml) at 170 °C for 10 h. The same working-up procedure as in the reaction of benzyl benzoate yielded 5.1 g (82 %) of *2-phenylbenzothiazole*.

Benzyl alcohol. (0.1 mol) was heated with S_8 (0.6 mol) in HMPA (15 ml) and aniline (30 ml) at 165 °C for 10 h. The worked-up reaction mixture (as in the reaction of benzyl benzoate) was recrystallized from EtOH to give 15.4 g (73 %) of *2-phenylbenzothiazole*. Column chromatography (elution with ether/light petroleum) of the worked-up NaOH-phase yielded 1.4 g (7 %) of *thiobenzanilide*.

Benzaldehyde. (0.1 mol) was heated with S_8 (0.6 mol in HMPA (15 ml) and aniline (30 ml) at 170 °C for 12 h. The worked-up reaction mixture (as in the reaction of benzyl benzoate) was recrystallized from EtOH to give 16.9 g (80 %) of *2-phenylbenzothiazole*.

Isolation of *N*-benzylidene aniline. Benzaldehyde (0.2 mol) was heated with S_8 (0.3 mol) in HMPA (15 ml) and aniline (20 ml) at 130–140 °C for 1 3/4 h. After cooling to room temperature the reaction mixture was poured into 300 ml of H_2O and 100 ml of ether. S_8 was filtered off. After ether extraction (4 × 100 ml), washing with H_2O (2 × 50 ml), drying ($MgSO_4$) and evaporation of the ether, distillation yielded 30.6 g (85 %) of *N-benzylidene aniline*, m.p. 54 °C (lit.[14] m.p. 53.5 °C). NMR ($CDCl_3$): 7.4 (m, 8 H); 7.9 (m, 2 H); 8.4 (s, 1 H). Benzylidene aniline (9.1 g) was heated with S_8 (0.3 mol) in HMPA (7.5 mol) and aniline (15 ml) at 170 °C for 40 min. The reaction mixture was worked up as in the reaction of benzyl benzoate.

The NaOH-phase yielded after acidification (1 M HCl) and recrystallization from EtOH 4.5 g (42 %) of *thiobenzanilide*.

REFERENCES

1. Perregaard, J., Thomsen, I. and Lawesson, S.-O. *Acta Chem. Scand. B 29* (1975) 538.
2. Perregaard, J., Thomsen, I and Lawesson, S.-O. *Acta Chem. Scand. B 29* (1975) 599.
3. Pryor, W. A. *Mechanism of Sulfur Reactions*, McGraw-Hill, New York 1962.
4. Carmack, M. and DeTar, D. F. *J. Amer. Chem. Soc. 68* (1946) 2029.
5. Nakajima, H., Chono, M., Tagucki, M., Sakurai, T. and Matsuo, N. *Ger. Pat.* 2129920; *Chem. Abstr. 76* (1972) 58996q.
6. Thomsen, I., Meyer, H. J., Perregaard, J. and Lawesson, S.-O. *To be published.*
7. Bogert, M. T. and Abrahamson, E. M. *J. Amer. Chem. Soc. 44* (1922) 826.
8. Vitan, M., Orosz, S. A., Velea, I., Dobrescu, D. Stoea, A. and Ciupea, C. *Rom. Pat.* 54969; *Chem. Abstr. 79* (1973) 66348.
9. Miller, P. E., Oliver, G. L., Dann, J. R. and Gates, J. W. *J. Org. Chem. 22* (1957) 664.
10. Porter, H. D. *J. Amer. Chem. Soc. 76* (1954) 127.
11. Maier, L. *Helv. Chim. Acta 53* (1970) 1216.
12. Wallach, O. and Hoffmann, M. *Justus Liebigs Ann. Chem. 184* (1877) 77.
13. Kindler, K. *Justus Liebigs Ann. Chem. 431* (1923) 225.
14. Pyl, G. *Ber. Deut. Chem. Ges. 60* (1927) 287.

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