A New, Efficient Synthesis of Thioloesters

Tomasz NOWICKI, Anna MARKOWSKA

Institute of Organic Chemistry, Technical University (Politechnika) Zwirki 36, 90-924 Łodz, Poland

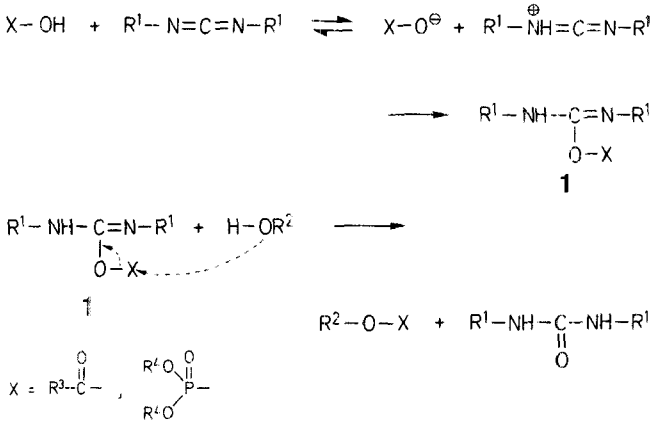
Piotr KIEŁBASINSKI, Marian MIKOŁAJCZYK*

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, Boczna 5, 90-362 Łodz, Poland

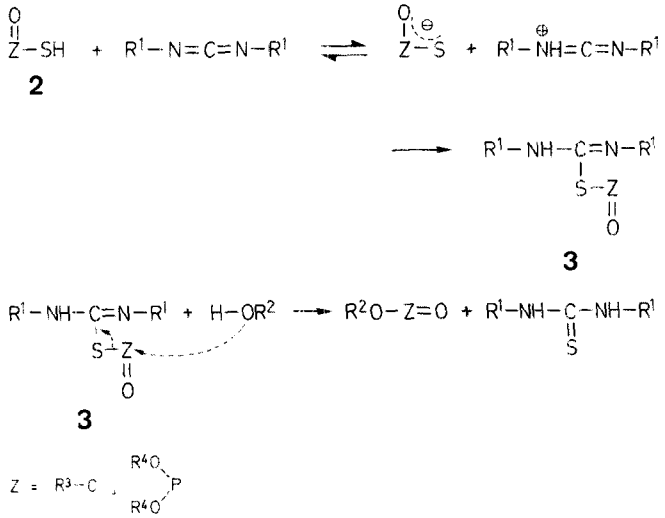
The reaction between phosphorothioic and thiocarboxylic acids and *O*-alkyl-*N,N*-dicyclohexylisoureas has been found to give the corresponding phosphorothiolates and thiolocarboxylates in high yields (65–95%), providing a new method for the thiophosphorylation and thiocarboxylation of alcohols.

In connection with our studies on biologically active thioloesters[1] we have become interested in developing a method for the synthesis of phosphorothiolates and thiolocarboxylates directly from the corresponding thioacids and alcohols. In this context, we have focused our attention on carbodiimides which are known to act as dehydrating agents in the synthesis of esters from alcohols and carboxylic or phosphoric acids[2] (Scheme **A**).

However, the same procedure cannot be applied to the synthesis of thioloesters because the first step of the reaction between carbodiimides and thiocarboxylic[3] or phosphorothioic[4] acids consists in the formation of *S*-acyl(phosphoryl)isothioureas (**3**). The eventual subsequent attack of an alcohol on this intermediate would result in the formation of the sulfur-free ester and thiourea as shown in Scheme **B**.

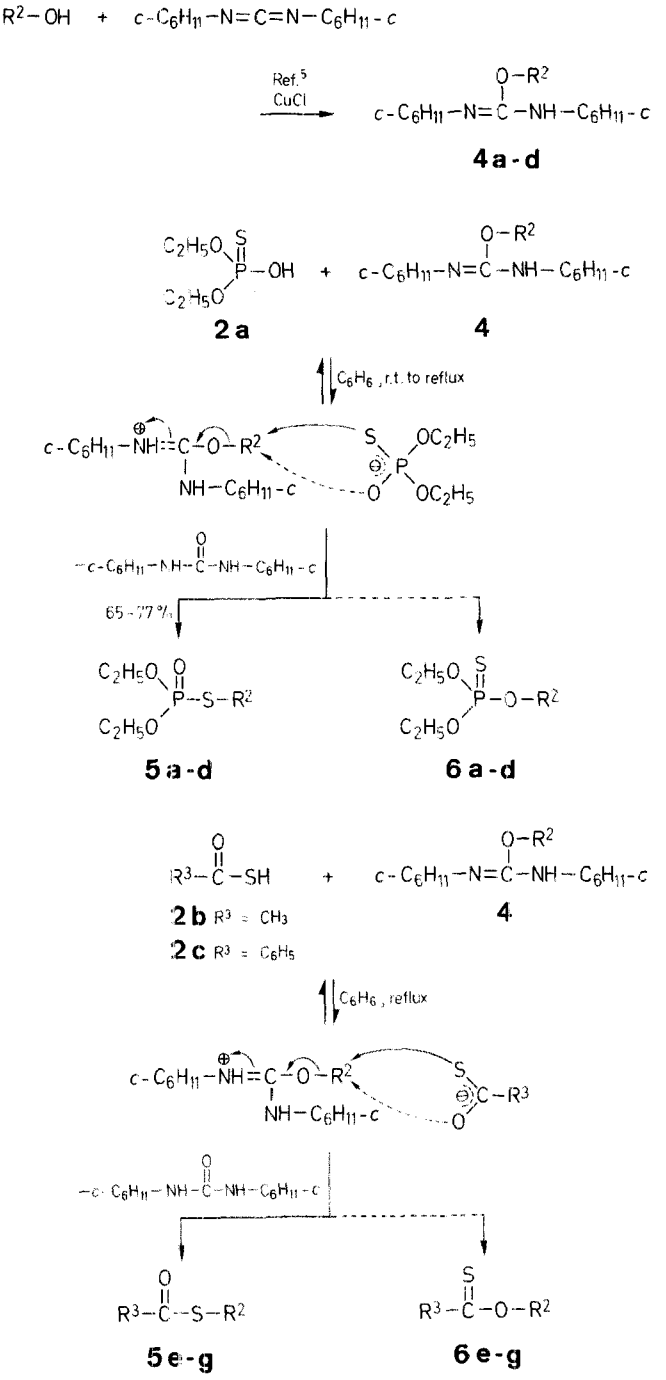


Scheme A



Scheme B

Therefore, it has become obvious that the synthesis of thioloesters may be realized if the reaction sequence shown in Scheme **B** is reversed. This means that an alcohol should be forced to react first with a carbodiimide to form the *O*-alkylisourea **(4)** which should then be attacked by a thioacid to form the corresponding thioester. Taking this into account, we have now developed a new synthesis of phosphorothiolates and thiolocarboxylates which involves the reaction of phosphorothioic and thiocarboxylic acids, respectively, with easily accessible *O*-alkyl-*N*,*N*-dicyclohexylisoureas[5] (Scheme **C**).



Scheme C

Table 1. Reaction of Thioacids **2** with *O*-Alkylisoureas **4**

Thioacid 2	*O*-Alkyl-isourea 4	Product 5/6 No	R^2	R^3	Yield [%] of 5 + 6	Pure 5	Ratio of 5 : 6
2a	**4a**	**a**	CH_3	–	90	77	90 : 10[b]
2a	**4b**	**b**	$C_6H_5CH_2$	–	96	72	92 : 8[b]
2a	**4c**	**c**	*i*-C_3H_7	–	94	68	90 : 10[b]
2a	**4d**	**d**	*i*-$C_3H_7CH_2$	–	90	65	100 : 0[b]
2b	**4b**	**e**	$C_6H_5CH_2$	CH_3	95	94[a]	100 : 0[c]
2c	**4c**	**f**	*i*-C_3H_7	C_6H_5	98	88[a]	90 : 10[c]
2c	**4b**	**g**	$C_6H_5CH_2$	C_6H_5	96	94[a]	100 : 0[c]

[a] After preparative T.L.C.
[b] From the ^{31}p-N.M.R. spectrum.
[c] From G.L.C./M.S. analysis.

Table 2. ^{1}H- and ^{31}P-N.M.R. Data of Thiolophosphates **5a–d**

Product	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	^{31}P-N.M.R. ($CDCl_3$/85% H_3PO_4) δ [ppm]
5a	1.5 (t, $J_{H,H}$ = 7.5 Hz, 6H, H_3CCH_2OP); 2.8 (d, $J_{H,P}$ = 15 Hz, 3H, H_3CSP); 4.4 (dq, $J_{H,H}$ = 7.5 Hz, $J_{H,P}$ = 9.5 Hz, 4H, H_3CCH_2OP)	26.0
5b	1.5 (t, $J_{H,H}$ = 7.5 Hz, 6H, H_3CCH_2OP); 4.4 (d, $J_{H,P}$ = 14.5 Hz, 2H, $C_6H_5CH_2SP$); 4.1–4.7 (dq, 4H, H_3CCH_2OP); 7.6 (m, 5H_{arom})	25.5
5c	1.5–2.0 [m, 12H, H_3CCH_2OP + $(H_3C)_2CHSP$]; 3.8 [m, 1H, $(H_3C)_2CHSP$]; 4.5 (dq, 4H, H_3CCH_2OP)	26.1
5d	1.1–2.0 [m, 13H, H_3CCH_2OP + $(H_3C)_2CHCH_2SP$]; 3.3 [dd, $J_{H,H}$ = 7.0 Hz, $J_{H,P}$ = 13 Hz, 2H, $(H_3C)_2CHCH_2SP$]; 4.2 (dq, 4H, H_3CCH_2OP)	26.8

It should be mentioned that an analogous procedure has already been applied to the synthesis of phosphates[6] and carboxylates[7]. However, in contrast to these example, in the case of the reaction between thioacids and *O*-alkylisoureas **(4)** a possibility of a bidirectional course has to be considered due to the ambident character of the monothioacid anions. Therefore, both thiolo- **(5)** and thionoesters **(6)** are expected to be produced.

In a typical procedure, a thioacid **(2)** was reacted with an *O*-alkylisourea **(4)** in a molar ratio 1:1 in boiling benzene. The reaction course was monitored by ^{31}P-N.M.R. spectrometry or by T.L.C. and the reaction appeared to be completed within 10 min to 1 h. We have found that in all cases the desired thioloesters **(5)** were formed in high yields, although they were usually accompanied with small amounts of the corresponding thionesters **(6)** (see Table 1). The thioloesters obtained could be easily purified by preparative T.L.C. or column chromatography. Their structures were established by spectral methods (^{1}H-, ^{31}P-N.M.R., mass) and on the basis of the literature data[8,9]. Table 2 summarizes the ^{1}H- and ^{31}-P-N.M.R. data for thiolophosphates **(5)** obtained in the present work.

In summary, the reaction described above may be recommended as an experimentally simple novel method for the thiophosphorylation and thiocarboxylation of alcohols. Its application to the synthesis of modified natural products with thioloester structures is being investigated. It should be mentioned that our procedure is an alternative to the synthesis of thiolcarboxylic acid esters[10] and thiolphosphoric acid esters[11] from alcohols and thioacids using the Mitsunobu reagent.

Mass spectra were recorded on a LKB 2091 mass spectrometer. ^{1}H-N.M.R. spectra were recorded on a Tesla BS 4887C and ^{31}P-N.M.R. spectra on a FT Jeol FX-60 instrument. G.L.C. analyses were performed on a Varian Aerograph 2700. *O*-Alkyl-*N,N*-dicyclohexylisoureas **4** were prepared from *N,N*-dicyclohexylcarbodiimide and appropriate alcohols according to the known procedures[5] and were used without further purification.

Reaction of 4 with *O,O*-Diethyl Phosphorothioic Acid (2a); General Procedure:

A solution of *O,O*-diethyl phosphorothioic acid (0.02 mol) in dry benzene (10 ml) is added dropwise with stirring to a solution af **4** (0.02 mol) in benzene (50 ml) at room temperature. The precipitation of *N,N'*-dicyclohexylurea is observed at this temperature only in the case of the reactions of **4a** and **4b** (see Table entry **a** and **b**). The reaction mixture is then refluxed until the reaction is completed (monitoring by T.L.C.: silica gel, cyclohexane/ethyl acetate: 5:1; R_F of the acid = 0.1). The precipitated urea is filtered off and the filtrate is concentrated in vacuo at room temperature. The ^{31}P-N.M.R. and T.L.C. analysis of the residue reveals the presence of phosphorothiolates **5** ($\delta^{31}{}_P$ = 25.0–26.5 ppm; R_F = 0.40–045) and phosphorothionates **6** as by-products ($\delta^{31}{}_P$ = 65.5–67.0 ppm; R_F = 0.7–0.8)[8]. Column chromatography of the residue performed on silica gel using cyclohexane/ethyl acetate (5:1) as eluent affords pure phosphorothiolates **5**. The yields of crude reaction products and pure phosphorothiolates **5** are given in Table 1. Physical properties of phosphorothiolates **5** were in accord with the literature data: for **5a, 5b** and **5d** see Ref.[12]; for **5c** see Ref.[13].

Reaction of 4 with Thiocarboxylic Acids (2b, 2c); General Procedure:

A solution of a thiocarboxylic acid (2 mmol) in benzene (2 ml) is added to a solution of **4** (2 mmol) in benzene (3 ml) and the mixture is refluxed (10 min in the case of **4b**, entry **e** and **g**; 1 hour for **4c**, entry **f**). The precipitated urea is filtered off and benzene is evaporated from the filtrate in vacuo. The residue is dissolved in pentane (≈ 5 ml) and the second crop of urea is filtered off. After evaporation of pentane, the crude product is chromatographed on a short silica gel column using ether as eluent. The product obtained is analysed by G.L.C./M.S., and then purified by means of preparative T.L.C.

Benzyl Thioloacetate **(5e)** is purified by preparative T.L.C. on silica gel using hexane: ether 10:1 as an eluent: yield: 94%; n_D^{20}: 1.5545 (Ref.[14], n_D^{25}: 1.5565).

M.S.: *m/e* = 166 (18%), 123 (25), 91 (100), 43 (74).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 2.48 (s, 3H); 4.31 (s, 2H); 7.48 ppm (br. s, 5H).

Isopropyl Thiolobenzoate **(5f)** *and Thionobenzoate* **(6f)**: Total yield of the crude mixture: 98%. The isomers were separated by means of preparative T.L.C. on silica gel using hexane: ether 30:1 as an eluent.

5f: $R_F \approx 0.33$, yield 88%, n_D^{22}: 1.5555 (Ref.[15], n_D^{29}: 1.5535).

M.S.: *m/e* = 180 (4), 105 (100), 77 (46), 43 (5).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.40 (d, 6H); 3.85 (sept., 1H); 7.26–7.55 (m, 3H); 7.89–7.99 ppm (m, 2H).

6f[16]: $R_F \approx 0.47$; yield: 9%.

M.S.: *m/e* = 180 (30%), 138 (44), 121 (39), 105 (100), 77 (61), 59 (6), 43 (19).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.48 (d, 6H); 5.96 (sept., 1H); 7.26–7.54 (m, 3H); 8.1–8.2 ppm (m, 2H).

Benzyl Thiolobenzoate **(5g)**[17]: after purification by preparative T.L.C. on silica gel (hexane/ether 10:1); yield: 94%.

M.S.: *m/e* = 228 (5%), 105 (100), 91 (14), 77 (44).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 4.25 (s, 2H); 7.03–7.58 (m, 8H); 7.78–8.06 ppm (m, 2H).

Received: April 9, 1985

[1] Młotkowska, B., Markowska, A. *Liebigs Ann. Chem.* **1984**, 1.

[2] For recent reviews on carbodiimides, see: Mikolajczyk, M., Kiełbasinski, P. *Tetrahedron* **1981**, *37*, 233. Williams, A., Ibrahim, I.T. *Chem. Rev.* **1981**, *81*, 589.

[3] Mikołajczyk, M., Kiełbasinki, P., Schiebel, H.M. *J. Chem. Soc. Perkin Trans. I* **1976**, 564.

[4] Mikołajczyk, M., Kiełbasinski, P., Basinski, W. *J. Org. Chem.* **1984**, *49*, 899.

[5] Mathias, L.D. *Synthesis* **1979**, 561.

[6] Khorana, H.G. *Can. J. Chem.* **1954**, *32*, 261 and 277.

[7] Vowinkel, E. *Chem. Ber.* **1967**, *100*, 16. Auterhoff, H., Oettmeier, R. *Arch. Pharm (Weinheim, Ger.)* **1975**, *308*, 732.

[8] Mark, V., Dungan, C.H., Crutfield, M.M., Van Wazer, J.R., in: *Topics in Phosphorus Chemistry*, Vol. 5, Grayson, M., Griffith, E.J., Eds., Interscience, New York, Sydney, 1967. Mastryukova, T.A., Zakharova, T.B., Kabachnik, M.I. *Izv. Akad. Nauk SSSR* **1963**, 2211; *C.A.* **1964**, *60*, 9882.
[9] Reid, E.E. *Organic Chemistry of Bivalent Sulfur*, Vol. IV, Chemical Publishing, Co. Inc., New York, 1962.
[10] Volante, R.P. *Tetrahedron Lett.* **1981**, *22*, 3119.
[11] Młotkowska, B., unpublished results.
[12] Ailman, D., Magee, R.J., in: *Organic Phosphorus Compounds*, Vol. 7, Kosolapoff, G.M., Maier, L., Eds., John Wiley & Sons, New York, London 1976, pp. 688, 701, 711.
[13] Muller, N., Lauterbur, P.C., Goldensen, J. *J. Am. Chem. Soc.* **1956**, *78*, 3557.
[14] Morse, B.K., Tarbell, D.S. *J. Am. Chem. Soc.* **1962**, *74*, 416.
[15] Chablay, A. *C.R. Acad. Sci. Ser. C* **1966**, *263*, 157.
[16] Sakurada, Y. *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.* **1926**, *9*, 237; *C.A.* **1927**, *21*, 2458.
[17] Fromm, E., Forster, A. *Liebigs Ann. Chem.* **1912**, *394*, 338.