J. prakt. Chem. 338 (1996) 763–765

Journal für praktische Chemie
Chemiker-Zeitung

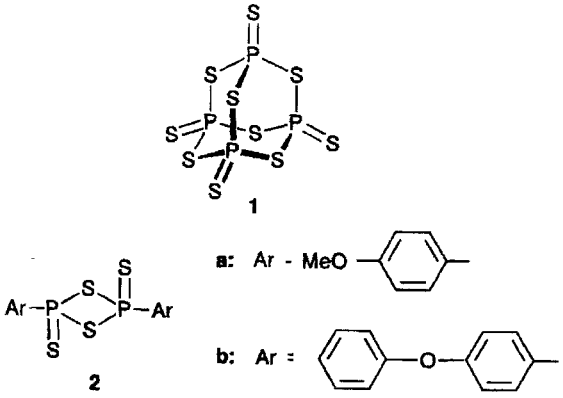
Tetraphosphorus Decasulfide, Revival of an Old Thionating Agent

K. Hartke and H.-D. Gerber

Marburg, Institut für Pharmazeutische Chemie, Universität

Received July 15th, 1996

Tetraphosphorus decasulfide (**1**) is a long known thionating agent for the conversion of carbonyl into thiocarbonyl groups [1, 2]. The normal procedure involves boiling of the carbonyl compound with a large excess of P_4S_{10} in an inert solvent such as toluene, xylene or pyridine. The reaction times are long and the yields in general low. A considerable progress has been made by the introduction of Lawesson's reagent, 2,4-bis-(*p*-methoxy)-1,3-dithiadiphosphetane-2,4-disulfide (**2a**), as a general thionating agent [3]. Meanwhile **2a** and several structural related dithiaphosphetanes such as **2b** [4] are used extensively for the conversion of carbonyl into thiocarbonyl groups [5].



Scheme 1

The thionation reactions with **2** can be run at room temperature or moderately elevated temperatures. Furthermore **2** is capable of transforming a large variety of carbonyl compounds into thiocarbonyl compounds, not only amides into thioamides but also lactones into thiolactones and esters into thioesters [3]. The main disadvantage in the use of **2** often lies in the difficulty found in separating product and reagent. This is normally done by column chromatography, which has to be repeated in unfavourable cases. Therefore efforts have been made to improve the results obtained with P_4S_{10} (**1**) as a very cheap thionating agent.

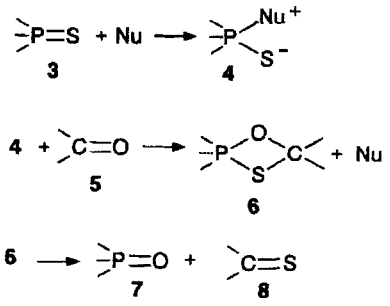
Raucher and Klein utilized the aid of ultrasonic-irradiation at 20–40 °C to transform amides into thioamides by P_4S_{10} [6]. Scheeren, Ooms and Nivard were obviously the first to propose the use of more polar solvents than toluene or xylene to improve the solubility of the reagent and the addition of sodium hydrogen carbonate as a suitable nucleophile to activate the P=S bond by nucleophilic attack [7]. They obtained fair to good yields with several aromatic ketones, amides, and some esters using mainly acetonitrile, diglyme, or diethyl ether at 30–40 °C. Dash, Dora, and Panda converted heterocyclic C=O groups of benzoxazine-4-ones, pyrazoline-4-ones and pyrimidine-2,5-diones into the corresponding thiones with P_4S_{10}/triethylamine in acetonitrile at room tem- perature [8a]. The yields reported ranged from 17% to 90%. P_4S_{10}/triethylamine in dichloromethane also transforms ef- fectively tropones into tropothiones (yields 62–96%) [8b]. According to Goel and Krolls P_4S_{10} reacts with 4 equivalents of *n*-butyllithium, methyllithium or phenyllithium to form a reagent that thionates lactams to thiolactams under mild conditions (10–60 °C).

Optimum thionation procedures have been elaborated by variation of the polar solvent and the nucleophilic base according to the principle proposed in Lit. [7]. Thus Brillon used P_4S_{10} and sodium carbonate (molar ratio 1:1) in tetrahydrofuran [10]. When mixing both reagents at room temperature a homogeneous solution is formed within 10–20 minutes. This solution is capable of thionating amides, peptides, and lactams at room temperature or slightly elevated temperatures (up to 50 °C) within a few hours affording good to excellent yields (general procedure A). In our hands the combination P_4S_{10} and sodium fluoride (molar ratio 1:2) in dimethoxyethane gave even better results [11] (general procedure B). The main advantages in following procedure A or B are:

- the extremely mild reaction conditions, in most cases room temperature,
- the high yields of thionation products generally obtained,
- the easy work-up procedure; most by-products are already eliminated with the alkaline water phase.

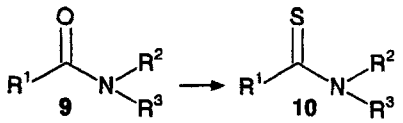
The exact nature of the thionating agent is still unknown. Obviously the attack of nucleophiles on P_4S_{10} gives rise to several species as indicated by complex ^{31}P NMR spectra

[9]. Therefore a probable reaction mechanism is merely based on speculation. The dissolution of P_4S_{10} in the polar solvent is mainly due to the addition of the nucleophile at the P=S bond (**2**) leading to the dipolar intermediate **3**, which attacks the C=O group exchanging ligands.



Scheme 2

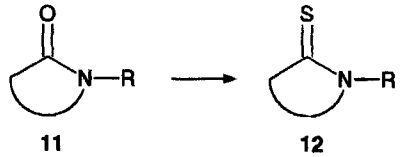
By the general procedure A or B a wide range of primary, secondary and tertiary amides **9** were effectively converted into thioamides **10** [10, 12]. The same is true for all kinds of lactams **11** [10, 12].



R^1 = H, alkyl, aryl

R^2, R^3 = H, alkyl

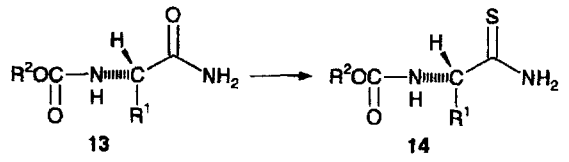
Scheme 3



R = H, alkyl

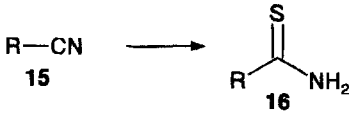
Scheme 4

Esters are generally not attacked and survive the thionation procedure. This means that *N*-protected α-amino amides **13** can be safely converted into *N*-protected α-amino thioamides **14** without racemization (yields of pure product 85–95%) [11].



Scheme 5

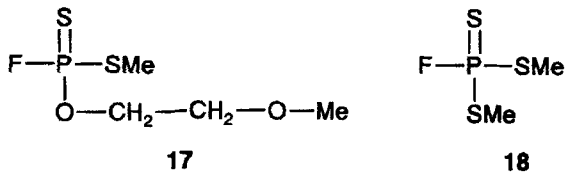
Following procedure B it is also possible to convert nitriles **15** directly into primary thioamides **16** [12]. The same aim can be acchieved with procedure A, using P_4S_{10} (9.0 mmol), anhydrous Na_2S (9.0 mmol) instead of Na_2CO_3 and the corresponding nitrile (1.8 mmol) [13].



R = aryl, alkyl

Scheme 6

The reagent combination P_4S_{10}/NaF in dimethoxyethane is capable of attacking the solvent [14]. Thus minor amounts of the main by-products **17** and **18** (molar ratio: 1:6) were isolated after longer reaction times. Separation of the liquid fluorophosphates **17** and **18** causes no problem with crystalline end products. With liquid end products, however, a purification by column chromatography is indispensible [15].



Scheme 7

Solvent attack by the reagents can be avoided in dichloromethane. In this case a catalytic amount of crown ether will accelerate the reaction (procedure C) [14].

General Procedures

A: In a flask fitted with a gas outlet, P_4S_{10} (2.0 g, 4.5 mmol) and Na_2CO_3 (0.47 g, 4.5 mmol) are added to THF (30 ml). The mixture is stirred vigorously for 10–20 min and the amide (3.75 to 2.25 mmol) is added. After completion of the thionation (about 1–8 h), a 10% aqueous solution of Na_3PO_4 (20 ml), AcOEt (15 ml) and hexane (15 ml) are respectively added. The aqueous layer is washed with AcOEt (1×10 ml). The organic layer is dried with $MgSO_4$ and then filtered on a silica gel pad. The crude thioamide can be further purified by chromatography on silica gel.

B: A suspension of P_4S_{10} (1.10 g, 2.5 mmol) and NaF (0.20 g, 4.75 mmol) in dry dimethoxyethane (10 ml) is stirred until a clear yellow solution results (about 30 min). Then the *N*-protected α-amino amide (1.67 mmol) **13** or the nitrile **15** (1.67 mmol) is added and stirring is continued for another 15 h. The reaction mixture is diluted with an aqueous solution of Na_2CO_3 (0.5 M, 10 ml) and extracted with *tert*-butylmethyl ether (2×10 ml). The organic phase is dried with Na_2SO_4, concentrated in vacuo, and the residue is chromatographed on silica gel with *tert*-butylmethyl ether/*n*-hexane 1:1.

C: P_4S_{10} (1.10 g, 2.5 mmol), KF (0.29 g, 5.0 mmol) and 18-

crown-6 (0.132 g, 0.5 mmol) are stirred in dry CH_2Cl_2 (30 ml) at room temperature for 1 h. To the cloudy suspension is added 1.25 mmol of the amide **9** or the lactam **11.** Stirring is continued for another 18 h. The reaction mixture is filtered and the filtrate worked up as indicated for procedure **B**.

References

[1] J. Wislicenus, Z. Chem. **1869**, 324. L. Henry, Ann. Chem. Pharm. **152** (1869) 148

[2] Review: E. Campaigne, Chem. Rev. **1** (1946) 39

[3] a) B. S. Pedersen, S. Scheibye, N. H. Nilsson, S.-O. Lawesson, Bull. Soc. Chim. Belg. **87** (1978) 223;
b) Review on Lawesson's reagent: M. P. Cava, M. I. Levinson, Tetrahedron **22** (1985) 5061

[4] G. Lajoie, F. Lépine, L. Maziak, B. Belleau, Tetrahedron Lett. **24** (1983) 3815

[5] Review on thionation methods: D. Brillon, Sulfur Reports **12** (1992) 297

[6] S. Raucher, P. Klein, J. Org. Chem. **46** (1981) 3558

[7] J. W. Scheeren, P. H. J. Ooms, R. J. F. Nivard, Synthesis **1973**, 149

[8] a) B. Dash, E. K. Dora, C. S. Panda, Heterocycles **19** (1982), 2093;
b) T. Machiguchi, T. Hasegawa, Y. Kano, Bull. Chem. Soc. Jpn. **66** (1993) 3639

[9] O. P. Goel, U. Krolls, Synthesis **1987**, 162

[10] D. Brillon, Synth. Commun. **20** (1990) 3085

[11] K. Hartke, S. Barrmeyer, J. Prakt. Chem. **338** (1996) 251

[12] S. Barrmeyer, Ph. D. thesis, University of Marburg **1994**

[13] D. Brillon, Synth. Commun. **22** (1992) 1397

[14] K. Hartke, H.-D. Gerber, unpublished results.

[15] a) Analytical data of **17**: ^{1}H NMR ($CDCl_3$): δ/ppm = 2.48 (dd, 6H, 2×SCH_3), J_{XH} = 19.2 and 1.6 Hz). – ^{13}C NMR ($CDCl_3$): δ/ppm = 16.44 (SCH_3, d, J_{XC} = 3.5 Hz). – ^{19}F NMR ($CDCl_3$): δ/ppm = –26.82 (d, J_{PF} = 1.17 kHz) (internal standard hexafluorobenzene). See also H. W. Roesky, Chem. Ber. **101** (1968) 2986
b) Analytical data of **18**: ^{1}H NMR ($CDCl_3$): δ/ppm = 2.44 (dd, 3H, SCH_3, J_{XH} = 18.4 and 1.6 Hz), 3.40 (s, 3H, OCH_3), 3.66 (m, 2H, $CH_3OC\underline{H}_2$), 4.34 (m, 2H, $POCH_2$). – ^{13}C NMR ($CDCl_3$): δ/ppm = 14.95 (SCH_3, d, J_{XC} = 4.6 Hz), 58.90 (OCH_3), 67,91 ($CH_3O\underline{C}H_2$, d, J_{XC} = 6.1 Hz), 70.66 ($POCH_2$, d, J_{XC} = 8.4 Hz). – ^{19}F NMR ($CDCl_3$): δ/ppm = –25.79 (d, J_{PF} = 1.15 kHz) (internal standard hexafluorobenzene).

Address for correspondence:
Prof. Dr. K. Hartke
Institut für Pharmazeutische Chemie
Universität Marburg
Marbacher Weg 6
D-35032 Marburg/Lahn