ChemComm

# New, efficient and chemoselective method of thioacylation, starting from carboxylic acids†

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***Received (in Liverpool, UK) 19th July 2000, Accepted 19th September 2000***
***First published as an Advance Article on the web 9th October 2000***

**_S_-Acylation of dithiophosphoric acids yields mixed anhydrides 3; they readily isomerize to _O_-thioacyl 4 and _S_-thioacyl monothiophosphates 5, which treated with the excess of dithiophosphoric acid 2 can be easily converted into thioacyl dithiophosphates 6, excellent thioacylating reagents.**

Thioacyl derivatives are mainly obtained by treating acyl derivatives with a thionating agent such as phosphorus pentasulfide or Lawesson's reagent.[1,2] Numerous other examples of sulfurating reagents have been reported (*e.g.* $R_3OBF_4$–NaHS,[3] $R_2PSX$,[4] $POCl_3$–$(Me_3Si)_2S$,[5] $(Et_2Al)_2S$,[1] $B_2S_3$[1] or $SiS_2$[1]) but are less well-known. Another strategy is to thioacylate nucleophiles with active derivatives of thiocarboxylic acids. Unfortunately, the known thioacylating agents (*e.g.* thioacyl halides,[1] thioacyl benzimidazolones,[6] thioacyl imidazoles, triazoles or tetrazoles,[1] thioacyloxybenzotriazoles,[7] thioacyl trifluorosulfonyl sulfides,[8] phenylmercury dithiocarboxylates[9] or bis(thioacyl) sulfides[10] *etc*.) show many disadvantages. They are generally unstable, expensive or their synthesis is complicated. In the case of less reactive reagents (like thioesters) reaction times are very long or the product cannot be obtained at all.[1] Most of the described reagents can only be prepared from dithiocarboxylic acids, which are scarcely obtainable commercially and are not easy to synthesise in high yield or to handle in pure form.

Here we report a new procedure for thioacylation with *S*-thioacyldithiophosphates, starting from carboxylic acids and dithiophosphoric acid. The usefulness of those kinds of reagents (namely thioacyl diphenylthiophosphinic sulfides) have been described by Kato *et al*.[11] but only derivatives of aromatic dithioacids were prepared by his group and the method of synthesis required cesium (or piperidinium) salts of dithiocarboxylic acids (general drawback). Moreover thioacyl diphenyldithiophosphinates are less reactive than dithiophosphates. We would like to describe a new and efficient method of synthesis of corresponding species and expand the scope of their applications (Scheme 1).‡

Acylation of dithiophosphoric acids (at the moment our best choice is 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane[12] (**2**)) yields mixed anhydrides of type **3** almost quantitatively (see Table 1). These compounds in solution isomerize to *O*-thioacylmonothiophosphates **4** and *S*-thioacylmonothiophosphates **5** (as we have proved, potential thioacylating reagents) but in an equilibrium mixture compounds **3** generally predominate.§ However, we have found that treatment of that mixture with excess of dithiophosphoric acid leads to the formation of mixed anhydrides of type **6** in high yields (see Table 2). Compounds of type **6** are relatively inert towards water and oxygen and are very good thioacylating agents. They react immediately with nitrogen and sulfur nucleophiles at rt. Thioacyl derivative **7** can be easily separated from water-soluble salts of thiophosphoric acids. Anhydrides **6** chemoselectively thioacylate nitrogen or sulfur nucleophiles in the presence of hydroxy groups. This property allows us to obtain *e.g.* hydroxythioamides (Table 3, **7g**, **7l**) or hydroxydithioesters (**7m**) or thiohydroxamic acids (**7e**, **7f**, **7k**) as well, from substrates with an unprotected oxygen atom. It is worth mentioning that these kinds of compound are not available *via* thionation of unprotected hydroxyamides, hydroxythiolesters or hydroxamic acids with Lawesson's reagent.[13]

In summary we have developed a new strategy of thioacylation, starting from carboxylic acids. In one pot the exchange of C=O into C=S occurs and at the same time activation of the thiocarboxyl function is performed. The method is simple and efficient and cheap reagents are used. The thioacylating agents formed are stable and can be stored for months without noticeable changes. Even thioanhydrides derived from aliphatic acids can be handled without special precautions. The reaction with *N*- or *S*-nucleophiles is very fast under ambient conditions and isolation of the product is very simple.

Our efforts to apply the isomerization of anhydrides of type **3** for the synthesis of thioacylating reagents are focused on a search for dithiophosphoric acids better suited for the described procedure. Our results will be published in a full paper soon.

We gratefully acknowledge the Polish State Committee for Scientific Research for financial support (Grant No. 3 T09A 061 16).

**Table 1** Acylation of dithiophosphoric acid **2**

| Entry | R | Chemical shift (ppm) $^{31}$P NMR | Yield (%) |
|---|---|---|---|
| **3a** | 1-Naphthyl | 69.6 | 100 |
| **3b** | Ph | 69.1 | 98 |
| **3c** | 4-PhOMe[a] | 70.1 | 85 |
| **3d** | 4-Ph$NO_2$ | 65.9 | 85 |
| **3e** | CH=$CH_2$Ph[a] | 69.7 | 93 |
| **3f** | Me | 69.1 | 89 |
| **3g** | Pr | 70.1 | 92 |
| **3h** | iPr | 70.6 | 98 |
| **3i** | tBu | 70.8 | 96 |
| **3j** | $CH_2$NPht | 65.8 | 82 |
| **3k** | $CH_2CH_2$NPht | 67.7 | 93 |
| **3l** | $CH_2$OPh | 67.9 | 90 |
| **3m** | $(CH_2)_4$COOMe | 69.2 | 100 |

[a] Due to fast isomerization obtained in mixtures with anhydride **4** (chemical shift $^{31}$P NMR of **4c**: 50.1 ppm; **4e**: 50.3 ppm).

**Table 2** Thioacyl dithiophosphates **6**

| Entry | R | Chemical shift (ppm) $^{31}$P NMR | Time/h | Yield (%) |
|---|---|---|---|---|
| **6a** | 1-Naphthyl | 67.8 | 1.5 | 90 |
| **6b** | Ph | 68.6 | 2 | 94 |
| **6f** | Me | 68.4 | 3 | 88 |
| **6g** | Pr | 68.5 | 3 | 92 |
| **6i** | tBu | 70.7 | 4 | 91 |
| **6m** | $(CH_2)_4$COOMe | 67.2 | 4 | 88 |

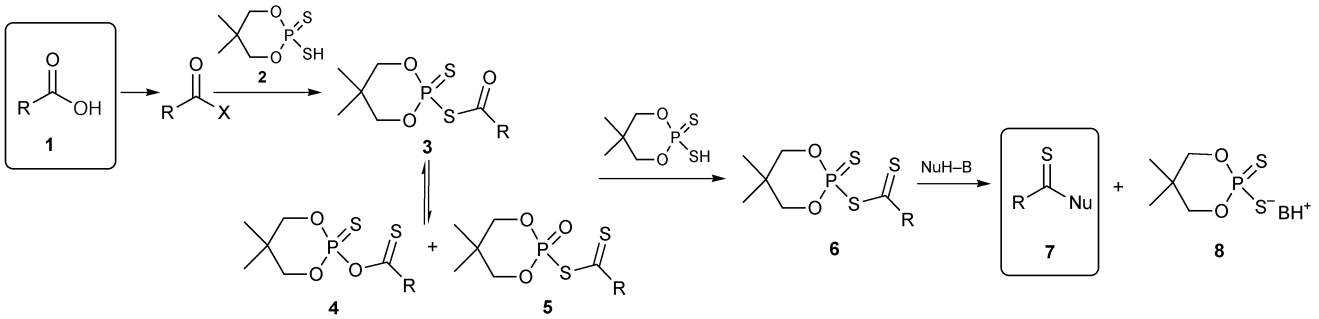
† Presented in part at 13th ICOS, Warsaw 2000, Poland, pp. 139.

DOI: 10.1039/b005911k

**Table 3** Thioacylations with dithiophosphates **6**

| Entry | R | Nucleophile | Product | Yield (%) |
|---|---|---|---|---|
| **7a** | Ph | Aq. $NH_3$ | $PhCSNH_2$ | 95 |
| **7b** | Ph | $PhNH_2$–$NEt_3$ | PhCSNHPh | 99 |
| **7c** | Ph | $(CH_2)_5NH$–$NEt_3$ | $PhCSN(CH_2)_5$ | 98 |
| **7d** | Ph | MeOH–$NEt_3$ | PhCSOMe | 0 |
| **7e** | Ph | MeNHOH·HCl–$NEt_3$ | PhCSN(OH)Me | 68 |
| **7f** | Ph | iPrNHOH·HCl–$NEt_3$ | PhCSN(OH)iPr | 73 |
| **7g** | Ph | $HOCH_2CH_2NH_2$–$NEt_3$ | $PhCSNHCH_2CH_2OH$ | 94 |
| **7h** | Me | $PhNH_2$–$NEt_3$ | MeCSNHPh | 88[a] |
| **7i** | Pr | $PhNH_2$–$NEt_3$ | PrCSNHPh | 96[a] |
| **7j** | tBu | $PhNH_2$–$NEt_3$ | tBuCSNHPh | 92 |
| **7k** | tBu | MeNHOH·HCl–$NEt_3$ | tBuCSN(OH)Me | 71 |
| **7l** | tBu | 2-$HOPhNH_2$–$NEt_3$ | 2-tBuCSNHPhOH | 99 |
| **7m** | tBu | $HOCH_2CH_2SH$–$NEt_3$ | $tBuCSSCH_2CH_2OH$ | 97 |
| **7n** | $(CH_2)_4COOMe$ | $(CH_2)_5N$–$NEt_3$ | $MeOCO(CH_2)_4CSN(CH_2)_5$ | 88[a] |

[a] Procedure B.




**Scheme 1** Conversion of carboxylic acids into thioacylating reagents and their reaction with nucleophiles.

## Notes and references

‡ *Acyl dithiophosphates* **3**, *typical procedure*: acyl chloride (5 mmol) is added to a solution of 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (**2**) (5 mmol) in 15 ml of benzene. The solution is cooled with iced water and subsequently pyridine or triethylamine (5 mmol) is added dropwise. Immediately, ammonium chloride precipitates. After 15 minutes the reaction mixture is filtered through a short layer of silica gel. Following solvent evaporation a pure enough product is obtained.

*Thioacyl dithiophosphates* **6**, *typical procedure*: A solution of 5 mmol of acyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide (**3**) and 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (**2**) (10 mmol) in 35 ml of benzene is heated under reflux for 2–6 h. Subsequently phosphoric thioacids **2** and **8** are removed by washing with an aq. solution of sodium carbonate and then water. The organic layer is then dried with magnesium sulfate and the benzene is evaporated. The crude product is used for thioacylation without further purification, or if necessary is purified by means of silica gel chromatography or crystallization.

*Thioacylation with thioacyl dithiophosphates* **6**, *typical procedure A:* A solution of amine or thiol (5 mmol) and pyridine or triethylamine (5.5 mmol) in benzene is added dropwise to a solution of thioacyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide (**6**). Triethylammonium (or pyridinium) dithiophosphate precipitates and can be removed by means of filtration or washing with water and aq. sodium carbonate. Drying and evaporation of the solvent generally yields pure enough product. If necessary, the thioacyl derivative can be purified by means of chromatography or crystallisation.

*Typical procedure B*: A solution of acyl 2-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) sulfide (**3**) (5 mmol) and 5,5-dimethyl-2-thiolo-2-thiono-1,3,2-dioxaphosphorinane (**2**) (10 mmol) in 35 ml of benzene is heated under reflux for 2–6 h. A solution of amine or thiol (5 mmol) and pyridine or triethyl amine (16.5 mmol) in benzene is then added. The resulting mixture is worked up as above.

§ On the basis of our $^{31}P$ NMR experiments we were able to estimate the composition of the equilibrium mixtures and additionally we managed to isolate a few examples of *S*- and *O*-thioacylmonothiophosphates (*e.g.* **4b**, **5a**,**b**,**i**) and to fully characterize them. Reactivity and the mechanism of formation of the species are under investigation. We would like to emphasize that apart from not well proven reports[14] of isomerization of anhydrides of type **3** to **4**, formation of compounds type **5** from **3** (or a mixture of **3** and **4**) have not been previously reported in the literature (excluding the speculations of Cherkasov,[15] which however do not agree with our results).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