1,3,2,4-Dithiadiphosphetane, 2,4-bis[(4 methylphenyl)thio]-2,4-disulfide

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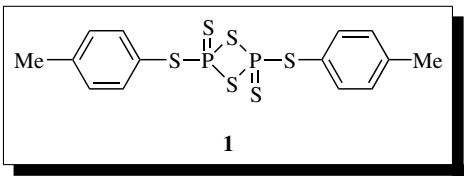
1,3,2,4-Dithiadiphosphetane, 2,4-bis[(4-methylphenyl)thio]-2,4-disulfide



1

[114234-09-2] $C_{14}H_{14}P_2S_6$ (MW 436.60)

(reagent used for the thionation of amides and lactams[1])

Alternate Name: 2,4-bis[(4-methylphenyl)thio]-1,3,2,4-dithiadiphosphetane-2,4-disulfide; 2,4-bis[(4-methylphenyl)thio]-1,3,2λ^5,4λ^5-dithiadiphosphetane-2,4-dithione; Davy-reagent *p*-tolyl.

Physical Data: mp 209–213 °C (dec).

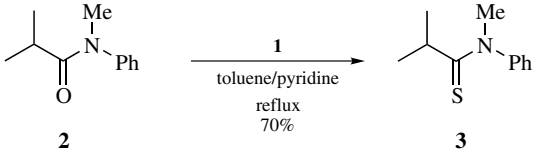
Solubility: soluble in pyridine, toluene, dioxane, and THF.

Form Supplied in: pale yellow crystals/solid; purum, >97.0%.

Preparative Methods: can be prepared by the reaction of P_4S_{10} (0.3 mol) and 4-methylthiophenol (thio-*p*-cresol; 1.0 mol) in toluene (500 ml), with 4 h at reflux temperature.

Purification: recrystallization from toluene.

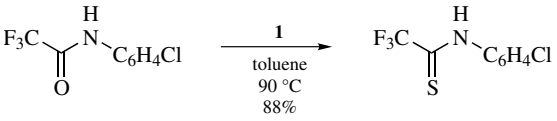
Thionation of Amides. 2,4-Bis[(4-methylphenyl)thio]-1,3,2,4-dithiadiphosphetane-2,4-disulfide (**1**) reacts with carboxamides to give the corresponding thioamides. Usually, this thionation reaction is performed in a 1:1 mixture of toluene and pyridine at 70–110 °C. For example, the treatment of *N*,2-dimethyl-*N*-phenylpropanamide (**2**) with **1** in toluene/pyridine under reflux for ca. 15 h leads to thioamide **3** in 70% yield (eq 1).[1] After only 3 h, 70% of the starting material (**2**) is consumed and **3** is obtained in 66% yield.



2 **3** (1)

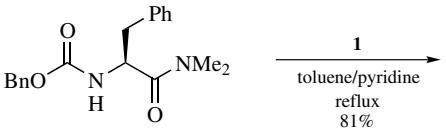
The thionation of carboxamides with **1** shows some remarkable selectivities:[1] the reagent is especially suited for the formation of *N*,*N*-disubstituted thiocarboxamides. Under similar conditions as described above, the transformations of 2-methyl-*N*-phenylpropanamide and benzamide gave the corresponding thioamides in only 27% and 4.5% yields, respectively. This selectivity is somehow complementary compared with that of Lawesson's reagent.

The thionation of trichloroacetamides with Lawesson's reagent fails, whereas the corresponding *N*-aryl and *N*-benzylthioacetamides are obtained in good yield on treatment with **1** in toluene.[2] For example, *N*-methyl-*N*-phenyltrichlorothioacetamide and *N*-(4-chlorophenyl)trifluorothioacetamide (**5**) have been prepared in 78% and 88% yields, respectively (eq 2).



4 **5** (2)

Thionation of Cbz-protected α-amino acid dimethylamides of type **6** proceeds smoothly under the standard conditions to give selectively Cbz-protected α-amino acid thioamides **7** (eq 3),[1] i.e., thionation of carboxamides is preferred to that of carbamates.



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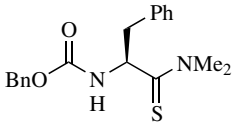
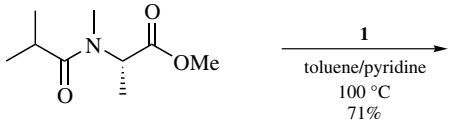


7 (3)

A similar selectivity is observed with respect to carboxamides and carboxylic esters; thionation of *N*-acylated α-amino acid esters of type **8** with **1** leads to thioamides **9** exclusively (eq 4).[3]



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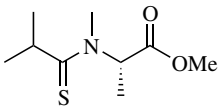
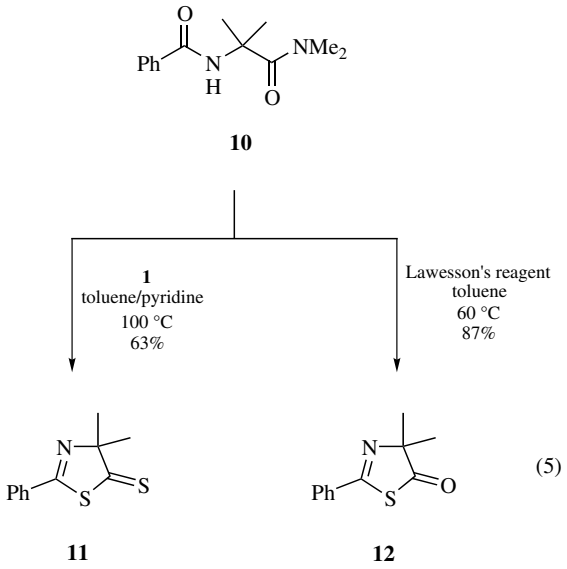


9 (4)

Synthesis of 1,3-Thiazole-5(4*H*)-thiones. The preferential thionation of *N*,*N*-disubstituted carboxamides can be used for a convenient synthesis of 2,4,4-trisubstituted 1,3-thiazole-5(4*H*)-thiones of type **11**. Treatment of *N*-acylated α,α-disubstituted α-amino acid amide (**10**) with **1** in toluene/pyridine at 100 °C gives **11** as the sole product.[1] In contrast, the analogous reaction with Lawesson's reagent leads exclusively to the corresponding 1,3-thiazol-5(4*H*)-one (**12**) (eq 5).[1,4–6]

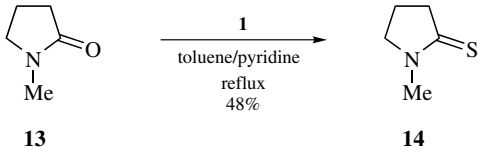


(5)

This difference can be rationalized by a reverse sequence of thionation of the diamide and the assumption that the analogs of **10** with a thiobenzoyl group undergo a spontaneous cyclization via elimination of dimethylamine to give 1,3-thiazole derivatives.

1,3-Thiazole-5(4*H*)-thiones of type **11** are also obtained by the thionation of *N*-acylated α,α-disubstituted α-amino acid thioamides with **1**.[1] In this case, the reaction with Lawesson's reagent parallels that with **1**.

Thionation of Lactams. The thionation of *N*-substituted lactams with **1** in toluene/pyridine provides the corresponding thiolactams, for e.g., *N*-methylpyrrolidin-2-one (**13**) is transformed into *N*-methylpyrrolidine-2-thione (**14**) (eq 6).[1] The observed selectivity in the case of lactams is similar to that of amides; the reaction of *N*-unsubstituted lactams with **1** is sluggish, i.e., the product pyrrolidine-2-thione is formed in very low yield.



(6)

Recently, thionation of an antitumor cyclic hexapeptide containing three -CO-NH- and three -CO-NMe- lactam groups has been studied.[7] The thionation with Lawesson's reagent occurs with high selectivity at the -CO-NH- group of Tyr-3 and only very small amounts of the product of dithionation at -CO-NH- of Tyr-3 and Tyr-6 are formed, whereas the reaction with **1** in dioxane yields two monothio and three dithio derivatives. The two main products are the same as obtained in the reaction with Lawesson's reagent, but their ratio is remarkably different. One of the minor dithionated products contains a -CS-NMe- group of Ala-2.

Related Reagents. 1,3,2,4-Dithiadiphosphetane, 2,4-bis (methylthio)-2,4-disulfide (Davy-reagent methyl);[8–10] 1,3,2,4-dithiadiphosphetane, 2,4-bis(ethylthio)-2,4-disulfide (Davy-reagent ethyl);[8,9] 1,3,2,4-dithiadiphosphetane, 2,4-bis(phenylthio)-2,4-di-

sulfide;[11] 1,3,2,4-dithiadiphosphetane, 2,4-bis[(4-methoxyphenyl)-thio]-2,4-disulfide;[8] 1,3,2,4-dithiadiphosphetane, 2,4-bis(4-methoxyphenyl)-2,4-disulfide (Lawesson reagent).[12,13]

1. Wipf, P.; Jenny, C.; Heimgartner, H., *Helv. Chim. Acta* **1987**, *70*, 1001–1011.
2. Braverman, S.; Cherkinsky, M.; Kedrova, L., *Tetrahedron Lett.* **1998**, *39*, 9259–9262.
3. Breitenmoser, R. A.; Heimgartner, H., *Helv. Chim. Acta* **2002**, *85*, 885–912.
4. Obrecht, D.; Heimgartner, H., *Chimia* **1982**, *36*, 78–81.
5. Obrecht, D.; Prewo, R.; Bieri, J. H.; Heimgartner, H., *Helv. Chim. Acta* **1982**, *65*, 1825–1836.
6. Jenny, C.; Heimgartner, H., *Helv. Chim. Acta* **1986**, *69*, 374–388.
7. Hitotsuyanagi, Y.; Matsumoto, Y.; Sasaki, S.; Suzuki, J.; Takeya, K.; Yamaguchi, K.; Itokawa, H., *J. Chem. Soc., Perkin Trans. 1* **1996**, 1749–1755.
8. Davy, H., *J. Chem. Soc., Chem. Commun.* **1982**, 457–458.
9. Davy, H.; Metzner, P., *J. Chem. Res. (S)* **1985**, 272.
10. Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S. O., *Tetrahedron* **1984**, *40*, 2047–2052.
11. Yokoyama, M.; Hasegawa, Y.; Hatanaka, H.; Kawazoe, Y.; Imamoto, T., *Synthesis* **1984**, 827–829.
12. Cherkasov, R. A.; Kutyrev, G. A.; Pudovik, A. N., *Tetrahedron* **1985**, *41*, 2567–2624.
13. Cava, M. P.; Levinson, M. J., *Tetrahedron* **1985**, *41*, 5061–5087.

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