Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Denis Brillon (1992) A New Thionation Reagent: Preparation of Primary Thioamides from Nitriles, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:10, 1397-1401

To link to this article: http://dx.doi.org/10.1080/00397919208021604

SYNTHETIC COMMUNICATIONS, 22(10), 1397-1401 (1992)

A NEW THIONATION REAGENT: PREPARATION OF PRIMARY THIOAMIDES FROM NITRILES

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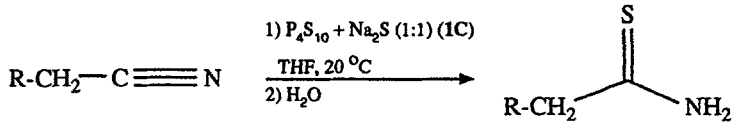
Abstract: Phosphorus decasulfide reacts with sodium sulfide (1:1 ratio) in tetrahydrofuran at 25 °C to afford an *in situ* reagent **1C** (5 eq.) that rapidly converts nitriles into thioamides at 20 °C.

As a continuation of our investigation on the use of *in situ* phosphorus decasulfide derivatives as thionation reagents,[1,2] we herein report the preparation of primary thioamide derivatives from methylene acidic acetonitriles with a new *in situ* reagent **1C**. Previous methods[2] for preparing thioamides from nitriles are the use of thioacetamide at high temperature,[3] thiophosphoric acid derivatives[4,5] or hydrogen sulfide.[6,7] Also, an *in situ* reagent described by Scheeren,[8] being a 1:6 ratio of phosphorus decasulfide/sodium bicarbonate used as a nucleophilic sulfuration reagent of ketones, gave traces amount of thioacetamide formed from acetonitrile used as the solvent. We demonstrated in the past that a reaction between phosphorus decasulfide/sodium carbonate (1:1) afford an electrophilic thionation reagent **1A** designed and found useful for the sulfuration of the R-C=O-NRR' moiety in general.[1,2] The empirical formula of *in situ* reagent **1A**, $(P_4S_{10}O)^{2-}Na_2^{2+}$, shows that it also possess a nucleophilic character in the thiophosphate groups.[8]

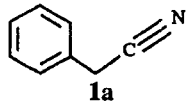
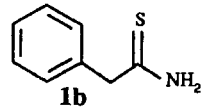
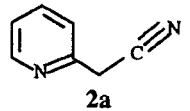
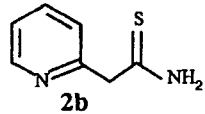
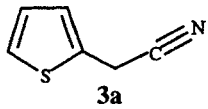
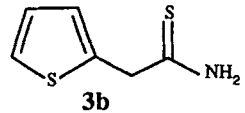
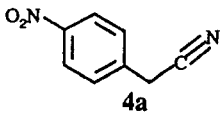
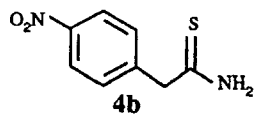
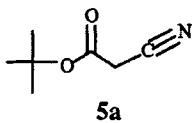
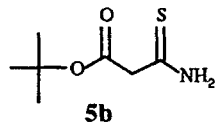
We found that 1.5 eq. of reagent **1A**[1] (prepared in THF) gives an optimized yield of 31% of thioacetamide from CH_3CN at 20 °C after 10 h. We also sulfurated phenylacetonitrile **1a** with **1A** using these conditions and obtained 27% of 2-phenylethanethioamide **1b**, but completion of the reaction could not be reached and heating the mixture led to lower yield; the other more electrophilic *in situ* reagent **1B** (1.8 eq.) we reported[1] nevertheless afforded 20% of **1b** after 5 h at 20 °C. These preliminary results indicated us along with the absence of water, required (1-2 eq.) in the use of *O,O*-diethylthiophosphoric acid in the sulfuration of nitriles,[4] that the ambivalent nucleophilic/electrophilic character of **1A** is necessary as might be rationalized[2] as follow: the thiophosphate group performs the nucleophilic attack on the nitrile group while a neutral P^v center is trapping the corresponding *in situ* thioimidate anion. So, by making appropriate processing changes, we thought possible to obtain a suitable *in situ* thionation reagent for nitriles. The reaction of a 1:1 ratio of phosphorus decasulfide and sodium sulfide[8] in tetrahydrofuran at 25 °C gives a stable and limpid solution of *in situ* reagent **1C** with all sulfur atoms as shown by the empirical formula: $(P_4S_{11})^{2-}$ Na_2^{2+}.



1a-5a **1b-5b**

The optimization in the preparation of thioamides led to the use of 5 eq. of this *in situ* reagent **1C** (0.45 M in THF) at 20 °C. The reagent **1C** converted 2-phenylacetonitrile **1a**, 2-pyridylacetonitrile **2a**, 2-thienylacetonitrile **3a**, 4-nitrophenylacetonitrile **4a** and *t*-butylcyanoacetate **5a** into the corresponding primary thioamides **1b-5b** (46-76%) in good yields after 3.5 h at 20 °C (Table 1).

Table 1. Preparation of thioamides from nitriles.

NITRILE	THIOAMIDE	YIELD[a] (%)
 **1a**	 **1b**	73
 **2a**	 **2b**	70
 **3a**	 **3b**	72
 **4a**	 **4b**	76
 **5a**	 **5b**	46

[a] isolated from chromatography after 3.5 h at 20 °C.

The work-up is easy since this *in situ* reagent **1C** readily dissolves in aqueous solutions such as sodium phosphate tribasic (gives a buffered solution at pH 5-6).

Despite the fact that the exact nature of **1C** cannot be ascertained from the complex ^{31}P NMR spectrum, the availability of this stable *in situ* reagent **1C** and its efficiency to convert rapidly nitriles into thioamides at 20 °C make its use especially advantageous over other known reagents.

Experimental

Phosphorus decasulfide (sold as the pentasulfide) from Aldrich or BDH was used. Anhydrous sodium sulfide was obtained after few hours under reduced pressure (1 Torr) at 100 °C. ^{1}H NMR spectra were recorded on a Bruker WH-400 spectrometer.

2-Phenylethanethioamide 1b. (General Procedure). P_4S_{10} (4.0 g, 9.0 mmol) is added to THF (20 mL) followed by anhydrous Na_2S (0.7 g, 9.0 mmol) and the mixture is stirred vigorously at 20-25 °C for 10 min. 2-Phenylacetonitrile **1a** (211 mg, 1.8 mmol) is then added. After 3.5 h at 20 °C, a 10% aqueous solution of Na_3PO_4 (25 mL), EtOAc (40 mL) and hexanes (20 mL) are respectively added. The aqueous layer is extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extracts are dried on $MgSO_4$ then filtered on a silica gel pad (1 g). The crude is purified by flash chromatography on silica gel (EtOAc/ hex 1:3) to give **1b** (198 mg, 73%). The solid is recristallized in CH_2Cl_2 and hexanes: mp 94- 95 °C. ^{1}H NMR δ 4.12 (s, 2 H, CH_2), 6.65 (m, 1 H, NH), 7.37 (m, 5 H, Ar), 7.62 (m, 1 H, NH); IR 3470, 3360, 2980, 1610, 1410 cm^{-1}. Exact mass calcd for C_8H_9NS 151.0457, found 151.0439.

2-(2-Pyridyl)ethanethioamide 2b. Following the general procedure: chromatography (EtOAc/hex/CH_2Cl_2 2:1:0 then 2:0:1). mp 87-88 °C (CH_2Cl_2/hex). ^{1}H NMR δ 4.22 (s, 2 H, CH_2), 7.30 (m, 1 H, Ar), 7.60 (m, 1 H, NH), 7.70 (m, 2 H, Ar), 8.55 (m, 1 H, Ar), 9.6 (m, 1 H, NH). IR 3240, 2980, 1600, 1445, 1410 cm^{-1}. Exact mass calcd for $C_7H_8N_2S$ 152.0409, found 152.0414. This compound slightly decompose on standing.

2-(2-Thienyl)ethanethioamide 3b. Following the general procedure: chromatography (EtOAc/hex/CH_2Cl_2 1:2:0 then 1:1: 1). mp 79-80 °C (CH_2Cl_2/hex). ^{1}H NMR δ 4.31 (s, 2 H, CH_2), 6.96 (m, 1 H, NH), 7.04 (m, 2 H, Ar),

7.29 (m, 1 H, Ar), 7.60 (m, 1 H, NH). IR 3470, 3260, 2990, 1605, 1405, 1230 cm^{-1}. Exact mass calcd for $C_6H_7NS_2$ 157.0021, found 156.9977.

2-(4-nitrophenyl)ethanethioamide 4b. Following the general procedure: chromatography (EtOAc/CH_2Cl_2 1:1). mp 139-140 °C (EtOAc/hex). ^1H NMR δ 4.15 (s, 2 H, CH_2), 6.75 (m, 1 H, NH), 7.51 (m, 3 H, Ar and NH), 8.22 (m, 2 H, Ar). IR 3380, 1610, 1530, 1355 cm^{-1}. Exact mass calcd for $C_8H_8N_2O_2S$ 196.0307, found 196.0328.

2-(*t*-Butyloxycarbonyl)ethanethioamide 5b. Following the general procedure: chromatography (EtOAc/hex 1:1 then 1:0). mp 90-91 °C (CH_2Cl_2/hex). ^1H NMR δ 1.47 (s, 9 H, CH_3), 3.74 (s, 2 H, CH_2), 7.73 (m, 1 H, NH), 9.02 (m, 1 H, NH). IR 3460, 2980, 1720, 1600, 1380, 1160 cm^{-1}. Exact mass calcd for $C_7H_{13}NO_2S$ 175.0668, found 175.0674.

Acknowledgements: The author thanks Western Ontario University for computer facilities and also A.C.W. and G.S. for their general supports.

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(Received in USA 17 December, 1991)