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Advanced reagent for thionation: Rapid synthesis of primary thioamides from nitriles at room temperature

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COMMUNICATION

Advanced reagent for thionation: Rapid synthesis of primary thioamides from nitriles at room temperature

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A series of aliphatic, aromatic and heterocyclic nitriles is thionated to give the corresponding thioamides in excellent yield using a newly developed reagent system of phosphorus pentasulfide and sodium sulfite or sodium dithionite at room temperature in a very short time (5–25 minutes). The microwave procedure of the reactions also is reported to afford the same products.

Keywords: Thioamides; Nitriles; Phosphorus pentasulfide; Sodium sulfite; Sodium dithionite

1. Introduction

Thioamides have been the subject of much interest in chemistry due to their potential role as intermediates in a variety of reactions including the formation of a nonsteroidal anti-inflammatory drug fentiazac [1], antithrombotic itazigrel [2], antagonist of histamine nizatidine [3] and also in novel heterocyclic ring systems [4].

Several methods for the preparation of thioamides from nitriles have been reported [5–12]. It is well known that the nitrile compounds are transformed to the corresponding thioamides using alkali metal hydrogen sulfides or ammonium sulfide [13], Dowex SH^- [14], sodium trimethyl silanethiolate [15] and $(P_4S_{11})Na_2$ [16]. Recently thioamide syntheses by microwave-assisted methods have been reported [17–21]. Conversion of amides, peptides and lactams to their thio analogues have also been reported [22] using P_4S_{10} and $NaHCO_3$ which actually produces *in situ* the thionation reagent $Na^{2+}(P_4S_{10}O)^{2-}$. Most recently simply phosphorous pentasulphide in different solvents, especially in ethanol under refluxing conditions, has been reported to give thioamides [23]. Thus, the development of new methods of thionation is a continuous challenge to many chemists to perform thionation under heterogeneous, anion-exchange resin [14], acidic [24–26], basic [27], under pressure using phase transfer catalysts [28] and high temperature [29] conditions.

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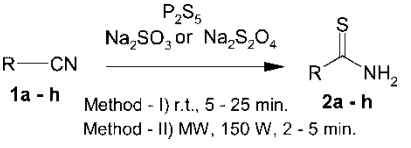
2. Results and discussion

Here, we report a useful straightforward, economic and efficient new method (scheme 1) for easy thionation of a series of aliphatic, aromatic and heterocyclic nitriles (**1a–h**) using a mixture of phosphorus pentasulfide and sodium sulfite or sodium dithionite in equivalent proportions at room temperature (method-I). The reactions are exothermic and the reaction mixture becomes hot within a few minutes. The most important aspect of this new procedure is that the completion of the reaction requires only a few minutes. The same reaction under microwave-assisted conditions (method-II) is also carried out and reported here.



SCHEME 1 Facile method for synthesis of primary thioamides.

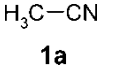
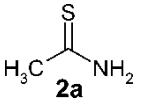
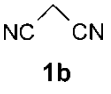
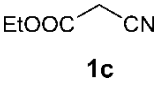
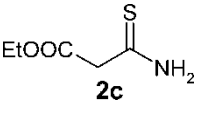
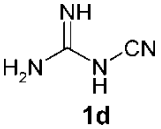
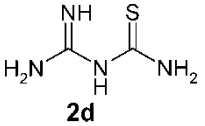
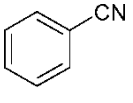
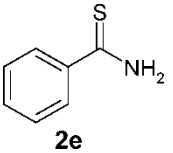
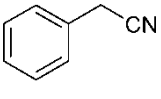
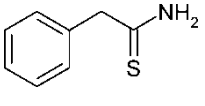
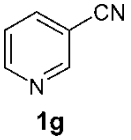
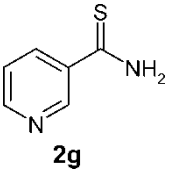
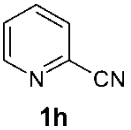
However, the conventional reactions at room temperature in this case have been found to be somewhat preferable compared to microwave assistance (table 1). Under microwave conditions, the products develop deep colour (yellow or brown to red) especially in the case of 2-cyanopyridine (entry 15), which is found to be most reactive. The thionation of 2-cyanopyridine **1 h** almost goes to completion by both the methods within a very short time. The results shown in table 1 clearly indicate the scope and generality of the methods with respect to aliphatic, aromatic and heterocyclic nitriles. Thus, the conventional method of simply mixing the nitrile with the newly developed reagent system (sodium sulfite or sodium dithionite and phosphorous pentasulfide) and stirring the mixture by a glass rod in a beaker or grinding them in a mortar by a pestle gives cleaner and better yields of thioamides compared to microwave condition.

The same reaction using the phosphorus pentasulfide and sodium sulfite or sodium dithionite in the presence of ethanol at room temperature also gives thioamides in good yields within a few minutes (5–20 minutes).

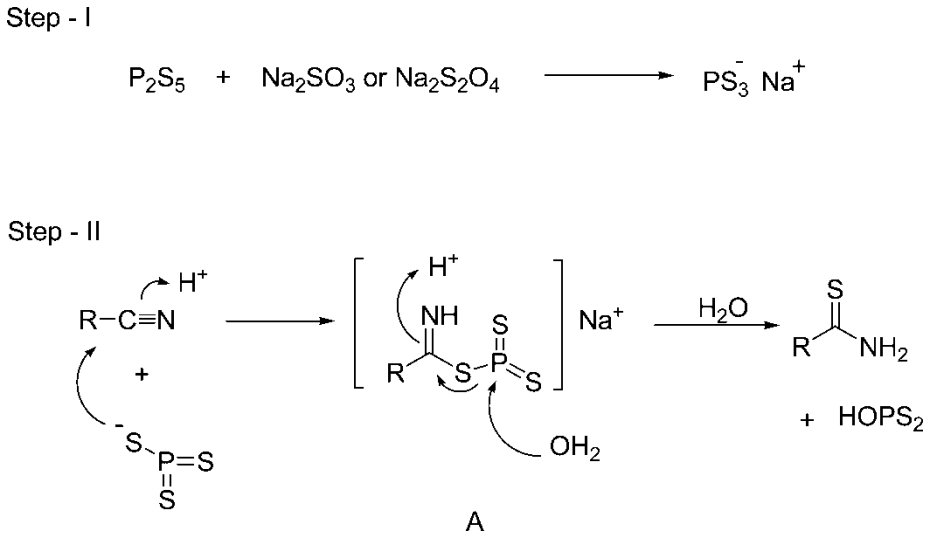
The reagent probably generates the thionating nucleophile (negatively charged phosphorous-linked thio nucleophile) by reducing the weak P=S bond or reductively cleaving the P-S bond (both dithionite or pentasulfide are reducing agents supplying electrons) of P_4S_{10} (P_2S_5 exists as tetraphosphorous decasulphide P_4S_{10}). The nucleophile readily attacks the electrophilic carbon of cyano group giving thioamide as product after aqueous work-up. A plausible mechanism of thioacetamide formation is shown in the scheme 2. It is suggested that PS_3^- represents the thionating nucleophile and this species is generated in the reaction medium by treatment of sodium sulfite or sodium dithionite with phosphorus pentasulfide. The aqueous work-up actually liberates the thioamide by nucleophilic attack by water on possible intermediate [**A**] followed by tautomeric shift of hydrogen from sulfur to nitrogen. The presence of reducing agent like sodium sulfite or sodium dithionite facilitates rapid liberation of sulfur nucleophile PS_3^- to form the possible intermediate [**A**] compared to use of other thionation reagents.

The NMR spectrum of thioacetamide shows that the two amide protons appear at two different positions where Ha appears at more downfield compared to Hb (7.54 and 6.84 ppm, respectively, for Ha and Hb). This may be due to the restricted rotation of the CN bond of thioamide group because of double bond character due to resonance (scheme 3) and also due

Table 1. Preparation of the thioamides **2a–h** from the nitriles **1a–h**.

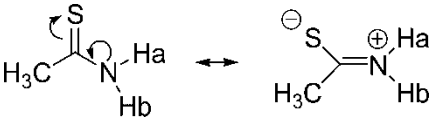
Entry	Substrate	Product	Time(min.)	Yield(%)[a]	Thioamide mp (°C)	Thioamide Ref. mp (°C[b])
1	 **1a**	 **2a**	20	80 (I)	112–114	(108–109)[8]
2			2	75 (II)		
3	 **1b**	 **2b**	25	70 (I)	208–212dec.	(211–212dec)[29]
4			3	55 (II)		
5	 **1c**	 **2c**	18	75 (I)	–	–
6			2	66 (II)		
7	 **1d**	 **2d**	22	60 (I)	210–215	–
8			3	55 (II)		
9	 **1e**	 **2e**	15	95 (I)	117–118	(118–119)[30]
10			2	80 (II)		
11	 **1f**	 **2f**	25	76 (I)	99–100	(96–97)[9]
12			3	62 (II)		
13	 **1g**	 **2g**	5	95 (I)	190–192	(190–192)[9,30]
14			1	90 (II)		
15	 **1h**	 **2h**	5	98 (I)	134–135	(136–137)[30]
16			20 sec.	92 (II)		

[a] Isolated yield of pure product. The parentheses refer to reaction condition Method-I: r.t., 5–25 min. Method-II: microwave irradiation at 150 W for 2–5 min. [b] The latter range in parentheses refers to literature melting points.



SCHEME 2 Possible mechanism for the formation of thioamides.

to closer proximity of Ha to sulfur of thioamide group giving rise to such deshielding effect compared to Hb.



SCHEME 3 Resonance forms of thioacetamide.

In conclusion, we have developed a new reagent system of phosphorus pentasulfide and sodium sulfite or sodium dithionite in equivalent proportions for an efficient and rapid synthesis of a series of aliphatic, aromatic and heterocyclic primary thioamides from the corresponding nitriles by both conventional reactions at room temperature as well as by microwave procedure.

3. Experimental

3.1 *Thioamides (entries 1–16); general procedure*

Method-I: A mixture of acetonitrile **1a** (0.786 g, 0.02 mol.), phosphorus pentasulfide (4.25 g, 0.02 mol.) and sodium sulfite (2.41 g, 0.02 mol.) or sodium dithionite (3.33 g, 0.02 mol.) was stirred by glass rod at r.t. for 20 min. Water (40 ml) was then added and mixture was extracted with CH_2Cl_2 (2×50 ml). The organic layer was washed well with brine, dried (Na_2SO_4) followed by evaporation with rotary evaporator affording a white crystalline solid which was further purified on silica gel (100–200 mesh) column chromatography using petroleum ether: CH_2Cl_2 (2:3) to give **2a** (1.14 g, 80%). The alternative way of performing the reaction in a mortar by just mixing the above substrate and the reagents and then grinding by the pestle also easily afforded the product in the same yield.

The above procedure works well also in the presence of the above thionation reagent in presence of solvent like ethanol. The above procedure was followed exactly in the same ratio of acetonitrile **1a,** phosphorus pentasulfide and sodium sulfite or sodium dithionite in the presence of ethanol (10 ml) and after usual aqueous work up afforded the desired thioacetamide **2a** (1.05 g, 74%).

Method-II: A mixture of acetonitrile **1a** (0.786 g, 0.02 mol.), phosphorus pentasulfide (4.25 g, 0.02 mol.) and sodium sulfite (2.41 g, 0.02 mol.) or sodium dithionite (3.33 g, 0.02 mol.) was placed in a microwave oven (BPL 800 G, the commercial name of the microwave oven) and then subjected to irradiation at 150 W for an optimized time (2 min). The resulting reaction mixture was cooled followed by the same above work-up procedure to afford the product **2a** (1 g, 75%).

Compound **2c**: Semisolid, FT-IR (KBr, ν): 3311, 3129, 2982, 1732, 1621, 1435, 1029 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm): 8.92 (br s, 1H, NH_2), 7.79 (br s, 1H, NH_2), 4.24 (q, 2H, $J = 7.0$), 3.86 (s, 2H), 1.32 (t, 3H, $J = 7.0$).

Compound **2d**: mp 210–215 °C, FT-IR (KBr, ν): 3407, 2922, 2852, 2255, 2128, 1653, 1408, 1003 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.52 (br s, 1H, NH), 7.09 (br s, 1H, NH_2), 6.94 (br s, 1H, NH_2), 6.22 (br s, 1H, NH), 5.87 (br s, 2H, NH_2).

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