JOC*Note*

Expeditious Microwave-Assisted Thionation with the System $PSCl_3/H_2O/Et_3N$ under Solvent-Free Condition

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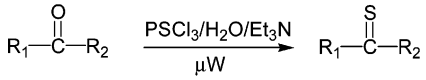

A novel thionation protocol for carbonyl compounds, with the system $PSCl_3/H_2O/Et_3N$ has been discovered. Clean, rapid, and efficient synthesis of a variety of thiocarbonyl compounds such as thioamides, thiolactams, thioketones, thioxanthones, and thioacridone can be achieved through this simple and convenient method under solventless condition with microwave irradiation.

Thionation of carbonyl compounds is an important organic transformation.[1] In view of their synthetic importance, several routes have been developed to gain access to thiocarbonyl compounds, and among them, C═O → C═S is the most exploited route. The mechanistic principle for majority of the methods employed is the nucleophilic attack of some suitable sulfur-containing agent on the carbon atom of a polar C═O bond leading to the substitution of oxygen by the sulfur. To effect this transformation, Lawesson's reagent[2] and P_4S_{10}, either alone or with additives,[3] are the reagents of choice. Many other useful reagents such as H_2S,[4] CS_2,[5] R_2PSX,[6] $(Et_2Al)_2S$,[7] NaSH,[8] TMS_2S,[9] elemental sulfur,[10] aq ammonium sulfide,[11] SiS_2,[12] HMDST,[13] etc. have also been reported. The described methods are in general solvent-mediated, where the nature of the solvent often constitutes a crucial factor. Reactions are usually performed in boiling toluene, xylene, chloroform, acetonitrile, or pyridine for long periods, and therefore, extensive workup and chromatographic purification become inevitable, which is another serious drawback. In consequence of the foregoing considerations, the development of novel synthetic strategies for thionation which have advantages with respect to short reaction time, mild reaction conditions, cleaner reactions, and simple isolation of the product are of paramount interest. In this note, we report a very convenient and efficient, solvent-free thionation of amides, lactams, ketones, xanthones, acridone with $PSCl_3/H_2O/Et_3N$. To our knowledge this represents the first general application of $PSCl_3$ as a thionating agent.

Due to the high nucleophilicity of sulfur and oxophilicity of phosphorus, $PSCl_3$ is an attractive candidate for an oxygen/sulfur exchange reaction and may reasonably be expected to convert carbonyl groups into their thiocarbonyl analogues. A survey of the literature revealed that thionation by $PSCl_3$ has scarcely been reported[14] and no attempt has been made so far to investigate the general applicability of this potential thionating agent. Hence, we set out to explore the ability of $PSCl_3$ for thionation. In order to ascertain the feasibility of this transformation *N*,*N*-diethyl-*m*-toluamide was selected as a model substrate, and conversion to its thio analogue was studied under a variety of conditions. In the first place, on the basis of literature precedence a solvent-mediated reaction of amide and $PSCl_3$ was attempted. A very slow reaction was found to occur in toluene under reflux. The conversion was modest even after long hours of reflux, and an increase in concentration of $PSCl_3$ also did not noticeably affect the outcome.

One interesting observation was that when the reaction is carried out under strictly anhydrous conditions, almost no conversion was found to occur. We assumed that, probably in the presence of water, $PSCl_3$ was getting hydrolyzed to thiophosphoric acid which may be responsible for thionation. Curiously, addition of water in the reaction mixture did indeed increase the rate of reaction. Although with $PSCl_3/H_2O$ thionation was improved, complete conversion could not be achieved.

(1) (a) Bernardi, F., Csizmadia, I. G., Mangini, A., Eds. *Organic Sulfur Chemistry*; Elsevier: New York, 1985. (b) Damani, L. A. *Sulfur-containing Drugs and Related Organic Compounds-Chemistry, Biochemistry and Toxicology*; Ellis Harwood: Chichester, 1989. (c) Block, E. *Reactions of organosulfur compounds*; Academic Press: New York, 1978. (d) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; John Wiley & Sons: New York, 1996. (e) Shaumann, E. Synthesis of Thioamides and Thiolactams. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: New York, 1991; Vol. 6, pp 419−434. (f) Duus, F. Thiocarbonyl Compounds. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; (g) Brillion, D. *Sulfur Rep*. **1992**, *1*, 297. (h) Polshettiwar, V.; Kaushik, M. P. *J. Sulfur Chem.* **2006**, *27*, 353−386.

(2) (a) Jesberger, M.; Davis, T. P.; Barner, L. *Synthesis* **2003**, 1929−1958. (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, 41, 5061−5087. (c) Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229−238. (d) Kaleta, Z.; Makowski, B.T.; Soos, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625−1628.

(3) (a) Hurd, R. N.; DeLaMater, G. *Chem. Rev.* **1961**, *61*, 45. (b) Wakabayashi, T.; Kato, Y.; Watanabe, K. *Jpn. Kokai Tokkyo Koho* **1978**, 78, 56, 662; *Chem. Abstr*. **1979**, *90*, 22818h. (c) Brillon, D. *Sulfur Rep.* **1992**, *12*, 297−338. (d) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461−6473.

(4) (a) Asquith, R. S.; Hammick, D. Ll.; Williams, P. L. *J. Chem. Soc.* 1948, 1181 (b) Fournier, C.; Paquer, D.; Vazeux, M. *Bull. Soc. Chim. Fr.* ***1975****, 2753.* (c) Sen, D. C. *J. Indian Chem. Soc.* **1935**, 12, 647; **1937**, *14*, 214.

(5) Zong, Z.-M.; Peng, Y.-L.; Liu, Z.-G.; Zhou, S.-L.; Wu, L.; Wang, X.-H.; Wei, X.-Y.; Lee, C. W. *Korean J. Chem. Eng.* **2003**, *20*(2), 235−238.

(6) (a) Oae, S.; Nakanishi, A.; Tsujimoto, N. *Chem. Ind*. **1972**, 575. (b) Pedersen, B. S.; Lawesson, S. O.; *Bull. Soc. Chim. Belg.* **1977**, *86*, 693.

(7) Ishii, Y.; Hirabayashi, T.; Imaeda, H.; Ito, Jpn, K. Patent 40441, 1974; *Chem. Abstr*. **1975**, *82*, 156074f.

(8) Bodine, J. J.; Kaloustian, M. K. *Synth. Commun.* **1982**, *12*, 787.

(9) Smith, D. C.; Lee, S. W.; Fuchs, P. L. *J. Org. Chem*. **1994**, *59*, 348−354.

(10) (a) Pedersen, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223−228. (b) Yang C. O-; Rotstein, D. M.; Labadie, S.S.; Walker K. A. M. *Synlett*, 1995, 655.

(11) Charette, A. B.; Grenon, M. *J. Org. Chem*. **2003**, *68*, 5792−5794.

(12) (a) Dean, F. M.; Goodchild, J.; Hill, A. W. *J. Chem. Soc*. (c), 1969, 2192−2195. (b) Dean, F. M.; Goodchild, J.; Hill, A. W.; Moore, S.; Zahman, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1335.

(13) Degl'Innocenti, A.; Capperucci A.; Castagnoli G.; Malesci. I. *Synlett* **1965** (**2005**).

(14) (a) Perrenaard, J.; Pedersen, B. S.; Lawesson, S.-O. *Acta Chem. Scand.* B31.460 (1977) (b) Pipko, S. E.; Simurova, N. V.; Shvadchak, V. V.; Bezgubenko, L. V.; Luk'yaneko, S. N. *Russ. J. Gen. Chem.* **2006**, *76*, 1019−1021.

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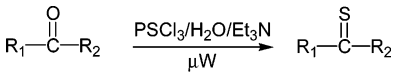
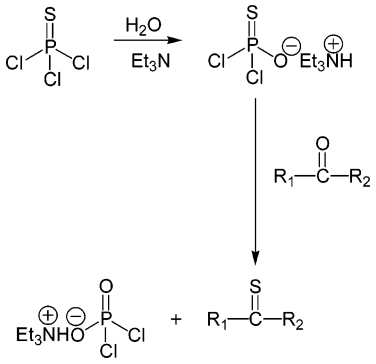
SCHEME 1. Thionation of Amides, Lactams, Ketones, and Xanthones



SCHEME 2. Possible Mechanism for Thionation



Next, we turned our attention on utilization of promoters to accelerate the reaction. Both acidic promoters[9] such as $POCl_3$, $SOCl_2$, oxalyl chloride, etc. and basic promoters[15] such as pyridine, Et_3N, and $NaHCO_3$ have been reported to assist in this transformation. After extensive examination of various promoters, organic basic promoters, i.e., triethyl amine and pyridine, were found useful in circumventing the problem. Non-nucleophilic organic bases such as diisopropyl ethyl amine were also investigated as an alternative promoter and were found to be effective. Acidic promoters and inorganic bases did not yield the desired result. All three bases, triethyl amine, pyridine, and diisopropyl ethyl amine, were found of equal utility, and any one of them can be used depending upon the convenience and availability. Keeping in view the less malodorous nature and common availability we utilized triethyl amine in most of our reactions. Further, we noted that addition of base was helpful only after the water had been added to the reaction mixture. Another important observation was that the amount of water required for the reaction is also critical. While optimizing the reaction with the reagent combination $PSCl_3/H_2O/Et_3N$, we noted that no conversion took place when an excess of water was used. On further inspection, the optimum quantity was found to be 1−1.2 mol of water/mol of $PSCl_3$. A possible explanation for this may be that in the first step chlorothiophosphoric acid was generated by the hydrolysis of $PSCl_3$ (Scheme 2). This was further assisted by the basic promoters. The active species then reacted with carbonyl compound to give the thionated product. To confirm this, a mixture of amide, water, and $PSCl_3$ in dry toluene was refluxed followed by addition of Et_3N; the contents were refluxed further whereupon complete thionation of the amide was observed. The inability of the reagent to thionate in the presence of excess of water may be explained by the fact that with excess of water more chloride groups of the reagent were replaced by hydroxyl groups. The greater electron-withdrawing effect of oxygen may render sulfur of the reagent insufficiently reactive toward the nucleophilic attack on carbonyl carbon. With the reagent combination $PSCl_3/H_2O/Et_3N$ in toluene complete thionation of *N*,*N*-diethyl-*m*-toluamide was achieved in 5 h. Other solvents found useful are benzene, dichloromethane, and chloroform all at reflux but less effective than toluene.

In recent years microwave-assisted synthesis has gained a lot of importance. A number of publications have demonstrated[16] that application of microwave energy offers several advantages including enhanced reaction rates. Furthermore, an additional advantage with $PSCl_3$ was that, since most of the substrates were either completely or partially soluble in it, there existed a scope for solventless synthesis. Accordingly, in an attempt to look for alternating reaction conditions/procedures efforts were directed toward a prospective microwave-assisted reaction under solventless condition.

In a typical microwave-assisted procedure water (1.0 mmol) was added to $PSCl_3$ (1.0 mmol), and the contents were microwaved for a short period. To this 1 mmol of carbonyl compound was added followed by 1.5 mmol of triethyl amine, and the contents were microwaved further. Reaction occurred immediately and went to completion within minutes. Having established optimum conditions for conversion of *N*,*N*-diethyl-*m*-toluamide to the corresponding thioamide (Table 1, entry 1), we explored the scope and limitation of this new thionation procedure.

A variety of compounds were investigated including substrates which posed problems with the reported thionating agents. The results of formation of various thionated products are summarized in Table 1. Secondary and tertiary amides underwent efficient thionation. In case of primary amides, nitriles were also formed as side products (Table 1, entries 5, 6) under the reaction conditions, and no attempts were made to optimize the reaction further. This reagent was particularly found useful for thionation of sparingly soluble amides such as nicotinamide, which is difficult to thionate due to its insolubility in commonly used solvents for thionation. Smooth thionation with $PSCl_3/H_2O/Et_3N$ took place, and thionicotinamide was isolated easily in good yield.

Encouraged by the facile thionation of amides, the utility of this method for thionation of lactams with different systems was studied. The method was found applicable for the synthesis of thiolactams also. Reaction with lactams occurred successfully under mild condition (Table 1, entries 7, 8, 9). 1-Vinyl-2-pyrrolidinone offered a noteworthy example. This compound was investigated as it has been reported to be a difficult substrate for thionation due to its highly sensitive nature.[9] Our initial attempts to thionate this compound following the protocol used for other amides and lactams, were not successful. The reaction mixture decomposed when the reaction was carried out at room temperature with $PSCl_3/H_2O/Et_3N$ in 1:1:1.5 mol ratio. However, satisfactory results were obtained with a slightly modified procedure.[17]

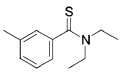
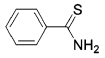
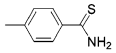
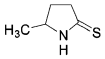
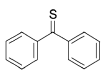
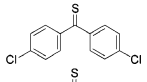
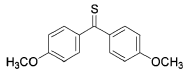
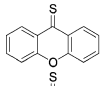
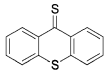
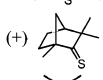
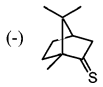
To further illustrate the generality of this reagent, different ketones and xanthones were investigated. It was inspiring to find that thio analogues of these compounds were efficiently synthesized by this method although a slightly higher amount

(15) (a) Barton, D. H. R. U. S. Patent 4011316, 1977; *Chem Abstr.* **1977**, *87*, 53490n. (b) Machiguchi, T.; Hoshino, M.; Kitahara, Y. *Jpn. Kokai Tokkyo Koho* 77,23,066, 1977; *Chem. Abstr.* **1977**, *82*, 102153r.

(16) (a) Loupy, A., Ed. *Microwave in Organic Synthesis*; Wiley-VCH: Weinheim, 2002. (b) Varma, R. S.; Kumar, D. *Org. Lett.* **1999**, 1, 697−700.

(17) Thionation procedure for 1-vinyl-2-pyrrolidinone: equimolar amount of $PSCl_3$ and water (0.005 mol) was taken in a test tube. To this triethyl amine was added dropwise at 0−5 °C with constant stirring till the contents were basic, this is followed by slow addition of 0.005 mol 1-vinyl-2-pyrrolidinone. Reaction mixture is then microwaved at 180 W for 3−4 min. Work up was carried by following the reaction workup procedure, method A.

TABLE 1. Thionation[f] of Carbonyl Compounds Using $PSCl_3/H_2O/Et_3N$

Entry	Product	Condition [SF, μW]	Time[a]	Temp. (°C)	Coversion[b] [Yield][c](%)	Workup method
1.		180W, TEA 180W, DIPEA 180W, Py	5 min. 5 min. 6 min.	60-70	99[89] 97[88] 99[89]	A
2.		180W, TEA 180W, DIPEA 180W, Py	1 min. 1 min. 1 min.	70-75	>99[92] 99[91] 98[91]	A
3.		180W, TEA	4 min.	70-75	99	-
4.		180W, TEA	4 min.	65-75	98[80]	A
5.		180W, TEA	6 min.	65-75	69[d][43]	A
6.		180W, TEA	5 min.	70-75	63[d]	-
7.		180W, TEA 180W, DIPEA 180W, Py	3 min. 3 min. 3 min.	70-80	99[84] 98[84] 97[82]	A
8.		180W, TEA	3 min.	70-80	96	-
9.		180W, TEA	5 min.	60-70	99	-
10.		180W, TEA	4 min.	70-80	87[42]	A[e]
11.		180W, TEA 180W, DIPEA 180W, Py	6 min. 7 min. 6 min.	80-90	94[78] 94[78] 93[76]	B
12.		180W, TEA 180W, DIPEA 180W, Py	3 min. 4min. 2min.	90-100	97[86] 94[85] 98[86]	A
13.		180W, TEA	5 min.	100-110	98	-
14.		180W, TEA	3 min.	90-95	98[92]	B
15.		180W, TEA	3 min.	70-80	99	-
16.		180W, TEA	4 min.	90-100	98	-
17.		180W, TEA	4 min.	65-75	98[89]	B
18.		300W, TEA	3 min.	100-110	98[92]	B
19.		180W, TEA	2 min.	70-80	99[90]	B
20.		180W, TEA 180W, Py	1.5 min. 1.5 min.	90-100	79[48] 75[46]	A
21.		180W, TEA	2 min.	90-100	81[52]	A

[a] Microwave exposure was intermittent (30 s/1 min duration) with 15 s break. [b] GC and HPLC conversion and identification by their MS data. [c] Isolated yield. [d] Nitrile was formed as a side product. [e] Reference 17. [f] SF, solvent-free; TEA, triethyl amine; DIPEA, diisopropyl ethyl amine; Py, pyridine. Mole ratio of $PSCl_3/H_2O$/base used for entries 1−9, 20−21 is 1:1:1.5, entries 11−16 is 2: 2:3, and entries 17−19 is 2.5:2.5:6 for 1 mol of carbonyl compound.

of $PSCl_3$ was used (Table 1, entries 12−19). The thionation potential of this system was also investigated for the preparation of sterically hindered optically active thioketones such as (+)-1,3,3-trimethyl-bicyclo[2.2.1]heptane-2-thione (**20**) and (-)-1, 7,

7-trimethyl-bicyclo[2.2.1]heptane-2-thione (**21**), and these compounds were obtained easily although the yields obtained were less. Since these compounds are highly volatile in nature and the reactions were carried out in open vessels, there was a loss of both reactant and product during the reaction.

Entries 13−16 indicate that this protocol has excellent functional group compatibility, and in this context thionation of isophorone, an α,β-unsaturated ketone, should be noted. This compound was readily converted to its thio analogue (entry 16). Similarly xanthione, thioxanthione, and thioacridone were also obtained conveniently in excellent yield.

In summary, a new protocol for rapid and efficient thionation of carbonyl compounds has been disclosed. This method has several advantages over the reported methods: extreme precaution in carrying out the reaction under completely anhydrous condition is not required, workup is very simple, and hazards of using solvents during reaction are minimized. Additionally, fast reaction, low consumption of solvent, mild reaction conditions, good to excellent yield, clean reaction, and readily obtainable, simple reagents make this method an attractive and useful alternative to the existing methods for thionation. The advantages associated with this method may lead to its wider application.

Experimental Section

Representative Experimental Procedure. To 0.51 mL (5 mmol) of $PSCl_3$ was added 0.09 mL (5 mmol) of water, and the mixture was microwaved (Samsung CE2977N operating at 2450 MHz) for 30 s. To this was added 0.95 mL (5 mmol) of *N*,*N*-diethyl-*m*-toluamide followed by dropwise addition of 0.76 mL (7.5 mmol) of triethyl amine. The temperature of the reaction mixture was maintained at 60−70 °C. Contents were mixed and microwaved further at 180 W for 4−5 min. Instantaneous reaction took place with simultaneous formation of thionated product. Microwave exposures were intermittent with 15 s break since it was necessary to mix the reaction mixture. Mixing was done gently with the help of glass thermometer, which also indicated the reaction temperature. The reaction was monitored by GC and TLC. On completion of the reaction the pure compound was obtained following the workup procedure, method A.

Yield 0.92 gm (89%); light yellowish crystals: mp 80−81 °C; ^{1}H NMR ($CDCl_3$/TMS-400 MHz): δ 1.14 (t, J = 7.2, 3H), 1.39 (t, J = 7.1, 3H), 2.34 (s, 3H), 3.44 (q, J = 7.1 Hz, 2H), 4.11 (q, 7.1 Hz, 2H), 7.11 (m, 4H); ^{13}C NMR ($CDCl_3$/TMS - 100.6 MHz): δ 200.55, 143.90, 138.27, 128.87, 128.35, 125.68, 121.96, 47.90, 46.11, 21.53, 13.98, 11.39; EIMS *m*/*z* 207 (M^+), 205, 192, 146, 135, 118, 91, 65, 51; Anal. Calcd for $C_{12}H_{17}NS$. C, 69.51; H, 8.26; N, 6.76; S, 15.47. Found: C, 69.67; H, 8.15; N, 6.84, S, 15.32.

Reaction Workup Procedures. Method A. Contents were adsorbed on silica, loaded on a column of silica gel, and eluted with the solvent of appropriate strength. Solvent removal afforded pure compound.

Method B. Contents were cooled, neutralized with Et_3N, and precipitated by addition of cold water. The insoluble thionated product obtained was filtered under vacuum and dried. Further purification, if required, can be achieved through recrystallization from the appropriate solvent. In the case of thionicotinamide, additional recovery was made by extracting the aqueous layer with ethyl acetate.

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Supporting Information Available: Copies of mass spectra for compounds **1**−**21**; ^{1}H NMR spectra of **1**, **2**, **4**, **5**, **7**, **10**−**12**, **14**, **17**−**21**; ^{13}C NMR spectra of **1**, **7**, **10**−**12**, **14**, **17**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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