Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 2315–2317
Tetrahedron Letters
ELSEVIER

# Alumina encapsulated phosphorus pentasulfide ($P_4S_{10}/Al_2O_3$) mediated efficient thionation of long chain amides

Vivek Polshettiwar*,† and M. P. Kaushik*

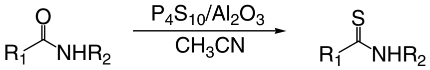
*Process Technology Development Division, Defence R&D Establishment, Jhansi Road, Gwalior 474 002, MP, India*

Received 5 December 2005; revised 1 February 2006; accepted 3 February 2006
Available online 20 February 2006

**Abstract**—Alumina encapsulated phosphorus pentasulfide ($P_4S_{10}/Al_2O_3$) was found to be an efficient solid supported reagent for the thionation of long chain amides. This method is advantageous in terms of use of inexpensive reagent, simple reaction processing, and clean product in good to excellent yield.

The amides and their thio analogues are an important constituent of many biologically active compounds and reactions of thioamides are important to the future development in polypeptides and protein chemistry.[1] The thioamide functional group is a relatively conservative replacement for the amide, differing in its electronic properties, hydrogen-bonding capacity, and photoreactivity.[1] A variety of reagents such as $P_2S_5$,[2] $R_3OBF_4$/NaSH,[3] $R_2PSX$,[4] $(Et_2Al)_2S$,[5] and $P_2S_5/Na_2CO_3$[6] have been utilized for thionation of carbonyl compounds. In recent years, Lawesson's reagent[7] (LR) and a combination of $P_4S_{10}$/HMDO (hexamethyl disiloxane)[8] have replaced $P_4S_{10}$ as the reagent of choice for many thionations. However, besides its high cost, LR results in the formation of by-products derived from the reagent itself, which cannot be easily removed by an extractive procedure and require chromatography, making the method more expensive. The combination of $P_4S_{10}$/HMDO is good in terms of reactivity but the use of HMDO makes the method expensive and the by-products formed need to be removed by column chromatography. There is still scope for improvement, as the existing methods require prolonged reaction times, aqueous work-up, high temperatures, or inconvenient reaction conditions for their execution.

Solid supported reagents have also been used in organic chemistry for many years.[9] A solid supported thionating reagent was therefore a particularly desirable target. A reagent that is anchored to a solid support may easily be removed from any solution by simple filtration. It is thus the facile purification method, which makes supported technology ideal, not only for single reaction synthesis, but also for robotic manipulation in high throughput multi-step syntheses.[10] The greatest advantages of reaction mediated by solid-supported reagents are that they can be optimized and scaled-up readily. Their flexibility in allowing both linear and convergent strategies to be selected is of considerable advantage to synthetic chemists building complex molecules.[11] Furthermore, handling supported-bound analogues of toxic, explosive, or malodorous reagents is often found to be safer and more convenient than handling the solution phase equivalents. Our aim in undertaking this work was to overcome the limitations and drawbacks of the reported methods. In our earlier letter,[12] we showed the efficiency of $P_4S_{10}/Al_2O_3$ for the thionation of ketones to thioketones. We were interested to synthesize and study thio-analogues of biologically active long chain amides[13] and in continuation of our work on solid supported reagents,[14] we decided to explore the utility of the reagent $P_4S_{10}/Al_2O_3$ for the synthesis of these long chain thioamides and herein, we report a simple, efficient, and economic method for the effective transformation of amides to thioamides using $P_4S_{10}/Al_2O_3$ in acetonitrile (Scheme 1).



Scheme 1.

---

*Keywords*: Thionation; Thioamide; Phosphorus pentasulfide; Alumina.

* Corresponding authors. E-mail addresses: vivekpol@yahoo.com; mpkaushik@rediffmail.com

† Present address: UMR CNRS-5076, Ecole Nationale Superieure de Chimie de Montpellier Cedex 05, France.

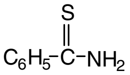
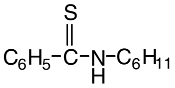
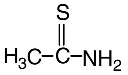
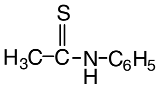
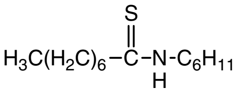
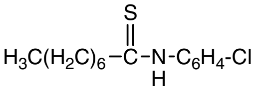
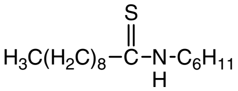
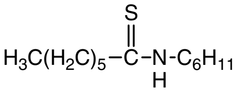
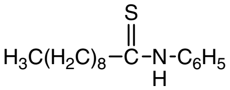
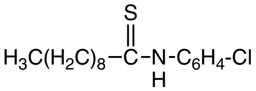
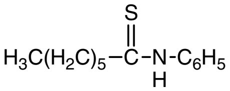
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.02.021

The reaction was carried out by refluxing a mixture of the amide and $P_4S_{10}/Al_2O_3$ in acetonitrile as a solvent. A series of experiments established that 0.5 mol of $P_4S_{10}/Al_2O_3$ per mole of amide were required to obtain maximum yield of the thioamide. Using standard conditions, the thionation of a series of amides was examined. Amides reacted smoothly with $P_4S_{10}/Al_2O_3$ under these reaction conditions to produce the corresponding thioamides in good to excellent yields. The results are summarized in Table 1.

This method has allowed us to transform amides into thioamides in reduced reaction time with quantitative yields and with high purity. The catalytic role of $Al_2O_3$ was also studied by carrying out the reaction in the absence of $Al_2O_3$ using $P_4S_{10}$ alone. It was found that the yield of the thioamides using the combination of $P_4S_{10}/Al_2O_3$ were greater than those with $P_4S_{10}$ alone (Table 1). Thionation by $P_4S_{10}$ alone produce highly condensed polythiophosphates. These species might be expected to be potent electrophiles, in analogy with $P_4O_{10}$, and therefore capable of promoting undesirable side reactions of both the carbonyl and thiocarbonyl derivatives. In fact, as the reaction with $P_4S_{10}$ proceeds, the general reaction environment becomes increasing electrophilic with each successive replacement of sulfur on phosphorus by oxygen. However, the $Al_2O_3$ in the reaction binds with these highly electrophilic species and scavenges them thereby raising the yield of the thionation product. Thus, the beneficial effect of $Al_2O_3$ is basically due to the scavenging of yield-lowering intermediates formed during the course of the reaction.

Although the yield and reaction times are comparable with LR, the $P_4S_{10}/Al_2O_3$ combination still offers advantages over LR. LR requires 2 mol of the reagent per mole of amides and the high equivalent weight of Lawesson's reagent means that the substrate comprises only a small percentage by weight of the crude reaction mixture, whereas $P_4S_{10}/Al_2O_3$ requires only 0.5 mol/

**Table 1.** Synthesis of thioamides using $P_4S_{10}/Al_2O_3$

| S. no. | Thioamide | R. time (h) | $P_4S_{10}/Al_2O_3$[15] Yield (%) | $P_4S_{10}$[16] Yield (%) |
|---|---|---|---|---|
| 1 |  $C_6H_5-\overset{\overset{S}{\|}}{C}-NH_2$ | 6 | 81 | 76 |
| 2 |  $C_6H_5-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_{11}$ | 5 | 85 | 62 |
| 3 |  $H_3C-\overset{\overset{S}{\|}}{C}-NH_2$ | 6 | 78 | 70 |
| 4 |  $H_3C-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_5$ | 6 | 79 | 62 |
| 5 |  $H_3C(H_2C)_6-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_{11}$ | 9 | 88 | 70 |
| 6 |  $H_3C(H_2C)_6-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_4-Cl$ | 10 | 80 | 56 |
| 7 |  $H_3C(H_2C)_8-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_{11}$ | 10 | 82 | 61 |
| 8 |  $H_3C(H_2C)_5-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_{11}$ | 11 | 79 | 62 |
| 9 |  $H_3C(H_2C)_8-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_5$ | 11 | 79 | 60 |
| 10 |  $H_3C(H_2C)_8-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_4-Cl$ | 11 | 81 | 60 |
| 11 |  $H_3C(H_2C)_5-\overset{\overset{S}{\|}}{C}-\underset{H}{N}-C_6H_5$ | 10 | 84 | 61 |

mol of amide making the method less expensive. The combination $P_4S_{10}/Al_2O_3$ also provides cleaner products in comparison to LR, which gives by-products, that are difficult to remove. Also this method is economic and practical as compared to the reported methods. The use of a solid support for $P_4S_{10}/Al_2O_3$ is advantageous over LR and $P_4S_{10}$/HMDO because this supported reagent is removed easily by filtration, avoiding an aqueous work-up and decreasing waste solvent.

In summary, we have developed an efficient, high yielding, and simple method for thionation of amides using $P_4S_{10}/Al_2O_3$, which offers the following advantages: (i) simple reaction processing and clean product, (ii) efficiency and economy gain through the use of readily accessible $P_4S_{10}/Al_2O_3$ as thionating agent, and (iii) good to excellent yield.

## Acknowledgments

We thank the referee for critical comments/suggestions, which helped us to modify the presentation and the content of this letter. Thanks are also due to DRDO, New Delhi, for financial support to V.P. during his Ph.D.

## References and notes

1. (a) Beckwith, A. L. J. Synthesis of amides. In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience, John Wiley and Sons: New York, London, 1970; p 96; (b) Hurd, R. N.; DeLamater, G. *Chem. Rev.* **1960**, *61*, 45.
2. (a) Brillon, D. *Sulfur Rep.* **1992**, *12*, 297–338; (b) Hofmann, A. W.; Gabriel, S. *Ber.* **1892**, *25*, 1578.
3. Bodine, J. J.; Kaloustian, M. K. *Synth. Commun.* **1982**, *12*, 787.
4. Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 693.
5. Ishi, Y.; Hirabayashi, T.; Imaeda, H.; Ito, K. *Jpn. Patent* **1974**, *40*, 441.
6. Shalaby, M. A.; Grote, C. W.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 9045.
7. (a) Pedersen, B. S.; Lawesson, S. O. *Tetrahedron* **1979**, *35*, 2433–2437; (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061–5087.
8. (a) Curphey, T. J. *Tetrahedron Lett.* **2000**, *41*, 9963–9966; (b) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461–6473; (c) Curphey, T. J. *Tetrahedron Lett.* **2002**, *43*, 371–373.
9. (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815; (b) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
10. (a) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A. G.; Hall, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239; (b) Gayo, L. M. *Biotechnol. Bioeng.* **1998**, *61*, 95.
11. Baxendale, I. R.; Ley, S. V. *Bioorg. Med. Chem. Lett.* **2000**, 1.
12. Polshettiwar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2004**, *45*, 6255.
13. Gannett, P. M.; Nagel, D. L.; Reilly, P. J.; Lawson, T.; Sharpe, J.; Toth, B. *J. Org. Chem.* **1988**, *53*, 1064–1071.
14. (a) Polshettiwar, V.; Kaushik, M. P. *Catal. Commun.* **2004**, *5*, 515; (b) Polshettiwar, V.; Kaushik, M. P. *Catal. Commun.* **2005**, *6*, 191; (c) Polshettiwar, V.; Nivsarkar, M.; Acharya, J.; Kaushik, M. P. *Tetrahedron Lett.* **2003**, *44*, 887; (d) Polshettiwar, V.; Nivsarkar, M.; Pardashani, D.; Kaushik, M. P. *J. Chem. Res.* **2004**, 474.
15. Experimental: The reagent was prepared as per our reported method.[12] The thionation of amide was carried out by refluxing 1 mol equiv of amide and 0.5 mol equiv of $P_4S_{10}/Al_2O_3$ with respect to $P_4S_{10}$ in acetonitrile. The reaction mixture was refluxed for the time given in Table 1 and monitored by GC. After completion of reaction the supported reagent was removed by filtration and solvent was evaporated. The resultant liquid is extracted with ether to yield thioamide, which was characterized by IR, GC–MS, and NMR analyses.
16. The thionation of amide was carried out by refluxing 1 mol equiv of amide and 0.5 mol equiv of $P_4S_{10}$ without alumina as per the above procedure. The reaction mixture was refluxed for the same time as that required for $P_4S_{10}/Al_2O_3$ method and yield was determined by GC and GC–MS.