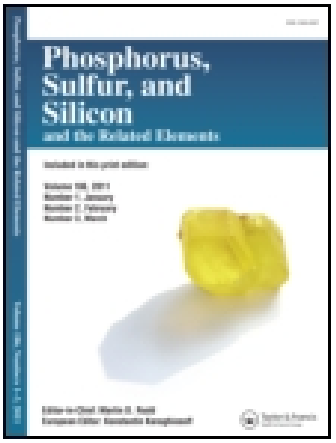


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Efficient α-Thiocyanation of Ketones Using Pyridinium Hydrobromide Perbromide

Liqiang Wu [a] & Xiaojuan Yang [b]
[a] School of Pharmacy , Xinxiang Medical University , Xinxiang , Henan , China
[b] College of Chemistry and Chemical Engineering , Xinxiang University , Xinxiang , Henan , China
Published online: 05 Apr 2012.

To cite this article: Liqiang Wu & Xiaojuan Yang (2012) Efficient α-Thiocyanation of Ketones Using Pyridinium Hydrobromide Perbromide, Phosphorus, Sulfur, and Silicon and the Related Elements, 187:6, 748-753, DOI: 10.1080/10426507.2011.616561

To link to this article: http://dx.doi.org/10.1080/10426507.2011.616561

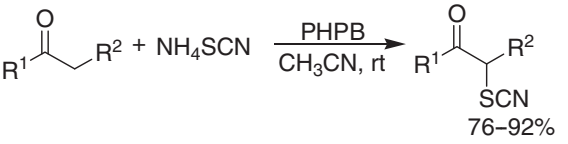
Phosphorus, Sulfur, and Silicon, 187:748–753, 2012

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2011.616561

EFFICIENT α-THIOCYANATION OF KETONES USING PYRIDINIUM HYDROBROMIDE PERBROMIDE

Liqiang Wu[1] and Xiaojuan Yang[2]
[1]*School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan, China*
[2]*College of Chemistry and Chemical Engineering, Xinxiang University, Xinxiang, Henan, China*

GRAPHICAL ABSTRACT



Abstract *The direct α-thiocyanation of ketones with ammonium thiocyanate has been achieved using pyridinium hydrobromide perbromide under mild and neutral conditions to produce α-ketothiocyanates in excellent yields and with high selectivity.*

Keywords Thiocyanation; ketones; ammonium thiocyanate; pyridinium hydrobromide perbromide; synthesis

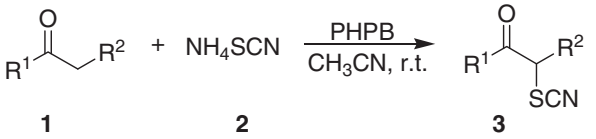
INTRODUCTION

Thiocyanate is a versatile synthon which can be readily transformed into other functional groups such as sulfide,[1] aryl nitrile,[2] thiocarbamate,[3] and thionitrile.[4] In particular, α-ketothiocyanates are useful intermediates in the synthesis of sulfur-containing heterocycles, such as thiazoles.[5] Some of these thiazoles exhibit herbicidal and other important biological activities.[6] Thus, the direct thiocyanation of ketones is of prime importance. The use of the bromodimethylsulfonium bromide/ammonium thiocyanate,[7] oxone/ammonium thiocyanate,[8] heteropoly acid/ammonium thiocyanate,[9] dichloroiodobenzene/lead(II) thiocyanate,[10] potassium peroxydisulphate/copper(II) complex,[11] I_2/ammonium thiocyanate,[12] $FeCl_3$/ammonium thiocyanate,[13] and NBS/ammonium thiocyanate[14] reagent systems have been reported for the direct thiocyanation of ketones. However, most of these reported methods involve the use of a large excess of strong oxidizing agents and toxic metal thiocyanates, resulting in low conversions due to the formation of complex mixtures of products, which limit their practical utility in organic synthesis. Since organosulfur compounds have

Received 31 May 2011; accepted 18 August 2011.
We are pleased to acknowledge the financial support from Xinxiang Medical University.
Address correspondence to Liqiang Wu, School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan 453003, China. E-mail: wliq1974@sohu.com

become increasingly useful and important in the field of drugs and pharmaceuticals, the development of simple, convenient, and efficient approaches for their synthesis is desirable.

Pyridinium hydrobromide perbromide (PHPB) is a solid complex of pyridine with bromine which is used as a source of bromine. It is more convenient to use definite small amounts of active bromine with this stable reagent than with bromine itself. It had been employed for bromination of ketones, acetals, alkenes, activated phenols, anilines and heterocycles as well as oxidation/dehydrogenation reagent.[15] However, the literature describing α-thiocyanation of ketones using PHBP is not available. In connection with our work on hydrobromide perbromide and bromide perbromide reagents,[16] we report herein the efficient α-thiocyanation of ketones using this reagent (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

Since the nature of solvent influences the rate of reaction, α-thiocyanation of acetophenone as a model substrate was performed in various solvents at room temperature. According to the data presented in Table 1, CH_3CN has been chosen as the best solvent for this purpose.

The next step was the optimization of the NH_4SCN:PHBP molar ratio for the thiocyanation reaction in CH_3CN. The results presented in Table 2 show that the optimized molar ratio of NH_4SCN:PHBP is 2:1. These data also show that an increase in the amount of NH_4SCN affected the yield or the rate of the reaction.

Encouraged by this result, we turned our attention to various acetophenones. Interestingly, several substituted acetophenones such as 4-chloro-, 4-nitro-, 4-methoxy-, 4-methyl-, 2-chloro-, 3-bromo-, and 2,4-dichloroacetophenone and 1-phenylbutan-1-one reacted rapidly with ammonium thiocyanate to afford the corresponding 2-thiocyanatoethanone

Table 1 Solvent optimization for the synthesis of 1-phenyl-2-thiocyanatoethanone[a]

Solvent	Time (h)	Yield (%)[b]
$CHCl_3$	1	87
CH_2Cl_2	1	90
EtOAc	1	88
n-Hexane	3	42
THF	2	85
CH_3CN	1	91
—	5	29

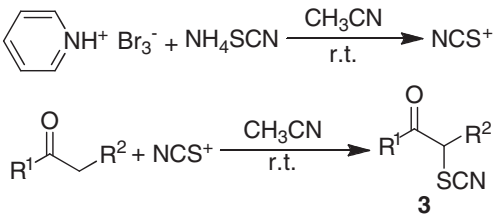
[a]Reaction conditions: acetophenone (1 mmol), NH_4SCN (2 mmol), and PHBP (1 mmol), r.t.
[b]Isolated yield.

Table 2 Optimization of NH_4SCN:PHBP molar ratio for the α-thiocyanation of acetophenone

Molar ratio NH_4SCN:PHBP	Time (h)	Yield (%)
1:2	3	23
1:1	2	53
1.2:1	2	65
1.5:1	2	79
2:1	1	91
2.1:1	1	90
2.2:1	1	90

derivatives (Table 3, entries **b–i**). In addition, various cyclic ketones, such as cyclohexanone, cyclopentanone, 1-tetralone, and indanone (Table 3, entries **j–m**), also participated effectively in this reaction. It is noteworthy that aliphatic ketones also gave the corresponding α-thiocyanated products in 76–87% yield (Table 3, entries **n–o**). In all cases, the reactions proceeded rapidly at room temperature with high regioselectivity. No bromination of the ketones was observed under the reaction conditions. All the products were characterized by ^{1}H NMR, IR, elemental analysis as well as by comparison with authentic samples. The IR spectra showed the characteristic peak of –SCN at 2122–2168 cm^{-1}.

Mechanistically, the reaction may proceed *via* the electrophilic substitution of acetophenone by NCS^+ intermediately generated in situ from PHPB and ammonium thiocyanate (Scheme 2).



Scheme 2

To illustrate the efficiency of the proposed method, Table 4 compares some of our results with some of those reported for relevant reagents in the literature, which demonstrates its significant superiority. Compared with some of the reported methods in Table 4, the present method has a better yield and a higher selectivity.

EXPERIMENTAL

NMR spectra were obtained with a Bruker AV-400 spectrometer at room temperature using TMS as internal standard. Coupling constants (J) are given in Hertz. Elemental analyses were performed with a Vario-III elemental analyzer. Melting points were determined with a XT-4 binocular microscope and are uncorrected. PHPB was prepared according to Englert and McElvain (1929).[17] Commercially available reagents were used throughout without further purification unless otherwise stated.

Table 3 α-Thiocyanation of ketones promoted by PHBP[a]

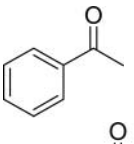
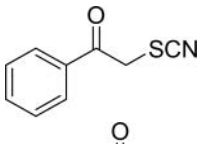
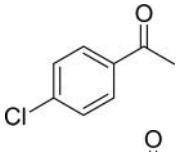
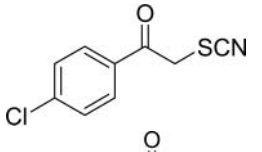
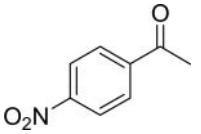
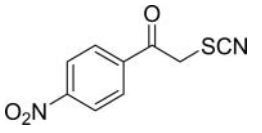
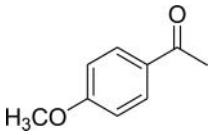
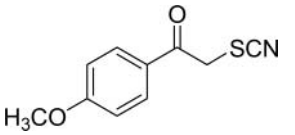
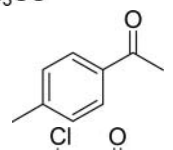
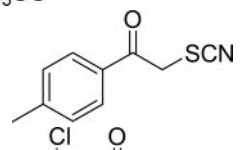
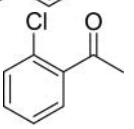
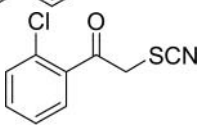
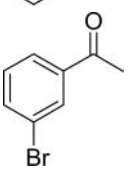
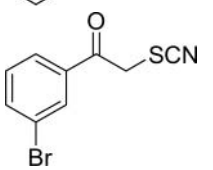
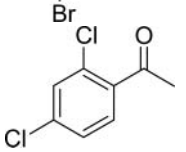
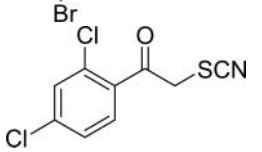
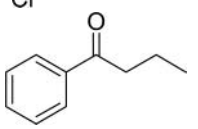
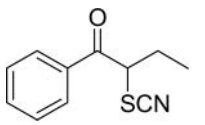
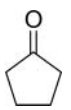
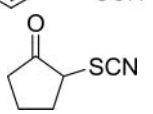
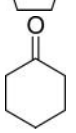
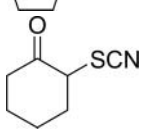
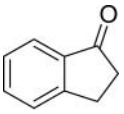
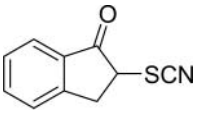
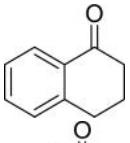
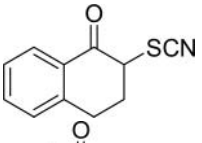
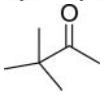
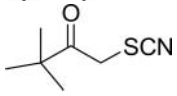
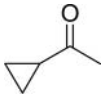
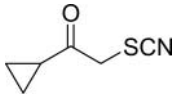
Entry	Ketone	Product	Time (h)	Yield (%)[b]	Reference[c]
a			1	91	Bhalerao et al. (2010)[7]
b			1.5	89	Bhalerao et al. (2010)[7]
c			2	92	Bhalerao et al. (2010)[7]
d			2	83	Bhalerao et al. (2010)[7]
e			2	83	Bhalerao et al. (2010)[7]
f			1.5	87	Chaskar et al. (2010)[9]
g			2	84	Chaskar et al. (2010)[9]
h			2	87	Bhalerao et al. (2010)[7]
i			2.5	80	Kumar et al. (2008)[8]
j			0.5	90	Bhalerao et al. (2010)[7]
k			0.5	92	Bhalerao et al. (2010)[7]

Table 3 α-Thiocyanation of ketones promoted by PHBP[a] *(Continued)*

Entry	Ketone	Product	Time (h)	Yield (%)[b]	Reference[c]
l			1.5	93	Chaskar et al. (2010)[9]
m			1.5	90	Chaskar et al. (2010)[9]
n			2	76	Kumar et al. (2008)[8]
o			2	87	Kumar et al. (2008)[8]

[a]Reaction conditions: ketone (1.0 mmol), NH_4SCN (2.0 mmol), and PHBP (1.0 mmol), r.t., CH_3CN.
[b]Isolated yield.
[c]All of the isolated products are known compounds and their spectra and physical data have been reported in the literature.[7–9]

α-Thiocyanation of Ketones: General Procedure

To a stirred solution of ammonium thiocyanate (2 mmol) and PHPB (1 mmol) in acetonitrile (10 mL) was added the respective ketone (1 mmol) at 0 °C and the resulting mixture was stirred at room temperature for the appropriate time (Table 3). After complete conversion, as indicated by TLC, the reaction mixture was quenched with water. The reaction mixture was successively extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The resulting product was purified by column chromatography on silica gel (200–300 mesh, ethyl acetate:hexane = 1:20) to afford pure **3**.

- 1-Phenyl-2-thiocyanatoethanone (**3a**)
  IR (KBr): $\nu = 2946, 2150$ (–SCN), 1672, 1591, 1420, 996, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.02–7.80$ (m, 2H), 7.66–7.25 (m, 3H), 4.78 (s, 2H); Anal. Calcd. for C_9H_7NOS: C 60.99, H 3.98, N 7.90, S 18.09%; Found: C 70.06, H 3.92, N 7.95, S 18.00%.

Table 4 PHBP-promoted α-thiocyanation of acetophenone compared with methods reported in the literature

Catalyst and conditions	Solvent	Time (h)	Yield (%)	Reference
$FeCl_3$ (100 mol%), r.t.	CH_2Cl_2	0.5	75	Yadav et al. (2008)[13]
Oxone (100 mol%), r.t.	MeOH	6	86	Kumar et al. (2008)[8]
Heteropolyacid (25 mol%), r.t.	$ClCH_2CH_2Cl$	0.3	86	Chaskar et al. (2010)[9]
NBS (100 mol%), r.t.	CH_3CN	4	85	Reddy et al. (2011)[14]
PHBP (100 mol%), r.t.	CH_3CN	1	91	This work

- 2-Thiocyanatocyclohexanone (**3k**)
  IR (KBr): $v = 2925, 2154$ (–SCN), 1702, 1455, 1129, 546; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 4.35$–4.20 (m, 1H), 2.85–2.38 (m, 3H), 2.20–1.73 (m, 5 H); Anal. Calcd. for C_7H_9NOS: C 54.17, H 5.84, N 9.02 S 20.66%; Found: C 54.11, H 5.92, N 9.12 S 20.60%.

CONCLUSION

In conclusion, we have found a convenient and selective method for α-thiocyanation of ketones using PHBP, a versatile, stable, inexpensive, and commercially available reagent.

REFERENCES

1. (a) Nguyen, T.; Rubinstein, M.; Wakselman, C. *J. Org. Chem.* **1981,** 46, 1938-1940; (b) Grieco, P. A.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978,** 43, 1283-1285.
2. Zhang, Z. H.; Liebeskind, L. S. *Org. Lett.* **2006,** 8, 4331-4333.
3. Riemschneider, R.; Wojahn, F.; Orlick, G. *J. Am. Chem. Soc.* **1951,** 73, 5905-5907.
4. Lee, Y. T.; Choi, S. Y.; Chung, Y. K. *Tetrahedron Lett.* **2007,** 48, 5673-5677.
5. (a) Kodomari, M.; Aoyama, T.; Suzuki, Y. *Tetrahedron Lett.* **2002,** 43, 1717-1720; (b) Aoyama, T.; Murata, S.; Arai, I.; Araki, N.; Takido, T.; Suzuki, Y.; Kodomari, M. *Tetrahedron* **2006,** 62, 3201-3213.
6. LeBlanc, B. W.; Jursic, B. S. *Synth. Commun.* **1998,** 28, 3591-3599.
7. Bhalerao, D. S.; Akamanchi, K. G. *Synth. Commun.* **2010,** 40, 799-807.
8. Kumar, M. A.; Reddy, K. R. K. K.; Reddy, M. V.; Reddy, C. S.; Reddy, C. D. *Synth. Commun.* **2008,** 38, 2089-2095.
9. Chaskar, A. C.; Yadav, A. A.; Langi, B. P.; Murugappan, A.; Shah, C. *Synth. Commun.* **2010,** 40, 2850-2856.
10. Prakash, O.; Kaur, H.; Batra, H.; Rani, N.; Singh, S. P.; Moriarty, R. M. *J. Org. Chem.* **2001,** 66, 2019-2023.
11. Maurya, R. A.; Kumar, A.; Ahamd, P. *Tetrahedron Lett.* **2007,** 48, 1399-1401.
12. Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Krishna, A. D. *Tetrahedron Lett.* **2007,** 48, 5243-5246.
13. Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Chary, D. N. *Synthesis*, **2008**, 1283-1287.
14. Reddy, B. V. S.; Reddy, S. M. S.; Madan, C. *Tetrahedron Lett.* **2011,** 52, 1432-1435.
15. Yang, S.-H. *Synlett* **2009**, 1351-1352.
16. (a) Wu, L.-Q.; Yang, C.-G.; Wu, Y.-F.; Yang, L.-M. *J. Chin. Chem. Soc.* **2009,** 56, 606-608; (b) Wu, L.-Q.; Wang, X.; Ma, W.-W.; Yang, F.-L. *J. Chin. Chem. Soc.* **2010,** 57, 616-621.
17. Englert, S. M. E.; McElvain, S. M. *J. Am. Chem. Soc.* **1929,** 51, 863-866.