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Molecular Iodine Mediated Preparation of Isothiocyanates from Dithiocarbamic Acid Salts

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We have developed a general economical and environmentally benign method for the preparation of isothiocyanates from the corresponding dithiocarbamic acid salts by using cheap and readily available reagent molecular iodine. This is perhaps the most efficient method reported so far for the synthesis of isothiocyanates. The reagent is easily available and nontoxic, and the precipitated sulfur can be removed easily; hence, this method is most suitable for large-scale synthesis.

Introduction

Isothiocyanates constitute an important class of molecules, which are frequently encountered in many natural products and pharmaceutically important compounds.[1] They are used as reagents for Edman peptide sequencing[2] and also serve as chemoselective electrophiles in bioconjugate chemistry, particularly for biological assays of DNA and proteins.[3] Isothiocyanates are key intermediates especially for the preparation of both sulfur- and nitrogen-containing organic heterocycles.[4] The conventional method used for their preparation involves the reaction of thiophosgene with amines.[5] However, the high toxicity of phosgene, its incompatibility with many functional groups, and the difficulties encountered in handling this reagent has led to the development of many other synthetic equivalents,[6] and thiocarbonyl transfer reagents are a case in point.[7] Isothiocyanates can also be prepared by the decomposition of dithiocarbamic acid salts with various reagents such as uranium- and phosphonium-based coupling agents,[8,9] tosylchloride,[10] di-*tert*-butyl dicarbonate,[11] hydrogen peroxide,[12] and ethylchlorocarbonate.[13]

Results and Discussion

Recently, we developed an excellent strategy for the preparation of isothiocyanates by diacetoxy iodobenzene (DIB) mediated decomposition of dithiocarbamate salts.[14] In spite of the superiority of the method, the expensive nature of the hypervalent iodine reagent became an obstacle for large-scale requirements. So, an alternative to hypervalent iodine for the decomposition of the dithiocarbamate salts was essential. Accordingly, it became incumbent upon us to modify this synthetic protocol. Because molecular iodine is thiophilic in nature,[15] we reasoned that it might also be equally effective for the decomposition of dithiocarbamates to their corresponding isothiocyanates. From the literature it is known that the reaction of thiourea with iodine gives a number of side products, in addition to the oxidized disulfide products.[16] However, when the triethylammonium salt of dithiocarbamate **1** (1 equiv.) was treated with iodine (1 equiv.) in the presence of triethylamine (1.5 equiv.) in acetonitrile, isothiocyanate **1a** was obtained in nearly quantitative yield in <10 min after the complete addition of iodine. The reaction temperature was generally maintained below 5 °C, but the reaction can also be carried out at room temperature. Addition of iodine to the suspension of the dithiocarbamate salt must be carried out slowly over a period of 10–15 min. The proposed mechanism is shown in (Scheme 1), which is supported by the isolation of the precipitated elemental sulfur. Alternatively, a mechanism proposed by some others, involving the formation of thiuram disulfide also cannot be ruled out.[12] When the dithiocarbamate salt was treated with iodine in the absence of any base, thiuram disulfide was isolated in good yield. The isothiocyanate was obtained in excellent yield when triethylamine and iodine were added to the isolated thiuram disulfide.

In these reactions, the most crucial aspect is the preparation of the dithiocarbamic acid salts,[10,12,17] and once the dithiocarbamate salts are obtained, iodine proved to be an effective reagent for their decomposition to the desired isothiocyanates in excellent yields. Thus, the use of molecular

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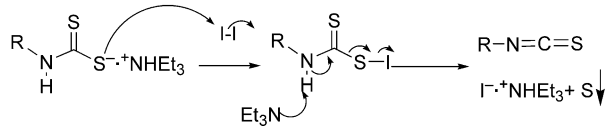
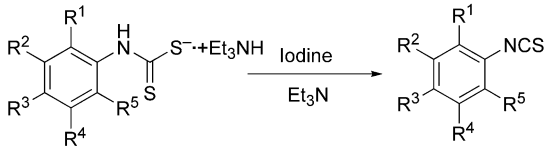
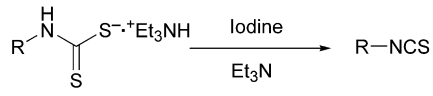


Scheme 1. Mechanism of formation of isothiocyanates from dithiocarbamate salts.

iodine overcomes many of the problems associated with the preparation of isothiocyanates. Employing this green synthetic protocol, several aromatic isothiocyanates were successfully prepared in high yields (Table 1). Aromatic substrates containing a chlorine atom in their *ortho*, *meta*, and *para* positions (i.e., **2**–**4**) gave isothiocyanates in excellent yields (94–97%) when iodine was used as the desulfurizing agent. This strategy was successful even when an electron-withdrawing substituent such as the NO_2 group (i.e., **5**) was attached to the aromatic ring. Through this strategy we were able to obtain excellent yields of aryl isothiocyanates **6a**–**12a** from substrates **6**–**12** having various substituents in the aromatic ring (Table 1).

Table 1. Preparation of isothiocyanates from dithiocarbamate salts and iodine.[a]

Substrate	Product[b]	% Yield[c]
		
1, R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**1a**	98
2, R^1 = Cl, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**2a**	97
3, R^1 = H, R^2 = Cl, R^3 =H, R^4 = H, R^5 = H;	**3a**	98
4, R^1 = H, R^2 = H, R^3 = Cl, R^4 = H, R^5 = H;	**4a**	94
5, R^1 = H, R^2 = NO_2, R^3 = H, R^4 = H, R^5 = H;	**5a**	96
6, R^1 = H, R^2 = H, R^3 = Br, R^4 = H, R^5 = H;	**6a**	98
7, R^1 = H, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;	**7a**	90
8, R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = H;	**8a**	98
9, R^1 = Me, R^2 = H, R^3 = Me, R^4 = H, R^5 = H;	**9a**	90
10, R^1 = Me, R^2 = H, R^3 = H, R^4 = H, R^5 = Me;	**10a**	95
11, R^1 = F, R^2 = H, R^3 = H, R^4 = H, R^5 = H;	**11a**	83
12, R^1 = F, R^2 = H, R^3 = F, R^4 = H, R^5 = H;	**12a**	94
		
13, α-Naphthyl	**13a**	91
14, *n*-Butyl	**14a**	65
15, Cyclohexyl	**15a**	84
16, Benzyl	**16a**	97
17, Furfuryl	**17a**	70

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. [c] Isolated yield.

Recently, we demonstrated the pK_a-dependent regioselective *N*-acylation of unsymmetrical 1,3-disubstituted thiourea.[17] Now, on the basis of the observation and mechanism proposed in Scheme 1, we have sufficient reason to believe that amines having a lower pK_a should yield the isothiocyanate better because of facile NH deprotonation. Triethylamine is sufficiently basic (pK_a 10.78) in comparison to aromatic amines (pK_a in the range 2.46 to 5.63), and the acidity of the dithiocarbamate-bound NH proton is expected to increase further upon salt formation. Other dithiocarbamate salts such as naphthyl compound **13** gave isothiocyanate **13a** in good yield. The decrease in the pK_a of the NH proton upon formation of the dithiocarbamate salt is further evidenced from the excellent formation of isothiocyanates **14a**–**16a** from alkylamines such as *n*-butyl (pK_a 10.77), cyclohexyl (pK_a 10.66), and benzylamine (pK_a 9.33), all of which have a similar basicity to that of triethylamine (10.78). Sensitive amines such as furfurylamine **17** gave isothiocyanate **17a** in moderate yield. Chiral amine **18** yielded isothiocyanate **18a** in excellent yield.

Conclusions

In conclusion, we have developed a general, economical, and environmentally benign method for the preparation of isothiocyanates from the corresponding dithiocarbamic acid salts. In comparison to the existing methods of the decomposition of the dithiocarbamic acid salts, our procedure is perhaps the simplest yet most efficient method for the synthesis of isothiocyanates. The reagent is cheap and nontoxic, and the precipitated sulfur can be removed easily. Although literature enumerates a number of procedures for the preparation of isothiocyanates, the simplicity, environmental acceptability, and cost effectiveness of our procedure makes it a practical alternative.

Experimental Section

Typical Procedure for the Preparation of 1a: To a stirred and ice-cooled suspension of dithiocarbamate **1** (540 mg, 2 mmol) in acetonitrile (5 mL) was added triethylamine (417 μL, 3 mmol). To this was added iodine (508 mg, 2 mmol) portionwise over a period of 30 min. A light-yellow-colored precipitate of sulfur started separating out during this period. The precipitated sulfur was filtered; the organic layer was concentrated and admixed with hexane (15 mL). The hexane layer was washed with 1 N HCl (2 × 5 mL) and water (1 × 5 mL). The organic layer was dried with anhydrous Na_2SO_4, concentrated under reduced pressure, and purified over a short column of silica gel (100% hexane) to give **1a** (259 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 125.8, 127.4, 129.6, 131.3, 135.3 ppm. IR (KBr): 3064.6, 2164.83, 2063.3, 1591.9, 1489.6, 1474.1, 1451.6, 1070.29, 927.6, 905.9, 749.6, 684.3 cm^{-1}.

Supporting Information (see footnote on the first page of this article): IR, ^{1}H NMR, and ^{13}C NMR spectra of the prepared compounds.

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[1] a) D. Xiao, A. A. Owolny, S. V. Singh, *J. Biol. Chem.* **2008**, *283*, 30151; b) S. L. Cuddihy, K. K. Brown, S. J. Thomson, M. B. Hampton, *Cancer Lett.* **2008**, *271*, 215; c) L. G. Wang, X. M. Liu, Y. Fang, W. Dai, F. B. Chiao, G. M. Puccio, J. Feng, D. Liu, J. W. Chiao, *Int. J. Oncol.* **2008**, *33*, 375; d) G. D. Stoner, A. A. Dombkowski, R. K. Reen, D. Cukovic, S. Salagram, L. S. Wang, J. F. Lechner, *Cancer Res.* **2008**, *68*, 6460; e) A. M. Bones, J. T. Rossiter, *Physiol. Plant.* **1996**, *96*, 194; f) Y. Zhang, T. Li, V. Gonzalez, *Mol. Cancer Ther.* **2003**, *2*, 1045; g) D. Xiao, V. Vogel, S. V. Singh, *Mol. Cancer Ther.* **2006**, *5*, 2931; h) K. Xu, P. J. Thornalley, *Biochem. Pharmacol.* **2000**, *6*, 221.

[2] a) P. Edman, *Arch. Biochem.* **1949**, *22*, 475; b) Z, I. Cabantchik, A. J. Rothstein, *Membrane. Biol.* **1974**, *15*, 227; c) D. Podhradsky, P. Oravec, M. Antalik, P. Kristian, *Collect. Czech. Chem. Commun.* **1994**, *59*, 213.

[3] a) S. Heckl, A. Sturzu, M. Regenbogen, A. Beck, G. Feil, A. Gharabaghi, H. Echner, *Med. Chem.* **2008**, *4*, 348; b) F. Meng, B. N. Manjula, P. K. Smith, S. A. Acharya, *Bioconjug. Chem.* **2008**, *19*, 1352; c) M. J. W. Ladden, X. Y. Ling, T. Gang, W. P. Bula, H. J. G. E. Gardeniers, D. N. Reinhoudt, J. Huskens, *Chem. Eur. J.* **2008**, *14*, 136; d) V. A. Vishwanath, J. M. Nclntosh, *Bioconjug. Chem.* **2006**, *17*, 1612; e) E.-M. Kim, H.-J. Jeong, I.-K. Park, C.-S. Cho, C.-G. Kim, H.-S. Bom, *J. Nucl. Med.* **2004**, *46*, 141; f) Y. Zhang, R. H. Kolm, B. Mannervik, P. Talalay, *Biochem. Bioph. Res. Co.* **1995**, *206*, 748; g) X. Guo, M. E. Meyerhoff, *Appl. Biochem. Biotechnol.* **1997**, *68*, 41; h) H. G. Lerchen, J. Baumgarten, N. Piel, V. Kolb-Bachofen, *Angew. Chem. Int. Ed.* **1999**, *38*, 3680; i) P. Laulia, M. B. Chanpark, Y. Yen, S. Q. Wang, C. M. Li, Y. C. Lam, *Small* **2008**, *4*, 69; j) S. Dong, M. Roman, *J. Am. Chem. Soc.* **2007**, *129*, 13810; k) W. Schubert, B. Bonnekoh, A. J. Pommer, L. Philipsen, R. Boeckelmann, Y. Malykh, H. Gollnick, M. Friedenberger, M. Bode, A. W. M. Dress, *Nat. Biotechnol.* **2006**, *24*, 1270.

[4] a) A. K. Muhkerjee, R. Ashare, *Chem. Rev.* **1991**, *91*, 1; b) H. Stephensen, F. Zaragosa, *J. Org. Chem.* **1997**, *62*, 6096; c) , B. J. Al-Hourani, K. Banert, N. Gomaa, K. Vrobel, *Tetrahedron* **2008**, *64*, 5590; d) D. Fajkusova, P. Pazdera, *Synthesis* **2008**, 1297; e) Y.-J. Wu, Y. Zhang, *Tetrahedron Lett.* **2008**, *49*, 2869; f) O. R. Thiel, C. Bernard, T. King, M. Dilmeghani-Serna, T. Bostick, R. D. Larson, M. M. Faul, *J. Org. Chem.* **2008**, *73*, 3508.

[5] E. Dyer, T. B. Johnson, *J. Am. Chem. Soc.* **1932**, *54*, 777.

[6] a) S. Kim, K. Y. Yi, *Tetrahedron Lett.* **1985**, *26*, 1661; b) F. Fischer, R. Gottfried, *J. Prakt. Chem.* **1965**, *30*, 230; c) F. Fischer, R. Gottfried, *Angew. Chem.* **1964**, *76*, 798; d) R. Gottfried, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 963; e) S. Kim, K. Y. Yi, *J. Org. Chem.* **1986**, *51*, 2613.

[7] a) C. Larsen, K. Stelliou, D. N. Harpp, *J. Org. Chem.* **1978**, *43*, 337; b) C. Larsen, D. N. Harpp, *J. Org. Chem.* **1981**, *46*, 2465; c) S. Kim, K. Y. Yi, *Tetrahedron Lett.* **1985**, *26*, 1661.

[8] a) U. Boas, M. H. Jakobsen, *J. Chem. Soc.* **1995**, 1995; b) U. Boas, B. Pedersen, J. B. Christensen, *Synth. Commun.* **1998**, *28*, 1223; c) U. Boas, H. G. Pedersen, J. B. Christensen, P. M. H. Heegaard, *Tetrahedron Lett.* **2004**, *45*, 269.

[9] P. Molina, N. Alajarin, H. Tamiaki, *Synthesis* **1982**, 596.

[10] R. Wong, S. J. Dolman, *J. Org. Chem.* **2007**, *72*, 3969.

[11] H. Munch, J. S. Hansen, M. Pittelkow, J. B. Christensen, U. Boas, *Tetrahedron Lett.* **2008**, *49*, 3117.

[12] G. Li, H. Tajima, T. Ohtani, *J. Org. Chem.* **1997**, *62*, 4539.

[13] J. E. Hodgkins, W. P. Reeves, *J. Org. Chem.* **1964**, *29*, 3098.

[14] H. Ghosh, R. Yella, J. Nath, B. K. Patel, *Eur. J. Org. Chem.* **2008**, 6189.

[15] F. Shibahara, A. Kitagawa, E. Yamaguchi, T. Murai, *Org. Lett.* **2006**, *8*, 5621.

[16] a) A. Claus, *Justus Liebigs Ann. Chem.* **1875**, *179*, 128; b) G. McGovan, *J. Prakt. Chem.* **1880**, *33*, 188; c) G. McGovan, *J. Chem. Soc.* **1887**, *51*, 378; d) E. A. Werner, *J. Chem. Soc.* **1912**, *101*, 2166; e) C. King, I. Ryden, *J. Am. Chem. Soc.* **1947**, *69*, 1813; f) C. B. Singh, H. Ghosh, S. Murru, B. K. Patel, *J. Org. Chem.* **2008**, *73*, 2924.

[17] a) S. Emami, A. Foroumadi, *Chin. J. Chem.* **2006**, *24*, 791; b) V. J. Sattigeri, A. Soni, S. Singhal, S. Khan, M. Pandya, P. Bhteja, T. Mathur, A. Rattan, J. M. Khanna, A. Mehta, *Arkivoc* **2005**, *ii*, 46.

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