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Isothiocyanates from Tosyl Chloride Mediated Decomposition of in Situ Generated Dithiocarbamic Acid Salts

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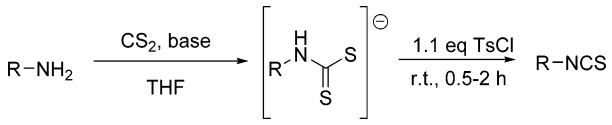
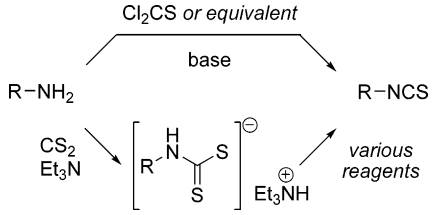


A facile and general protocol for the preparation of isothiocyanates from alkyl and aryl amines is reported. This method relies on a tosyl chloride mediated decomposition of a dithiocarbamate salt that is generated in situ by treatment of an amine with carbon disulfide and triethylamine. Utilizing this protocol, we have prepared 19-alkyl- and arylisothiocyanates in moderate to excellent yield.

The isothiocyanate moiety is found in many natural products and is also useful as a reactive functional group in chemical synthesis. For example, isothiocyanates are synthesized by glucosinolates as part of cruciferous plants' defense mechanism[1] and certain examples have been reported to possess anticancer properties.[2] Isothiocyanates are also used in the synthesis of various sulfur-containing heterocycles, including thiohydantoins, thiopyrimidones, thioquinazolones, mercaptoimidazoles, thioamidazolones, and benzothiazines.[3] Numerous synthetic methods have been developed to convert readily available amines into the isothiocyanate analogue (Scheme 1). While thiophosgene has often been employed for this transformation,[4] its high toxicity and incompatability with many functional groups limit its general use. Various thiophosgene equivalents have been developed; however, most are not readily available and often do not afford comparable reactivity.[3] An alternative approach relies on reagent-promoted decomposition of dithiocarbamic acid salts into isothiocyanates. The required dithiocarbamic acid salts may be generated in situ by treatment of an amine with carbon disulfide (CS_2) in the presence of triethylamine (Et_3N).[5] Reagents and conditions known to affect decomposition of

SCHEME 1. Methods for Conversion of Amines to Isothiocyanates



dithiocarbamic acid salts into isothiocyanates are often harsh (phosgene, phosphorus oxytrichloride, hydrogen peroxide, sodium hypochlorite,[6] cyanogen chloride,[7] sulfur dioxide,[8] or ethyl chloroformate with hydroxide[5]) or result in intractable byproducts (stoichiometric metal salts, carbodiimides,[3] phosphonium salts,[9] 2-chloro-1-methylpyridinium salts,[10] and di-2-pyridyl carbonate[11]).

We have recently reported that after acylation of a given hydrazide with an isothiocyanate, the related thiosemicarbazide may subsequently be cyclized into a 2-amino-1,3,4-oxadiazole by tosyl chloride (TsCl).[12] To access a wide variety of thiosemicarbazides, we sought to develop an effective, mild, and general method for the conversion of amines into isothiocyanates. We reasoned that since TsCl facilitated elimination of H_2S from thiosemicarbazides, it might also prove effective for decomposition of dithiocarbamic acid salts to the related isothiocyanates. Furthermore, TsCl, Et_3N, and CS_2 are all inexpensive commercial chemicals, which makes this a cost-effective strategy.

Alkyldithiocarbamic acid salts were readily generated at room temperature in THF by the slow addition (1 h) of 1 equiv of CS_2 to a solution of the requisite primary amine and 3.3 equiv of Et_3N.[13] Gratifyingly, upon addition of TsCl to derived unpurified salts, complete conversion to the isothiocyanate was observed in <30 min at room temperature. For example, benzylisothiocyanates (Table 1, entries 1−4) were successfully prepared in 78−97% yield utilizing this protocol. Linear and branched alkylisothiocyanates (entries 5−8) were obtained in 75−96% yield. Alkylamines possessing sterically encumbering secondary or tertiary carbon centers adjacent to the amine (entries 9−11) were also obtained in good yield (71−99%). In the case of tritylamine (entry 12), the dithiocarbamic acid salt was not formed, even after 18 h.[14]

The synthesis of dithiocarbamates from arylamines proved to be more challenging and often required longer reaction times and excess CS_2 and Et_3N to effect complete conversion. The

(1) Bones, A. M.; Rossiter, J. T. *Physiol. Plant.* **1996**, *96*, 194−208.
(2) (a) Zhang, Y.; Li, T.; Gonzalez, V. *Mol. Cancer Ther.* **2003**, *2*, 1045−1052. (b) Xiao, D.; Vogel, V.; Singh, S. V. *Mol. Cancer Ther.* **2006**, *5*, 2931−2945.
(3) Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91* (1), 1−24 and references therein.
(4) Dyer, E.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54* (2), 777−787.
(5) (a) Hodgkins, J. E.; Ettlinger, M. G. *J. Org. Chem.* **1956**, *21* (4), 404−405. (b) Hodgkins, J. E.; Reeves, W. P. *J. Org. Chem.* **1964**, *29* (10), 3098−3099.
(6) (a) Drobnica, L.; Kristian, P.; Augustin, J. In *The Chemistry of Cyanates and Their Thio Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1977; Part 2, pp 1003−1221. (b) Hartmann, A. *Methoden Org. Chem.* (*Houben-Weyl*) **1983**, *E4*, 834.
(7) Giesselmann, G.; Schreyer, G.; Vanheertum, R. *Chem. Abstr.* **1978**, *87*, 38871u.
(8) Fujinami, T.; Ashida, M.; Sakai, S. *Chem. Abstr.* **1978**, *89*, 108570n.
(9) Furukawa, I.; Abe, N.; Hashimoto, S. *Chem. Express* **1988**, *3* (4), 215−218.
(10) Shibanuma, T.; Shiono, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 573−574.
(11) Kim, S.; Ko, Y. K. *Chem. Abstr.* **1987**, *107*, 154037g.
(12) Dolman, S. J.; Gosselin, F.; O'Shea, P. D.; Davies, I. W. *J. Org. Chem.* **2006**, *71* (25), 9548−9551.
(13) Salt formation was monitored by ^{1}H NMR (DMSO-d_6) analysis of aliquots taken from the the reaction mixture.

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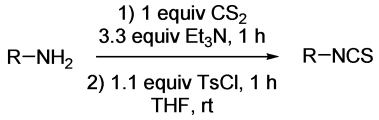
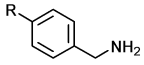
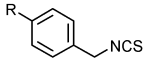
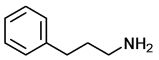
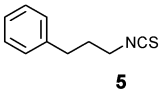
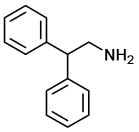
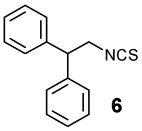
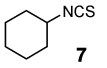
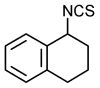
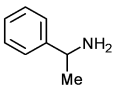
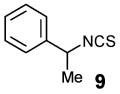
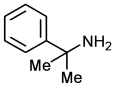
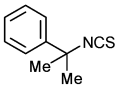
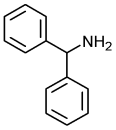
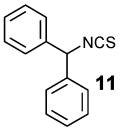
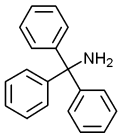
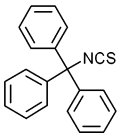
TABLE 1. Preparation of Isothiocyanates via TsCl-Mediated Dithiocarbamic Acid Decomposition[a]

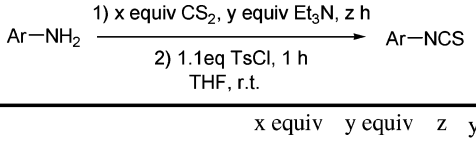


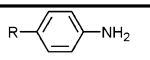
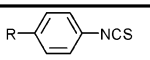
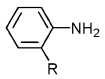
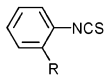
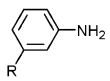
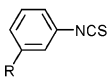
entry	amine	isothiocyanate	yield[b] (%)
			
1		**1** R = H	78
2		**2** R = OMe	96
3		**3** R = Br	97
4		**4** R = CF_3	80
5		 **5**	75
6		 **6**	76
7		 **7**	77
8		 **8**	96
9		 **9**	99
10		 **10**	97
11		 **11**	71
12		 **12**	0

[a] Reaction conditions: The substrate was treated with 1 equiv of CS_2 and 3.3 equiv of Et_3N in THF at 22 °C. After the solution was stirred for 1 h, 1.1 equiv of TsCl was added at 0 °C, and the was mixture allowed to warm to 22 °C over 1 h. [b] Isolated yield after purification via column chromatography on silica gel.

necessary reaction time and amount of each reagent are included in Table 2. In general, electron-rich arylamines more readily formed their corresponding dithiocarbamic acid salts and isothiocyanates. For example, various electron donating groups in both the para and ortho positions (Table 2, entries 1, 2, 6, 7,

TABLE 2. Preparation of Isothiocyanates via TsCl-Mediated Dithiocarbamic Acid Decomposition[a]



entry	amine	isothiocyanate	x equiv CS_2	y equiv Et_3N	z h	yield[b] (%)
						
1		**13** R = H	1.25	5.5	20	72
2		**14** R = OMe	1	4.4	1.5	97
3		**15** R = Br	2	4.4	0.5	77
4		**16** R = F	1	3.3	2	84
5		**17** R = Cl	1	3.3	20	34
6		**18** R = OH	1	3.3	20	54
						
7		**19** R = OMe	2	4.4	20	95
8		**20** R = Me	2	4.4	20	80
						
9		**21** R = Br	2	4.4	20	65

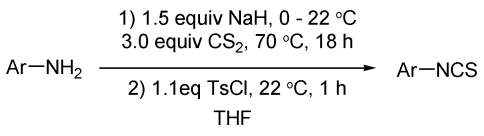
[a] Reaction conditions: The substrate was treated with *x* equiv of CS_2 and *y* equiv of Et_3N in THF at 22 °C. After the solution was stirred for *z* h, 1.1 equiv of TsCl was added at 0 °C, and the mixture was allowed to warm to 22 °C over 1 h. [b] Isolated yield after purification via column chromatography on silica gel.

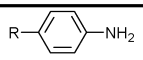
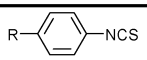
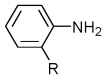
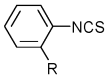
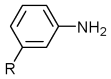
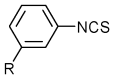
and 8) afforded good to excellent yields of 54−97%. When halides were placed in the para or meta position (entries 3−5 and 9) longer reaction times were required to access the dithiocarbamic acid salt, but the isothiocyanates were still obtained in reasonable yields, ranging from 34% to 84%. However, when strongly electron-withdrawing groups (such as CF_3, NO_2, CN, or CO_2Me) were placed in the para or meta position, dithiocarbamic acid salts could not be obtained under these conditions even after prolonged reaction times. We also observed that halide substituents in the ortho position prevented conversion of the amine to their corresponding dithiocarbamic acid salts. Thus, isothiocyanates derived from these electron-deficient amines could not be obtained utilizing this protocol.

In an effort to improve the reactivity of electron-poor arylamines, we investigated higher reaction temperatures in a variety of solvents. Using *p*-trifluoromethylaniline as a test substrate, we found that after 20 h of reflux in THF, dioxane, or DME, no dithiocarbamic acid salt was observed.[13] Addition of 5 mol % of DMAP to a refluxing mixture of *p*-trifluorom-

(14) To the best of our knowledge, neither the dithiocarabamic acid salt nor isothiocyanate have been successfully prepared from tritylamine. Trityl isothiocyanate has been prepared from trityl halides (Iliceto, A.; Fava, A.; Mazzuccato, U. *J. Org. Chem.* **1960**, *25* (8), 1445−1447) trityl alcohol (Kniezo, L.; Bernat, J. *Synth. Commun.* **1990** *20* (4), 509−513), and triphenylmethane (Bacon, R. G. R.; Guy, R. G. *J. Chem. Soc.* **1961**, 2428−2436).

TABLE 3. Preparation of Isothiocyanates via TsCl-Mediated Dithiocarbamate Decomposition[a]



entry	amine	isothiocyanate	yield[c] (%)
			
1		**22** R = CF_3	63
2		**23** R = CO_2Me	89
3		**24** R = NO_2	0
4		**25** R = CN	0
			
5		**26** R = Br	55
6		**27** R = Cl	53
			
7		**28** R = CF_3	41

[a] Reaction conditions: The substrate was treated with 1.5 equiv of NaH in THF at 0 °C; after the solution was warmed to 22 °C, 3 equiv of CS_2 was added over 1 h. The mixture was then stirred at reflux for 20 h. After the solution was cooled to 0 °C, 2.2 equiv of Et_3N and 1.1 equiv of TsCl were added, and the mixture was stirred at 22 °C for 1 h. [b] Isolated yield after purification via column chromatography on silica gel.

ethylaniline, Et_3N, and CS_2 in THF also failed to afford the dithiocarbamate salt. We next investigated the use of stronger bases to generate the more nucleophilic amide anions prior to CS_2 addition. After testing various bases, the use of NaH was found to be ideal. After 20 h at reflux, full conversion to the dithiocarbamic acid salt was observed[13] and the mixture was cooled to room temperature, then treated with tosyl chloride. In this manner, we were able to obtain reasonable yields of several aryl-isothiocyanates with strong electron-withdrawing groups such as CO_2Me and CF_3 (Table 3, entries 1, 2, and 7, 41−89% yield). This method was also effective for *o*-halide substitiuents (entries 5 and 6, 53−55% yield). Disappointingly, neither NO_2- nor CN-substituted anilines afforded clean conversion to the related dithiocarbamic acid salts, and after treatment with TsCl, no isothiocyanate was isolated (entries 3 and 4).[15]

We have developed a general, economical, and simple one-pot method for the preparation of a variety of alkyl- and arylisothiocyanates from amines and CS_2 via TsCl-mediated decomposition of the corresponding dithiocarbamic acid salts. By comparison, previously reported methods for dithiocarbamate decomposition were not as mild or high yielding. While formation of dithiocarbamic acid salts from arylamines proved more difficult, use of excess reagents and longer reaction times generally afforded the desired intermediates. In the case of electron-deficient arylamines, it was necessary to employ NaH and higher temperature to achieve high conversion to the dithiocarbamic acid salts. However, in all cases, once the dithiocarbamic acid salt was obtained, TsCl proved an effective reagent for decomposition to the desired isothiocyanate

Experimental Section

Representative Procedure for Alkylamines. A 50 mL round-bottomed flask was charged with 3-propylphenylamine (1.6 mL, 11.0 mmol), triethylamine (5.0 mL, 36.2 mmol), and THF (10 mL), then cooled with an ice bath under N_2 atmosphere. Carbon disulfide (0.66 mL, 11.0 mmol) was then added to the reaction mixture by syringe pump over 0.5 h. After the addition was completed, the mixture was stirred at room temperature. After 1 h, ^{1}H NMR of an aliquot indicated that conversion into dithiocarbamate salt was complete. The reaction mixture was cooled with an ice bath, tosyl chloride (2.3 g, 12.1 mmol) was added, and the reaction was allowed to warm to room temperature. After 0.5 h, 1 N HCl (10 mL) and MTBE (10 mL) were added to the mixture. The aqueous layer was separated and back extracted with MTBE (10 mL). The organic layers were then combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to obtain an oil, which was passed through a silica plug with 100% hexane as eluent. 3-Propyl phenylisothiocyanate (1.48 g) was obtained as a colorless oil in 75% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (m, 2H), 7.20 (m, 3H), 3.64 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H), 1.94 (q, J = 10.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 140.4, 128.5, 128.4, 126.2, 44.3, 32.0, 30.9. IR 3061.1 (m), 3025.5 (m), 2925.4 (m), 2857.7 (m), 2181.4 (s), 2088.9 (s).

Representative Procedure for Arylamines. A 50 mL round-bottomed flask was charged with *p*-bromoaniline (1.89 g, 11.0 mmol), Et_3N (5.03 mL, 36.2 mmol), and THF (10 mL), then cooled with an ice bath under N_2 atmosphere. CS_2 (0.66 mL, 11.0 mmol) was added by syringe pump over 0.5 h. More CS_2 (0.66 mL, 11.0 mmol) and Et_3N (1.8 mL, 12.1 mmol) were added after ^{1}H NMR of an aliquot indicated incomplete conversion into the dithiocarbamate. Once conversion of the salt was completed, (18 h) the mixture was cooled with an ice bath and TsCl (2.30 g, 12.1 mmol) was added. The reaction was stirred at room temperature for 1 h. The material was subjected to workup (as above) and 1.76 g of *p*-bromophenyl isothiocyanate was obtained in 77% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 134.6, 132.7, 129.4, 127.9, 120.6. IR 2923.6 (w), 2076.5 (m).

Representative Procedure for Electron Poor Arylamines with NaH as Base. A 50 mL round-bottomed flask was charged with 4-aminobenzotrifluoride (1.38 mL, 11.0 mmol), THF (10 mL), and sodium hydride (60% in mineral oil; 0.66 g, 16.5 mmol) in an ice bath under N_2 atmosphere. CS_2 (1.98 mL, 32.9 mmol) was added via syringe pump as the reaction was brought up to room temperature over 1 h. The mixture was then refluxed at 75 °C for 20 h. The mixture was then cooled on an ice bath, and TsCl (2.30 g, 12.1 mmol) and Et_3N (3.35 mL, 26.1 mmol) were added. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was subjected to workup (as above) and column chromatography to yield 1.44 g of *p*-CF_3-phenyl isothiocyanate in 63% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 8.4 Hz), 7.64 (d, J = 8.4 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.0, 134.0, 127.7 (q, J = 32.2 Hz), 126.9, 126.8, 122.3 (t, J = 270 Hz). IR 3447.3 (s), 2923.7 (m), 2090.7 (s).

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) To the best of our knowledge, 1-isothiocyanato-4-nitrobenzene has never been reported. 1-Isothiocyanato-4-cyanobenzene has been prepared from 4-nitroaniline with thiophosgene in 50 % yield (Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2000**, *65* (8), 8669−8674).