Indium-mediated Allylation of Heteroaryl, Benzyl, and Cinnamyl Thiocyanates: A Novel Route for 3-(Allylsulfanyl)-1*H*-indoles

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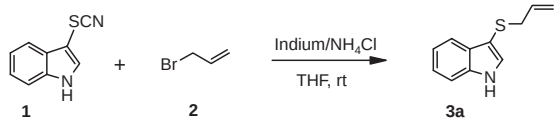
(Received July 29, 2008; CL-080735; E-mail: yadavpub@iict.res.in)

Heteroaryl, benzyl, and cinnamyl thiocyanates undergo smooth allylation with allyl bromide in the presence of indium or zinc metal in THF at room temperature to produce the corresponding allyl sulfides in good yields and with high selectivity.

The indole nucleus is frequently found in medicinal chemistry and is considered a "privileged scaffold."[1] In particular, 3-sulfanylindoles are used as COX-2 inhibitors in medicinal chemistry.[2] These motifs are very common in various drugs for the treatment of HIV, obesity, cancer, heart diseases, and allergies.[3,4] Thiocyanates have proven to be valuable tools for the synthesis of a wide range of organo-sulfur compounds.[5] Numerous reports in the literature concerning their applications attest to their growing importance. In particular, aryl thiocyanates are potential precursors for the synthesis of novel organo-sulfur compounds.[6] Furthermore, aryl thiocyanates can be easily transformed into various sulfur functional groups such as thiophenols by reduction with lithium aluminum hydride and aryl nitriles/disulphides by aromatic Grignard reagents.[7] Recently, samarium metal has been utilized for the reductive allylation of alkyl thiocyanates and diaryl disulfides.[8] During the last decade, indium has emerged as a metal of high potential in organic synthesis because it possesses certain unique properties. Indium metal is unaffected by air or oxygen at ambient temperatures and can be handled safely without any apparent toxicity. In addition, indium exhibits low heterophilicity in organic reactions and thus oxygen- and nitrogen-containing functional groups are usually well tolerated by organo-indium reagents.[8,9] Moreover, indium-assisted reactions display low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity.[10–16] However, there have been no previous reports on the allylation of heteroaryl thiocyanates using allylindium bromide.

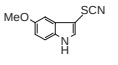
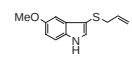
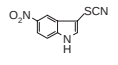
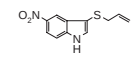
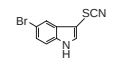
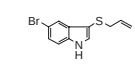
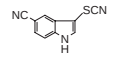
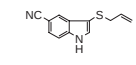
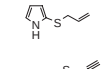
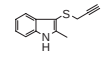
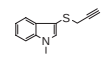
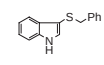
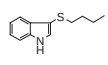
In this article, we report a simple and convenient method for the preparation of 3-(allylsulfanyl)indoles by means of the allylation of 3-thiocyanatoindoles using indium metal and allyl bromide. Initially, we attempted allylation of 3-thiocyanatoindole (**1**) with 2.1 equiv of allyl bromide (**2**) in the presence of indium metal. The reaction proceeded smoothly in THF at room temperature to produce 3-(allylsulfanyl)-1*H*-indole (**3a**) in 87% yield (Scheme 1).

This result provided incentive for further study of reactions with various 3-thiocyanatoindoles such as 2-methyl-, 2-carboethoxy-, 7-ethyl-, 2-phenyl-, *N*-benzyl-, *N*-methyl-, 5-methoxy-, 5-nitro-, 5-bromo-, and 5-cyano derivatives to furnish the corresponding 3-(allylsulfanyl)indoles (Entries b–k, Table 1). This method is well tolerated with substrates bearing ester, nitro,

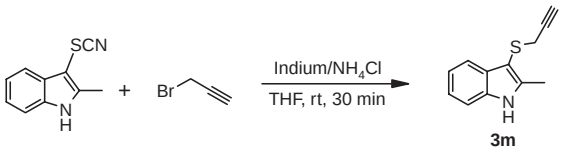


Scheme 1.

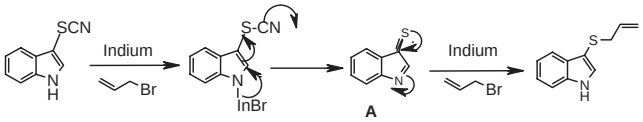
Table 1. Indium-mediated allylation of thiocyanates

Entry	Substrate (**1**)	Substrate (**2**)	Product[a]	Time/min	Yield/%[b]
a				2	87
b		"		25	92
c		"		20	90
d		"		25	91
e		"		15	94
f		"		30	88
g		"		25	86
h		"		15	90
i		"		30	85
j		"		20	87
k		"		20	86
l		"		30	83
m				30	70
n				30	75
o				25	80
p				45	71
q				30	78[c]
r				35	73[c]
s				10	80
t		"		20	90

[a]All products were characterized by NMR, IR, and mass spectrometry. [b]Yield refers to pure products after chromatography. [c]5–7% α-adduct was observed by NMR spectra of crude product.



Scheme 2.



Scheme 3.

bromo, and cyano functionalities (Entries c, i, j, and k, Table 1). Interestingly, the allylation of 2-thiocyanatopyrrole gave the respective 2-(allylsulfanyl)pyrrole in 83% yield (Entry l, Table 1). However, treatment of 2-methylindole and *N*-methylindole with 2-propynylindium bromide generated in situ from metallic indium and 2-propynyl bromide in THF over 30 min gave the 2-propynyl sulfides in 70 and 75% yields respectively (Entries m and n, Table 1, Scheme 2).

Similarly, benzyl bromide and *n*-butyl bromide reacted with 3-thiocyanatoindole (**1**) to furnish the corresponding *S*-benzyl and *S*-butyl derivatives respectively (Entries o and p, Table 1). However, reaction of 3-thiocyanatoindole with crotyl and cinnamyl bromides gave γ-adducts as major products (Entries q and r, Table 1). Next, we examined the reactivity of benzyl and cinnamyl thiocyanates. Interestingly, these thiocyanates also underwent smooth allylation with allyl bromide under identical conditions to provide the corresponding benzyl and cinnamyl allylsulfides respectively in good yields (Entries s and t, Table 1). This method works well for both electron rich as well as electron deficient substrates. Both N-protected and unprotected indoles participated in this reaction (Table 1). This method offers several advantages such as high conversions, mild reaction conditions, greater selectivity, cleaner reaction profiles, and operational simplicity. The scope and generality of this process is illustrated with respect to various indolyl thiocyanates and the results are presented in Table 1.[17] The limitation of this methodology is that alkyl thiocyantes failed to undergo allylation under these conditions. Mechanistically, it is known that indium reacts with allyl bromide to generate allylindium species,[9] which subsequently reacts with indole to give intermediate A.[18] The reaction of intermediate A with allyl bromide would furnish the desired allyl sulfide (Scheme 3).

In case of alkyl-susbstituted thiocyanates (Entries s and t), the reaction may proceed via the single-electron-transfer (SET) process as described previously.[8]

In summary, we have developed an efficient method for the preparation of 3-(allylsulfanyl and 2-propynylsulfanyl)indoles by means of the allylation and 2-propynylation of 3-thiocyanatoindoles. In addition to its simplicity and mild reaction conditions, this method provides good yields of products with high selectivity, which makes it a useful and attractive process for the synthesis of 3-susbtituted indoles.

References and Notes

1 R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**; G. W. Gribble, *J. Chem. Soc., Perkin Trans 1* **2000**, 1045; S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875.

2 Y. Maeda, M. Koyabu, T. Nishimura, S. Uemura, *J. Org. Chem.* **2004**, *69*, 7688; J. A. Campbell, C. A. Broka, L. Gong, K. A. M. Walker, J.-H. Wang, *Tetrahedron Lett.* **2004**, *45*, 4073.

3 T. M. Williams, T. M. Ciccarone, S. C. MacTough, C. S. Rooney, S. K. Balani, J. H. Condra, E. A. Emini, M. E. Goldman, W. J. Greenlee, L. R. Kauffman, J. A. O'Brien, V. V. Sardana, W. A. Schleif, A. D. Theoharides, P. S. Anderson, *J. Med. Chem.* **1993**, *36*, 1291; R. Silvestri, G. D. Martino, G. L. Regina, M. Artico, S. Massa, L. Vargiu, M. Mura, A. G. Loi, T. Marceddu, P. L. Colla, *J. Med. Chem.* **2003**, *46*, 2482.

4 I. Avis, A. Martinez, J. Tauler, E. Zudaire, A. Mayburd, R. Abu-Ghazaleh, F. Ondrey, J. L. Mulshine, *Cancer Res.* **2005**, *65*, 4181; G. D. Martino, G. L. Regina, A. Coluccia, M. C. Edler, M. C. Barbera, A. Brancale, E. Wilcox, E. Hamel, M. Artico, R. Silvestri, *J. Med. Chem.* **2004**, *47*, 6120; C. D. Funk, *Nat. Rev. Drug Discovery* **2005**, *4*, 664; S. S. Khandekar, D. R. Gentry, G. S. V. Aller, P. Warren, H. Xiang, C. Silverman, M. L. Doyle, P. A. Chambers, A. K. Konstantinidis, M. Brandt, R. A. Daines, J. T. Lonsdale, *J. Biol. Chem.* **2001**, *276*, 30024.

5 A. W. Erian, S. M. Sherif, *Tetrahedron* **1999**, *55*, 7957.

6 J. L. Wood, in *Organic. Reactions*, ed. by R. Adams, John Wiley & Sons, New York, **1946**, Vol. 3, Chap. 6; R. G. Guy, in *The Chemistry of Cyanates and Their Thio Derivatives*, ed. by S. Patai, John Wiley & Sons, New York, **1977**, Part 2, Chap. 18, p. 819.

7 F. D. Toste, F. Laronde, I. W. J. Still, *Tetrahedron Lett.* **1995**, *36*, 2949; M. S. Grant, H. R. Snyder, *J. Am. Chem. Soc.* **1960**, *82*, 2742.

8 Z.-P. Zhan, K. Lang, *Chem. Lett.* **2004**, *33*, 1370.

9 H. L. Phil, *Bull. Korean Chem. Soc.* **2007**, *28*, 17.

10 J. Podlech, T. C. Maier, *Synthesis* **2003**, 633.

11 B. C. Ranu, *Eur. J. Org. Chem.* **2000**, 2347.

12 J. S. Yadav, B. V. S. Reddy, K. S. Reddy, K. B. Reddy, *Tetrahedron Lett.* **2002**, *43*, 1549.

13 J. S. Yadav, A. Bandyopadhyay, B. V. S. Reddy, *Tetrahedron Lett.* **2001**, *42*, 6385.

14 J. S. Yadav, S. Anjaneyulu, M. M. Ahmed, B. V. S. Reddy, *Tetrahedron Lett.* **2001**, *42*, 2557.

15 J. S. Yadav, A. Bandyopadhyay, B. V. S. Reddy, *Synlett* **2001**, 1608.

16 J. S. Yadav, B. V. S. Reddy, P. Vishnumuthy, S. K. Biswas, *Tetrahedron Lett.* **2007**, *48*, 6641.

17 General procedure: A mixture of allyl bromide/2-Propynyl bromide (2.1 mmol) and indium (2.1 mmol) was stirred in THF at room temperature for 15–20 min to dissolve the metal. Then thiocyanate (1 mmol) was added and the reaction stirred for the appropriate time (Table I). After complete conversion as indicated by TLC, the reaction mixture was quenched with aqueous saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:7) to afford the pure product (Caution: Work-up to be carried out with utmost care to avoid possible toxicity of indium cyanide towards skin. See Supporting Information.[19]

18 J. S. Yadav, B. V. S. Reddy, P. M. Reddy, C. Srinivas, *Tetrahedron Lett.* **2002**, *43*, 5185.

19 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

Published on the web (Advance View) September 20, 2008; doi:10.1246/cl.2008.1082