

Hydrothiolation of Unactivated Alkynes Catalyzed by Indium(III) Bromide

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Indium(III) bromide is found to catalyze efficiently the hydrothiolation of unactivated alkynes with various thiols under mild conditions to produce the corresponding dithioacetals in excellent yields. However, addition of aromatic thiols on aromatic alkynes gave the β -vinyl sulfides in high yields. This new procedure offers significant advantages such as high conversions, short reaction times, and simplicity in operation.

The sulfur-containing natural products and synthetic materials coupled with the utility of sulfur-based reagents in synthetic organic chemistry illustrates the need for efficient and versatile strategies for the construction of sulfur-containing molecules.¹ Consequently, various synthetic methods have been developed for the conversion of alkynes into a variety of sulfur-containing compounds by hydrothiolation.² The hydrothiolation is one of the most attractive methods for the formation of disulfides and β -vinyl sulfides, which are valuable as synthetic intermediates in total synthesis and as precursors to a wide range of functionalized molecules. As a result, several methods such as radical, nucleophilic, and metal-catalyzed hydrothiolation using aryl- and alkyl-thiols have been reported under various reaction conditions.^{3–6} In addition, hydrothiolation of activated alkynes by thiols has also been reported to furnish 1,1-disulfides (dithianes).⁷ However, there have been no reports on hydrothiolation of unactivated alkynes with aryl- and alkylthiols.

Recently, indium tribromide has received increasing attention as a water-tolerant green Lewis acid catalyst for various organic transformations demonstrating highly chemo-, regio-, and stereoselective results.⁸ Compared to conventional Lewis acids, it has advantages of water stability, recyclability, operational simplicity, strong tolerance to oxygen- and nitrogen-containing substrates and functional groups, and it can often be used in catalytic amounts.

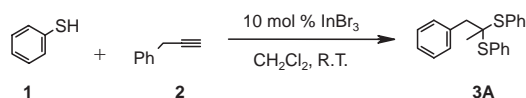
In continuation of our interest on the catalytic use of indium(III) reagents for various organic transformations,⁹ we herein disclose a mild and efficient methodology for the hydrothiolation of unactivated alkynes using indium(III) bromide as the novel catalyst. Initially, we attempted the nucleophilic addition of benzenethiol (**1**) onto 3-phenyl-1-propyne (**2**) in the presence of 10 mol % of indium(III) bromide. The reaction proceeded rapidly at room temperature to produce [2,2-di(phenylsulfanyl)propyl]benzene (**3A**) in 96% yield (Scheme 1, Entry A, Table 1). Similarly, 4-phenyl-1-butyne was also participated well in this reaction (Entry B, Table 1). The remarkable catalytic activity of InBr_3 provided the incentive for further

reactions of thiols with various alkynes. Interestingly, aromatic thiols such as benzenethiol, *p*-thiocresol, and naphthalene-2-thiol reacted readily with 1-octyne to produce the corresponding dithioacetals (Entries A–E, Table 1). Like aromatic thiols, aliphatic thiols such as *n*-butanethiol and ethanethiol also under-

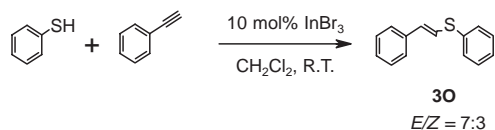
Table 1. Hydrothiolation of alkynes with thiols using 10 mol % of indium(III) bromide in dichloromethane

Entry	Thiol 1	Alkyne 2	Product ^a 3	Time/min	Yield/% ^b
A				20	96
B				25	98
C				25	98
D				20	96
E				25	95
F				20	98
G				20	95
H				25	98
I				20	96
J				30	98
K				25	95
L				30	96
M				20	96
N				25	98
O				25	96 (7:3) ^c
P				20	94 (6:4) ^c
Q				20	95 (7:3) ^c
R				30	92 (6:4) ^c
S				20	90
T				15	92

^aAll the products were characterized by ¹H NMR, IR, and mass spectrometry. ^bYield refers to pure products after chromatography. ^cE/Z ratio was determined by ¹H NMR spectrum of crude product.



Scheme 1.

**Scheme 2.****Table 2.** The effects of various indium(III) reagents for the preparation of **3A**

Entry	Catalyst (10 mol %)	Conditions	Time/min	Yield/% ^a
1	InCl ₃	CH ₂ Cl ₂ , R.T.	30	70
2	In(OTf) ₃	CH ₂ Cl ₂ , R.T.	30	60
3	In(ClO ₄) ₃	CH ₂ Cl ₂ , R.T.	30	40
4	InBr ₃	H ₂ O, R.T.	30	0
5	InBr ₃	CH ₂ Cl ₂ , R.T.	30	96
5	InBr ₃	MeOH, R.T.	30	20
5	InBr ₃	CH ₃ CN, R.T.	30	80
5	InBr ₃	Et ₂ O, R.T.	30	30

^aYield refers to pure product after chromatography.

went smooth addition onto alkynes (Entries F, J, and L, Table 1). In addition to this, aliphatic alkynes such as 1-heptyne and 1-hexyne were participated efficiently in this reaction (Entries G–N, Table 1). Subsequently, we have investigated the reaction of aromatic thiols with aromatic alkynes. Unlike aliphatic alkynes, the reaction of aromatic alkynes with aromatic thiols in the presence of 10 mol % of indium(III) bromide gave vinylic sulfides as a mixture of E/Z isomers favoring E isomer. For example, treatment of phenylacetylene with benzenethiol gave (*E*)-phenyl(styryl)sulfane (**30**) as a mixture of E/Z isomers in 7:3 ratios (Entry O, Scheme 2, Table 1).

The (E/Z) ratio of the products was determined by the ¹H NMR spectrum of the crude product. Similarly, substituted benzenethiols reacted well to give the corresponding vinylic sulfides (Entries P–T, Table 1). However, treatment of diphenylacetylene with benzenethiol for 30 min afforded 1,2-disulfide in 90% yield (Entry S, Table 1). Furthermore, the reaction of ethyl 1-phenylpropiolate with benzenethiol gave mono-adduct (Entry T, Table 1). In all cases, the reactions proceeded rapidly at room temperature with high efficiency. To compare the selectivity, phenylacetylene was treated with benzenethiol in the presence of various catalysts. The exomethylene products are obtained when using transition metals such as Ni(acac)₂, Pd(OAc)₂, or PdCl₂(PhCN)₂ arising from the Markovnikov-type addition. By using 10 mol % of InBr₃, anti-Markovnikov-type, β-vinyl sulfides are obtained with excellent regioselectivity. In the absence of catalyst, no reaction was observed even after long reaction times (10–20 h). As solvent, dichloromethane gave the best results. The scope and generality of this process is illustrated in Table 1. The effects of various indium(III) catalysts such as InBr₃, InCl₃, In(OTf)₃, and In(ClO₄)₃ were tested and the results are presented in Table 2. Of these catalysts, InBr₃ was found to be the most effective in terms reaction time and conversion.

In summary, we have developed a rapid and efficient protocol for the preparation of dithioacetals and β-vinyl sulfides from alkynes and thiols using indium(III) bromide as a novel catalyst. The notable features of this procedure are mild reaction conditions, high to quantitative yields, operational simplicity, cleaner reaction profile, and very short reaction times, which make it a useful and attractive strategy for the direct conversion of aliphatic alkynes to dithioacetals.

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