

Dehydrosulfurization of Aromatic Thioamides to Nitriles Using Indium(III) Triflate

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Abstract

The efficient dehydrosulfurization of thioamides to nitriles was carried out using indium(III) triflate as a catalyst. Based on the results of the initial study, the optimal reaction conditions required 5 mol% of indium(III) triflate with toluene as the practical solvent. Various thioamides were successfully converted to nitriles in high yields.

Keywords

Indium(III) Triflate, Dehydrosulfurization, Thioamide, Nitriles

1. Introduction

Functional group conversions are of significant importance in the field of organic synthesis. Hence, the development of novel functional group conversions is a world-wide pursuit. Organosulfur compounds have been recognized as highly useful precursors, or synthons, in order to demonstrate functional group transformation [1]. Due to their considerable versatility and unique reactivity, thioamides are receiving increased attention, and many precedent interconverting reactions have been introduced. However, the dehydrosulfurization of thioamides to nitriles is often implemented under harsh reaction conditions that require elongated reaction times. Several studies that have focused on the dehydrosulfurization of thioamides to nitriles have used reagents such as diphosphorus tetraiodide [2], 2, 4-dichloro-5-nitropyrimidine [3], and aryl chlorothionoformate [4] or a combination of reagents like $S_8/NaNO_2/NH_3$ [5] and benzyl chloride/tetra-*n*-butylammonium bromide as a phase transfer catalyst [6]. In alternative conversions of thioamides to nitriles, researchers have employed metal reagents by intro-

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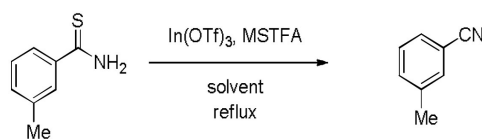
ducing reactions with silver carboxylates [7] [8], manganese oxide [9], and *n*-butyltin oxide [10]. Ogura *et al.* has reported for the dehydrosulfurization of thioamides to nitriles by using selenium-based and tellurium-based reagents [11]-[15], while Enthaler *et al.* has reported using iron-based and zinc-based reagents [16] [17]. We have studied the catalytic utility of indium reagents, and reported the chemical application of indium reagents, including an efficient conversion of primary amides to nitriles using catalytic indium(III) triflate [18]-[24]. In ongoing research, we have found that the catalytic use of indium(III) triflate facilitates the dehydrosulfurization of thioamides to nitriles. Herein, we describe the details of our study.

2. Results and Discussion

Using 3-methyl thiobenzamide as the starting substrate, a search for the optimal conditions of dehydrosulfurization was attempted, as presented in **Table 1**. The amount of *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) was fixed at 3.5 equivalents, as established in our previous report (**Figure 1**) [24], and thus the catalytic amount of indium(III) triflate and appropriate solvents were investigated. The entries using toluene as the solvent afforded the expected products (**Table 1**, entries 1 and 2), whereas the entries using THF ended with no reactions (**Table 1**, entries 3 and 4). The use of 5 mol% of indium(III) triflate was also discovered as one of the key factors for the optimal reaction conditions (**Table 1**, entry 2).

Once the optimal conditions for the dehydrosulfurization of thioamides to nitriles were obtained, we next examined their applicability. Various aromatic thiobenzamides were subjected to dehydrosulfurization reactions. As shown in **Table 2**, the reactions proceeded smoothly to give the corresponding nitriles in good to excellent yields [24]. The alkyl group substituents, such as methyl on the aromatic ring and the *tert*-butyl groups were inert under the reaction conditions of dehydrosulfurization, and gave high yields (**Table 2**, entries 1, 3, and 5) [25] [26]. The dehydrosulfurization reactions of halogenated aromatic thioamides were carried out without dehalogenation (**Table 2**, entries 2 and 7) [27]. Also, the reaction led to the desired nitriles without damaging methoxy functionality (**Table 2**, entries 4 and 6). Consequently, the scope of the silyl protecting groups was investigated. The conversion reaction was successfully conducted maintaining both *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyldiphenylsilyl (TBDPS) functionalities, and furnished the desired products in excellent order (**Table 2**, entries 8 and 9), which supported the mildness of the reaction conditions by not affecting the acid labile silyl functionalities. Furthermore, these reaction processes were extended to bicyclic aromatic compounds. The dehydrosulfurization reactions starting with naphthalene-1-thiocarboxamide and naphthalene-2-thiocarboxamide provided the corresponding nitriles in excellent yields (**Table 2**, entries 10 and 11). In addition, the entry using 2,2-diphenylthioacetamide, which is a non-aromatic, afforded the desired nitrile product in an 84% yield (**Table 2**, entry 12) [28].

Table 1. Reactions in the search for optimal conditions.



Entry	Solvent	MSTFA	In(OTf) ₃	Reflux Time (h)	Yield ^a (%)
1	toluene	3.5 eq.	10 mol%	3	86
2	toluene	3.5 eq.	5 mol%	3	quant
3	THF	3.5 eq.	10 mol%	3	N.R.
4	THF	3.5 eq.	5 mol%	3	N.R.

^aIsolated yields.

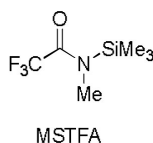


Figure 1. Structure of *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA).

Table 2. Dehydrosulfurization of aromatic thioamides to nitriles.

Entry	Starting substrate	Product	Reflux Time (h)	Yield ^a (%)
1			3	quant
2			2	84
3			3	52
4			3	88
5			3	85
6			3	quant
7			3	94
8			2	quant
9			3	86
10			3	94
11			2	97
12			2.5	84

3. Conclusion

In conclusion, we have established an efficient method for the dehydrosulfurization of thioamides to nitriles in the presence of a catalytic amount of indium(III) triflate. Many aromatic thioamides were subjected to these reaction conditions, and provided the corresponding nitriles in good to excellent yields. The dehydrosulfurization reaction conditions were sufficiently mild, so as to not cleave the acid labile silyl functionalities. Further mechanistic investigations are ongoing.

4. Experimental

4.1. Materials and Instruments

All reagents were of analytical grade and were purchased commercially and used without further purification. All reactions were carried out under an argon atmosphere using magnetic stirring unless otherwise noted. ¹H NMR and ¹³C NMR spectral data were recorded on a JEOL JMTC-500 spectrometer using TMS as an internal standard.

4.2. General Experimental Procedure

The starting thioamide substrates (1 mmol) and In(OTf)₃ (5 mol%) were dissolved in dehydrated toluene (6 mL) contained in a 100 mL flask equipped with a magnetic stirrer and a reflux condenser. MSTFA (3.5 mmol) was added using a syringe at room temperature. The reaction mixture was heated at reflux for 3 h, and was monitored for completion by TLC. After the reaction mixture was cooled to room temperature, the solvent was washed with aqueous solutions and concentrated by rotary evaporation. Flash column chromatography on silica gel furnished the corresponding nitrile product, which was confirmed by spectroscopy [24]-[28].

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