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Highly-Efficient Conversion of Primary Amides to Nitriles Using Indium(III) Triflate as the Catalyst

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Abstract

Indium(III) triflate, a trivalent indium reagent, was shown to be a highly-efficient catalyst for the conversion of primary amides to the corresponding nitriles. The successful reactions required 5 mol% of indium(III) triflate, and toluene was proved to be the most suitable solvent. Various amides were subjected to this method, and each produced the corresponding nitriles in excellent yields.

Keywords

Indium(III) Triflate; Primary Amides; Nitriles

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1. Introduction

The development of efficient methods for the preparation of nitriles has been receiving extensive attention in organic synthesis because of important applications in the fields of chemistry and biochemistry [1]. Nitriles are common building blocks that are used in chemical industries for the production of pharmaceutically or agrochemically valuable agents. The known classic protocols for the synthesis of aryl nitriles include the Sandmeyer

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reaction of aryldiazonium salts and the cyanation of aryl halides by metal cyanides in the presence of transition metal catalysts [2]-[5]. Recently, the direct transformation of methyl arenes to the corresponding aryl nitriles has been reported, which uses sodium azide as the nitrogen source and is promoted by copper salt [6].

Another practical method to form nitriles is the dehydration of primary amides. There are a number of reports concerning the dehydration of primary amides conducted with stoichiometric amounts of acidic reagents such as P_2O_5 [7], [8], $POCl_3$ [9], $SOCl_2$ [10]-[12], aryl chlorothionoformate [13], trifluoroacetic anhydride [14], and trichloroisocyanuric acid [15]. However, in many cases, implementation with these acidic reagents may not be appropriate, particularly for compounds that possess acid sensitive substrates. In this regard, more recently, metalcatalyzed methods for the transformation of primary amides to nitriles have been introduced as efficient alternatives. Various successful applications have been reported, utilizing a variety of metals including Ru, Rh, W, Pd, V, Re, and U [16]-[25]. Also, Fe, Cu, and Zn, which are known to be abundant and environmentally safe elements, have shown practical applicability to this transformation [26]-[30]. Another rare metal, In, as trivalent $InCl_3$, has been used to accelerate the dehydration of oximes and arenes with benzyl alcohols [31], [32]. After studying the chemical utility of trivalent indium reagents [33]-[36], we conducted a preliminary investigation into the use of trivalent indium reagents for the conversion of primary amides. As part of our ongoing investigations, $In(OTf)_3$ was found to be a suitable and highly-efficient catalyst for transforming primary amides to nitriles in combination with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) [26]-[30], which has unique dehydrating properties as described in recent reports (**Figure 1**). Herein, we report the details of this study.

2. Results and Discussion

Initially, to the starting substrate, *para*-toluamide, we attempted the reactions using 10 and 5 mol% of $In(OTf)_3$ (**Table 1**, entries 1 and 2). The behaviour of these reactions was quite identical with regard to reaction time and yield. Consequently, the use of different amounts of MSTFA was investigated, keeping toluene as the solvent. However, the result was a diminished yield, as we anticipated (**Table 1**, entries 3 and 4). In order to confirm the selection of a solvent, three starting primary amides were subjected to the same competent reaction conditions. In all cases, the reactions employing toluene furnished nitriles in excellent yields (**Table 1**, entries 6 and 8), whereas the reactions using THF gave insufficient outcomes (**Table 1**, entries 5, 7 and 9).

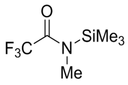
With the optimized parameters in hand, we investigated the scope and applicability of various aromatic and aliphatic amides. As shown in **Table 2**, many benzamide derivatives were converted to the corresponding nitriles in excellent yields. The substituents on the aromatic ring, such as halogen and alkyl groups, were inert through the course of the reactions. In particular, primary amides of phenol and aniline derivatives gave the nitriles successfully in excellent yields without requiring tedious chemical protecting procedures of the *para*-hydroxy and *meta*-amino groups (**Table 2**, entries 6 and 8). Furthermore, the limitations of the protecting groups were examined. The *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyl-diphenylsilyl (TBDPS) groups were resistant to the reaction conditions yielding the silyl-maintained products [37] in good order (**Table 2**, entries 9 and 10). Consulting the previous report [26]-[30], these results suggest that the reaction condition employing catalytic $In(OTf)_3$ is mild enough to maintain acid labile silyl protecting groups.

The study was then extended to bicyclic and aliphatic compounds under the same reaction processes. Overall, the conversion reactions were applicable to bicyclic and aliphatic compounds, as indicated in **Table 3**. Comparing 1- and 2-naphthamides, 2-naphthamide resulted in a highly improved yield of nitriles (**Table 3**, entries 1 and 2). Aliphatic primary amides were also similarly transformed to the corresponding nitriles in good to excellent yields (**Table 3**, entries 3, 4 and 5). Especially, it is notable that the reaction with oleamide, which possesses a double bond in the middle of elongated chain, successfully furnished the desired nitrile as good as in a 94% yield (**Table 3**, entry 3).

The proposed reaction mechanism involving MSTFA were reported by Enthaler and co-workers [25]-[27]. In this case, also, the pathway can be similar, though further investigation is needed.

3. Conclusion

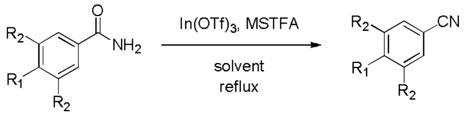
In summary, we have developed a highly efficient method for the conversion of primary amides to nitriles using $In(OTf)_3$ as the catalyst. These reactions produced both aromatic and aliphatic nitriles in excellent yields. The reactions were accomplished while maintaining acid labile silyl protecting functionalities. Further development



MSTFA

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

Table 1. Reactions in the search for optimal conditions.



Entry	R_1, R_2	Solvent	$In(OTf)_3$, MSTFA	Time (h)	Yield[a] (%)
1	Me, H	toluene	10 mol%, 3.5 eq	3	70
2	Me, H	toluene	5 mol%, 3.5 eq	3	70
3	Me, H	toluene	5 mol%, 2.5 eq	3	63
4	Me, H	toluene	5 mol%, 1.5 eq	3	32
5	Me, H	THF	5 mol%, 3.5 eq	3	42
6	H, OMe	toluene	5 mol%, 3.5 eq	3	quant
7	H, OMe	THF	5 mol%, 3.5 eq	3	65
8	H, Cl	toluene	5 mol%, 3.5 eq	3	quant
9	H, Cl	THF	5 mol%, 3.5 eq	3	39

[a] Isolated yields.

of the method is in progress.

4. Experimental

4.1. Materials and Instruments

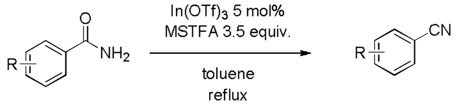
All reagents were of analytical grade purchased commercially and used without further purification. All reactions were carried out under argon using magnetic stirring unless otherwise noted. ^1H NMR and ^{13}C NMR spectral data were recorded on a JEOL JMTC-500 spectrometer using TMS as internal standard.

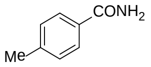
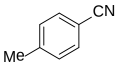
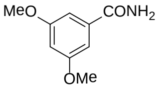
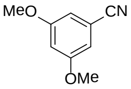
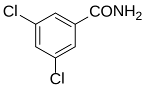
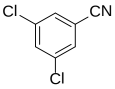
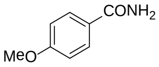
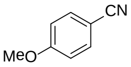
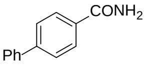
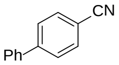
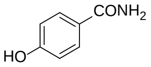
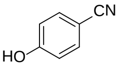
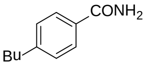
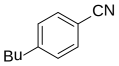
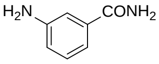
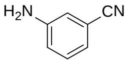
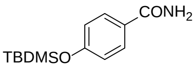
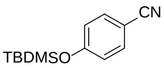
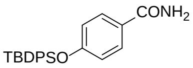
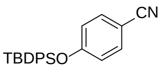
4.2. General Experimental Procedure

The starting benzamide substrates (1 mmol) and $In(OTf)_3$ (5 mol%) were dissolved in dehydrated toluene (5 mL) contained in a 100 mL flask equipped with a magnetic stirrer and a reflux condenser, and 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 concentrated by rotary evaporation. Flash column chromatography on silica gel furnished the corresponding nitrile product, which was confirmed by spectroscopy.

4-(*tert*-butyldimethylsilyloxy)benzonitrile: ^1H NMR (500 MHz, $CDCl_3$) $\delta = 7.54$ (2H, d, $J = 8.5$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 0.98 (9H, s), 0.23 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 159.7$, 134.0, 120.8, 119.2, 104.6, 25.5, 18.2, −4.4.

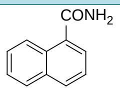
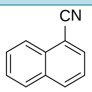
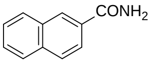
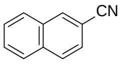
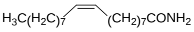
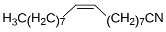
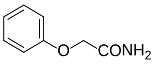
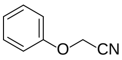
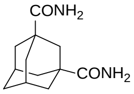
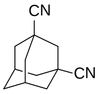
Table 2. Conversion of aromatic primary amides to nitriles.



Entry	Starting substrate	Product	Time (h)	Yield[a] (%)
1			3	70
2			3	quant
3			3	quant
4			3	quant
5			3	quant
6			3	quant
7			3	94%
8			4	quant
9			3	98%
10			3	81%

[a] Isolated yields.

Table 3. Conversion of bicyclic and aliphatic primary amides to nitriles.

Entry	Starting substrate	Product	Time (h)	Yield[a] (%)
1			3	75
2			3	quant
3			3	94
4			3	69
5			3	quant

[a] Isolated yields.

4-(*tert*-butyldiphenylsilyloxy)benzonitrile: ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 7.67$ (4H, dd, $J = 8.0$ and 2.0 Hz), 7.48 - 7.37 (8H, m), 6.79 (2H, d, $J = 8.5$ Hz), 1.10 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 159.5$, 135.3, 133.8, 131.7, 130.3, 128.0, 120.6, 119.2, 104.4, 26.3, 19.4.

Acknowledgements

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