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Facile Preparation of α-Aryl Nitriles by Direct Cyanation of Alcohols with TMSCN Under the Catalysis of InX_3

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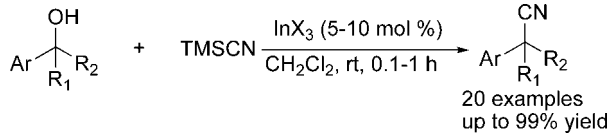
ABSTRACT



A convenient and efficient synthesis of α-aryl nitriles was developed by direct cyanation of alcohols with TMSCN under the catalysis of Lewis acid. Using 5−10 mol % of $InBr_3$ as the catalyst, a variety of benzylic alcohols can be converted to the corresponding nitriles in 5−30 min with yields of 46−99%.

α-Aryl nitriles represent one class of important compounds with extensive biological activities and utility in organic synthesis. For example, verapamil (**1**)[1] is used clinically for the treatment of chronic obstructive pulmonary disease and hypertension. As synthetic intermediates, α-aryl nitriles are potentially valuable precursors for the synthesis of well-known drugs such as indoprofen (**2**),[2] cicloprofen (**3**),[3] and naproxen (**4**)[4] as shown in Figure 1. Furthermore, α-aryl nitriles are also versatile building blocks for constructing the corresponding amides, aldehydes, ketones, primary amines, and heterocycles.[5] Accordingly, several useful strategies for the synthesis of α-aryl nitriles have been developed over the decades, typically including nucleophilic substitution of a benzylic halide,[6] photochemical aromatic cyanomethylation,[7] dehydration of amides,[8] hydrocyanation of olefins,[9] acylations of silyl ketene imines,[10] and coupling reactions of nitriles with aryl halides,[11] among others.[12] When an alcohol is used as the starting material for the synthesis of

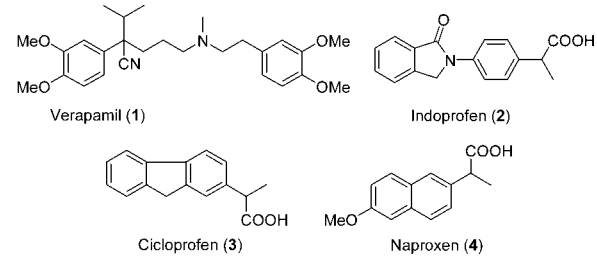


Figure 1. Verapamil and some derivatives of α-aryl nitriles.

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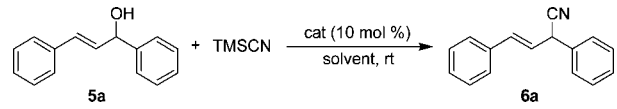
the corresponding nitrile, at least two viable synthetic routes can be envisaged, i.e., a prior transformation of the alcohol into the corresponding halide or related compounds that have good leaving potential followed by cyanation or, alternatively, via direct conversion of the corresponding alcohols using various cyanating reagent systems.[13] Although direct cyanation of alcohols constitutes a particularly attractive synthetic route to nitriles in terms of both starting material accessibility and economy concerns, unfortunately many of the direct cyanation protocols developed suffered from shortcomings such as the use of stoichiometric activating reagents and (or) tedious workup procedures, which would to some extent hamper their practical utilizations.[13]

Recently, direct substitutions of the hydroxyl group in alcohols by various nucleophiles such as allyl-, alkynyl-, and propargylsilanes,[14] 1,3-dicarbonyl compounds,[15] amides[16] or amines,[17] and so on[18] under the catalysis of Lewis acids (such as FeX_3, BiX_3, or InX_3, etc. X = Cl, Br, or OTf) have been of much research interest. In these reactions, the hydroxyls in alcohols can be directly substituted by the desired nucleophiles without the need for prior transformation into the groups that have good leaving potentials. It has been assumed that at least in some of these reactions the alcohols are activated toward nucleophilic substitution by interaction with the oxophilic Lewis acids.[14c] Inspired by these results, we envisaged that a direct transformation of alcohols to the corresponding α-aryl nitriles might also be feasible in the presence of a suitable Lewis acidic catalyst/cyanating agent combination. Herein, we report an InX_3[14a−c,15a,19] catalyzed cyanation protocol for α-aryl alcohols using TMSCN (trimethylsilyl cyanide) as the cyanating agent, affording the corresponding α-aryl nitriles efficiently in high yields under mild reaction conditions.

The work was started by testing the cyanation of allylic alcohol **5a** with TMSCN in dichloromethane in the presence of a catalytic amount (10 mol %) of $FeCl_3$. The reaction proceeds smoothly at room temperature with complete substrate conversion in 30 min, albeit with only a moderate yield of isolated allylic cyanide **6a** (41%). Encouraged by this result, various Lewis acids as well as the reaction conditions were further screened for the catalysis (Table 1). As shown in Table 1, the bismuth(III) halides ($BiCl_3$ or $BiBr_3$) are more efficient for the reaction than $FeCl_3$, affording the target nitrile in good

Table 1. Optimization of the Reaction Conditions for Lewis Acid Catalyzed Cyanation of **5a**[a]



entry	cat.	TMSCN (equiv)	solvent	time (h)	yield (%)[b]
1	$FeCl_3$	2	CH_2Cl_2	0.5	41
2	$BiCl_3$	2	CH_2Cl_2	0.5	88
3	$BiBr_3$	2	CH_2Cl_2	0.5	73
4	$AuCl_3$	2	CH_2Cl_2	2	82
5	$In(OTf)_3$	2	CH_2Cl_2	2	78
6	$InCl_3$	2	CH_2Cl_2	0.5	93
7	$InBr_3$	2	CH_2Cl_2	0.1	98
8	/	2	CH_2Cl_2	10	0
9	$InBr_3$	1	CH_2Cl_2	0.5	67
10	$InBr_3$	2	THF	2	trace
11	$InBr_3$	2	dioxane	2	23
12	$InBr_3$	2	toluene	0.5	81
13	$InBr_3$	2	$ClCH_2CH_2Cl$	0.5	99
14	$InBr_3$	2	CH_3CN	0.5	87
15	$InBr_3$	2	*n*-hexane	5	41
16[c]	$InBr_3$	2	CH_2Cl_2	1	95

[a] All the reactions were carried out by dropwise addition of a solution of **5a** in the specified solvent to a stirred suspension of TMSCN and the metal salt (10 mol %) in the same solvent over 30 min (or less), and the resulting mixtures were stirred therein at room temperature for the specified time periods. [b] Yield of the isolated product. [c] 0.05 equiv of $InBr_3$ was used.

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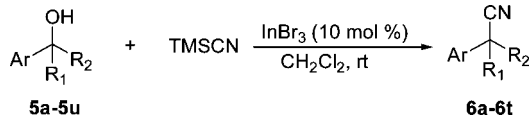
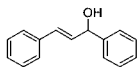
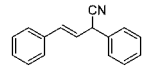
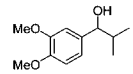
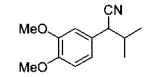
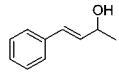
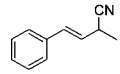
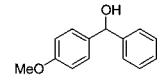
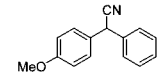
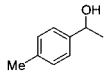
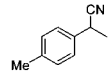
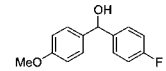
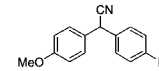
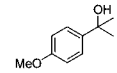
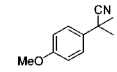
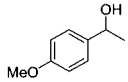
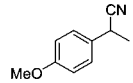
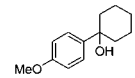
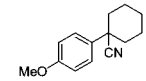
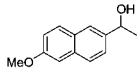
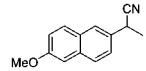
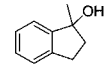
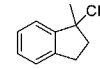
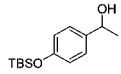
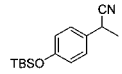
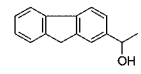
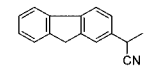
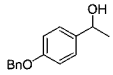
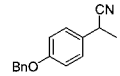
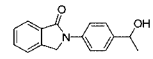
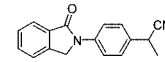
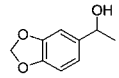
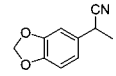
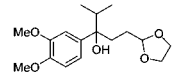
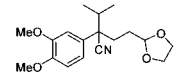
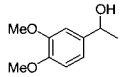
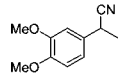
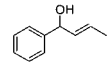
Table 2. $InBr_3$-Catalyzed Direct Cyanation of Alcohols **5a**−**5u** with TMSCN[a]



5a-5u **6a-6t**

entry	alcohol **5**	time (h)	nitrile **6** (yield)	entry	alcohol **5**	time (h)	nitrile **6** (yield)
1	 **5a**	0.1	 **6a** (98%)	12	 **5l**	0.2	 **6l** (89%)
2	 **5b**	0.2	 **6b** (84%)	13	 **5m**	0.5	 **6m** (84%)
3	 **5c**	0.5	 **6c** (59%)	14	 **5n**	0.5	 **6n** (85%)
4	 **5d**	0.5	 **6d** (46%)	15	 **5o**	0.1	 **6o** (89%)
5	 **5e**	0.1	 **6e** (99%)	16	 **5p**	0.5	 **6p** (93%)
6	 **5f**	0.5	 **6f** (96%)	17	 **5q**	0.2	 **6q** (79%)
7	 **5g**	0.2	 **6g** (98%)	18	 **5r**	0.5	 **6r** (95%)
8	 **5h**	0.5	 **6h** (92%)	19	 **5s**	0.2	 **6s** (95%)
9	 **5i**	0.2	 **6i** (96%)	20[b]	 **5t**	10	 **6t** (56%)
10	 **5j**	0.2	 **6j** (96%)	21	 **5u**	0.2	**6b** (86%)
11	**5k**	0.1	**6k** (99%)				

[a] Reaction conditions: a solution of **5** (0.25 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a suspension of TMSCN (0.5 mmol) and $InBr_3$ (10 mol %) in CH_2Cl_2 (0.5 mL) over the specified time period (<30 min) at room temperature, followed by stirring the resulting mixture for an extended time period or immediate workup. [b] $InCl_3$ was used as the catalyst instead of $InBr_3$.

yields under identical conditions (entries 2 and 3). $AuCl_3$ and $In(OTf)_3$ were also found to be effective catalysts for the reaction, giving the cyanation product in good yields (78−80%) in somewhat prolonged reaction periods (entries 4 and 5). Among the examined metal salts, $InCl_3$ and $InBr_3$ turned out to be optimal in terms of reaction efficiency, affording the cyanation product in excellent yields within short reaction periods (entries 6 and 7), presumably as a result of the moderate Lewis acidity and water/alcohol tolerance of the indium(III) species.[14c,20] A control experiment indicated that under the

(20) Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764.

test conditions the reaction was negligible in the absence of a catalyst (entry 8). Lowering the amount of the nucleophile TMSCN from 2 equiv (relative to that of the alcohol) to 1 is obviously unfavorable for the reaction, as the yield of the desired product decreased considerably, probably owing to more side product formation (chalcone and 1,3-diphenylpropene were isolated from the reaction system as the byproducts due to the disproportionation of **5a** under the experimental conditions) by competing reactions under lower nucleophile concentration (entries 9 vs 7). Screening the solvents for $InBr_3$-catalyzed reaction revealed that CH_2Cl_2 or 1,2-dichloroethane (DCE) was optimal (entries 7 and 13), whereas coordinating solvents such as THF or dioxane were deleterious to the catalysis (entries 10 and 11). Furthermore, when the catalyst loading of $InBr_3$ was reduced to 5 mol %, the cyanation product could still be obtained in high yield within a slightly prolonged reaction period (entry 16).

Subsequently, we proceeded to examine the substrate scope of the alcohol cyanation protocol for the preparation of α-aryl nitriles with $InBr_3$ as the catalyst (Table 2). As shown in the table, most of the tested benzylic alcohols can smoothly react with TMSCN in high efficiency (usually less than 10 min) under the optimized conditions, giving the corresponding nitriles in good to excellent yields. For the reaction involving the dissymmetric allylic alcohol **5b**, only one of the two potential isomers was isolated in good yield (entry 2).[21] While only moderate yield of the nitrile was obtained for the cyanation of *ortho*-methoxy substituted 1-phenyl ethanol **5d** (entry 4), the presence of the same substituent at the *para*-position of the α-phenyl ring of the substrate was obviously beneficial for the reaction (entry 5). Although the exact reason for such a dramatic difference in reactivity is unclear, the electronic and/or steric effect of the *ortho*-methoxy group in substrate **5d** should be responsible for the result observed. For the reactions of other analogous substrates, it is obvious that the electron-donating groups at the *para*-position of benzylic alcohols consistently gave the corresponding nitriles in high yields (entries 6−14). Furthermore, for the cyanation of the sterically more demanding tertiary alcohols, which are known to be difficult substrates for other cyanation approaches, good to excellent yields of nitriles were obtained (entries 15−17). To our delight, the precursors for cicloprofen and indoprofen, respectively, can also be efficiently obtained in high yields by this protocol (entries 18 and 19). Intriguingly, when alcohol **5t** was subjected to the cyanation condition with $InBr_3$ as the catalyst, an intractable mixture was obtained. Further screening of a variety of Lewis acids revealed that $InCl_3$ was an effective catalyst for the transformation of **5t**, affording the nitrile product **6t**, a key intermediate, in 56% yield (entry 20). Therefore, the present protocol has provided an alternative facile synthesis of verapamil.[10,11a]

(21) ^{1}H NMR spectrum of the crude reaction products indicated that a regioisomer of **6b** is also formed as the minor product (14%) (see page S55 in Supporting Information).

However, it is worth noting that alcohol substrates including primary alcohols, such as $PhCH_2OH$, 4-$MeOC_6H_4CH_2OH$, or (*E*)-3-PhCH═$CHCH_2OH$, and secondary 1-phenyl ethanol were found to be not amenable to this catalytic cyanation protocol. In the reactions of alcohols bearing electron-deficient aryl substituents, such as 1-(4-fluorophenyl)ethanol, 1-(4-nitrophenyl)ethanol, or 1-(pyridin-2-yl)ethanol, the corresponding cyanation products were not obtained under otherwise identical reaction conditions, which might be attributed to the difficulty in the formation of a carbo-cationic intermediate.

Although the exact mechanism of this In(III)-catalyzed cyanation reaction is unclear at the present stage, we speculate that the catalytic cycle might involve some type of carbenium intermediates[14c,15d] formed by the heterolytic cleavage of the C−O bond of the alcohols with the assistance of Lewis acidic In(III) (and TMSCN). Experimental evidence in support of this proposal was observed in the cyanation of enantioenriched (*S*)-**5e** (90% ee), where racemic cyanation product **6e** was isolated in high yield (92%). In addition, when (*E*)-1-phenylbut-2-en-1-ol (**5u**), a regioisomer of **5b**, was submitted to the cyanation reaction, the essentially identical yield of **6b** (entry 2 vs 21 in Table 2) and regioisomer distribution[21] of cyanation products to the case of **5b** were observed (see also pp S54−55 in Supporting Information), indicating the involvement of a delocalized carbocation in the catalytic process.

In summary, we have developed a new and efficient catalytic protocol for the preparation of α-aryl nitriles via a direct cyanation of appropriate alcohols. Using InX_3 (X = Br or Cl) as the catalyst, a variety of α-aryl alcohols can be converted to the corresponding nitriles commonly within 5−30 min in good to excellent yields under mild reaction conditions. Of special importance, the method was demonstrated to be very convenient for the synthesis of the key nitrile precursors for some clinically important compounds such as verapamil (**1**), indoprofen (**2**), cicloprofen(**3**), and naproxen (**4**). Further development of a catalytic asymmetric version of this method is in progress in our laboratory.

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Supporting Information Available: A general experimental procedure and spectroscopic data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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