Tetrahedron 65 (2009) 4351–4355

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of α-aryl nitriles through $B(C_6F_5)_3$-catalyzed direct cyanation of α-aryl alcohols and thiols

Gurusamy Rajagopal[†], Sung Soo Kim[*]

Department of Chemistry, Inha University, Incheon 402-751, South Korea

ARTICLE INFO

Article history:
Received 29 January 2009
Received in revised form 23 March 2009
Accepted 24 March 2009
Available online 1 April 2009

Keywords:
Direct cyanation
α-Aryl alcohols
α-Aryl thiols
Lewis acid

ABSTRACT

Various α-aryl nitriles have been prepared in excellent yield from the corresponding α-aryl alcohols employing 3 mol % of $B(C_6F_5)_3$ (**1**) as Lewis acid catalyst and $(CH_3)_3SiCN$ (TMSCN) as cyanide source. Cyano transfer from TMSCN to alcohol proceeds within short reaction time at rt. α-Aryl thiols also produce corresponding nitriles in good to excellent yield at reflux condition.

1. Introduction

Nitriles are valuable intermediates that can be transformed to a variety of biologically important substances such as oxazoles,[1] thiazoles,[2] triazoles,[3] oxadiazoles,[4] and tetrazoles.[5] α-Arylnitriles are potentially valuable precursors for the synthesis of well known drugs such as verapamil,[6] indoprofen,[7] cicloprofen, and naproxen.[8] Direct substitutions of the hydroxyl group in alcohols by various nucleophiles such as allyl-, alkynyl-, and propargylsilanes,[9] 1,3-dicarbonyl compounds,[10] amides[11] or amines,[12] and so on[13] using the Lewis acid catalysts have aroused much research interest. In these reactions, the hydroxyl groups in alcohols can be directly substituted by the desired nucleophiles without the need for prior transformation into the groups that have good leaving potentials. Aryl nitriles are usually synthesized from aryl halides using stoichiometric amount of copper(I) cyanide, which has been known for over 80 years.[14] Nitriles are also prepared by dehydration of amides and aldoximes,[15] acylations of silyl ketene imines,[16] hydrocyanation of olefins,[17] and displacement of aryl triflates.[18] Microwave-assisted preparation of aryl nitriles has been reported too.[19] Recently palladium catalyzed cyanation of aryl and heteroaryl chlorides has appeared in the literature.[20]

The conversion of an alcohol into the corresponding nitrile is a fundamental synthetic process for carbon chain elongation. It is usually performed through prior conversion of hydroxyl group to halides and sulfonates. However, there are only a few reports on the direct cyanation of alcohols into nitriles in one-pot procedure.[21] Reagent system composed of TMSCN and $InBr_3$ in CH_2Cl_2 was reported as a convenient and efficient system for cyanation of secondary alcohols.[22]

While various Lewis acids are employed in modern organic synthesis, boron based reagents still remain prominent as a result of their high Lewis acid strength and ready availability. The strong organometallic Lewis acid, $B(C_6F_5)_3$ **1**, has emerged in recent years as a viable alternative to BF_3.[23] Owing to its uniqueness and commercial availability, its applications in organic synthesis are growing and have been reviewed.[24]

The first commercial application of **1** was introduced as the cocatalyst in metallocene mediated olefin polymerization.[25] The functional group transformation by **1** was initially undertaken by Ishihara et al. for aldol type reaction.[26] Recently, the applications of **1** are found in hydrosilation of alcohols,[27a] enones,[27b] carbonyl groups,[27c] and imines, [27d] stereoselective transformation of epoxides,[27e] tritylation of alcohols,[27f] allylstannation of aromatic alehydes,[27g] allylation of secondary benzyl acetates,[27h] Ferrier azaglycosylation with sulfonamides and carbamate,[27i] reduction of carbonyl group to methylene,[27j] cleavage of aryl and alkyl ether with hydrosilanes,[27k,l] aziridines' ring opening,[27m] and hydrogenation of imines.[27n]

2. Results and discussion

We have developed several catalytic methods for the oxidation of alcohols[28] and cyanosilylation of carbonyl compounds.[29] Herein

---

[*] Corresponding author. Tel.: +82 32 860 7678; fax: +82 32 867 5604.
E-mail address: sungsoo@inha.ac.kr (S.S. Kim).

[†] Present address: Dept. of Chemistry, Govt. Arts College (Men), Nandanam, Chennai 600 035, India.

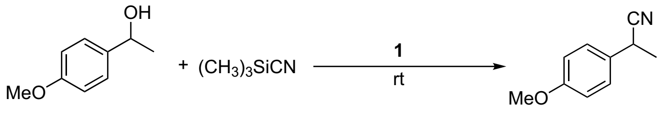
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.03.073

we report **1** as a simple and effective catalyst for the direct cyanation of α-aryl alcohols with TMSCN at rt. This can be the first example of borane catalyzed cyanation of alcohols.

To obtain the optimized reaction conditions, we have chosen the reaction of 4-methoxy-α-methylbenzyl alcohol with TMSCN in the presence of $B(C_6F_5)_3$ as Lewis acid catalyst. First we examined the solvent suitability for this reaction. The data in Table 1 indicate that CH_3CN is the most appropriate solvent (entries 1–9). CH_2Cl_2 also acts as a good solvent for this system with little longer reaction time (entry 7). The solvent-free reaction gave only good yield of the corresponding nitrile (entry 10). To determine the effect of catalytic loading for improving the yield, we have performed the reaction with 1–20 mol % of $B(C_6F_5)_3$ in CH_3CN. We have found that the reaction proceeds to give 94% yield with 3 mol % of the catalyst (entry 4). TMSCN and n-Bu_4NCN were also tested for the cyanation reaction as cyanide source. In terms of yield and reaction time, TMSCN gave the best results (entry 4). We have therefore chosen entry 4 (Table 1) as the optimum reaction condition for cyanation of α-aryl alcohols.

Having established the standard conditions, the scope of this protocol was examined for various α-aryl alcohols (Table 2). *sec*-1-Phenylethanol (entry 1) and its *para*-substituted derivatives (entries 2–6) are efficiently converted to corresponding α-aryl nitriles in relatively short reaction time. It is worthwhile to note that the recently reported $InBr_3$ catalyzed protocol[22] is not amenable to *sec*-1-phenylethanol for cyanation reaction. Our system, however, gives excellent yield for the same substrate. *ortho*-Di substituted α-aryl alcohol underwent smooth cyanation and gave moderate yield (entry 7). The change of phenyl to naphthyl group (entries 8 and 9) hardly influences the reactivity and also the yield. Benzhydrol underwent smooth cyanation and gave an excellent yield (entry 10). The reactions of benzhydrols having chlorine and fluorine atoms at *para*-position gave the corresponding α-aryl nitriles in high yields (entries 11 and 12). Furthermore, sterically hindered triphenylmethanol, which is known to be a difficult substrate for cyanation reaction, gave excellent yield in short reaction time (entry 13). This may indicate that steric hindrance is no longer important for the cyanation. It should be noted that alcohol having additional methylene group in the side chain was also proved as good substrate for cyanation reaction (entry 14). Good yields were obtained for *ortho*-methoxy substituted 1-phenylpropanaol

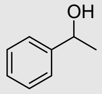
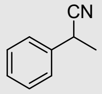
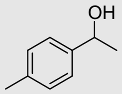
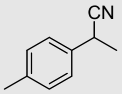
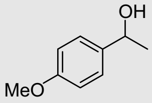
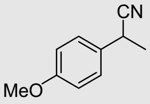
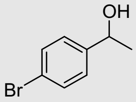
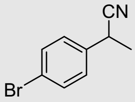
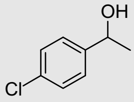
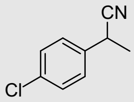
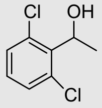
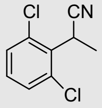
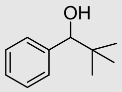
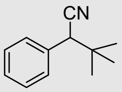
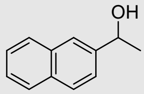
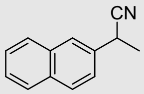
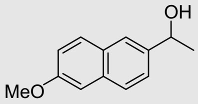
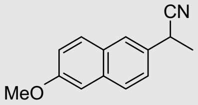
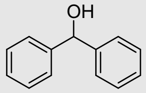
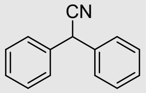
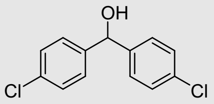
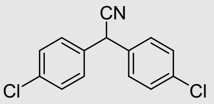
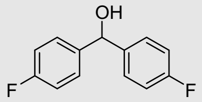
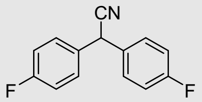
Table 1
Direct cyanation of 4-methoxy-α-methylbenzyl alcohol under various reaction conditions[a]



Entry	Catalyst loading (mol %)	Solvent	Time (min)	Yield[b]
1	20	CH_3CN	30	96
2	10	CH_3CN	30	96
3	5	CH_3CN	60	95
4	3	CH_3CN	55	94
5	2	CH_3CN	90	95
6	1	CH_3CN	180	90
7	3	CH_2Cl_2	70	93
8	3	CH_3Cl	180	40
9	3	THF	240	50
10	3	No solvent	120	75
11	3	CH_3CN	120	50[c]

[a] Reagent and condition: 1.0 mmol of 4-methoxy-α-methylbenzyl alcohol, 1.0 mmol of TMSCN.
[b] Isolated yield.
[c] n-Bu_4NCN (5.0 mmol) was used as cyanide source.

Table 2
$B(C_6F_5)_3$-catalyzed direct cyanation of α-aryl alcohols with TMSCN at rt[a]

Entry	Substrate	Time (min)	Product	Yield[b]
1	 **(1a)**	60	 **(1b)**	90
2	 **(2a)**	60	 **(2b)**	90
3	 **(3a)**	55	 **(3b)**	94
4	 **(4a)**	70	 **(4b)**	90
5	 **(5a)**	60	 **(5b)**	89
6	 **(6a)**	70	 **(6b)**	85
7	 **(7a)**	60	 **(7b)**	92
8	 **(8a)**	60	 **(8b)**	90
9	 **(9a)**	60	 **(9b)**	92
10	 **(10a)**	60	 **(10b)**	93
11	 **(11a)**	60	 **(11b)**	91
12	 **(12a)**	60	 **(12b)**	90