ORGANIC LETTERS

2011
Vol. 13, No. 20
5608–5611

Lewis Acid Catalyzed Direct Cyanation of Indoles and Pyrroles with *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS)

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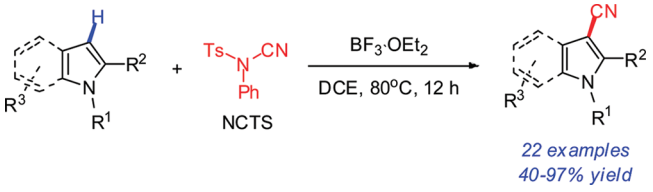
Received August 29, 2011

ABSTRACT



$BF_3 \cdot OEt_2$-catalyzed direct cyanation of indoles and pyrroles using a less toxic, bench-stable, and easily handled electrophilic cyanating agent *N*-cyano-*N*-phenyl-*para*-toluenesulfonamide (NCTS) affords 3-cyanoindoles and 2-cyanopyrroles in good yields with excellent regioselectivity. The substrate scope is broad with respect to indoles and pyrroles.

Aryl nitriles are important constituents of pharmaceuticals, agrochemicals, dyes, and natural products.[1] In addition, the nitrile moiety also serves as a key intermediate for a broad range of functional group transformations leading to the formation of amines, aldehydes, acids, ketones, amides, and heterocycles.[2] The Rosenmund–von Braun reaction[3] and the Sandmeyer reaction[4] represent two classical methods for the introduction of a cyano group onto the aromatic ring, where copper(I) cyanide is used as the cyanating reagent. In recent decades, nucleophilic transition-metal-catalyzed cyanation of aryl halides using KCN,[5] $Zn(CN)_2$,[6] acetone cyanohydrin,[7] trimethylsilyl cyanide,[8] and $K_4[Fe(CN)_6]$[9] as cyanating agents has emerged as a useful alternative for the preparation of aryl nitriles. Advances in transition-metal-catalyzed C–H bond functionalization have also enabled the direct cyanation of aromatic compounds.[10] However, severe drawbacks of cyanide sources including the notorious toxicity or the generation of stoichiometric amounts of metal wastes prevent their wide application in academic laboratories and the

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10.1021/ol202335p
Published on Web 09/14/2011

pharmaceutical industry. Moreover, the efficiency of these transformations is hampered by the high affinity of cyanide toward transition-metal-based catalytic systems, which often results in the rapid formation of stable cyanide complexes and deactivation of transition-metal catalysts.[11]

To circumvent this problem, electrophilic cyanation is among the most promising approaches to access aryl nitriles. To date, electrophilic cyanation of reactive organometallic species (i.e., Grignard reagents,[12] organolithium reagents,[13] organozinc reagents,[14] arylstannanes[15]) have been investigated. However, most of the established electrophilic cyanations need highly toxic cyanogen halides, either used as cyanating sources directly or to prepare electrophilic cyanating agents.[16] Moreover, the presence of a highly reactive carbon−metal bond somehow undermines the functional group tolerance of this type of method. Therefore, new methodologies enabling the direct electrophilic cyanation through aromatic C−H bond functionalization using environmentally friendly cyanating reagents under mild conditions would be highly desirable for the synthetic organic community.

During our search for less toxic and easily handled electrophilic cyanating agents, we were attracted to NCTS (**1**). NCTS is a bench-stable crystalline compound first synthesized by Kurzer in 1949.[17] It is noteworthy that NCTS is readily synthesized in an environmentally benign fashion from inexpensive phenylurea by dehydrative tosylation in pyridine without the use of toxic cyanogen halides. However, to our surprise the potential of this N−CN bond containing compound as an electrophilic cyanating reagent was not evaluated until very recently.[18] In 2011, Beller and co-workers reported a Rh-catalyzed cyanation of arylboronic acids with NCTS as a cyanating agent.[18a] Furthermore, they have developed an electrophilic cyanation through the reaction of NCTS with aromatic Grignard reagents.[18b]

On the other hand, indoles are ubiquitous motifs in natural products and pharmaceutical agents.[19] Currently, most commonly used methods for the cyanation of indoles proceed through a stepwise manner where isocyanates are employed.[20] Kita and co-workers reported an intriguing hypervalent iodine(III)-mediated direct cyanation which is believed to proceed through a single electron transfer (SET) process.[21] However, due to the highly reactive nature of the hypervalent iodine(III) reagent, this methodology suffers from inferior yields and poor regioselectivity with regard to indole substrates. Recently, cyanation through transition-metal-catalyzed C−H bond functionalization has attracted great attention.[10] For example, Ding and Jiao reported Pd-catalyzed cyanation of indoles by using *N*,*N*-dimethylformamide as a cyanating agent.[10j] As a continuation of our interest in developing an environmentally benign cyanation process,[10g] and also inspired by the recent development of cyanation with electrophilic cyanating agents, we decided to explore the possibility of electrophilic cyanation through direct C−H bond functionalization.

Initial investigations were aimed at promoting the cyanation of *N*-substituted indoles with NCTS **1**. At the beginning of our research, indole derivatives with various *N*-protecting groups (e.g., −Bn, −TIPS, −Ts, etc.) were screened, and we were disappointed to find that NCTS was ineffective in all the cyanation studies. At this stage, we reasoned that a Lewis acid might serve to activate the cyanating agent NCTS and render the desired cyanation reaction as favorable. After conducting an extensive survey of Lewis acids, to our delight, it was observed that a *catalytic* amount of $BF_3 \cdot OEt_2$ (Table 1, entry 8) uniquely facilitated the desired cyanation. Other conventionally used Lewis acids such as $Zn(OTf)_2$, $FeCl_3$, $AlCl_3$, and $Sm(OTf)_3$ (Table 1, entries 1−4) proved to be poor catalysts for this reaction. With the use of $In(OTf)_3$ and AgOTf, only low to moderate yields of the 3-cyanated product were observed (Table 1, entries 5 and 6, respectively). Interestingly, $AuCl_3$, a superior catalyst for the electrophilic halogenation of aromatic compounds,[22,23] failed to afford any cyanated product except a trace amount of undesired 3-chlorinated indole (Table 1, entry 7). Finally, no desired

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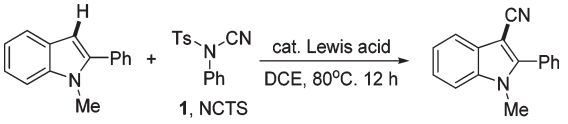
product was observed through the use of a catalytic amount of Brønsted acids (e.g., TFA, entry 9). Under optimal conditions, treatment of 1-methyl-2-phenyl-1*H*-indole with NCTS in the presence of catalytic $BF_3 \cdot OEt_2$ in DCE at 80 °C for 12 h delivered the cyanated product in 93% yield (Table 1, entry 8).

Table 1. Screening of Lewis Acid Catalysts[a]

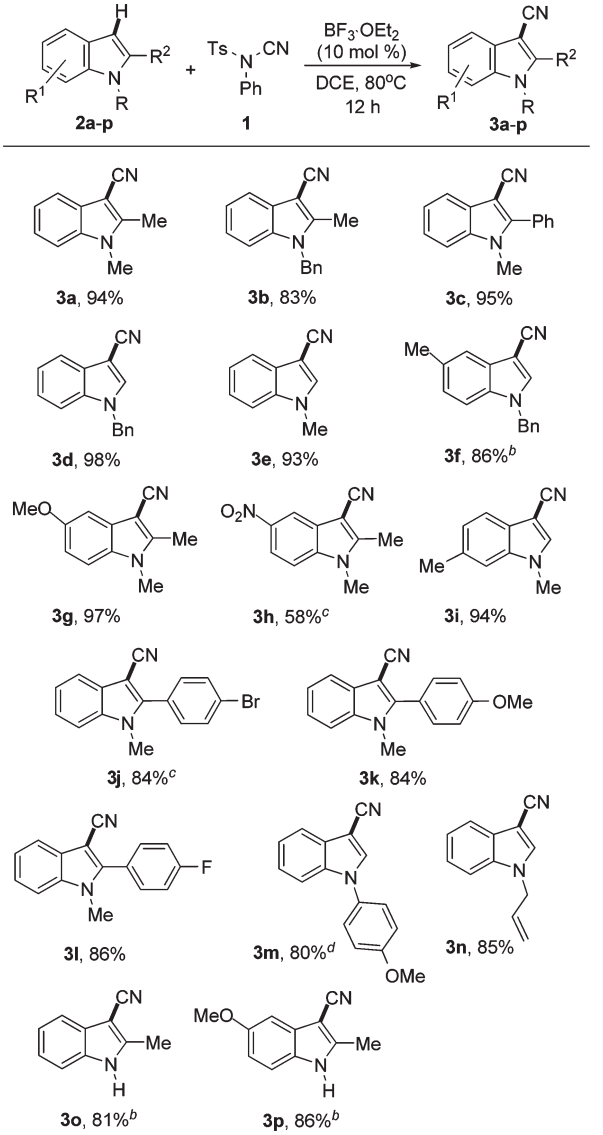


entry	cat. (mol %)	yield (%)[b]
1	$Zn(OTf)_2$ (20)	N.R.[c]
2	$FeCl_3$ (20)	N.R.
3	$AlCl_3$ (10)	N.R.
4	$Sm(OTf)_3$ (20)	N.R.
5	AgOTf (20)	<20
6	$In(OTf)_3$ (20)	47
7	$AuCl_3$ (8)	–[d]
8	**$BF_3 \cdot OEt_2$ (10)**	**97(93)**[e]
9	TFA (10)	N.R.

[a] Unless otherwise noted, the reaction conditions are as follows: indole (0.24 mmol, 1.2 equiv), NCTS **1** (0.20 mmol, 1.0 equiv), DCE (0.2 mL). [b] Yield determined based on GC-MS analysis using dodecane as internal standard. [c] N.R.: no reaction occurred. [d] Only trace amount of undesired 3-chlorinated product was observed. [e] Isolated yield in parentheses.

With the optimized reaction conditions in hand, a wide range of indole substrates were investigated in the $BF_3 \cdot OEt_2$-catalyzed cyanation process with NCTS (Scheme 1). 2-Substituted indoles afforded the corresponding cyanated products in excellent yields (Scheme 1, **3a**–**c**). More satisfyingly, we found that, in the absence of a substituent at the C2 position, the cyanation proceeded regioselectively to furnish 3-cyanoindoles as the only products (Scheme 1, **3d**–**e**). In this regard, this newly established protocol is superior over the previously reported palladium-catalyzed cyanation procedure, where indoles without C2 substituents were troublesome substrates due to the insuppressible formation of homocoupling byproducts.[10g] C5- and C6-substituted indoles were found to be suitable substrates (Scheme 1, **3f** and **3i**). Moreover, an electron-donating methoxy group (Scheme 1, **3g**) and an electron-withdrawing nitro group (Scheme 1, **3h**) at the C5 position were well-tolerated, although in the latter case a stoichiometric amount of $BF_3 \cdot OEt_2$ was needed to achieve a satisfactory conversion of the 5-nitro-substituted indole substrate to product **3h**. In addition to this, indoles bearing an electron-donating *para*-methoxyphenyl group (Scheme 1, **3k**) or electron-withdrawing *para*-bromophenyl and *para*-fluorophenyl groups (Scheme 1, **3j** and **3l**, respectively) at the C2 position were also found to be excellent substrates. Notably, the highly susceptible bromide moiety toward transition-metal catalysis remains intact under this cyanation protocol, allowing for further cross-couplings and demonstrating the advantage of this methodology. *N*-*para*-Methoxylphenyl and *N*-allyl indoles (Scheme 1, **3m** and **3n**) were successfully transformed into 3-cyanoindoles. Finally, the cyanation of free indoles proceeded smoothly as well (Scheme 1, **3o** and **3p**).

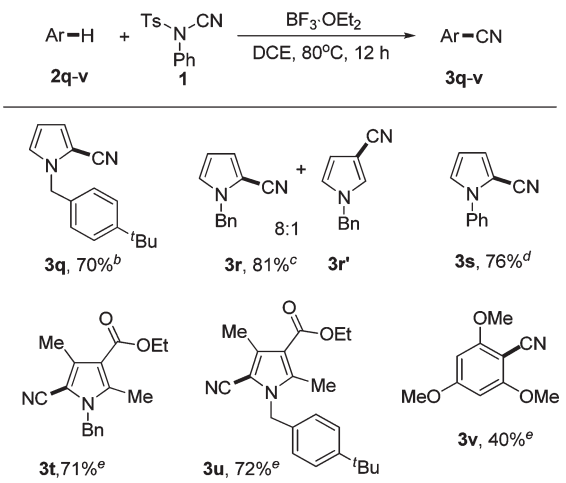
Scheme 1. $BF_3 \cdot OEt_2$-Catalyzed Cyanation of Indoles[a]



[a] Unless otherwise noted, the reaction conditions are as follows: indole (0.48 mmol, 1.2 equiv), NCTS **1** (0.40 mmol, 1.0 equiv), DCE (0.4 mL). All the yields refer to isolated yield. [b] 40 mol % $BF_3 \cdot OEt_2$ was used. [c] 100 mol % $BF_3 \cdot OEt_2$ was used. [d] 20 mol % $BF_3 \cdot OEt_2$ was used.

Encouraged by the success in the direct electrophilic cyanation of indoles, we next attempted to extend the substrate scope to pyrroles and arenes (Scheme 2). Gratifyingly, pyrroles were also found to be suitable substrates for this reaction, although higher amounts of $BF_3 \cdot OEt_2$ were often needed and the yield was slightly lower than in the case of cyanation with indoles. While *N*-benzyl pyrrole

Scheme 2. $BF_3 \cdot OEt_2$-Catalyzed Cyanation of Pyrroles[a]



[a] The reaction conditions are as follows: pyrrole or arene (0.48 mmol, 1.2 equiv), NCTS **1** (0.40 mmol, 1.0 equiv), DCE (0.4 mL). All the yields refer to isolated yields. [b]20 mol % $BF_3 \cdot OEt_2$ was used. [c]40 mol % $BF_3 \cdot OEt_2$ was used. The ratio of **3r** and **3r′** was 8:1 based on GC-MS analysis. The yield refers to the isolated product of **3r**. [d]150 mol % $BF_3 \cdot OEt_2$ was used. [e]100 mol % $BF_3 \cdot OEt_2$ was used.

afforded a mixture of 2- and 3-cyanated products (Scheme 2, **3r** and **3r′**, 8:1), the cyanation of *N-para-tert*-butyl pyrrole proceeded in a regiospecific manner (Scheme 2, **3q**). The reaction also worked well with pyrroles bearing three substituents including an electron-withdrawing ester group (Scheme 2, **3t** and **3u**). To further probe the scope of this transformation, we subjected a variety of arenes to the standard or slightly modified reaction conditions. It was observed that the reaction became sluggish in most cases, yet to our gratification, the cyanation of electron-rich 1,3,5-trimethoxybenzene still afforded a moderate yield through the use of 1 equiv of $BF_3 \cdot OEt_2$ (Scheme 2, **3v**).

In summary, we have developed a mild $BF_3 \cdot OEt_2$-catalyzed protocol for the direct cyanation of indoles and pyrroles using a bench-stable, easily handled, and less toxic electrophilic cyanating agent NCTS. The reaction is broad in scope with respect to indole and pyrrole substrates. This methodology does not use transition metal catalysts and provides an effective and practical means for accessing 3-cyanoindoles and 2-cyanopyrroles. Designing and developing novel electrophilic cyanating reagents to enable direct cyanation of other aromatic compounds based on a catalytic C–H bond functionalization strategy are currently underway in our laboratory.

Acknowledgment. The project is supported by the 973 Program (No. 2009CB825300) and NSFC (Grant Nos. 20832002, 20821062, 20902005, 21072009). The authors acknowledge Xi Wang for providing samples of *N*-substituted indoles for reactivity test.

Supporting Information Available. Experiment procedure, characterization data, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.