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A Convenient Synthesis of Benzonitriles via Electrophilic Cyanation with *N*-Cyanobenzimidazole

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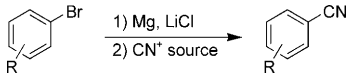
Benzonitriles constitute an important part of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.[1] In addition, the nitrile group serves as a valuable intermediate for a multitude of transformations into other functional groups, such as benzoic acid derivatives, benzylamines, benzaldehydes, and heterocycles.

The synthesis of aromatic nitriles can be achieved in numerous ways. Ammoxidation is the method of choice in industry on ton-scale synthesis,[2] whereby toluene derivatives are reacted with oxygen and ammonia at high temperature (300–550 °C) in the presence of a heterogeneous fixed-bed catalyst. However, lack of functional group tolerance and the harsh reaction conditions make this method not suitable for the preparation of functionalized benzonitriles.

Direct cyanation is probably the most versatile route to prepare functionalized benzonitriles. Traditional stoichiometric methods such as the Rosenmund–von Braun reaction of aryl halides[3] and diazotization of anilines with subsequent Sandmeyer reaction[4] have been replaced in recent years by transition-metal-catalyzed cyanations.[5] Hence, notable advancements for the catalytic cyanation of aryl halides using various cyanation reagents such as KCN,[6] $Zn(CN)_2$,[7] acetone cyanohydrin,[8] trimethylsilyl cyanide (TMSCN),[9] and $K_4[Fe(CN)_6]$[10] have been reported. However, a general problem in these reactions is the high affinity of cyanide towards Pd-, Ni-, and Cu-based catalysts, which often results in fast deactivation of the catalytic system. Therefore, the development of new methods is of continuing academic interest.

Recently, we developed a convenient protocol for the electrophilic fluorination of aryl and heteroaryl Grignard reagents applying pyridinium fluorides.[11] Inspired by this work and our long standing interest in the synthesis of benzonitriles,[10,12] we got attracted by the idea to directly synthesize benzonitriles from aryl Grignard reagents (Scheme 1). We envisioned that in situ generation of functionalized Grignard reagents[13,14] and the subsequent electrophilic cyanation should result in the desired benzonitriles. Such an approach is different from the known syntheses of benzonitriles and makes use of an electrophilic cyanation reagent under mild conditions. Electrophilic cyanations have been less studied compared to nucleophilic cyanations.[15] Examples using aromatic nucleophiles include cyanations of arylzinc reagents with tosyl cyanides,[16] directed lithiation followed by electrophilic cyanation with phenyl cyanate or *p*-toluenesulfonyl cyanide,[17] reaction of 3-pyridyllithium with *N*-cyanoimidazole,[18] reaction of aryltrimethylstannanes with cyanogen chloride in the presence of aluminum chloride,[19] and reaction of aryllithium compounds with pentachlorobenzonitrile.[20] With regard to aryl Grignard reagents so far the nucleophilic displacement of *p*-toluenesulfonyl cyanide and phenylmagnesium bromide,[21] and cyanation with 2-pyridyl cyanate have been investigated.[22]



Scheme 1. Synthesis of benzonitriles via electrophilic cyanation.

At the beginning of our work we prepared different *N*-cyano reagents, such as *N*-cyano-4-(*N*,*N*-dimethylamino)pyridinium tetrafluoroborate (**4**), *N*-cyano-4-methoxypyridinium tetrafluoroborate (**5**), *N*-cyanophthalimide (**6**), and *N*-cyanobenzimidazole (**7**),[23,24] either by treating the corresponding pyridine derivative with cyanogen bromide in the presence of silver tetrafluoroborate or by the reaction of the corresponding amide and amine with cyanogen bromide and triethylamine (for more details see Supporting Information). Next, these reagents were tested in the Grignard–cyanation sequence of 4-bromotoluene (**1**) to give 4-methylbenzonitrile (**2**) (Scheme 2).

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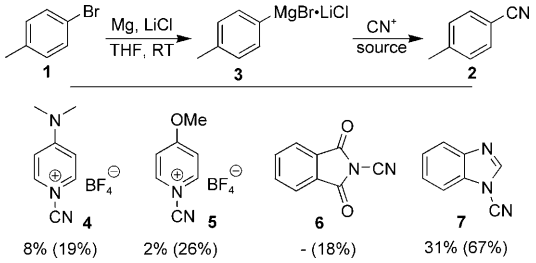
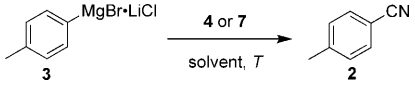


Scheme 2. Cyanation of 4-$MeC_6H_4MgBr{\cdot}LiCl$ using various cyanation reagents: **3** (0.5 mmol), CN^+ source (0.75 mmol), heptane (2 mL), 0 °C, 1.5 h. Yields are determined by GC with hexadecane as internal standard and yield of toluene is given in parenthesis.

In our model reaction we converted **1** into the corresponding aryl Grignard **3** in presence of LiCl, according to the procedure developed by Knochel and co-workers.[25] Based on our previous experience in electrophilic fluorinations, the cyanation was performed in heptane at 0 °C. As shown in Scheme 2, reaction of **3** with **4** and **5** gave **2** only in poor yield of 8 and 2%, respectively. As major product toluene was obtained. No cyanation product at all was observed in the reaction with **6**. However, cyanation with **7** resulted in the formation of **2** in 31% yield. To the best of our knowledge **7** has not been applied for the synthesis of benzonitriles via electrophilic cyanations.

In order to further improve the results, the influence of critical reaction parameters (temperature, solvent) were investigated in more detail, utilizing **4** and **7** as cyanation reagents. Selected results are shown in Table 1. Cyanation with **4** at elevated temperature in heptane gave the product in 43% yield and a similar trend was observed with **7** (Table 1, entries 1 and 4). In addition, changing the solvent from heptane to THF showed a significant positive influence on the cyanation. Thus, cyanation of **3** with **4** or **7** in THF at 0 °C provided **2** in 37 and 86% yield, respectively, and good selectivity (Table 1, entries 2 and 5). Notably, compared to metal-catalyzed cyanations the reaction is carried out at mild conditions (Table 1, entries 3–4).

Table 1. Variation of temperature and solvents in the cyanation of 4-$MeC_6H_4MgBr{\cdot}LiCl$.[a]



Entry	CN^+ Source	T [°C]	Solvent	Yield[b] **2** [%]
1	**4**	0→RT[c]	heptane	43
2	**4**	0	THF	37
3	**4**	0→RT[c]	THF	38
4	**7**	0→RT[c]	heptane	72
5	**7**	0	THF	86 (77)[d]

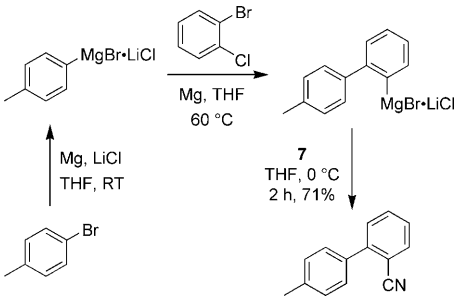
[a] Reaction conditions: **3** (0.5 mmol), CN^+ source (0.75 mmol), solvent (2 mL), 1.5 h. [b] Determined by GC with hexadecane as internal standard. [c] Grignard reagent **3** was added at 0 °C and warmed up to RT and stirred for 1.5 h. [d] Isolated yield is given in parenthesis.

After having identified suitable reaction conditions, we were interested in the scope and limitations of the procedure using different aryl Grignard reagents. As seen in Table 2, the cyanation of aryl Grignard reagents has substantial scope. Simple aromatic substrates, such as 4-methyl- and 4-methoxyphenylmagnesium bromides react smoothly to provide the corresponding benzonitriles in high yields (Table 2, entries 1 and 3). Notably, both electron-rich and electron-poor substrates were efficiently cyanated leading to the products in good isolated yield (Table 2, entries 3, 4, 10 and 11). Likewise, sterically demanding as well as non-hindered benzonitriles are readily accessible in good yield from the corresponding arylmagnesium bromides (Table 2, entries 8, 6, 5, 2 and 3, 9, 7, 1). Moderate to high yields were obtained in the cyanation of functionalized- (vinyl) and hetero- (pyridine, benzothiophene) arylmagnesium bromides (Table 2, entries 12–14). Notably, in case of the pyridyl substrate the arylmagnesium species was prepared by halogen–magnesium exchange.

Finally, we were interested in the possibility to apply this novel electrophilic cyanation procedure in a domino Grignard-coupling–cyanation sequence. Such a reaction would allow for the straightforward access of 2-biaryl- and 2-heteroarylarylnitriles.

The most prominent derivative of this class of compounds is 2-(4-tolyl)benzonitrile, which is the central intermediate for several angiotensin II antagonists.[26]

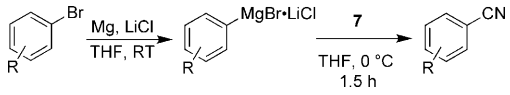
To our delight the coupling of 4-tolylmagnesium bromide with benzyne, generated from 2-chloro-1-bromobenzene and magnesium, followed by cyanation with *N*-cyanobenzimidazole gave the desired product in 71% isolated yield (Scheme 3). As shown in Scheme 4, similar coupling reactions can be performed with various Grignard reagents. All reactions proceeded smoothly in good yield to the corresponding 2-cyanobiaryls. To the best of our knowledge these transformations constitute the first examples of domino Grignard-coupling–cyanation reactions.

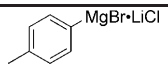
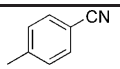
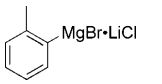
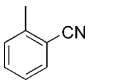
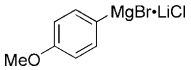
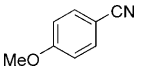
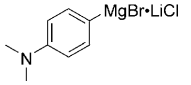
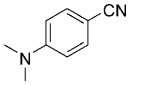
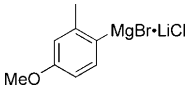
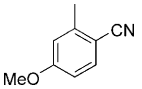
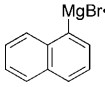
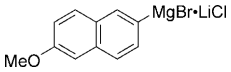
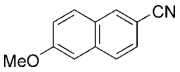
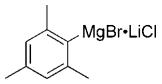
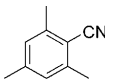
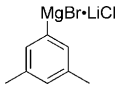
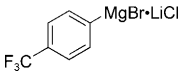
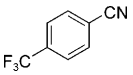
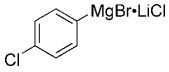
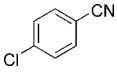
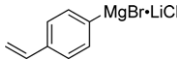
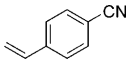
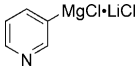
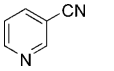
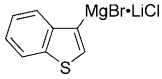
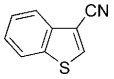


Scheme 3. Synthesis of 2-(4-tolyl)benzonitrile via domino Grignard-coupling–cyanation sequence.

In summary, an electrophilic cyanation of aryl and heteroaryl Grignard reagents applying *N*-cyanobenzimidazole has been developed. This methodology could be further applied

Table 2. Scope and limitations of the cyanation of ArMgBr·LiCl with **7**.[a]



Entry	ArMgBr·LiCl	Product	Yield[b] [%]
1			77
2			68
3			82
4			86
5			81
6			79
7			83
8			80
9			82
10			64
11			78
12			73
13[c]			61
14			76

[a] Reaction conditions: ArMgBr·LiCl (1 mmol), **7** (1.5 mmol), THF (3 mL), 0 °C, 1.5 h. [b] All are isolated yields. [c] Grignard reagent was prepared via Br/Mg exchange with *i*PrMgCl·LiCl.

towards a novel domino Grignard-coupling–cyanation strategy to obtain 2-cyano-1,1′-biaryls starting from simple aryl bromides. Easy access of many benzonitrile derivatives and mild reaction conditions are notable features of the present electrophilic cyanation procedure.

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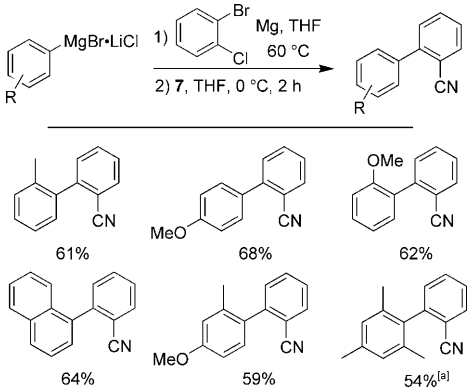

Scheme 4. Domino Grignard-coupling–cyanation for the synthesis of 2-cyano-1,1′-biaryls. [a] **4** was used as cyanation reagent at 50 °C.

Keywords: arenes · benzimidazole · cyanides · electrophilic cyanation · Grignard reaction

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