

A State-of-the-Art Cyanation of Aryl Bromides: A Novel and Versatile Copper Catalyst System Inspired by Nature

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This work is dedicated to Prof. Dr. Bernhard Lücke on the occasion of his 70th birthday

Abstract: A general protocol for the cyanation of aryl halides with the nontoxic cyanide source $K_4[Fe(CN)_6]$ using copper catalysis and a ligand system based on 1-alkylimidazoles is presented. The advantages of this system are the high selectivity, a unique substrate range, easy handling, and inexpensive reagents.

Keywords: alkyimidazoles • bromoarenes • copper • cyanation • nitriles

Introduction

Benzonitriles are of general interest for organic synthesis as an integral part of dyes, herbicides, agrochemicals, pharmaceuticals, and natural products.^[1] In addition, the nitrile group also serves as an important intermediate for a multitude of possible transformations into other functional groups, such as benzoic acid derivatives, benzylamines, benzaldehydes, and heterocycles.

Benzonitriles can be prepared in numerous ways. Typically, the introduction of a cyanide group is the most direct and versatile route to prepare functionalized benzonitriles. For more than a century stoichiometric methods prevailed in the laboratory and in industry. These methods included especially the Rosenmund-von Braun reaction of aryl halides^[2] and the diazotization of anilines with subsequent Sandmeyer reaction.^[3] Owing to (over)stoichiometric amounts of metal waste, such processes do not meet today's criteria of sustainable synthesis. On ton-scale the method of choice in industry is ammoxidation,^[4] in which the corresponding toluene derivatives are allowed to react with oxygen and ammonia at high temperature (300–550 °C) in the presence of heterogeneous fixed-bed catalysts.^[5] However, lack of functional

group tolerance and the harsh reaction conditions make this method less suitable for functionalized benzonitriles.

In the early 1970s the introduction and development of transition-metal-catalyzed C–C coupling reactions have dramatically changed the way functionalizations of arenes are performed. In this regard the first palladium-catalyzed cyanation of aryl halides was introduced in 1973 by Takagi et al. using aryl bromides and iodides with potassium cyanide as cyanating agent.^[6] Since then various catalysts have been developed for the coupling of aryl halides with cyanide. These are transition metal complexes based on palladium, nickel, and more recently copper. Clearly so far, palladium complexes have dominated as catalysts in cyanation reactions because they tolerate a wider variety of functional groups and are less sensitive to air and humidity than nickel catalysts, and they are more active than copper catalysts.

A general problem of metal-catalyzed cyanations is the high affinity of cyanide towards typical Pd-, Ni-, and Cu-based catalysts. Often a fast deactivation of the catalytic system is observed by the formation of stable cyanide complexes, and catalysis proceeds in general with low efficiency. To overcome this problem, typically, solvents are applied in which standard cyanide sources such as NaCN, KCN, and $Zn(CN)_2$ ^[7] have a very low solubility.^[8] We and others have shown that organic, for example, tetramethylethylenediamine (tmeda),^[9] and inorganic, for example, Zn and Zn salts,^[10] additives are beneficial for the regeneration of the catalytically active metal center. Another elegant approach is the slow dosage of the corresponding cyanide source, for example, acetone cyanohydrin^[11] or trimethylsilyl cyanide (TMSCN),^[12] which keeps the cyanide concentration low and leads to a higher catalyst productivity. Other recent de-

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velopments include microwave activation,^[13] and the application of novel catalyst systems.^[14] However, most of these developments have drawbacks such as toxicity of the cyanide source and comparably high catalyst costs (low catalyst productivity).

In 2004, we described for the first time catalytic cyanations with potassium hexacyanoferrate(II) $K_4[Fe(CN)_6]$, which has the advantage of being essentially the least toxic cyanide source conceivable. While all known other cyanation sources, for example, KCN (LD_{Lo} (oral, human) = 2.86 mg kg^{-1}), are highly poisonous, $K_4[Fe(CN)_6]$ is nontoxic (the LD_{50} of $K_4[Fe(CN)_6]$ is lower than that for NaCl!) and even used in the food industry for metal precipitation. Important for practical applications $K_4[Fe(CN)_6]$ is commercially available on ton-scale and even cheaper than KCN.^[15] Our new approach has proven its initial value in both palladium-^[16] and copper-catalyzed cyanations,^[17] and has been adopted nicely by Ozawa,^[14a] Weissman, and Gelman and co-workers.^[18]

Recently, we discovered that novel copper catalysts containing imidazole ligands allow the cyanation of heteroaryl bromides.^[19] Here, we report a full account of our work on the development of a new and improved copper-based catalyst system, which enables for the first time efficient cyanations of all kinds of aromatic and heteroaromatic bromides. Importantly, notoriously difficult substrates react in excellent yield and selectivity, making the method applicable on an industrial scale.

The first catalytic variant of the Rosenmund-von Braun reaction was reported by Buchwald and co-workers,^[20] who used 10 mol % of CuI and 100 mol % of *N,N'*-dimethylethylenediamine (dmeda). Subsequently, Taillefer and co-workers^[21] demonstrated that this reaction also proceeds in the presence of 20 mol % 1,10-phenanthroline as ligand. Both methods still relied upon highly toxic cyanide sources such as NaCN or KCN. In our initial investigations on copper-catalyzed cyanations with potassium hexacyanoferrate(II) we demonstrated the necessity of dmeda as the ligand for catalysis. Unfortunately, the amount (stoichiometric with respect to the aryl halide) and price of the bidentate amine dmeda is prohibitive for practical applications of the system. Additionally, a number of potentially interesting substrates, especially heterocycles, could not be converted by any of the methods. Thus, in a joint collaboration we set the goal to develop a copper-based catalyst system, which is industrially feasible and should have a broader substrate scope than previously known systems.

To compare new and known in situ copper catalysts, the cyanation of 3,5-bis(trifluoromethyl)bromobenzene was studied as a model reaction. The resulting product 3,5-bis(trifluoromethyl)benzonitrile is a versatile intermediate for fine chemical syntheses.

As shown in Table 1 the application of the known Cu/dmeda system was unsatisfactory with less than 20% yield of the desired benzonitrile and a wide spectrum of side products, among them 3,5-bis(trifluoromethyl)benzamide and the reductive dimerization product 3,3',5,5'-tetrakis(tri-

Table 1. Cu-catalyzed cyanation of 3,5-bis(trifluoromethyl)bromobenzene.^[a]














Entry	Ligand	Additive (mol %)	<i>T</i> [°C]	Conv. [%] ^[b]	Yield [%] ^[b]	Sel. [%]
1 ^[c,d]		Na_2CO_3 (20), KI (20)	140	98	15	15
2 ^[d,e]		Na_2CO_3 (20), KI (20)	140	97	40	41
3 ^[e]	—	—	140	73	71	97
4		—	160	66	65	98
5	—	—	160	4	0	0
6		—	160	99	98	99
7		—	160	97	87	90
8		—	160	62	35	56
9		—	160	5	3	60
10		—	160	13	10	77
11 ^[d]		—	160	16	7	44
12		—	160	9	2	22
13		—	160	10	2	20
14		—	160	5	0	0

[a] Reaction conditions: 2 mmol 3,5-bis(trifluoromethyl)bromobenzene, 20 mol % $K_4[Fe(CN)_6]$, 10 mol % CuI, 200 mol % ligand, 2 mL toluene, 200 μ L tetradecane (internal GC standard), 16 h. [b] Determined by GC. [c] NMP as solvent. [d] 100 mol % ligand. [e] 1-Methylimidazole as solvent.

fluoromethyl)biphenyl (Table 1, entry 1). Inspired by nature we assumed that imidazoles might be superior ligands to control the stability and selectivity of the copper catalyst. This idea developed from the fact that the most abundant metal-binding amino acid in nature is histidine. In fact, in most metalloenzymes the actual binding site contains at least one, and in some cases up to three histidine units per metal atom.^[22] Apart from iron, manganese, molybdenum, and zinc, also copper is present in such metalloenzymes.^[23] Following this idea, in exploratory experiments we used 1-methylimidazole as a mimic of histidine due its reasonable price and availability, and limited side-reactions.

To our delight the use of 1-methylimidazole as solvent—to ensure sufficient binding to the metal center—resulted in a yield of 71% of the desired product (Table 1, entry 3)! Surprisingly, the addition of Na_2CO_3 , KI, or dmeda, which were necessary in previous cyanation protocols, gave significantly lower yields (Table 1, entry 2). Further experiments showed that 1-methylimidazole can also be used as an additive in toluene as solvent (Table 1, entry 4). Without any 1-

Table 2. Comparison of different cyanation protocols for "difficult" substrates.^[a]

Entry	Substrate	T [°C]	Metal precursor (mol %)	Ligand (mol %)	Additive (mol %)	Conv. [%] ^[b]	Yield [%] ^[b]	Sel. [%]
1		140	Pd(OAc) ₂ (0.1)	dppf (0.2)	Na ₂ CO ₃ (100)	32	8	25
2		120	CuI (10)	dmeda (100)	KI (20)	100	0	0
3 ^[c]		160	CuI (10)	1-BuIm ^[d] (200)	–	98	80	82
4		130	Pd(OAc) ₂ (0.5)	dppp (2)	Na ₂ CO ₃ (20)	48	30	63
5		140	Pd(OAc) ₂ (0.5)	dppf (1)	Na ₂ CO ₃ (20)	20	8	40
6		160	Cu(BF ₄) ₂ ·6H ₂ O (10)	dmeda (100)	Na ₂ CO ₃ (20), KI (20)	96	0	0
7 ^[e]		140	CuI (10)	–	–	100	>99	99
8		140	Pd(OAc) ₂ (0.1)	dppf (0.2)	Na ₂ CO ₃ (20)	0	0	–
9		140	CuI (10)	dmeda (100)	Na ₂ CO ₃ (20), KI (20)	86	0	0
10 ^[e]		140	CuI (10)	–	–	100	99	99
11		140	Pd(OAc) ₂ (0.1)	dppf (0.2)	Na ₂ CO ₃ (20)	5	0	0
12		140	CuI (10)	dmeda (100)	Na ₂ CO ₃ (20), KI (20)	87	0	0
13 ^[c]		160	CuI (10)	1-BuIm ^[d] (200)	–	100	95	95

[a] Reaction conditions: 2 mmol substrate, 20 mol % K₄[Fe(CN)₆], 10 mol % CuI, 2 mL NMP, 200 μL tetradecane (internal GC standard), 16 h. [b] Determined by GC; average of 2 parallel experiments. [c] Toluene as solvent. [d] 1-Butylimidazole. [e] 1-Methylimidazole as solvent.

methylimidazole present no reaction takes place (Table 1, entry 5). Next, a series of commercially available imidazoles and similar ligands were tested. The more electron-rich and lipophilic 1-butylimidazole performed best, with an almost quantitative yield (98 %; Table 1, entry 6). At this point it is interesting to note that to the best of our knowledge 1-alkylimidazoles have not been used as ligands in coupling reactions of aryl halides before our work.^[24] Clearly, imidazoles might be useful ligands for other Cu-catalyzed reactions (amination, ether formation, etc.), too.^[25]

Interestingly, even imidazole itself is capable of generating an active cyanation catalyst. The decreased product yield (35 %) can be explained by the lower solubility of imidazole in toluene and the increased hydrolysis of the nitrile, which is catalyzed by free imidazole (Table 1, entry 8). Histidine, the starting point of our biomimetic search, gave only a very low yield, because of low solubility and side-reactions of the ligand (Table 1, entry 9). Noteworthy, other typical nitrogen ligands such as pyridine or 2,2'-bipyridine gave only low yields of 3,5-bis(trifluoromethyl)benzotrile (<10 %; Table 1, entries 10 and 11, respectively). The same holds true for 1-methylpyrazole, *N*-methylpyrrole, and benzothiazole (Table 1, entries 12–14) although they are structurally related to 1-methylimidazole.

The new protocol was then applied to the cyanation of notoriously problematic substrates (nitroarenes, heteroarenes), which have so far been difficult to convert by known catalysts with potassium hexacyanoferrate(II) and other cyanide sources. To demonstrate the significant advantages the new Cu/alkylimidazole system is compared in Table 2 to previously described Pd- and Cu/dmeda-catalysts.^[16–25] By palladium catalysis, nitroarenes such as 4-bromonitrobenzene (Table 2, entries 1–3) gave the corresponding nitrobenzotriles only in traces. Here, reduction of the nitro group and formation of azo compounds are observed as side-reactions. Also the copper-based method with dmeda as ligand led to decomposition of the starting material. However, in

the presence of 1-alkylimidazole a high yield (80 %) of the desired product is obtained.

With respect to applications, probably the most interesting class of substrates for metal-catalyzed coupling reactions is bromoheteroarenes.^[26] In general, these substrates are more difficult to activate due to the formation of less- or nonstable transition-metal/substrate and product complexes. For example, it is well known that 2-bromopyridine (Table 2, entries 4–7) forms catalytically inactive dimers of oxidative addition products.^[27] By applying the novel Cu/imidazole catalyst a remarkable increase in yield and activity is observed. Similarly dramatic improvements are seen for 2-bromothiazole (Table 2, entries 8–10), and 5-bromopyrimidine (Table 2, entries 11–13) as substrates.

Finally, 31 different bromoarenes and bromoheteroarenes were tested in the Cu-catalyzed cyanation (Table 3). It should be noted that a proper choice of reaction conditions can be crucial for the success of the reaction (Table 3, entries 2 and 3). In general, 1-butylimidazole is the best ligand. Most of the substrates, both electron-poor, for example, 2-bromonitrobenzene (Table 3, entry 1), and electron-rich ones such as 2-bromoanisole or 4-bromoaniline (Table 3, entries 19 and 20) gave good to very good yields and selectivities.

Notably, substrates with primary amino groups, which did not react to the corresponding benzotriles in the presence of palladium catalysts, readily gave the desired products (Table 3, entries 20, 24, and 25). Additionally, heterocyclic substrates also perform well (Table 3, entries 22–28). Pyridines, thiophenes, thiazoles, indoles, and furans deliver fair to excellent yields of the corresponding nitriles. A particularly interesting feature becomes apparent when the yields of differently sterically hindered isomers are compared. With 2- and 4-bromonitrobenzene (92 % versus 80 %, Table 3, entries 1 and 32) as well as the three increasingly hindered compounds 4-bromotoluene, 2-bromotoluene, and 2,6-dimethylbromobenzene (70, 85, and 89 %, Table 3, en-

Table 3. Scope and limitations of the copper-catalyzed cyanation.^[a]




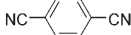


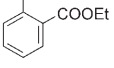
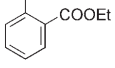



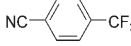



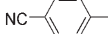






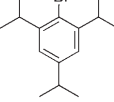
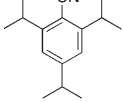
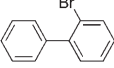
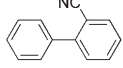
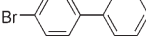
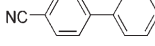
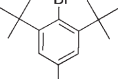
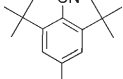
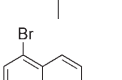
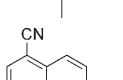


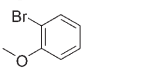
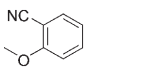


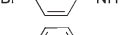
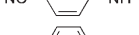
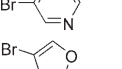
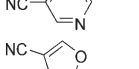







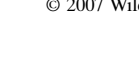












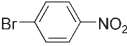
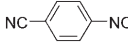


Entry	Substrate	Product	Method ^[b]	Conv. ^[c] [%]	Yield ^[c] [%]	Sel. [%]
1			A ^[e]	100	92	92
2			B ^[f]	94	75	80
3			A ^[f]	36	31	86
4			A ^[e]	100	92	92
5			A ^[f]	84	83	99
6			A ^[f]	87	86	99
7			A ^[d,f]	97	78	80
8			A ^[f]	72	70	98
9			A ^[f]	86	85	99
10			A ^[f]	90	89	99
11			A ^[f]	86	85	98
12			A ^[f]	90	85	95
13			A ^[f]	85	77	90
14			A ^[f]	78	73	94
15			A ^[f]	30	29	97
16			C ^[g]	64	63	99
17			A ^[f]	87	85	98
18			A ^[f]	75	75	100
19			A ^[f]	83	75	90
20			A ^[f]	78	69	88
21			A ^[f]	63	61	97
22			A ^[f]	87	82	94
23			A ^[f]	58	49	84
24			B ^[f]	55	53	96
25			B ^[e]	100	93	93

Table 3. (Continued)

Entry	Substrate	Product	Method ^[b]	Conv. ^[c] [%]	Yield ^[c] [%]	Sel. [%]
26			B ^[e]	70	67	96
27			A ^[f]	71	68	96
28			B ^[e]	63	58	92
29			A ^[f]	25	25	100
30			B ^[e]	100	> 99	99
31			A ^[f]	100	95	95
32			A ^[f]	98	80	82
33			B ^[e]	100	> 99	99

[a] Reaction conditions: 2 mmol substrate, 20 mol % dry $K_4[Fe(CN)_6]$, 10 mol % CuI, 2 mL solvent, 200 μ L tetradecane (internal standard for GC), 16 h. [b] Method A: 200 mol % 1-butylimidazole, solvent = toluene; Method B: solvent = 1-methylimidazole; Method C: 200 mol % 1-butylimidazole, solvent = *o*-xylene. [c] Determined by GC; average of 2 parallel experiments. [d] 40 mol % $K_4[Fe(CN)_6]$, product = phthalic acid dinitrile. [e] 140 °C. [f] 160 °C. [g] 180 °C.

tries 8–10, respectively), the more sterically hindered starting material gives the better yields! This is in sharp contrast to most known palladium-catalyzed coupling reactions and might be an indication of a fundamental mechanistic difference between copper- and palladium-catalyzed cyanations.

Following this trend 2-isopropylbromobenzene and the very hindered 2,4,6-tri(isopropyl)bromobenzene (Table 3, entries 11 and 12) gave excellent yields (85 % both)! 2-Bromobiphenyl and 4-bromobiphenyl (Table 3, entries 13 and 14) were cyanated in about 75 % yield. Notably, the challenging 1-bromo-2,4,6-tri(*tert*-butyl)benzene gave the corresponding benzonitrile in a respectable 63 % yield (Table 3, entry 16), with an almost perfect selectivity. At this point, a few comments about the reaction temperature are appropriate: Although the commonly used temperature (140–160 °C) may seem high, the observed chemoselectivity demonstrates that side-reactions are occurring only to a very low extent. Moreover, it is often forgotten that, on a larger scale, such reaction temperatures are beneficial compared to room temperature.

In summary, we have developed a general protocol for the cyanation of aryl and heteroaryl bromides. Using biomimetic Cu/imidazole catalysts an easy and practical synthesis of nearly all kinds of benzonitriles is possible. Typically, reactions proceed with high yield and selectivity applying the environmentally benign cyanide source $K_4[Fe(CN)_6]$, and it is not necessary to exclude air or moisture. Of special importance is the cyanation of previously difficult substrates, especially functionalized heterocycles, amino-substituted arenes, and sterically hindered arenes, which is an important feature for practical applications. We believe that our novel

procedure is the most environmentally benign and general cyanation protocol for aryl bromides known to date.

Experimental Section

General: All chemicals are commercially available and were used without further purification. 1-Methylimidazole was distilled once at reduced pressure, *N*-methylpyrrolidone (NMP) was dried over CaH_2 and also distilled at reduced pressure. Toluene and *o*-xylene (>99.5 % quality) were used without drying after a triple cycle of vacuum and argon. New products were fully characterized after isolation (NMR and IR spectroscopy, mass spectrometry, elemental analysis), or in the case of commercially available products by comparison of GC-MS data.

General procedure

$K_4[Fe(CN)_6] \cdot 3H_2O$ was ground to a fine powder and dried in vacuum (ca. 2 mbar) at 80 °C overnight. Dry $K_4[Fe(CN)_6]$ (0.4 mmol), copper precursor (0.2 mmol), the additive, and aryl halide (2 mmol) were placed in a pressure tube under argon. Tetradecane (200 μ L, internal standard for GC) and solvent (2 mL) were added. The pressure tube was sealed and heated for 16 h at the temperature specified in the tables. After the mixture had been cooled to room temperature, dichloromethane (3 mL) was added and the mixture was analyzed by GC. Conversion and yield were calculated as an average of two parallel runs. For isolation of the products the reaction mixture was washed with water, and the organic phase was dried over Na_2SO_4 . After evaporation of the solvents the residue was subjected to column chromatography (silica, hexane/ethyl acetate).

Selected analytical data of 3,5-bis(trifluoromethyl)benzonitrile: 1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.14 ppm (br s, 3H; CH_o , CH_p); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 133.3 (q, $J_{C,F}$ = 35 Hz; C_m), 132.3 (br q, $J_{C,F}$ = 3 Hz; C_o), 126.6 (hept., $J_{C,F}$ = 3.5 Hz; C_p), 122.2 (q, $J_{C,F}$ = 273 Hz; CF_3), 116.0 (CN), 114.9 ppm (C_i); HR-MS: calculated for $C_9H_5F_6N$: 239.01642; found: 239.016259.

Selected analytical data of pyrimidine-5-carbonitrile: 1H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.42 (s, 1H; H_{C2}), 9.04 ppm (s, 2H; H_{C4}/H_{C6});

¹³C NMR (75 MHz, CDCl₃, 300 K): δ = 160.5 (C2), 159.5 (C2/C4), 114.0 (C=N), 110.2 ppm (C5); MS (EI, 70 eV); *m/z* (%): 105 (80), 78 (70), 51 (100); HR-MS: not possible due to low volatility of the compound.

Selected analytical data of 2,4,6-tri(*tert*-butyl)benzotrile: ¹H NMR (300 MHz, CDCl₃, 300 K): δ = 7.38 (s, 2H), 1.57 (s, 18H), 1.33 ppm (s, 9H); ¹³C NMR (CDCl₃, 75 MHz, 300 K): δ = 153.2, 152.6, 119.3, 118.8, 103.8 (C_{ipso}), 34.0, 33.3, 28.8, 28.1 ppm; HR-MS: calculated for C₁₉H₂₉N: 271.22945; found: 271.228865.

Selected analytical data of 2,4,6-tri(isopropyl)benzotrile: ¹H NMR (300 MHz, CDCl₃, 300 K): δ = 6.98 (s, 2H), 3.48 (hept, *J* = 7 Hz, 2H), 2.87 (hept, *J* = 7 Hz, 1H), 1.24 ppm (d, *J* = 7 Hz, 18H); ¹³C NMR (CDCl₃, 75 MHz, 300 K): δ = 147.9, 147.4, 123.6, 122.3, 34.1, 33.6, 24.1, 23.2 ppm; HR-MS: calculated for C₁₆H₂₃N: 229.18250; found: 229.182347.

Selected analytical data of 2-isopropylbenzotrile: ¹H NMR (CDCl₃, 300 MHz, 300 K): δ = 7.61 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.55 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.40 (bd, *J* = 7.6 Hz, 1H), 7.28 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 3.39 (hept, *J* = Hz, 1H), 1.32 ppm (d, *J* = 6.9 Hz, 6H); ¹³C NMR (CDCl₃, 75 MHz, 300 K): δ = 152.4, 133.0, 132.9, 126.3, 125.9, 118.2, 111.7, 32.4 (C_o), 23.2 ppm (CH₃); HR-MS: calculated for C₁₀H₁₁N: 145.08860; found: 145.088320.

Selected analytical data of 2-amino-5-fluoronicotinitrile: ¹H NMR (CDCl₃, 300 MHz, 300 K): δ = 8.16 (d, *J* = 3 Hz, 1H); 7.46 (dd, *J* = 3 Hz, *J* = 7 Hz, 1H), 5.14 ppm (br s, 2H); ¹³C NMR (CDCl₃, 75 MHz, 300 K): δ = 156.2 (C2), 151.9 (C5, *J*_{C,F} = 247 Hz), 141.4 (C6, *J* = 25 Hz), 127.6 (C4, *J* = 22 Hz), 115.3 (C=N), 90.9 ppm (C3); HR-MS: calculated for C₆H₄FN₃: 137.03838; found: 137.038247.

Selected analytical data of thiazole-2-carbonitrile: ¹H NMR (CDCl₃, 300 MHz, 300 K): δ = 8.09 (s, 1H), 7.74 ppm (s, 1H); ¹³C NMR (CDCl₃, 75 MHz, 300 K): δ = 145.3, 136.7, 125.0, 112.7 ppm; HR-MS: calculated for C₄H₂N₂S: 109.99332; found: 109.993126.

Selected analytical data of isoquinoline-4-carbonitrile: ¹H NMR (CDCl₃, 300 MHz, 300 K): δ = 9.43 (s, 1H), 8.91 (s, 1H), 8.19 (dd, *J* = 8.4 Hz, *J* = 1 Hz, 1H), 8.11 (dt, 1H), 7.95 (ddd, *J* = 8 Hz, *J* = 7 Hz, *J* = 1 Hz, 1H), 7.80 ppm (ddd, *J* = 8 Hz, *J* = 7 Hz, *J* = 1 Hz, 1H); ¹³C NMR (CDCl₃, 75 MHz, 300 K): δ = 156.3, 148.4, 134.5, 133.1, 129.2, 128.5, 127.6, 124.1, 115.9, 106.0 ppm; HR-MS: calculated for C₁₀H₆N₂: 154.05255; found: 154.052270.

Acknowledgements

The authors thank Dr. W. Baumann, Dr. C. Fischer, Mrs. S. Buchholz, Mrs. S. Schareina and Ms. K. Reincke for analytical support. Generous support from the state Mecklenburg-Vorpommern, the BMBF, the Deutsche Forschungsgemeinschaft (Leibniz prize), and Saltigo GmbH are gratefully acknowledged.

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Received: January 18, 2007
Published online: May 7, 2007