Aryl Nitriles

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Direct Transformation of Methyl Arenes to Aryl Nitriles at Room Temperature**

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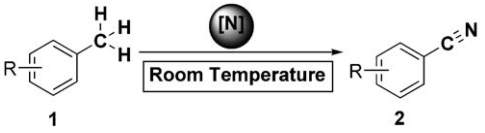
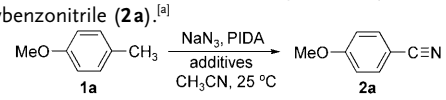
The development of novel methods for the preparation of aryl nitriles is of long-standing interest to organic chemists because of the importance of these compounds in chemistry and biology. Moreover, they are also versatile building blocks in the synthesis of natural products, pharmaceuticals, agricultural chemicals, materials, and dyes.[1] In the past several decades, three general strategies for the synthesis of aryl nitriles have been developed: 1) the replacement approach, in which aryl nitriles are obtained by introducing a nitrile group through Sandmeyer reaction[1] of aryldiazonium salts or by the transition-metal-mediated cyanation of aryl halides with a cyanide source which generally is toxic;[2] 2) the dehydration approach, for example, dehydration of aryl amides[3a,b] or oximes,[3c,d] or oxidative dehydration of benzylic amines or alcohols with ammonia;[3e,f] and 3) direct C–H functionalization, one of the most exciting topics in concise and economical organic synthesis.[4] In this context an even more attractive but challenging issue is the direct ammoxidation of substituted methyl arenes.[5] However, the low selectivity and harsh reaction conditions (reaction temperatures of 630–730 K) required because of the high C–H bond dissociation energy limit their application in organic synthesis. Hence, the direct transformation of methyl arenes to aromatic nitriles under mild conditions still remains of great value. Herein, we demonstrate a novel and efficient copper-promoted transformation of substituted methyl arenes to aryl nitriles by the cleavage of three C–H bonds under mild and neutral conditions [Eq. (1)].



(1)

We began our evaluation of this direct transformation with the reaction of *para*-methylanisole (**1a**; Table 1). Gratifyingly, when NaN_3 was chosen as the nitrogen source, the reaction in the presence of phenyliodonium diacetate (PIDA) in acetonitrile at room temperature provided 4-methoxybenzonitrile (**2a**) in 42% yield (Table 1, entry 3). This product was not observed when the reaction was carried out in the absence of either NaN_3 or PIDA (Table 1, entries 1 and 2). Notably, catalytic amounts of CuCl facilitated this transformation, giving **2a** in 55% yield (cf. Table 1, entries 3 and 4). The oxidant played an essential role in this transformation. Attempts at using other organic or inorganic oxidants such as ceric ammonium nitrate (CAN), $Mn(OAc)_3$, and PhIO were not successful (see Table S3 in the Supporting Information). The yield of **2a** decreased to 8% when Me_3SiN_3 was used instead of NaN_3 (Table 1, entry 7). Further studies indicated that the efficiency of this transformation was not affected by the addition of water, base, or Lewis acid (see Tables S3 and S4 in the Supporting Information). We screened a number of different parameters (see the Supporting Information) and found that the direct transformation facilitated by $CuSO_4{\cdot}5H_2O$ using acetonitrile as the solvent at room temperature was the most efficient (58% yield, Table 1, entry 8). The optimized conditions providing the highest yield (71%) are listed in entry 9, Table 1. The yields decreased when the salts of other metals such as Co, In, Zn, or Fe were

Table 1: The direct transformation of *para*-methylanisole (**1a**) to 4-methoxybenzonitrile (**2a**).[a]



Entry	NaN_3 [equiv]	PIDA [equiv]	Additive (equiv)	*t* [h]	Yield of **2a** [%][b]
1	0	3.2	none	12	0
2	4.0	0	none	12	0
3	4.0	3.2	none	3	42
4	4.0	3.2	CuCl (0.1)	2	55
5[c]	4.0	3.2	CuCl (0.1)	12	trace
6[d]	4.0	3.2	CuCl (0.1)	3	53
7[e]	0	3.2	$CuSO_4{\cdot}5H_2O$ (0.05)	3	8
8	4.0	3.2	$CuSO_4{\cdot}5H_2O$ (0.05)	3	(58)
9[f]	**4.0**	**3.2**	**$CuSO_4{\cdot}5H_2O$ (0.05)**	**6**	**70 (71)**
10[f]	4.0	3.2	none	6	(60)
11[f]	8.0	6.4	none	6	(64)

[a] Reaction conditions: **1a** (0.5 mmol), NaN_3, PIDA, additive in acetonitrile at 25 °C under N_2. [b] Yields determined by GC using *n*-dodecane as the internal standard, the number in parentheses refers to the yield of isolated product. [c] The reaction was carried out at 0 °C. [d] The reaction was carried out at 50 °C. [e] Me_3SiN_3 was used instead of NaN_3. [f] NaN_3 and PIDA were added in three portions.

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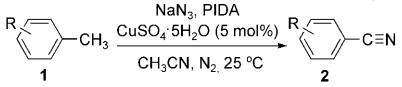
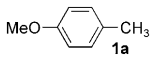
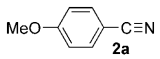
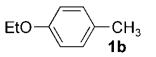
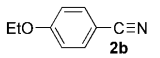
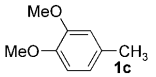
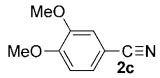
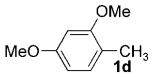
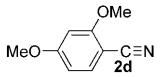
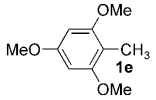
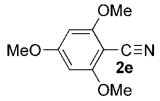
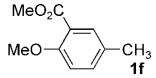
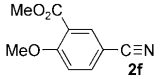
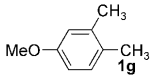
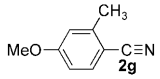
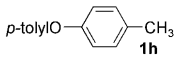
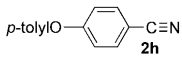
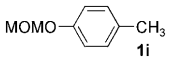
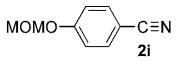
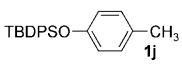
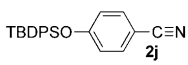
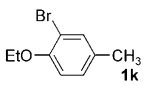
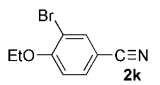
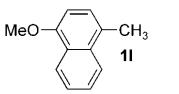
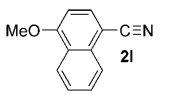
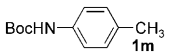
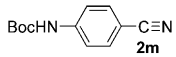
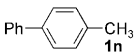
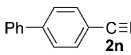
employed instead of $CuSO_4 \cdot 5H_2O$ (see Table S4 in the Supporting Information). Even with loadings of 8.0 equiv NaN_3 and 6.4 equiv PIDA, the yield did not increase significantly in the absence of the copper salt (cf. Table 1, entries 9–11).

As this reaction proceeds under mild and neutral conditions, it may be useful for the preparation of functionalized aryl nitriles from the corresponding toluenes avoiding the decomposition of the functional group. To explore the substrate scope, we examined a wide range of substituted toluenes. Reactions of *para*-heteroatom-substituted toluenes with electron-donating groups proceeded efficiently (Table 2). Substrates with substituents at the *meta* and *ortho* positions could be smoothly transformed into the corresponding aryl nitriles, which indicated that steric interactions did not significantly affect the reactivity (Table 2, entries 3–7 and 11). It is noteworthy that the *para* substituents, which serve as the directing groups, are important for this transformation. Hence, **1g** reacted highly regioselectively to give **2g**, in which the *meta* methyl group is untouched, in 76% yield (Table 2, entry 7). Furthermore, *para* hydroxy groups protected as methoxymethyl (MOM) and *tert*-butyldiphenylsilyl (TBDPS) ethers, protecting groups that are easily cleaved, are amenable to further functional group transformations and can serve as efficient directing groups (Table 2, entries 9 and 10). Moreover, halogen-substituted toluenes are also suitable substrates leading to halogen-substituted aryl nitriles (Table 2, entry 11). Intriguingly, protected *para*-toluidines reacted smoothly (**2m** was formed in 44% yield; Table 2, entry 13); in contrast, the synthesis of these *para*-aminobenzonitriles by other methods from simple and inexpensive starting materials would normally require at least three steps. Notably, *para*-methylbiphenyl also exhibited good reactivity, and 4-phenylbenzonitrile (**2n**) was obtained in 45% yield (Table 2, entry 14).

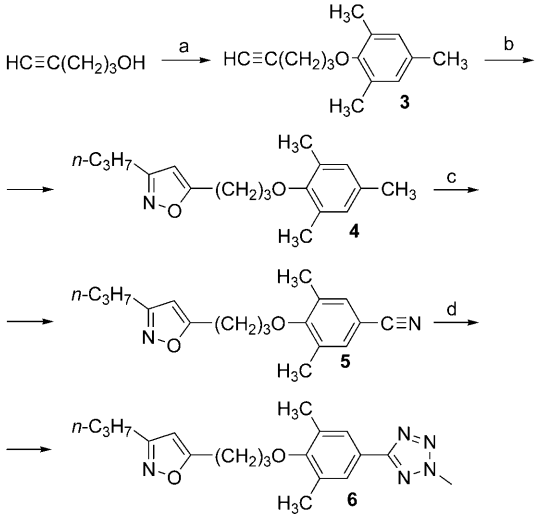
Table 2: Direct transformation of methyl arenes **1** to aryl nitriles **2**.[a]



Entry	Substrate	Product	Yield [%][b]
1	 **1a**	 **2a**	71
2	 **1b**	 **2b**	65
3	 **1c**	 **2c**	86
4	 **1d**	 **2d**	96
5	 **1e**	 **2e**	52
6	 **1f**	 **2f**	31
7	 **1g**	 **2g**	76
8	 **1h**	 **2h**	83
9	 **1i**	 **2i**	50
10	 **1j**	 **2j**	95
11	 **1k**	 **2k**	29
12	 **1l**	 **2l**	77
13	 **1m**	 **2m**	44
14	 **1n**	 **2n**	45

[a] Reaction conditions: **1** (0.5 mmol), NaN_3 (2.0 mmol), PIDA (1.6 mmol), $CuSO_4 \cdot 5H_2O$ (0.025 mmol) in acetonitrile (4 mL) at 25 °C under N_2. [b] Yield of isolated product. Boc = *tert*-butoxycarbonyl.

This transformation provides diverse opportunities for application to organic synthesis. For example, tetrazole analogue **6** related to Disoxaril[6] (Scheme 1) has broad-

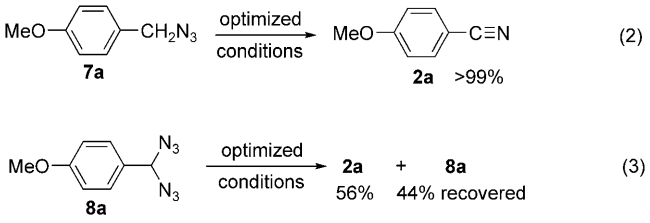


Scheme 1. Synthesis of a tetrazole analogue related to Disoxaril. Reagents and conditions: a) 1. TsCl, pyridine, −20 to −10 °C, 96%; 2. 2,4,6-trimethylphenol, K_2CO_3, butan-2-one, reflux, 90%; b) *n*-C_3H_7CH=NOH, *N*-chlorosuccinimide, pyridine, $CHCl_3$, 75%; c) NaN_3, PIDA, $CuSO_4 \cdot 5H_2O$, CH_3CN, 25 °C, 32%; d) 1. NaN_3, NH_4Cl, DMF, 120 °C; 2. CH_3I, K_2CO_3, CH_3CN, 60 °C, 50% for 2 steps. Ts = toluenesulfonyl.

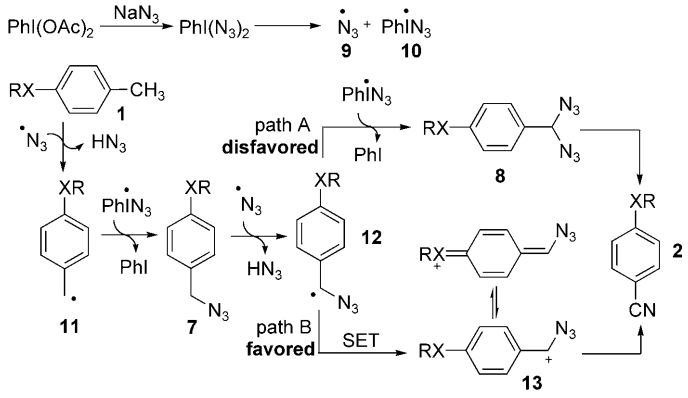
spectrum antipicornavirus activity, exhibiting MIC_{80} values on the order of 0.20 μM for 15 rhinovirus serotypes. In the reported method, tetrazole analogue **6** was prepared from 4-hydroxy-3,5-dimethylbenzonitrile.[6] Alternatively, we envisioned that **6** could be synthesized with our presented transformation as the key step from inexpensive and easily available 2,4,6-trimethylphenol.[7] The aryl nitrile intermediate **5** was prepared with high regioselectivity from the functionalized methyl arene **4** as the key step; this trans-

formation could hardly be realized by the gas-phase ammoxidation of methyl arenes with ammonia and molecular oxygen.[5] Tetrazole analogue **6** was prepared in an overall yield of 10%, which is similar to that of the reported method from 4-hydroxy-3,5-dimethylbenzonitrile;[6] however, in the former case the starting material (2,4,6-trimethylphenol) is much cheaper than 4-hydroxy-3,5-dimethylbenzonitrile.[7]

During this process, small amounts of benzylic azide **7** were observed. To probe the reaction mechanism, **7a** and **8a** were subjected to the optimized conditions. Interestingly, **7a** was cleanly converted to **2a** [Eq. (2)]. However, **8a** provided **2a** in 56% yield with 44% recovery of **8a** [Eq. (3)].



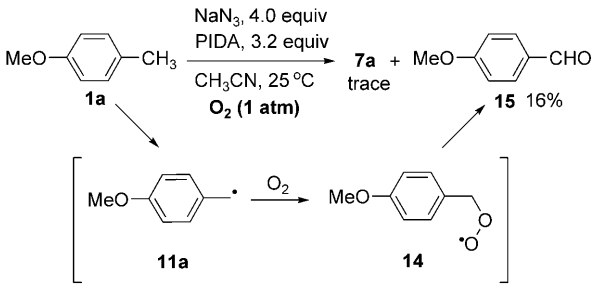
On the basis of these preliminary results, a reasonable mechanism of this transformation is hypothesized (Scheme 2). Radical species **9** and **10** are initially produced



Scheme 2. Proposed mechanism for the direct transformation.

through the reaction of PIDA and NaN_3.[8] Then the azide radical **9** attacks substrate **1** to generate the benzylic radical **11**, followed by the formation of benzylic azide **7**.[9] Since the conversion of **7a** to **2a** was not observed in the absence of PIDA or NaN_3 (see Equations S1 and S2 in the Supporting Information), these results indicate that the reaction between PIDA and NaN_3 generating radical species **9** and **10** is important for this transformation. We hypothesize that further abstraction of a proton from benzylic azide **7** by the radical **9** forms radical **12**. Although path A via intermediate **8** is possible,[10] we consider that the transformation is more likely to occur through path B, because **8** was not detected during this transformation and the result of Equation (3) is also unreasonable. In path B the benzylic cation **13** is produced through copper-promoted single electron transfer (SET)[11] of **12** oxidated by PIDA.[8a] Then cation **13**, which is stabilized by the α-N_3 and *para* substituent on the aromatic ring, undergoes a rearrangement like the Schmidt reaction[12] to afford product **2**.

Some deliberate reactions for an in-depth understanding of the mechanism have been investigated (see Scheme 3 and the Supporting Information). When the reaction of *para*-methylanisole (**1a**) was conducted under O_2, 4-methoxybenzaldehyde (**15**) was obtained in 16% yield along with a trace of benzylic azide **7a** (Scheme 3); the transformation of **1a** was



Scheme 3. The reaction of *para*-methylanisole (**1a**) in the presence of O_2.

completely inhibited by dioxygen. On the other hand, the formation of 4-methoxybenzaldehyde (**15**) implicates that the process proceeds via radical intermediate **11a**. Radical **11a** is then trapped by dioxygen to provide peroxy radical **14**,[13] which is eventually converted into 4-methoxybenzaldehyde (Scheme 3).[14] Neither **2a** nor **15** were observed in the absence of NaN_3 (see the Supporting Information).

In summary, we have developed a unique and novel method for the direct transformation of methyl arenes to aryl nitriles at room temperature. To the best of our knowledge, this is the first direct conversion of a methyl group to a cyano group under mild and neutral conditions. During this transformation, three C–H bonds are cleaved. This observation not only provides a new synthetic tool for constructing synthetically and medicinally important aryl nitriles, but also offers an opportunity to achieve C–H functionalization under mild conditions. Further studies on the reaction scope and synthetic applications are ongoing in our group.

Experimental Section

4-methoxybenzonitrile (**2a**):[15] 4-Methoxytoluene (**1a**) (0.5 mmol, 61 mg) was added to a mixture of PIDA (0.53 mmol, 172 mg), NaN_3 (0.67 mmol, 44 mg), and $CuSO_4 \cdot 5H_2O$ (0.025 mmol, 6.2 mg) in acetonitrile (4 mL) at −40 °C under N_2, and then the reaction mixture was degassed. The reaction mixture was stirred at room temperature for 2 h, then two further portions of PIDA (171 mg each time) and NaN_3 (44 mg each time) were added, once every 2 h. After further 2 h, the resulting mixture was filtered, concentrated to dryness, and purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford 47 mg (71%) of **2a** as a solid: ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.51$ (d, $J = 8.9$ Hz, 2H), 6.87 (m, $J = 8.9$ Hz, 2H), 3.78 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 162.8$, 133.9, 119.2, 114.7, 103.9, 55.5 ppm; IR (neat): $\tilde{\nu} = 2924$, 2219, 1606,

1510, 1461, 1260, 1176, 1024, 832 cm^{-1}; MS (70 eV): *m/z* (%) 133.1 (M^+, 100).

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