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Pharmaceutical-Oriented Selective Synthesis of Mononitriles and Dinitriles Directly from Methyl(hetero)arenes: Access to Chiral Nitriles and Citalopram

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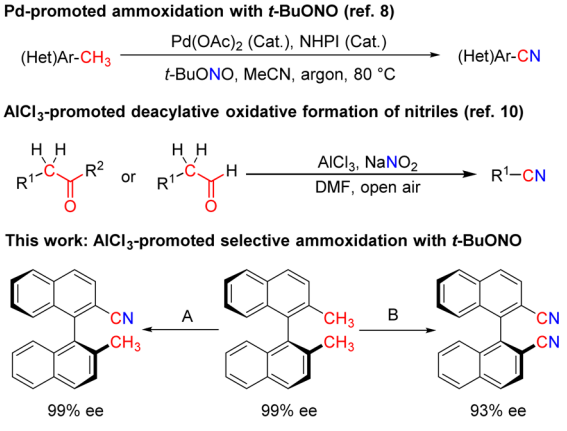
Supporting Information

ABSTRACT: A pharmaceutical-oriented, transition-metal-free, cyanide-free one-step direct transformation of methylarenes to aryl nitriles is described. For the dimethylarenes, the selectivity can be well-controlled to form mononitriles or dinitriles. Enantioenriched nitriles can also be synthesized by this method. As a pharmaceutically practical method, the antidepressant drug citalopram was synthesized from cheap and commercially abundant *m*-xylene on a gram scale in high yield, avoiding transition-metal residues and toxic cyanides.

Among the numerous well-established approaches to nitriles, the one-step direct construction of aryl nitriles, especially dinitriles, under transition-metal-free and cyanide-free conditions is important in pharmaceutical-oriented organic synthesis.[1] In the conventional approaches[2,3] or transition-metal-catalyzed cross-coupling reactions to give nitriles, toxic organic or inorganic cyanides have generally been used as the nitrile sources.[4−6] For a pharmaceutical-oriented nitrile formation method, following requirements should be matched to avoid heavy-metal residues as well as toxics: (i) transition-metal-free; (ii) cyanide-free; (iii) selectivity-controllable and functional- or protecting-group-tolerant. Methyl(hetero)arenes are cheap and industrially abundant feedstocks, and thus, the synthesis of aryl nitriles by ammoxidation of methyl(hetero)-arenes under mild conditions should be valuable indeed. The catalytic one-step direct oxidative conversion of methyl-(hetero)arenes into aryl nitriles is straightforward but still under development,[7−9] although a multistep conversion of methylarenes to nitriles has been reported.[9c] Two major drawbacks must be overcome for the existing methods:[7,8] (i) the involvement of transition-metal catalysts, which results in metal residues,[7,8] and (ii) the need for strongly electron-donating substituents on the substrate.[7] For example, in both previously reported catalytic one-step direct conversions of methylarenes to nitriles, transition metals such as copper and palladium have been used as catalysts.[7,8] In the copper-catalyzed reaction, only highly electron-efficient substrates can be transformed.[7] Nevertheless, a pharmaceutical-oriented, transition-metal-free, cyanide-free, one-step direct synthesis of aryl nitriles from methyl(hetero)arenes under mild and catalytic conditions is desired.

In the previous work on transition-metal-free deacylative cyanide-free access to aryl and aliphatic nitriles from ketones and aldehydes with $NaNO_2$ and $AlCl_3$ as reagents,[10] $AlCl_3$ proved to be a powerful Lewis acid for converting oxime intermediates to nitriles, although $AlCl_3$ was claimed to be ineffective in the previous report.[8] We recently found that the *t*-BuONO−$AlCl_3$ system is very efficient for either electron-efficient or electron-deficient methylarenes. The selectivity for mononitriles versus dinitriles could be controlled well (Scheme 1). Herein we report our results and the application of this reaction for the synthesis of enantioenriched nitriles as well as the antidepressant drug citalopram from cheap and industrially abundant *m*-xylene.

Scheme 1. Selectivity-Controllable One-Step Direct Transformation of Methyl(hetero)arenes to Mononitriles or Dinitriles[a]



[a]Conditions A: $AlCl_3$ (cat.), NHPI (cat.), *t*-BuONO, MeCN (0.1% H_2O), argon, 80 °C. Conditions B: Two cycles of conditions A.

First, the dimethylarene *p*-xylene (**1a**) was chosen as the starting material to assess the reaction conditions as well as the selectivity control over mono- versus dinitrile formation.

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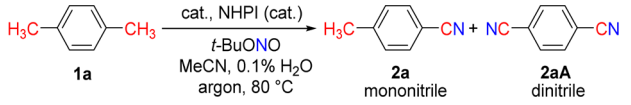
Without catalyst, only a 9% yield of **2a** was obtained with recovery of the starting material **1a** (Table 1, entry 1). The

Table 1. Reaction Conditions: Selectivity for Mononitriles versus Dinitriles[a]



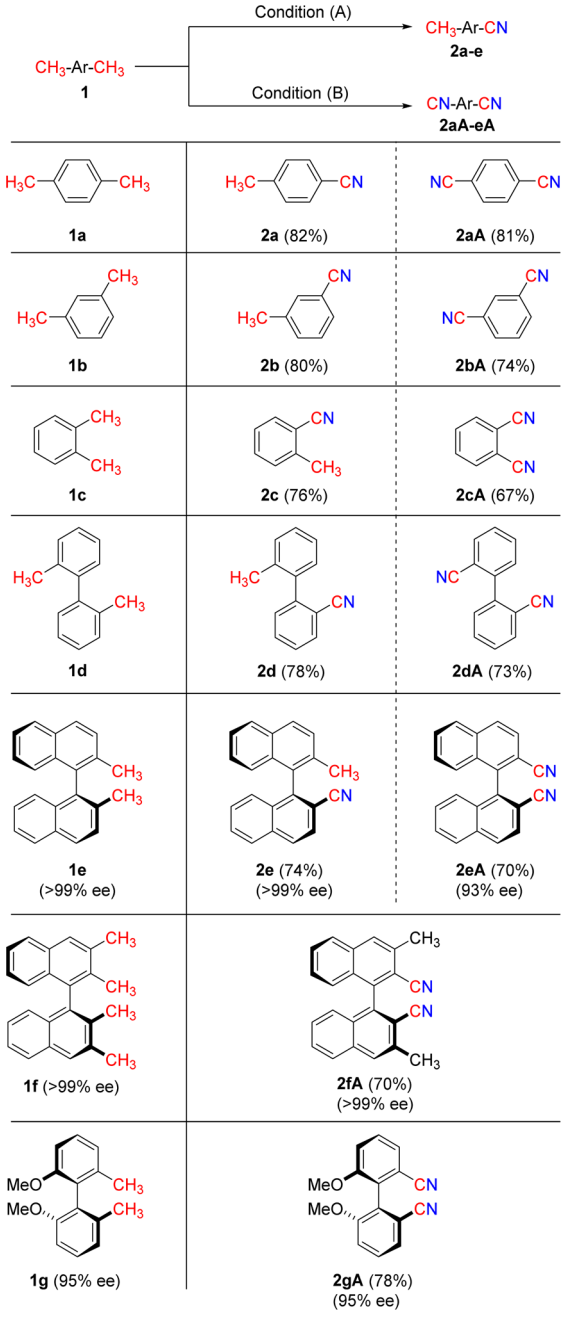
entry	cat (%)	H_2O	yield (%)[b] 2a	2aA
1	—	none	9	0
2	$AlCl_3$(30)	none	74	0
3	$AlCl_3$(10)	0.1%	39	0
4	$AlCl_3$ (5)	0.1%	26	0
5	$AlCl_3$ (30)	0.1%	**82**	0
6[c]	$AlCl_3$ (30)	0.1%	0	**81**
7	$AlBr_3$ (30)	0.1%	53	0
8	$Al(NO_3)_3$ (30)	0.1%	47	0
9	$Al_2(SO_4)_3$ (20)	0.1%	41	0
10	$Al(ClO_4)_3$ (30)	0.1%	2	0
11	$Al(O^iPr)_3$ (30)	0.1%	0	0
12	$GaCl_3$ (10)	0.1%	70	0
13	$Ga(OTf)_3$ (10)	0.1%	57	0
14	$InCl_3$ (10)	0.1%	63	0
15	$BF_3{\cdot}Et_2O$ (30)	0.1%	45	0
16	$SnCl_2{\cdot}2H_2O$ (30)	0.1%	34	0
17	$[RuCl_2(p\text{-cymene})]_2$	0.1%	21	0[g]
18	$Sc(OTf)_3$ (0.3)	0.1%	9	0
19	HCl (100)	none	0	0
20[d]	$CuSO_4{\cdot}5H_2O$	—	trace	0
21[e]	$Pd(OAc)_2$	—	77	0
22[f]	$Pd(OAc)_2$	—	52	41

[a]Conditions A: **1a** (0.5 mmol), *t*-BuONO (1.5 mmol), NHPI (0.15 mmol), dry MeCN (1 mL), H_2O (10 μL), 80 °C, argon. [b]Determined by ^1H NMR analysis. [c]Conditions B: Two cycles of conditions A. [d]Using the method in ref 7: $CuSO_4{\cdot}5H_2O$ (5 mol %), $PhI(OAc)_2$ (3.2 equiv), NaN_3 (4 equiv). [e]Using the method in ref 8: $Pd(OAc)_2$ (5 mol %), NHPI (30 mol %), *t*-BuONO (3.0 equiv). [f]Two cycles of the Pd catalytic conditions in ref 8. [g]10 mol % [Ru] was used.

reaction in the presence of 30 mol % $AlCl_3$ afforded mononitrile **2a** in 74% yield (entry 2), although $AlCl_3$ was addressed to be unreactive in the previous report.[8] A trace amount of water proved to be essential to improve the yield from 74% to 82% (entry 5). However, HCl gave no conversion (entry 19), indicating that $AlCl_3$ itself promotes the transformation. Under conditions A, mononitrile **2a** was obtained as the single product, whereas conditions B afforded only dinitrile **2aA** (entries 5 and 6). The selectivity was thus well-controlled. Other aluminum salts were also investigated to explore the effect of the counteranion on the reactivity of the Lewis acid (entries 7–11). In fact, the stronger aluminum Lewis acids gave some lower yields. For example, $Al(ClO_4)_3$ gave only a 2% yield of **2a**, which is much lower than that obtained with $AlCl_3$ or $Al(NO_3)_3$. Gallium and indium chlorides also gave relatively good yields of **2a** (entries 12–14). Low yields were obtained with $SnCl_2$ and $[RuCl_2(p\text{-cymene})]_2$ (entries 16 and 17). The very strong Lewis acid $Sc(OTf)_3$ was not efficient (entry 18). Thus, with respect to the previous methods, Cu catalysis using $PhI(OAc)_2$ and NaN_3 as reagents gave no **2a** at all (entry 20), and Pd catalysis using *t*-BuONO and *N*-hydroxyphthalimide (NHPI) gave a yield comparable to that with $AlCl_3$ (entry 21). However, the synthesis of the dinitrile under Pd catalysis afforded **2aA** in only 41% yield with 52% residue of **1a** (entry 22). Thus, the $AlCl_3$-promoted one-step direct transformation of **1a** to **2a** or **2aA** is more efficient than previous methods. Generally, salts of the group 13 metals are suitable catalysts for this reaction.

Next, the selectivity-controllable conversion of methylarenes was evaluated using various dimethylarenes, as demonstrated in Scheme 2. Various xylenes were subjected to the mono- and dinitrile formation conditions, and mononitriles **2a–c** and

Scheme 2. Selectivity Control: Mononitriles versus Dinitriles[a]



[a]Conditions A: **1** (0.5 mmol), $AlCl_3$ (0.15 mmol), NHPI (0.15 mmol), *t*-BuONO (1.5 mmol), CH_3CN (1.0 mL, containing 0.1% H_2O), 80 °C, argon. Conditions B: two cycles of conditions A. Isolated yields are shown.

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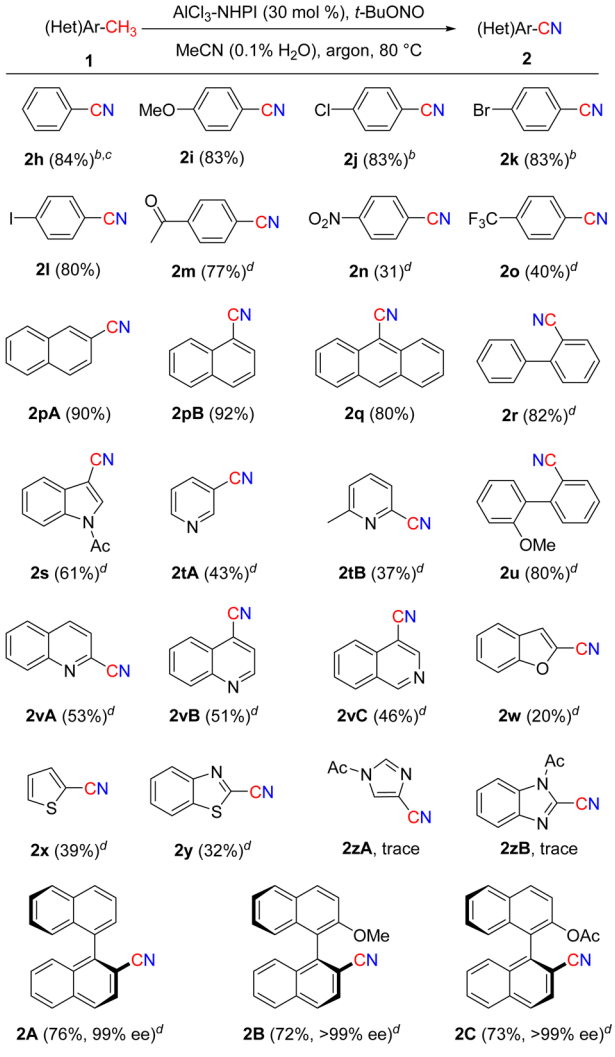
dinitriles **2aA–cA**, respectively, were obtained in high yields. The reaction of 2,2′-dimethylbiphenyl (**1d**) could also be well-controlled, affording mononitrile **2d** and dinitrile **2dA** in high yields. With respect to chiral nitriles, enantioenriched 2,2′-dimethyl-1,1′-binaphthalene (**1e**) gave mononitrile **2e** with >99% retention of the ee, and moreover, chiral dinitrile **2eA** was obtained with 93% ee retention in 70% yield. Chiral dinitriles **2fA** and **2gA** were also obtained in high yields with >95% ee. What should be pointed out is that a method for the preparation of such enantioenriched nitriles has not been well-established.

The scope of this method was further investigated under the standard conditions A. Various substituted toluenes were subjected to the standard conditions to afford the corresponding nitriles in generally high yields (Scheme 3, **2h–o**). Besides electron-rich methylarenes, electron-deficient methylarenes (**2m–o**) and methylheteroarenes (**2s**, **2t**, **2v–2y**) were all converted to he corresponding nitriles, whereas the Cu–PhI(OAc)$_2$–N$_3$ system could not achieve this. Most methylheteroarenes could converted to the corresponding nitriles in generally moderate yields except imidazole substrates (**2zA** and **2zB**). Other arenes including methylnaphthalenes and 9-methylanthracene could all be smoothly converted to the desired nitriles in high yields (**2p** and **2q**). Chiral nitriles **2A–C** were obtained in high yields with excellent ee retention, providing easy and practical access to enantioenriched chiral nitriles.

This method was successfully employed in the gram-scale total synthesis of the antidepressant drug citalopram from the cheap, commercially abundant starting material *m*-xylene (**1b**) (Scheme 4). The traditional synthesis of citalopram involves twice using Grignard reagents, which can easily react with the nitrile group, resulting in a decreased yield.[11] The present method avoids this problem and does not involve transition metals or cyanide. First, by means of this selectivity-controllable method, **1b** was converted to mononitrile **2b** in 83% yield. A bromination–reduction process yielded intermediate **4**, which was further coupled with ketone **5** to give **6**. Finally, 1 g of citalopram was obtained from **6** in an overall yield of 18.5% from *m*-xylene using this transition-metal-free, cyanide-free one-step direct reaction as the initial step.[12]

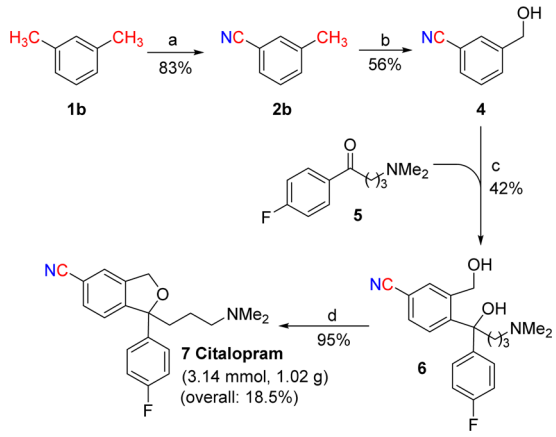
The reaction mechanism has been discussed in detail in previous work by Zhang and Wang.[8] Without AlCl$_3$, **1a** can be converted to oxime **8a** (eq 1), which can be further transformed to nitrile **2a** in high yield (eq 2). Therefore, this reaction should pass through the same pathway as that proposed previously.[8]

Scheme 3. Mononitriles[a]

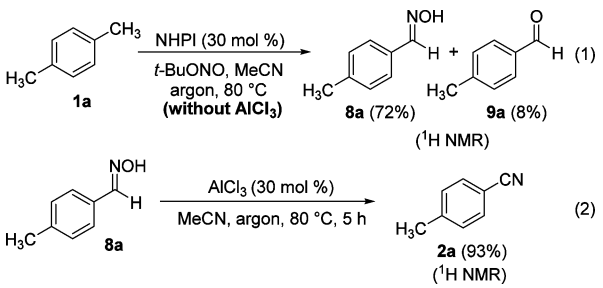


[a]Condition (A): **1** (0.5 mmol), AlCl$_3$ (0.15 mmol), NHPI (0.15 mmol), *t*-BuONO (1.5 mmol), CH$_3$CN (1.0 mL, 0.1% H$_2$O), 80 °C, argon. Isolated yields are shown. [b]Conditions B: same as conditions A except with 0.25 mmol of AlCl$_3$ and 0.5 mmol of NHPI. [c]GC yield. [d]Conditions C: same as conditions B except at 90 °C.

Scheme 4. Gram-Scale Synthesis of the Antidepressant Drug Citalopram from *m*-Xylene[a]



[a]Conditions: (a) AlCl$_3$–NHPI, *t*-BuONO, CH$_3$CN (0.1% H$_2$O), argon, 83%. (b) NBS, (PhCO)$_2$O, CCl$_4$, reflux, 10 h; then AgNO$_3$ THF, reflux, 5.5 h; then NaBH$_4$, MeOH, RT, 4 h, 56%. (c) *t*-BuLi, TMEDA, THF, argon, −78 °C to RT, 42%. (d) 60% H$_2$SO$_4$, 95%.



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In conclusion, a pharmaceutical-oriented, transition-metal-free, cyanide-free one-step direct transformation of methylarenes to aryl nitriles has been developed. The selectivity can be controlled to form mononitriles or dinitriles merely by switching two standard reaction conditions. Enantioenriched chiral nitriles can also been synthesized by this method. As a pharmaceutically practical method, the antidepressant citalopram was synthesized from cheap and commercially abundant *m*-xylene on a gram-scale in high yield. This method is promising for the large-scale synthesis of nitrile-containing pharmaceuticals under transition-metal-free and cyanide-free conditions using simple and cheap reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00180.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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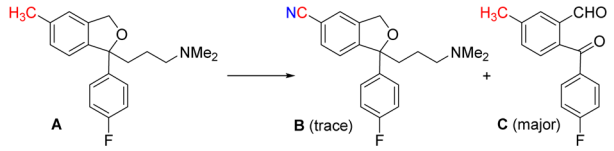
(12) Late-stage introduction of nitrile in the synthesis of citalopram was initially tried. However, the benzylic position adjacent to the oxygen atom is more reactive, and thus, the decomposition product **C** was obtained as the major product:



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