Tetrahedron 67 (2011) 958–964

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

One-pot conversion of aromatic bromides and aromatics into aromatic nitriles via aryllithiums and their DMF adduct

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ARTICLE INFO

Article history:
Received 8 November 2010
Received in revised form 29 November 2010
Accepted 30 November 2010
Available online 7 December 2010

Keywords:
Molecular iodine
Aq ammonia
n-Butyllithium
Aryllithium
Aromatic nitrile
DMF

ABSTRACT

Various aromatic bromides and iodides were smoothly converted into the corresponding aromatic nitriles in good to moderate yields by the treatment with *n*-butyllithium and subsequently DMF, followed by treatment with molecular iodine in aq NH_3. The same treatment of typical aromatics and heteroaromatics with *n*-butyllithium and subsequently DMF, followed by treatment with molecular iodine in aq NH_3 also provided the corresponding aromatic nitriles in good yields. Moreover, the same treatment of aromatic bromides and aromatics with half amount of DIH (1,3-diiodo-5,5-dimethylhydantoin) instead of molecular iodine worked effectively to give the corresponding aromatic nitriles, respectively, in good yields. These reactions are novel and environmentally benign one-pot methods for the preparation of aromatic nitriles from aromatic bromides and aromatics, respectively, through the formation of aryllithiums and their DMF adducts.

1. Introduction

Aromatic nitriles are one of the most important synthetic transformation precursors because they can be easily converted into esters, amides, carboxylic acids, amines, amidines, ketones, and nitrogen-containing heterocycles, such as tetrazoles, and are used as pharmaceuticals and liquid crystals, and as synthetic intermediates for agricultural chemicals, pharmaceuticals, and functional materials.[1] For example, Citalopram hydrobromide® (treatment of alcohol dependency), Periciazine® (anti-psychotic drug), Fadrozole® (oncolytic drug), Letrozole® (breast cancer therapy), Bicalutamide (prostatic cancer and breast cancer therapy), and Etravirine (anti-HIV) are pharmaceutically important aromatic nitriles,[2] and 4-cyano-4′-pentylbiphenyl is a typical liquid crystal material. The general methods for the preparation of aromatic nitriles include the dehydration of aromatic amides with $SOCl_2$, TsCl/Py, P_2O_5, $POCl_3$, $COCl_2$, or Ph_3P/CCl_4, the reaction of carboxylic acids with chlorosulfonylisocyanate ($ClSO_2NCO$) and DMF,[3a] palladium-catalyzed decarboxylative conversion of arenecarboxylic acids into aromatic nitriles with $Pd(OTf)_2$, Ag_2CO_3, and cyanhydrin,[3b] the reaction of esters with Me_2AlNH_2,[3a] and the Sandmeyer reaction of aromatic diazonium ion with toxic CuCN.[3a,4] Aromatic aldehydes can be also used for the preparation of aromatic nitriles via the dehydration of the corresponding aldoximes formed.[5] Recently, the direct conversion of aromatic bromides into the corresponding aromatic nitriles has been actively studied with CuCN at DMF refluxing temperature,[6a] $Pd(OAc)_2 \cdot K_4[Fe(CN)_6]$ at 120 °C,[6b] Pd·(binaphthyl)P(^tBu)$_2$·Zn$(CN)_2$·Zn at 80–95 °C,[6c] $Pd_2(dba)_3 \cdot Zn(CN)_2 \cdot$DPPF at 80–120 °C,[6d] Pd$(tmhd)_2 \cdot K_4[Fe(CN)_6]$ at 80 °C,[6e] $Zn(CN)_2 \cdot Pd_2(dba)_3$ at 100 °C,[6f] Pd/C·CuI·$K_4[Fe(CN)_6] \cdot 3H_2O$ at 130–140 °C,[6g] CuI·alkylimidazole·Pd/C·CuI·$K_4[Fe(CN)_6]$ at 140–180 °C,[6h] $Zn(CN)_2 \cdot Pd_2(dba)_3 \cdot$dppf·Zn·$ZnBr_2$ at 95 °C,[6i] CuO·Pd·$K_4[Fe(CN)_6]$ at 120 °C,[6j] Pd$(OAc)_2 \cdot Cu(OAc)_2 \cdot K_4[Fe(CN)_6]$[6k] at 130 °C, and CuI·$K_4[Fe(CN)_6]$[6l] at 175 °C, all of which require toxic metal cyanides. More recently, the direct and catalytic cyanation of aromatics containing a 2-pyridyl group via C–H bond cleavage with $Cu(OAc)_2 \cdot$TMSCN,[7a] Pd$(OAc)_2 \cdot$CuBr·CuCN,[7b] which requires toxic metal cyanides again, and $Pd(OAc)_2 \cdot CuBr_2 \cdot$DMF·aq NH_3 at 130 °C,[7c] was reported. The another one-pot cyanation of arenes via iridium-catalyzd C–H borylation of arenes and copper-mediated cyanation was reported recently with B_2pin_2, $[Ir(cod)OMe]_2$, followed by treatment with $Cu(NO_3)_2$ and Zn$(CN)_2$ at 100 °C.[7d] To the best of our knowledge, one-pot preparations of aromatic nitriles from aromatics are extremely limited. One well-established method is the reaction of highly electron-rich aromatics with $ClSO_2NCO$ to form *N*-chlorosulfonyl amides and the subsequent treatment with DMF to provide aromatic nitriles, together with the evolution of SO_3 and HCl.[8] However, its synthetic utility is limited to highly electron-rich aromatics alone. Thus, today, there are no practical and general methods for the environmentally benign and efficient one-pot preparation of aromatic nitriles from aromatic

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doi:10.1016/j.tet.2010.11.109

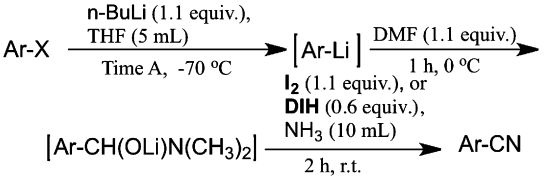
bromides and aromatics. Clearly an environmentally benign, economical, and efficient approach for the one-pot preparation of aromatic nitriles from aromatic bromides and aromatics is urgently required. On the other hand, molecular iodine is one of the simplest oxidants currently available. It is highly affordable and has very low toxicity. In view of environmentally benign organic synthesis, molecular iodine has been used in various organic reactions, including the oxidation of alcohols or aldehydes to esters, the oxidation of sulfides to sulfoxides, the oxidation of cyclohexenones to benzene rings, the introduction of protecting groups, the deprotection of protecting groups, iodocyclization, carbon–carbon bond formation, and the formation of heterocycles.[9]

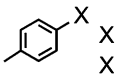
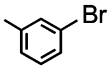
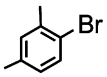
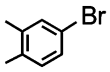
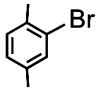
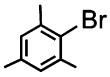
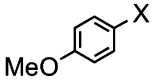
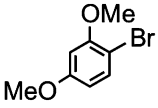
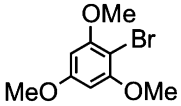
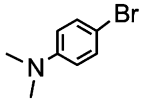
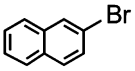
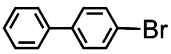
Recently, we reported a direct, efficient, practical, and low-toxicity method for the oxidative conversion of benzylic alcohols and benzylic halides into the corresponding aromatic nitriles using molecular iodine in aq NH_3.[10g–i] In those reactions, aromatic aldehydes could be also smoothly converted into the corresponding aromatic nitriles with molecular iodine in aq NH_3.[10b,10g,11] As part of our studies on the use of molecular iodine for organic synthesis,[10] we would like to report herein a facile and environmentally benign one-pot conversion of aromatic bromides and aromatics into the corresponding aromatic nitriles in detail. Very recently, we reported the first practical metal-free one-pot conversion of electron-rich aromatics into the corresponding aromatic nitriles in good yields, via the formation of aromatic *N*,*N*-dimethyliminium salts with $POCl_3$ and DMF, followed by the treatment with molecular iodine in aq NH_3.[12] However, that reaction required highly electron-rich aromatics, such as dimethoxybenzenes, trimethoxybenzenes, methoxynaphthalenes, indoles, 2-alkylfurans, and 2-alkylthiophenes, because the first step involves the formation of aromatic *N*,*N*-dimethyliminium salts via electrophilic substitution on aromatics, using $POCl_3$ and DMF (the Vilsmeier–Haack reaction), and in one case, the introduction of cyano group into benzothiophene and benzofuran was not successful. Therefore, we designed an environmentally benign one-pot conversion of aromatic bromides and aromatics into the corresponding aromatic nitriles via aryllithium, using DMF and molecular iodine in aq NH_3.

2. Results and discussion

n-Butyllithium (1.67 M solution in hexane) was added dropwise to a solution of *p*-bromotoluene in THF at −70 °C. After 30 min, the resulting mixture was warmed at 0 °C and stirred for 5 min. Then, DMF was added and the obtained mixture was stirred at 0 °C. After 1 h at the same temperature, aq NH_3 (28–30%) and I_2 were added and the obtained mixture was stirred for 2 h at rt to provide 4-methylbenzonitrile in 80% yield, as shown in Table 1 (entry 1).[13] After removal of ether from the ether extract of reaction mixture, the purity of 4-methylbenzonitrile was over 80%. The same treatment of 3-methylbromobenzene, 2-methylbromobenzene, 2,4-dimethylbromobenzene, 3,4-dimethylbromobenzene, 2,5-dimethylbromobenzene, 2,4,6-trimethylbromobenzene, *p*-bromoanisole, 2,4-dimethoxybromobenzene, 2,4,6-trimethoxybromobenzene, and 4-(dimethylamino)bromobenzene gave the corresponding aromatic nitriles, respectively, in good to moderate yields (Table 1, entries 4–10, 12–14). After removal of ether from the ether extracts of reaction mixtures, the purity of aromatic nitriles was in the range of 65–80%. When 2,4-dimethylbromobenzene and 3,4-dimethylbromobenzene were used, 2,6-dimethylbenzonitrile and 2,3-dimethylbenzonitrile were formed as by-product via the isomerization of the formed carbanions, respectively (entries 6, 7). Using the same procedure, 1-bromonaphthalene, 2-bromonaphthalene, and 4-bromobiphenyl also provided the corresponding aromatic nitriles in good yields (Table 1, entries 15, 17, 18). 2-Bromopyridine gave

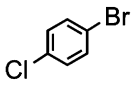
Table 1
Conversion of aromatic bromides into aromatic nitriles



Entry	Ar-X	Time A (h)	Yields (%)[a]	
			I_2	*DIH*
1	 X = Br	0.5	80	75
2	X = Cl	0.5	0	0
3	X = I	0.5	70	68
4		0.5	76	70
5		0.5	68	73
6		0.5	62 (15)[b]	62 (16)[b]
7		0.25	74 (20)[c]	61 (18)[c]
8		0.5	62	64
9		0.5	99[d]	80[d]
10	 X = Br	0.5	76	81
11	X = I	0.5	70	—
12		0.5	95[d]	83[d]
13		0.5	59	61
14		2.0[e]	86	79
15	 X = Br	0.5	60[d]	51[d]
16	X = I	0.5	64[d]	61[d]
17		0.5	83	60
18		0.5	64	63

(*continued on next page*)

Table 1 (*continued*)

Entry	Ar-X	Time A (h)	Yields (%)[a]	
			I_2	*DIH*
19		0.5	66	47[f]
20		0.5	67	55

[a] Reaction was performed on a 5 mmol scale. Isolated yield.
[b] Yield of 2,6-dimethylbenzonitrile.
[c] Yield of 2,3-dimethylbenzonitrile.
[d] DMF (1.5 equiv) was added.
[e] I_2 (1.5 equiv) or DIH (1.0 equiv) was added and the third step was 4 h.
[f] DIH (1.0 equiv) was added.

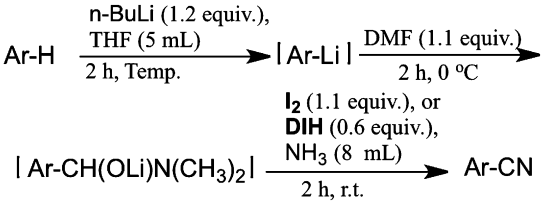
2-cyanopyridine in good yield using the same procedure (Table 1, entry 19). Under the present conditions, *p*-chlorotoluene did not provide 4-methylbenzonitrile at all (entry 2), while the same treatment of *p*-iodotoluene, *p*-iodoanisole, and 1-iodonaphthalene gave the corresponding aromatic nitriles in good yields (Table 1, entries 3, 11, 16). Therefore, the same reaction of *p*-bromochlorobenzene with *n*-butyllithium, and subsequently DMF, followed by treatment with I_2 in aq NH_3 gave *p*-chlorobenzonitrile in good yield, as shown in Table 1 (entry 20).

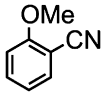
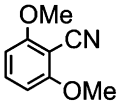
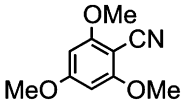
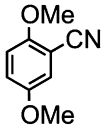
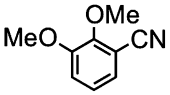
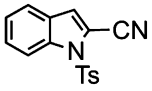
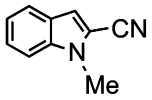
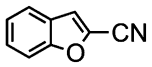
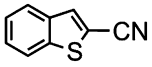
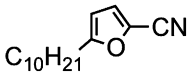
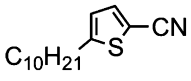
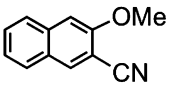
1,3-Diiodo-5,5-dimethylhydantoin (DIH) has two N—I bonds and therefore, a half amount of DIH, instead of I_2, in aq NH_3 provided the corresponding aromatic nitriles in good to moderate yields, as shown in Table 1 (right column). Thus, *n*-butyllithium was added dropwise to a solution of *p*-bromotoluene in THF at −70 °C. After 30 min, the resulting mixture was warmed at 0 °C and stirred for 5 min. Then, DMF was added and the obtained mixture was stirred at 0 °C. After 1 h at the same temperature, aq NH_3 and DIH were added and the obtained mixture was stirred for 2 h at rt to provide 4-methylbenzonitrile in 75% yield, as shown in Table 1 (entry 1, right column). The reactivity of DIH is almost the same as that of molecular iodine. When 2,4-dimethylbromobenzene and 3,4-dimethylbromobenzene were used, 2,6-dimethylbenzonitrile and 2,3-dimethylbenzonitrile were formed again as by-product via the isomerization of formed carbanions, respectively (entries 6, 7, right column).

The one-pot conversion of dialkylbenzenes, trialkylbenzenes, anisoles, benzothiophene, benzofuran, and pyridine into the corresponding aromatic nitriles with the previous methods ($POCl_3$·DMF, and I_2 in aq NH_3)[12] did not succeed at all. Therefore, the present method should be very useful for the conversion of aromatic bromides and iodides into the corresponding aromatic nitriles, using *n*-butyllithium, DMF, and molecular iodine or DIH in aq NH_3, as aromatic bromides and iodides can be prepared directly from aromatics. Moreover, known one-pot methods for the preparation of aromatic nitriles from aromatic bromides have drawbacks, thus they require expensive Pd and toxic metal cyanide, and the reactions are conducted at high temperature.[6]

Then, *n*-butyllithium was added dropwise into a solution of 1,3-dimethoxybenzene in THF at 0 °C and the obtained mixture was stirred for 2 h at the same temperature. Thereafter, DMF was added and the obtained mixture was stirred at 0 °C. After 2 h at the same temperature, aq NH_3 and I_2 were added and the reaction mixture was stirred for 2 h at rt to give 2,6-dimethoxybenzonitrile in 91% yield, as shown in Table 2 (entry 2). After removal of ether from the ether extract of reaction mixture, the

Table 2
Conversion of aromatic into aromatic nitriles

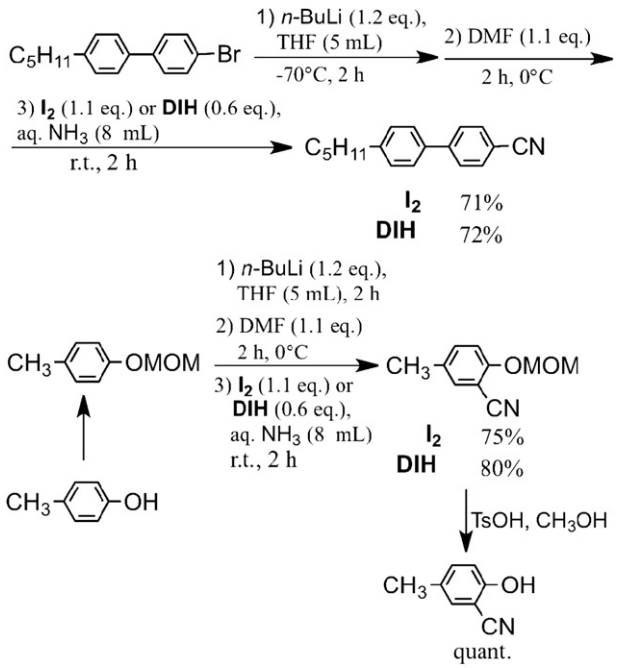


Entry	Ar-CN	Temp.	Yields (%)[a]	
			I_2	*DIH*
1		0 °C	74	68
2		0 °C	91	94
3		0 °C	61	79
4		0 °C	92	91
5		0 °C	76	56
6		rt[b]	42	41
7		0 °C → rt	65	63
8		0 °C[d]	68	75
9		0 °C	70	51
10		0 °C[d]	49 (20)[c]	47 (21)[c]
11		0 °C	90	74
12		0 °C[d]	65	53
13		0 °C	79	74

[a] Reaction was performed on a 4 mmol scale. Isolated yield.
[b] LDA (2.2 equiv) was added instead of *n*-BuLi.
[c] Yield starting material.
[d] The third step was 4 h, and I_2 (1.5 equiv) or DIH (0.75 equiv) was used.

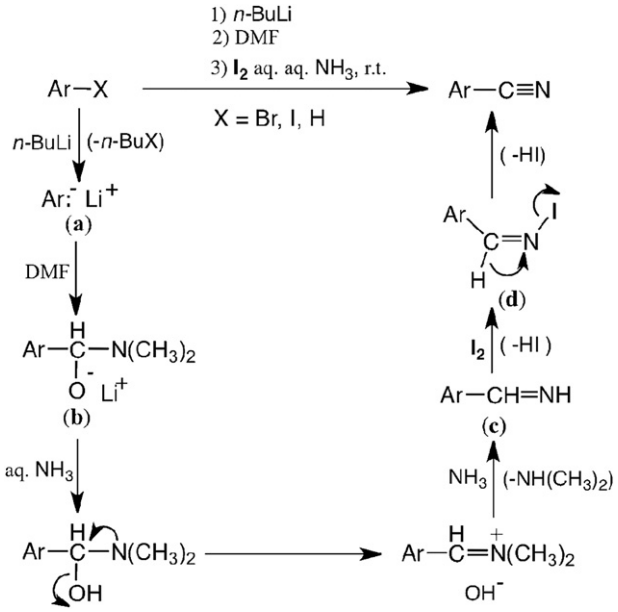
purity of 4-methylbenzonitrile was over 80%. Under the same conditions, anisole, 1,3,5-trimethoxybenzene, 1,4-dimethoxybenzene, 1,2-dimethoxybenzene, *N*-tosylindoles, *N*-methylindole, benzofuran, benzothiophene, 2-decylfuran, 2-decylthiophene, and 2-methoxynaphthalene could be converted into the corresponding aromatic nitriles in good to moderate yields (Table 2, entries 1, 3–5, 7–13). After removal of ether from the ether extracts of reaction mixtures, the purity of aromatic nitriles was in the range of 60–80%. 1,3-Difluorobenzene was also converted into the corresponding aromatic nitrile containing fluorine atoms in moderate yield, by the present procedure using LDA instead of *n*-butyllithium (Table 2, entry 6). The reactivity of DIH is again almost the same as that of I_2 (Table 2, right column).

Then, the synthetic application of the present reactions was carried out. 4-Cyano-4′-pentylbiphenyl, which is a typical liquid crystal material, was prepared in good yield from the reactions of 4-bromo-4′-pentylbiphenyl with *n*-butyllithium at −70 °C, and subsequently DMF at 0 °C, followed by the reaction with molecular iodine or DIH in aq NH_3 at rt, as shown in Scheme 1. The hydroxy group of *p*-cresol was protected with an MOM group, and *O*-MOM protected *p*-cresol was treated with *n*-butyllithium at 0 °C and subsequently DMF. This was followed by the reaction with molecular iodine or DIH in aq NH_3 and then methanolysis with *p*-TsOH in methanol to provide 2-cyano-4-methylphenol in good yield.



Scheme 1. Synthetic Application.

A plausible reaction mechanism is shown in Scheme 2. The initial step is the formation of aryllithium (**a**) by the reaction of aromatic bromide or aromatics with *n*-butyllithium. Then, aryllithium (**a**) reacts with DMF to generate adduct (**b**). The addition of molecular iodine or DIH, and aq NH_3 induces the formation of aromatic imine (**c**), which further reacts with molecular iodine or DIH to form *N*-iodo aromatic imine (**d**). Once *N*-iodo aromatic imine (**d**) is formed, HI elimination smoothly occurs by NH_3 to generate aromatic nitrile.[10g–j]



Scheme 2. Possible Reaction Pathway for Nitrile.

3. Conclusion

Various electron-rich and electron-deficient aromatic bromides, such as bromotoluenes, bromodimethylbenzenes, bromotrimethylbenzene, bromoanisole, bromonaphthalenes, bromobiphenyl, and bromopyridine could be smoothly converted into the corresponding aromatic nitriles in good to moderate yields by treatment with *n*-butyllithium and subsequently DMF, followed by treatment with molecular iodine or DIH in aq NH_3. The same treatment of typical aromatics and heteroaromatics, such as anisole, dimethoxybenzenes, trimethoxybenzenes, benzothiophene, *N*-methylindole, *N*-tosylindole, benzofuran, alkylthiophene, and alkylfuran with *n*-butyllithium and subsequently DMF, followed by treatment with molecular iodine or DIH in aq NH_3 provided the corresponding aromatic nitriles in good yields. The present reactions are novel and practical one-pot methods for the preparation of aromatic nitriles from aromatic bromides and aromatics through the formation of aryllithiums and their DMF adducts.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded with JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. Chemical shifts are expressed in parts per million downfield from TMS in δ units. Mass spectra were recorded on JMS-HX110, JMS-T100GCV, and Thermo LTQ Orbtrap spectrometers. IR spectra were measured with a JASCO FT-IR4100 spectrometer. Melting points were determined on a YAMATO Melting Point electrothermal apparatus MP-21 in open capillary tubes and are uncorrected. Kieselgel 60 F_{254} was used for TLC, Silica gel 60 (Kanto Kagaku Co.) was used for column chromatography, and Wakogel B-5F was used for preparative pTLC.

4.2. Typical experimental procedure for the conversion of aromatic bromides into aromatic nitriles with I_2

n-Butyllithium (1.67 M solution in hexane, 3.3 mL, 5.5 mmol) was added dropwise to a solution of *p*-bromotoluene (855 mg, 5.0 mmol) in THF (5 mL) at −70 °C. After 30 min, the resulting

mixture was warmed and stirred for 5 min at 0 °C. Then, DMF (0.43 mL, 5.5 mmol) was added and the obtained mixture was stirred at 0 °C. After 1 h at the same temperature, aq NH_3 (10 mL, 150 mmol) and I_2 (1.40 g, 5.5 mmol) were added and the obtained mixture was stirred for 2 h at rt. The reaction mixture was quenched with satd aq Na_2SO_3 (15 mL) and extracted with Et_2O (3×20 mL). The organic layer was washed with brine and dried over Na_2SO_4 to provide 4-methylbenzonitrile in over 80% purity. The product was purified by a short column chromatography on silica gel (Hexane/EtOAc=9:1) to give pure 4-methylbenzonitrile in 80% yield as a colorless solid.

4.3. Typical experimental procedure for the conversion of aromatic bromides into aromatic nitriles with DIH

n-Butyllithium (1.67 M solution in hexane, 3.3 mL, 5.5 mmol) was added dropwise to a solution of *p*-bromotoluene (0.86 g, 5.0 mmol) in THF (5 mL) at −70 °C. After 30 min, the resulting mixture was stirred for 5 min at 0 °C and then DMF (4.25 mL, 5.5 mmol) was added and the obtained mixture was stirred at 0 °C. After 1 h at the same temperature, aq NH_3 (10 mL, 150 mmol) and DIH (1.14 g, 3.0 mmol) were added and the resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched with satd aq Na_2SO_3 (15 mL) and extracted with ether (3×20 mL). The organic layer was washed with brine and dried over Na_2SO_4 to provide 4-methylbenzonitrile in over 75% purity. The product was purified by a column chromatography on silica gel (Hexane/EtOAc=9:1) to give pure 4-methylbenzonitrile in 75% yield as a colorless solid.

Most aromatic nitriles mentioned in this work are commercially available and were identified by comparison with the authentic samples.

4.3.1. 4-Methylbenzonitrile. Mp 26–28 °C (commercial, Mp 26–28 °C); IR: 2227 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.41 (s, 3H), 7.26 (d, *J*=8.1 Hz, 2H), 7.52 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.7, 109.2, 119.1, 129.7, 131.9, 143.6.

4.3.2. 3-Methylbenzonitrile. Oil (commercial); IR: 2229 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.38 (s, 3H), 7.32–7.47 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.8, 111.9, 118.8, 128.8, 129.0, 132.2, 133.4, 139.0.

4.3.3. 2-Methylbenzonitrile. Oil (commercial); IR: 2225 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.54 (s, 3H), 7.26 (t, *J*=7.6 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 1H), 7.58 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.0, 112.3, 117.8, 126.0, 130.0, 132.1, 132.3, 141.5.

4.3.4. 2,4-Dimethylbenzonitrile. Mp 23–24 °C (commercial, Mp 23–25 °C); IR: 2221 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.36 (s, 3H), 2.47 (s, 3H), 7.05 (d, *J*=8.0 Hz, 1H), 7.10 (s, 1H) 7.43 (d, *J*=8.0 Hz, 1H).

4.3.5. 3,4-Dimethylbenzonitrile. Mp 63–64 °C (commercial, Mp 64–67 °C); IR: 2224 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.29 (s, 3H), 2.32 (s, 3H), 7.21 (d, *J*=7.8 Hz, 1H), 7.39 (d, *J*=7.8 Hz, 1H), 7.41 (s, 1H).

4.3.6. 2,5-Dimethylbenzonitrile. Oil (commercial); IR: 2227 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.33 (s, 3H), 2.48 (s, 3H), 7.18 (d, *J*=7.9 Hz, 1H), 7.27 (d, *J*=7.9 Hz, 1H), 7.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=19.6, 20.3, 112.2, 118.0, 129.8, 132.3, 133.3, 135.8, 138.4.

4.3.7. 2,4,6-Trimethylbenzonitrile. Mp 50–51 °C (lit.[10i] Mp 54–55 °C); IR: 2218 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=2.32 (s, 3H), 2.47 (s, 6H), 6.92 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.6, 21.5, 110.2, 117.6, 128.1, 141.9, 142.7.

4.3.8. 4-Methoxybenzonitrile. Mp 54–55 °C (commercial, Mp 57–59 °C); IR: 2216 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=3.86 (s, 3H), 6.95 (d, *J*=8.9 Hz, 2H), 7.59 (d, *J*=8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=55.5, 103.8, 114.7, 119.2, 133.9, 162.8.

4.3.9. 2,4-Dimethoxybenzonitrile. Mp 93–94 °C (commercial, Mp 93–94 °C); IR: 2219 cm^{-1}; ^1H NMR ($CDCl_3$, 500Hz), δ=3.86 (s, 3H), 3.90 (s, 3H), 6.46 (s, 1H), 6.51 (d, *J*=8.5 Hz, 1H), 7.48 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.6, 55.9, 93.8, 98.4, 105.7, 116.9, 134.8, 162.8, 164.6.

4.3.10. 2,4,6-Trimethoxybenzonitrile. Mp 139–140 °C (commercial, Mp 143–145 °C); IR: 2212 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=3.86 (s, 3H), 3.89 (s, 6H), 6.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=55.6, 56.0, 83.7, 90.2, 114.6, 163.6, 165.3.

4.3.11. 4-(N,N-dimethyamino)benzonitrile. Mp 74–75 °C (commercial, Mp 75 °C); IR: 2210 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=3.04 (s, 6H), 6.64 (d, *J*=9.1 Hz, 2H), 7.47 (d, *J*=9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=39.9, 97.2, 111.3, 120.7, 133.3, 152.4.

4.3.12. 1-Naphthonitrile. Mp 35–36 °C (commercial, Mp 36–38 °C); IR: 2219 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=7.49 (t, *J*=7.9 Hz, 1H), 7.59 (t, *J*=8.2 Hz, 1H), 7.67 (t, *J*=8.2 Hz, 1H), 7.89 (d, *J*=7.9 Hz, 1H), 7.91 (d, *J*=7.9 Hz, 1H), 8.05 (d, *J*=8.2 Hz, 1H), 8.22 (d, *J*=8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=110.0, 117.7, 124.8, 124.9, 127.4, 128.4, 128.5, 132.2, 132.5, 132.8, 133.2.

4.3.13. 2-Naphthonitrile. Mp 68–70 °C (commercial, Mp 66–70 °C); IR: 2225 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=7.58–7.68 (m, 3H), 7.88–7.93 (m, 3H), 8.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=109.3, 119.2, 126.3, 127.6, 128.0, 128.4, 129.0, 129.2, 132.2, 134.1, 134.6.

4.3.14. 4-Cyanobiphenyl. Mp 85–88 °C (commercial, Mp 85–87 °C); IR: 2225 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.44 (t, *J*=7.3 Hz, 1H), 7.49 (t, *J*=7.3 Hz, 2H), 7.59 (d, *J*=7.3 Hz, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.73 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=110.8, 118.9, 127.1, 127.6, 128.6, 129.0, 132.5, 139.0, 145.6.

4.3.15. 2-Cyanopyridine. Mp 24–25 °C (commercial, Mp 24–27 °C); IR: 2236 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.56 (dd, *J*=7.8 and 4.6 Hz, 1H), 7.73 (d, *J*=7.8 Hz, 1H), 7.88 (t, *J*=7.8 Hz, 1H), 8.74 (d, *J*=4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=117.0, 126.9, 128.3, 133.4, 136.9, 150.8.

4.3.16. 4-Chlorobenzonitrile. Mp 92–95 °C (commercial, Mp 90–93 °C); IR: 2226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.48 (d, *J*=8.8 Hz, 2H), 7.61 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=110.7, 117.9, 129.6, 133.3, 139.5.

4.4. Typical experimental procedure for the conversion of aromatics into aromatic nitriles with I_2

n-Butyllithium (1.67 M solution in hexane, 2.9 mL, 4.8 mmol) was added dropwise into a solution of 1,3-dimethoxybenzene (0.55 g, 4.0 mmol) in THF (5 mL) at 0 °C and the mixture was stirred for 2 h at the same temperature. Then, DMF (0.34 mL, 4.4 mmol) was added to the mixture and the obtained mixture was stirred at 0 °C. After 2 h at the same temperature, aq NH_3 (8 mL, 120 mmol) and I_2 (1.12 g, 4.4 mmol) were added and stirred for 2 h at rt. The reaction mixture was quenched with satd aq Na_2SO_3 (15 mL) and was extracted with Et_2O (3×20 mL). The organic layer was washed with brine and dried over Na_2SO_4 to provide 2,6-dimethoxybenzonitrile in over 80% purity. The product was purified by a short column chromatography on silica gel (Hexane/EtOAc=3:1) to give pure 2,6-dimethoxybenzonitrile in 91% yield as a colorless solid.

4.5. Typical experimental procedure for the conversion of aromatics into aromatic nitriles with DIH

n-Butyllithium (1.67 M solution in hexane, 2.9 mL, 4.8 mmol) was added dropwise to a solution of 1,3-dimethoxybenzene (0.55 g, 4.0 mmol) in THF (5 mL) at 0 °C. After 2 h, DMF (0.34 mL, 4.4 mmol) was added to the mixture and the obtained mixture was stirred at 0 °C. After 2 h at the same temperature, aq NH_3 (8 mL, 120 mmol) and DIH (0.91 g, 2.4 mmol) were added and the resulting mixture was stirred for 2 h at rt. The reaction mixture was quenched with satd aq Na_2SO_3 (15 mL) and was extracted with ether (3×20 mL). The organic layer was washed with brine and dried over Na_2SO_4 to provide 2,6-dimethoxybenzonitrile in over 80% purity. The product was purified by a column chromatography on silica gel (Hexane/EtOAc=3:1) to give pure 2,6-dimethoxybenzonitrile in 94% yield as a colorless solid.

4.5.1. 2-Methoxybenzonitrile. Oil (commercial); IR: 2228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ=3.92 (s, 3H), 6.96–7.04 (m, 2H), 7.51–7.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=55.8, 101.3, 111.1, 116.3, 120.6, 133.4, 134.3, 161.0.

4.5.2. 2,6-Dimethoxybenzonitrile. Mp 117–119 °C (commercial, Mp 119–123 °C); IR: 2220 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=3.90 (s, 6H), 6.56 (d, *J*=8.5 Hz, 2H), 7.44 (t, *J*=8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.1, 91.2, 103.4, 114.0, 134.7, 162.6.

4.5.3. 2,4,6-Trimethoxybenzonitrile. Mp 139–140 °C (commercial Mp 143–145 °C); IR: 2212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=3.86 (s, 3H), 3.89 (s, 6H), 6.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.6, 56.0, 83.7, 90.2, 114.6, 163.6, 165.3.

4.5.4. 2,5-Dimethoxybenzonitrile. Mp 79–82 °C (commercial, Mp 81–85 °C); IR: 2224 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=3.78 (s, 3H), 3.89 (s, 3H), 6.91 (d, *J*=9.0 Hz, 1H), 7.05–7.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=48.9, 49.3, 94.7, 105.5, 109.3, 110.5, 113.8, 146.1, 148.7.

4.5.5. 2,3-Dimethoxybenzonitrile. Mp 41–42 °C (commercial, Mp 43–46 °C); IR: 2228 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=3.89 (s, 3H), 4.03 (s, 3H), 7.07–7.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0, 61.7, 107.0, 116.3, 116.9, 124.4, 124.5, 151.7, 152.6.

4.5.6. 2,6-Difluorobenzonitrile. Oil (commercial Mp 25–28 °C); IR: 2241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.05–7.10 (m, 2H), 7.58–7.67 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=92.5 (s), 109.1 (s), 112.2 (dd, J_1=6.2, J_2=3.8 Hz), 135.5 (t, *J*=10.5 Hz), 163.3 (*J*=257.5 Hz).

4.5.7. 2-Cyano-N-tosylindole. Mp 160–161 °C (lit.[14] Mp 160–162 °C); IR: 1173, 1377, 2227 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=2.37 (s, 3H), 7.27 (d, *J*=8.2 Hz, 2H), 7.32–7.38 (m, 2H), 7.52–7.60 (m, 2H), 7.90 (d, *J*=8.4 Hz, 2H), 8.21 (d, *J*=8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.6, 108.9, 112.2, 114.5, 122.5, 123.0, 124.7, 127.1, 127.4, 128.6, 130.2, 134.3, 136.6, 146.1.

4.5.8. 2-Cyano-N-methylindole. Mp 70–73 °C; IR: 2223 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=3.91 (s, 3H), 7.16 (s, 1H), 7.21 (t, *J*=6.8, 1H), 7.34–7.44 (m, 2H), 7.66 (d, *J*=8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=31.4, 110.0, 110.1, 112.6, 113.6, 121.3, 122.2, 125.7, 126.0, 137.9; HRMS(APCI) $[M]^+$, calcd for $C_{10}H_8N_2$=156.0682, found=156.0681.

4.5.9. Benzofuran-2-carbonitrile. Oil (lit.[15]); IR: 2227 cm^{-1}; ^1H NMR ($CDCl_3$:500 MHz) δ=7.36 (t, *J*=7.5 Hz, 1H), 7.46 (s, 1H), 7.49–7.58 (m, 2H), 7.68 (d, *J*=7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=111.8, 112.0, 118.4, 122.5, 124.5, 125.4, 127.2, 128.4, 155.6.

4.5.10. Benzothiophene-2-carbonitrile. Oil (commercial, Mp 24–28 °C); IR: 2217 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=7.43 (t, *J*=7.6 Hz, 1H), 7.48 (t, *J*=7.6 Hz, 1H), 7.77–7.85 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=109.4, 114.3, 122.2, 125.1, 125.6, 127.7, 134.8, 137.2, 141.0.

4.5.11. 5-Decylfuran-2-carbonitrile. Oil; IR: 2229 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ=0.88 (t, *J*=7.0 Hz, 3H), 1.21–1.38 (m, 14H), 1.65 (quintet, *J*=7.1 Hz, 2H), 2.66 (t, *J*=7.1 Hz, 2H), 6.11 (d, *J*=3.4 Hz, 1H), 6.99 (d, *J*=3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.0, 22.6, 27.5, 28.1, 28.9, 29.1, 29.2, 29.4, 29.5, 31.8, 106.9, 111.9, 123.0, 124.2, 162.5; HRMS (FAB) $[M+H]^+$, calcd for $C_{15}H_{24}NO$=234.1858, found=234.1861.

4.5.12. 5-Decylthiophene-2-carbonitrile. Oil; IR: 2218 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=0.88 (t, *J*=7.1 Hz, 3H), 1.23–1.38 (m, 14H), 1.67 (quintet, *J*=7.5 Hz, 2H), 2.83 (t, *J*=7.5 Hz, 2H), 6.78 (d, *J*=3.6, Hz, 1H), 7.43 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 22.5, 28.8, 29.0, 29.1, 29.3, 29.6, 29.9, 31.2, 31.7, 106.6, 114.3, 124.7, 137.4, 154.2; HRMS(FAB) $[M+H]^+$, calcd for $C_{15}H_{24}NS$=250.1629, found=250.1636.

4.5.13. 3-Methoxy-2-naphthonitrile. Mp 123–125 °C (lit.[16] Mp 125 °C); IR: 2224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=4.02 (s, 3H), 7.19 (s, 1H), 7.43 (dd, *J*=6.8 and 7.2 Hz, 1H), 7.58 (dd *J*=6.8 and 7.2 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.79 (d, *J*=8.2 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.9, 103.3, 106.2, 116.4, 125.0, 126.8, 127.3, 128.1, 129.3, 135.9, 136.1, 156.0.

4.5.14. 4-Cyano-4′-pentylbiphenyl. Oil (commercial); IR: 2226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.8 Hz, 3H), 1.28–1.38 (m, 4H), 1.58–1.68 (m, 2H), 2.62 (t, *J*=7.7 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 7.46 (d, *J*=8.2 Hz, 2H), 7.57–7.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.9, 22.4, 30.9, 31.3, 35.4, 110.3, 118.8, 126.9, 127.2, 129.0, 132.3, 136.2, 143.6, 145.3.

4.5.15. 2-(methoxymethoxy)-5-methylbenzonitrile. Mp 59–61 °C; IR: 2225 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ=2.31 (s, 3H), 3.52 (s, 3H), 5.26 (s, 2H), 7.12 (d, *J*=8.6 Hz, 1H), 7.31 (d, *J*=8.6 Hz, 1H), 7.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=20.2, 56.5, 94.8, 102.6, 114.9, 116.5, 131.6, 133.5, 135.0, 157.0; HRMS(ESI)$[M+H]^+$, calcd for $C_{10}H_{12}O_2N$=178.0863, found=178.0861.

4.5.16. 2-Hydroxy-5-methylbenzonitrile. Mp 100–102 °C; IR: 2234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.28 (s, 3H), 6.12–6.65 (br, 1H), 6.90 (d, *J*=8.6 Hz, 1H), 7.24–7.3(m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=20.1, 90.0, 116.5, 130.5, 132.5, 135.6, 156.5; HRMS(ESI) $[M+H]^+$, calcd for C_8H_8ON=134.0600, found=134.0603.

Acknowledgements

Financial support in the form of a Grant-in-Aid for Scientific Research (No. 20550033) from the Ministry of Education, Culture, Sports, Science, and Technology in Japan, Iodine Research Project in Chiba University, Academia Showcase Research Grant from the Japan Chemical Innovation Institute (JCII), and Futaba Electronics Memorial Foundation, is gratefully acknowledged.

References and notes

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