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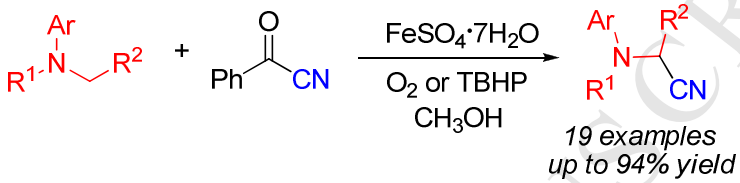

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ABSTRACT

An iron-mediated oxidative cyanation of tertiary amines with benzoyl cyanide and molecular oxygen or TBHP has been achieved. This reaction furnished α-cyanated tertiary amines under mild reaction conditions in good to excellent yields (up to 94%) with great diversity (19 examples). The cascade process involves an iron-catalyzed oxidation of tertiary amine. Our protocol features safety cyanation reagent, acid-free conditions, inexpensive iron catalyst, and aerobic oxidation.

1. Introduction

α-Aminonitriles are important building blocks in organic synthesis because they can be readily converted into various compounds with multifunctionalities, including α-amino acids and 1,2-diamines. Preparation of α-aminonitriles by traditional Streck reaction,[1,2] a three-component reaction from carbonyl, amine, and cyanide, has been well documented. Alternative approach using α-cyanation of tertiary amines attracted much attention since the late 1960s by using anodic oxidation of amine to iminium and a sequential nucleophilic trap by Et_4NCN[3] or NaCN.[4] Since then, several chemical oxidation methods were reported in the literature, such as chorine dioxide,[5] hypervalent iodine,[6,7] and molecular iodine as well.[8] By using visible-light, photo-catalyzed oxidative cyanation of tertiary amines has recently been realized with low organic dye loading.[9-12] Beyond electro-oxidation, chem-oxidation, and photo-oxidation, transition metal catalyzed oxidative cyanation of tertiary amines becomes unique due to several advantages, such as controllable reaction conditions, high catalytic efficiencies, simple facilities, operational safety, and environmental benignity.[13,14] In this blooming field, several research groups made great contributions. In 1993, Miura and co-workers reported a preliminary work using $FeCl_3$ as the catalyst and molecular oxygen as oxidant.[15] However, only five 4-substituted N,N-dimethylanilines were presented as starting materials, all of which contaminated with N-methylformanilides in approximate 2:1 ratio. Keeping up with the successful example of ruthenium-catalyzed oxidation of β-lactam for the synthesis of fourth-generation antibiotics,[16,17] Murahashi pioneered the development of $RuCl_3$-catalyzed oxidative cyanation of tertiary amines with sodium cyanides using O_2 or H_2O_2 in acid environment.[18-20] Meanwhile, Li and co-workers developed the CuBr-catalyzed cross-dehydrogenative coupling between tetrahydroisoquinoline and manolonitrile in the presence of TBHP under acid-free condition, which produced the cyanated product in 36% yield.[21] Afterwards, in order to have high efficiency, high yield, and safe operation, several catalyst systems based on various transition metals were disclosed, including V_2O_5,[22] $FeCl_2$,[23] polymer supported iron(II) phthalocyanines,[24] iron oligopyridine complexes,[25] gold-complex,[26] and rhenium-complex.[27] However, these transition metal-catalyzed reactions all lead to by-product formation. Taking *N*,*N*-dimethylaniline as an example, its oxidation could produce *N*-methylformanilide[15] and *N*-methylaniline,[25,28] both of them derived from the oxidation of tertiary amine.

In this paper, we would like to report an iron-mediated oxidative cyanation of tertiary amines with benzoyl cyanide using molecular oxygen or TBHP as oxidant. The reaction furnished α-cyanated tertiary amines under mild reaction conditions in good to excellent yields.

2. Results and discussion

Attracted by the thriving chemistry of transition metal-catalyzed oxidative cyanation of tertiary amine[13] and our previous work on benzyl cyanide as the safe cyanating reagent,[29,31] we primarily

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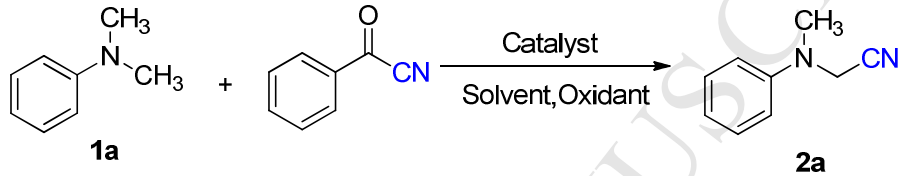
designed the oxidative cyanation reaction of *N,N*-dimethylaniline (**1a**) using the combination of "CuBr + *t*-BuOOH TBHP) + $PhCH_2CN$".[21] To our disappointment, no satisfied results were obtained from benzyl cyanide. By altering benzyl cyanide to benzoyl cyanide,[32] the yields changed drastically. The reaction of benzoyl cyanide with **1a** in the presence of CuI and TBHP provided the desired cyanated product **2a** in 36% yield (Table 1, entry 1), while $Cu(OAc)_2$ and $Pd(OAc)_2$ gave **2a** in 10% and 62% yields, respectively (Table 1, entries 2 and 3).

By changing the catalyst to various iron catalysts, $FeSO_4•7H_2O$ was found to be optimal in comparison with $FeCl_3$, $FeCl_3•7H_2O$, $FeCl_2$, Fe_2O_3, $Fe(NO_3)_3•9H_2O$, and $Fe_2(SO_4)_3$ (Table 1, entries 4-10). Yield of **2a** increased to 84% (Table 1, entry 7). Optimal amounts of $FeSO_4•7H_2O$, TBHP, and PhCOCN were found to be 0.05, 1.5, and 1.2 equivalents, respectively (Table 1, entries 11-17). The suitable reaction temperature was determined to be at room temperature (Table 1, entries 14, 18 and 19). It was also found that the reaction largely depended upon the solvents and oxidants. When 1,4-dioxane, dichloromethane, tetrahydrofuan or toluene was used as solvent, on reaction was observed. DMSO (Table 1, entry 20), acetonitrile (Table 1, entry 21) and ethanol (Table 1, entry 22) provided **2a** in 75%, 55% and 36% yields, respectively. DMF (Table 1, entry 23) and isopropanol (Table 1, entry 24) did not work. Without TBHP, the reaction could be carried out under air, but presented poor yield (Table 1, entry 25). Slightly improved yields were obtained when hydrogen peroxide (Table 1, entry 26) or benzoyl peroxide (Table 1, entry 27) was used as oxidant. The situation changed when molecular oxygen was used. By screening other conditions under O_2 (Table 1, entries 29-31), the optimal reaction conditions were established. When the mixture of **1a** (0.5 mmol), PhCOCN (0.6 mmol), and (5 mol % $FeSO_4•7H_2O$) in methanol (2.0 mL) reacted under O_2 at room temperature for 16 hours, **2a** was prepared in 91% isolated yield (Table 1, entry 29).

Table 1
Optimization of the reaction conditions[a]



1a **2a**

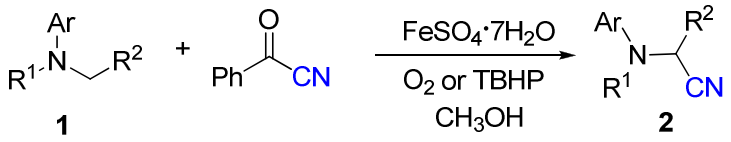
Entry	Catalyst (equiv)	Oxidant (equiv)	PhCOCN (equiv)	Solvent	Yield (%)[b]
1	CuI (0.1)	TBHP (2.5) / air	1.2	CH_3OH	36
2	$Cu(OAc)_2$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	10
3	$Pd(OAc)_2$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	62
4	$FeCl_3$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	63
5	$FeCl_3•7H_2O$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	52
6	$FeCl_2$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	69
7	$FeSO_4•7H_2O$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	84
8	Fe_2O_3 (0.1)	TBHP (2.5) / air	1.2	CH_3OH	35
9	$Fe(NO_3)_3•9H_2O$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	30
10	$Fe_2(SO_4)_3$ (0.1)	TBHP (2.5) / air	1.2	CH_3OH	65
11	$FeSO_4•7H_2O$ (0.05)	TBHP (2.5) / air	1.2	CH_3OH	86
12	$FeSO_4•7H_2O$ (0.15)	TBHP (2.5) / air	1.2	CH_3OH	82
13	$FeSO_4•7H_2O$ (0.05)	TBHP (1.0) / air	1.2	CH_3OH	83
14	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	CH_3OH	88
15	$FeSO_4•7H_2O$ (0.05)	TBHP (2.0) / air	1.2	CH_3OH	86
16	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.0	CH_3OH	75
17	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.5	CH_3OH	88
18	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	CH_3OH	38[c]
19	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	CH_3OH	85[d]
20	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	DMSO	75
21	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	CH_3CN	55
22	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	EtOH	36
23	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	DMF	0
24	$FeSO_4•7H_2O$ (0.05)	TBHP (1.5) / air	1.2	*i*-PrOH	0
25	$FeSO_4•7H_2O$ (0.1)	air	1.2	CH_3OH	9
26	$FeSO_4•7H_2O$ (0.1)	H_2O_2 (2.5) / air	1.2	CH_3OH	15
27	$FeSO_4•7H_2O$ (0.1)	$(PhCOO)_2$ (2.5) / air	1.2	CH_3OH	12
28	$FeSO_4•7H_2O$ (0.1)	O_2	1.2	CH_3OH	91
29	$FeSO_4•7H_2O$ (0.05)	O_2	1.2	CH_3OH	91
30	$FeSO_4•7H_2O$ (0.05)	O_2	1.2	CH_3OH	91[d]
31	$FeSO_4•7H_2O$ (0.05)	O_2	1.2	CH_3OH	45[c]

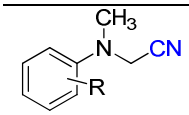
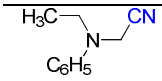
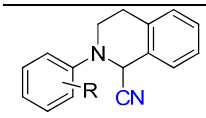
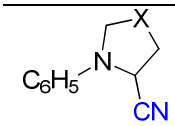
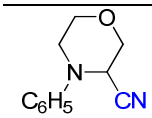
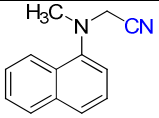
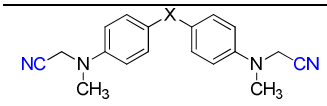
[a] Reaction conditions: **1a** (0.5 mmol), solvent (2 mL), room temperature, 16 h.
[b] Isolated yield.
[c] 0 °C.
[d] 50 °C.

With the optimal reaction conditions in our hand, we investigated the substrate diversity and the results are summarized in Table 2. It was found that reaction heavily relied on the substrate structure. We thereby used the TLC to track each reaction. Under the same conditions, **2b** and **2c** were obtained in 94% and 85% yields. With the methyl group occupied on the ortho position of *N,N*-dimethylaniline, **2d** was obtained in 83% yield by raising the reaction temperature to reflux. With bromomine atom occupied on the para-position of *N,N*-dimethylaniline, **2e** was obtained in 78% yield. For 4-chloro-*N,N*-dimethylaniline, the cyanated product **2f** was obtained in 50% yield when the reaction was carried out under O_2. An improved yield (65%) of **2f** was obtained when the reaction was performed using TBHP as oxidant. With fluorine atom occupied on the para-position of *N,N*-dimethylaniline, **2g** was obtained in 68% yield by refluxing for 24 h. When the para-position of N,N-

Table 2.

Preparation of α-cyanated tertiary amines **2** [a]



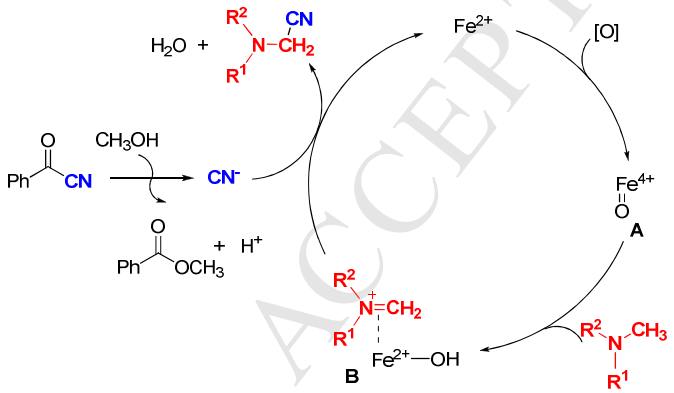
Product		Reaction conditions	Yield (%)[b]
	**2a:** R = H	O_2, 5 mol % [Fe], rt, 16 h	91
		1.5 equiv TBHP, 5 mol % [Fe], rt, 16 h	88
	2b: R = 4-Me	O_2, 5 mol % [Fe], rt, 16 h	94
		1.5 equiv TBHP, 5 mol % [Fe], rt, 16 h	89
	2c: R = 3-Me	O_2, 5 mol % [Fe], rt, 16 h	85
	2d: R = 2-Me	O_2, 5 mol % [Fe], reflux, 14 h	83
	2e: R = 4-Br	O_2, 5 mol % [Fe], rt, 20 h	78
	2f: R = 4-Cl	O_2, 10 mol % [Fe], 35 °C, 36 h	50
		1.5 equiv TBHP, 10 mol % [Fe], rt, 20 h	65
	2g: R = 4-F	O_2, 5 mol % [Fe], reflux, 24 h	68
	2h: R = 4-MeO	O_2, 10 mol % [Fe], reflux, 36 h	41
	2i: R = 4-CO_2Et	3 equiv TBHP, 20 mol % [Fe], reflux, 24 h	82
	**2j**	O_2, 5 mol % [Fe], rt, 24 h	53
	**2k:** R = H	O_2, 10 mol % [Fe], reflux, 24 h	70
	2l: R = 4-MeO	O_2, 10 mol % [Fe], reflux, 24 h	68
	2m: R = 4-CN	O_2, 10 mol % [Fe], reflux, 24 h	45
	**2n:** X = CH_2	O_2, 20 mol % [Fe], reflux, 36 h	20
		1.5 equiv TBHP, 20 mol % [Fe], rt, 24 h	80
	2o: X= CH_2CH_2	O_2, 20 mol % [Fe], 60 °C, 36 h (solvent-free)	35
		1.5 equiv TBHP, 20 mol % [Fe], rt, 24 h	68
	**2p**	1.5 equiv TBHP, 20 mol % [Fe], rt, 36 h	51
	**2q**	1.5 equiv TBHP, 10 mol % [Fe], 60 °C, 24 h	34
	**2r:** X = CH_2	O_2, 10 mol % [Fe], reflux, 30 h	9
		3 equiv TBHP, 10 mol % [Fe], reflux, 30 h	80
	2s: X = CO	3 equiv TBHP, 20 mol % [Fe], reflux, 24 h	70

[a] Reaction conditions: **1** (0.5 mmol), benzoyl cyanide (0.6 mmol), $FeSO_4$•$7H_2O$ (5~20 mol %), CH_3OH (2 mL).
[b] Isolated yield.

dimethylaniline was substituted by methoxyl, a relatively lower yield was observed. In this case, **2h** was prepared in 41% yield even when the catalyst amount was increased to 10 mol % and the reaction mixture was refluxed for 36 hours. For ester group substituted N,N-dimethylaniline, the desired product **2i** was not obtained under O_2 condition. However, changing the oxidant to TBHP led to successful preparation of **2i** in 82% yield.

Regioselective oxidation was observed on *N*-Me instead of N-Et in case of N-ethyl-N-methylaniline. For this case, **2j** was isolated in 53% yield. The cyclical amines were examined and high regioselectivity was also observed. Thus, *N*-phenyl-tetrahydroisoquinoline, *N*-(*p*-methoxyphenyl)-tetrahydroiso-quinoline and *N*-(*p*-cyanophenyl)-tetrahydroisoquinoline gave **2k, 2l** and **2m** in 70%, 68% and 45% yields, respectively. The reaction of *N*-phenylpyrrolidine and *N*-phenylpiperidine under O_2 conditions provided the corresponding products **2n** and **2o** in relatively lower yields. When TBHP was used, the yields of **2n** and **2o** were improved to 80% and 68% yields, respectively. *N*-Both phenylmorpholine and *N*,*N*-Dimethylnaphthalen-1-amine did not react under an oxygen atmosphere. Using TBHP as oxidant, they offered the corresponding products **2p** and **2q** in 51% and 34% yields, respectively. 4,4'-Methylenebis(*N*,*N*-dimethylaniline) furnished the bicyanated product **2r** in 9% yield under O_2 even after refluxing for 30 hours. When 3.0 equivalents of TBHP were used, we achieved **2r** in 80% yield. Bis(4-(dimethylamino)phenyl)methanone furnished the bicyanated product **2s** in 70% yield with excellent regioselectivity. So far, we provided 19 examples with the nice substrate diversity in yields varied from 20% to 94%.

Referring to the iron-oxo complexes in many non-heme iron catalyzed oxidations[33,34] and previous reports on transition metal-catalyzed oxidation of tertiary amines,[20,24,25] we postulated a possible reaction mechanism (**Scheme 1**). The low valence $FeSO_4$•$7H_2O$ is oxidized into iron-oxo species (**A**) in the presence of TBHP or oxygen. Followed by the electron and hydrogen transfer, the iminium intermediate **B** is formed as the key intermediate and subsequently trapped by the in situ generated cyanide anion from benzoyl cyanide.



Scheme 1. Possible reaction mechanism.

3. Conclusion

In conclusion, we have developed a feasible method for the preparation of 2-cyanoamines from benzoyl cyanide and readily available tertiary amines. More examples were presented with nice diversity. The reaction proceeded in a cascade way, including an iron-catalyzed oxidation of tertiary amine to iminium ions and trapping them by cyanide anion. Several features about this protocol should be mentioned: safety cyanation reagent, acid-free conditions, inexpensive iron catalyst, and aerobic oxidation.

4. Experimental

4.1 General

Unless stated otherwise, commercially available reagents and solvents were used as received. Flash column chromatography was performed using 200-300 mesh silica gel. Visualization on TLC was achieved by the use of UV light (254 nm). NMR spectra were obtained at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts were quoted relative to tetramethylsilane (TMS) as internal standard and reported in ppm. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, t = triplet, m = multiple. High-resolution mass spectra (HRMS) were recorded using TOF-EI. Melting points were measured with a micro melting point apparatus.

4.2 Typical procedure for the synthesis of 2a

Method A: The mixture of $FeSO_4$•$7H_2O$ (6.95 mg, 0.025 mmol), N,N-dimethylaniline (60.55 mg, 0.5 mmol), benzoyl cyanide (78.62 mg, 0.6 mmol) in CH_3OH (2.0 mL) was stirred under an oxygen atmosphere at room temperature for 16 hours. After the tertiary amine was completely consumed (checked by TLC), the reaction mixture was filtrated and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to afford **2a** (66.5 mg, 91% yield) as a yellow oil.

Method B: The mixture of $FeSO_4$•$7H_2O$ (6.95 mg, 0.025 mmol), N,N-dimethylaniline (60.55 mg, 0.5 mmol), benzoyl cyanide (78.62 mg, 0.6 mmol), and TBHP (70% aqueous solution, 108 μL, 0.75 mmol) in CH_3OH (2.0 mL) was stirred under air at room temperature for 16 hours. After the tertiary amine was completely consumed, the reaction mixture was filtrated and concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 4:1) to afford **2a** (64.3 mg, 88% yield) as a yellow oil.

4.3 Characterization data

*4.3.1. 2-(Methyl(phenyl)amino)acetonitrile (**2a**).* (Method A, 66.5 mg, 91% yield); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H), 6.90 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 129.6, 120.2, 115.8, 115.0, 42.3, 39.3.

*4.3.2. 2-(Methyl(p-tolyl)amino)acetonitrile (**2b**).* (Method A, 75.2 mg, 94% yield); yellow solid; mp 55-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.97 (s, 2H), 2.82 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 130.2, 129.9, 115.8, 115.5, 42.9, 39.6, 20.6.

*4.3.3. 2-(Methyl(m-tolyl)amino)acetonitrile (**2c**).* (Method A, 68.0 mg, 85% yield); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.8, 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.58 (m, 2H), 4.04 (s, 2H), 2.89 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 139.5, 129.5, 121.3, 115.9, 115.9, 112.3, 42.5, 39.4, 22.0.

*4.3.4. 2-(Methyl(o-tolyl)amino)acetonitrile (**2d**).* (Method A, 66.4 mg, 83% yield); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-

7.15 (m, 3H), 7.10-7.01 (m, 1H), 3.82 (s, 2H), 2.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 133.1, 131.6, 127.1, 125.2, 120.9, 115.9, 45.3, 41.2, 18.0.

4.3.5. 2-((4-Bromophenyl)(methyl)amino)acetonitrile ***(2e)***. (Method A, 87.4 mg, 78% yield); yellow solid; mp 35-36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.2 Hz, 2H), 6.71 (d, *J* = 9.2 Hz, 2H), 4.12 (s, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 132.5, 116.6, 115.5, 112.7, 42.3, 39.5.

4.3.6. 2-((4-Chlorophenyl)(methyl)amino)acetonitrile ***(2f)***. (Method B, 58.5 mg, 65% yield); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.12 (s, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 129.5, 125.4, 116.2, 115.5, 42.5, 39.6.

4.3.7. 2-((4-Fluorophenyl)(methyl)amino)acetonitrile ***(2g)***. (Method A, 55.8 mg, 68% yield); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04-6.98 (m, 2H), 6.86-6.83 (m, 2H), 4.02 (s, 2H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7 (J_{C-F} = 238.1 Hz), 144.6 (J_{C-F} = 2.3 Hz), 117.2 (J_{C-F} = 7.8 Hz), 116.2 (J_{C-F} = 22.2 Hz), 115.6, 43.5, 40.0.

4.3.8. 2-((4-Methoxyphenyl)(methyl)amino)acetonitrile ***(2h)***. (Method A, 36.1 mg, 41% yield); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 4H), 4.00 (s, 2H), 3.70 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 142.4, 118.0, 115.7, 115.0, 55.8, 44.2, 40.2.

4.3.9. Ethyl 4-((cyanomethyl)(methyl)amino)benzoate ***(2i)***. (Method B, 89.4 mg, 82% yield); yellow solid; mp 63-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.17 (s, 2H), 3.02 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.0, 131.6, 121.3, 115.5, 113.0, 60.8, 41.5, 39.3, 14.6.

4.3.10. 2-(Ethyl(phenyl)amino)acetonitrile ***(2j)***. (Method A, 42.4 mg, 53% yield); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.6 Hz, 2H), 6.86-6.71 (m, 3H), 4.05 (s, 2H), 3.35 (q, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 129.8, 120.0, 116.7, 115.1, 46.5, 39.7, 12.5.

4.3.11. 2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile ***(2k)***. (Method A, 81.9 mg, 70% yield); yellow solid; mp 95-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.2 Hz, 2H), 7.25-7.14 (m, 4H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 5.44 (s, 1H), 3.74-3.64 (m, 1H), 3.41 (ddd, *J* = 12.4, 10.8, 4.0 Hz, 1H), 3.08 (ddd, *J* = 16.4, 10.8, 6.0 Hz, 1H), 2.89 (dt, *J* = 16.4, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 134.9, 129.9, 129.7, 129.1, 128.7, 127.4, 127.2, 122.2, 118.1, 117.9, 53.5, 44.5, 28.9.

4.3.12. 2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile ***(2l)***. (Method A, 89.8 mg, 68% yield); white solid; mp 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.19 (m, 4H), 7.09 (dd, *J* = 8.8, 4.4 Hz, 2H), 6.98-6.85 (m, 2H), 5.38 (s, 1H), 3.79 (s, 3H), 3.58 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.51-3.36 (m, 1H), 3.21-3.06 (m, 1H), 2.93 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 142.7, 134.5, 129.8, 129.6, 128.8, 127.2, 126.9, 121.1, 117.8, 114.9, 55.8, 55.7, 45.0, 28.8.

4.3.13. 2-(4-Cyanophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile ***(2m)***. (Method A, 58.3 mg, 45% yield); yellow solid; mp 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 9.0 Hz, 2H), 7.39-7.31 (m, 3H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 5.60 (s, 1H), 3.90-3.79 (m, 1H), 3.68-3.52 (m, 1H), 3.19-3.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 135.0, 134.2, 129.7, 129.5, 129.1, 127.7, 127.3, 119.7, 117.7, 115.0, 103.0, 50.5, 44.1, 28.5. HRMS (EI) Calcd. for $C_{17}H_{13}N_3$:259.1109([M]$^+$), found: 259.1113.

4.3.14. 1-Phenylpyrrolidine-2-carbonitrile ***(2n)***. (Method B, 68.8 mg, 80% yield); gray solid; mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 8.0 Hz, 2H), 6.83 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 4.55 (d, *J* = 6.4 Hz, 1H), 3.51-3.40 (m, 1H), 3.41-3.26 (m, 1H), 2.48-2.36 (m, 1H), 2.34-2.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 129.8, 119.6, 118.6, 113.0, 49.4, 47.8, 31.9, 24.3.

4.3.15. 1-Phenylpiperidine-2-carbonitrile ***(2o)***. (Method B, 63.3 mg, 68% yield); yellow solid; mp 60-61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 8.8, 7.2 Hz, 2H), 7.00 (dd, *J* = 8.3, 7.7 Hz, 3H), 4.63 (t, *J* = 3.4 Hz, 1H), 3.44 (d, *J* = 12.0 z, 1H), 3.03 (ddd, *J* = 12.1, 9.6, 2.5 Hz, 1H), 2.11-1.94 (m, 2H), 1.91-1.78 (m, 2H), 1.75-1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 129.7, 122.5, 118.6, 117.5, 52.3, 46.9, 29.5, 25.4, 20.5.

4.3.16. 4-Phenylmorpholine-3-carbonitrile ***(2p)***. (Method B, 48.0 mg, 51% yield); white solid; mp 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 4.43 (s, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 4.10 (d, *J* = 11.2 Hz, 1H), 3.91 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.80-3.70 (m, 1H), 3.29 (dd, *J* = 7.9, 2.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 129.9, 123.0, 117.6, 116.3, 68.4, 67.2, 51.4, 45.8.

4.3.17. 2-(Methyl(naphthalen-1-yl)amino)acetonitrile ***(2q)***. (Method B, 33.3 mg, 34% yield); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.05 (m, 1H), 7.84 (dd, *J* = 7.2, 2.2 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.54-7.45 (m, 2H), 7.45-7.39 (m, 1H), 7.30 (dd, *J* = 7.4, 0.9 Hz, 1H), 4.06 (s, 2H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 135.0, 128.9, 128.8, 126.4, 126.4, 125.9, 125.6, 123.0, 117.4, 115.7, 46.3, 41.5.

4.3.18. 2,2'-((Methylenebis(4,1-phenylene))bis(methylazanediyl))diacetonitrile ***(2r)***. (Method B, 121.7 mg, 80% yield); yellow solid; mp 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.3 Hz, 4H), 6.80 (d, *J* = 8.4 Hz, 4H), 4.11 (s, 4H), 3.86 (s, 2H), 2.95 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 133.5, 130.0, 115.9, 115.4, 42.7, 40.2, 39.6.

4.3.19. 2,2'-((Carbonylbis(4,1-phenylene))bis(methylazanediyl))diacetonitrile ***(2s)***. (Method B, 111.4 mg, 70% yield); yellow solid; mp 183-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.7 Hz, 4H), 6.83 (d, *J* = 8.8 Hz, 4H), 4.27 (s, 4H), 3.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 150.6, 132.3, 128.9, 115.6,

112.7, 41.3, 39.2. HRMS (EI) Calcd. for $C_{19}H_{18}N_4O$: 318.1481 ($[M]^+$), found: 318.1480.

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Supplementary data

Copies of NMR spectra (^1H and ^{13}C) for **2a**-**2s** and HRMS of **2m** and **2s**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.

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