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PAPER

Oxidative aromatic C–N bond formation: convenient synthesis of *N*-amino-3-nitrile-indoles *via* FeBr₃-mediated intramolecular cyclization†

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A variety of functionalized *N*-amino-3-nitrile-indole derivatives are obtained *via* an intramolecular hetero-cyclization of 2-aryl-3-substituted hydrazono-alkylnitriles using FeBr₃ as a single electron oxidant. This approach allows the *N*-moiety on the side-chain to be annulated to the benzene ring during the final synthetic step *via* direct oxidative aromatic C–N bond formation.

Introduction

For a class of nitrogen heterocyclic compounds with particular substitution patterns, *N*-amino substituted indole derivatives show significant pharmacological properties,¹ which include but are not limited to analgesic,^{1a} anticonvulsant,^{1b} and antioxidative^{1c,d} effects. In addition, some *N*-pyridylamino indole derivatives have found wide applications as acetylcholinesterase inhibitors for the treatment of Alzheimer's disease.²

Several methods for the construction of these compounds have been developed (Fig. 1).^{3,4} A literature survey shows that those methods can be generalized into following categories: (1) the *N*-aminoindole compound was synthesized using *N*-functionalized aniline (e.g. nitroso aniline, phenylhydrazine, or diphenyldiazene, etc.) as starting material (Fig. 1, Path a).^{3b–f} (2) *N*-Amination of the indole skeletons, *via* the hygroscopic hydroxylamine-*O*-sulfonic acid (HOSA) or related reagents remains overwhelmingly as the most applied method for constructing this interesting class of compounds (Fig. 1, Path b).^{1d,2a,3i,4} (3) The *N*-moiety was annulated to the benzene ring with an indispensable *ortho* halogen substituent as the last synthetic step. This approach can provide efficient syntheses of *N*-aminoindole derivatives *via* transition metal-catalyzed intramolecular cyclization (Fig. 1, Path c).^{3a,3g,h}

In continuation of our work on the synthesis of indole compounds with different substitution patterns,⁵ we reported herein that *N*-amino-3-nitrile-indoles **2** can be achieved *via* a novel iron(III)-mediated intramolecular oxidative hetero-cyclization of 2-aryl-3-substituted hydrazonoalkylnitriles **1** (Table 2), which contains the following features: (1) the indole ring formation allows the *N*-moiety to be annulated to the benzene ring during the last synthetic step, which enables the functionalization of the benzenoid part with a variety of substituents at an early stage. (2)

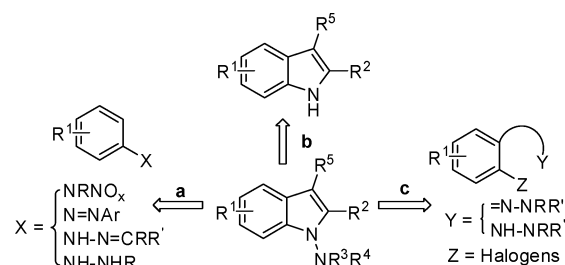


Fig. 1 General strategies for the syntheses of *N*-aminoindoles.

The annulation can be directly realized *via* oxidative C–N bond formation. (3) The presence of a halogen substituent at the *ortho* position to the side-chain is unnecessary.

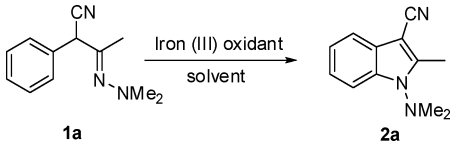
Result and discussion

We firstly subjected hydrazone substrate **1a** (Table 1) to FeCl₃ in CH₂Cl₂ to test the feasibility of the reaction. To our delight, the reaction did produce the desired *N,N*-dimethylaminoindole **2a**. However, the yields (10–20%) at complete consumption of **1a** were far from satisfactory (Table 1, entries 1–4). In each case, a significant amount of unisolated polar byproducts (baseline by TLC) were formed, which were probably derived from strong complexation of HCl or iron(III) salts (both are Lewis acids) with the amino moiety in the hydrazone **1a** (Lewis base). Further optimization study by using **1a** as the substrate (Table 1) showed that 1,2-dichloroethane (DCE) is a more desirable solvent than CH₂Cl₂ since 2.5 equiv. of FeCl₃ in DCE provided a better yield (36%) under the conditions (Table 1, entry 5). It was also found that increasing the dosage of FeCl₃ to 3 equivalents led to an obvious decrease in the yield (Table 1, entries 3–6). Finally, we found that the replacement of FeCl₃ with FeBr₃ provided the cyclized products in much improved yields (Table 1, entries 11–14). Attempts to counteract the complexation *via* the introduction of a milder Lewis base, such as acetic anhydride or propylene oxide (PO) only resulted in lower yields (Table 1, entries 12–13).

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Table 1 Oxidative condition screening for the cyclization of substrate **1a**^a

				
Entry	Oxidant (equiv.)	Solvent	Time/h	Yield ^b (%)
1	FeCl ₃ (2.0)	CH ₂ Cl ₂	2 ^c	10
2	FeCl ₃ (2.2)	CH ₂ Cl ₂	1	16
3	FeCl ₃ (2.5)	CH ₂ Cl ₂	0.5	20
4	FeCl ₃ (3.0)	CH ₂ Cl ₂	0.5	15
5	FeCl ₃ (2.5)	DCE	0.5	36
6	FeCl ₃ (3.0)	DCE	0.5	30
7	FeCl ₃ (2.5)	CHCl ₃	0.5	32
8	FeCl ₃ (2.5)	THF	0.5	10
9	FeCl ₃ (2.5)	toluene	0.5	5
10	FeCl ₃ (2.5)	CH ₃ CN	1	23
11	FeBr ₃ (2.5)	DCE	0.5	60
12	FeBr ₃ (2.5)	DCE-Ac ₂ O	0.5	51
13	FeBr ₃ (2.5)	DCE-PO	0.5	43
14	FeBr ₃ (2.5)	DCE-CH ₃ NO ₂	0.5	57

^a Reaction conditions: **1a** (1 mmol) and iron(III) oxidant in 10 mL of solvent at room temperature. ^b Yield of isolated product after chromatography. ^c The substrate was not totally consumed, even though the reaction mixture was refluxed for 12 h.

Moreover, the introduction of polar nitromethane to enhance the solubility of FeBr₃ did not benefit the yield (Table 1, entry 14).⁶

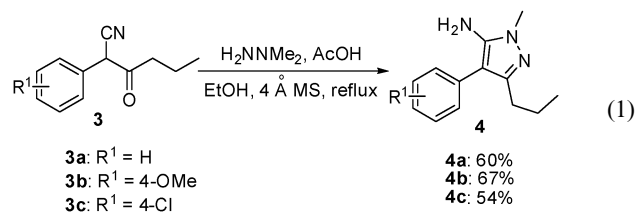
Under the most optimal reaction conditions (Table 1, entry 11), the scope and limitations of this reaction were further explored. It is expected that each hydrazine substrate **1**, prepared from α -aryl- β -ketonitrile **3** and 1,1-dimethylhydrazine *via* condensation,⁷ should possess two isomers. However, the ¹H NMR spectra indicated that only hydrazones **1a–b**, **1i** and **1o** exist as a mixture of *trans* and *cis* isomers, with the *trans* isomers predominating for **1c–h**, **1j–n** and **1p–q**.^{5b,8} The results listed in Table 2 demonstrate that both the electron-withdrawing and electron-donating aromatic substituents can be tolerated and all reactions proceed to afford a variety of *N,N*-dimethylaminopyrazoles in moderate yields (Table 2, entries 1–14). The reaction was also shown to be compatible with multiple substituents on the benzene ring (Table 2, entries 3–4 and 12).

Meta-substituted aromatic reactants have the possibility of producing two regioisomeric products. However, for substrates **1f–h**, only **2f–h** were obtained, respectively, by silica gel chromatography as the major regioisomeric products.

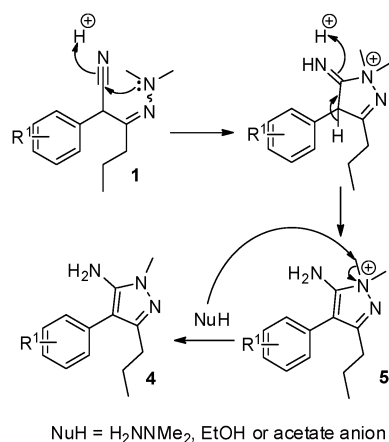
An extension of the application of this heterocyclization methodology is to generate N-containing heterocycles containing aromatic systems other than benzene. An example of this application is the synthesis of the two unknown heterocycles **2m** and **2n** with yields close to 50%.

It is worth noting that our attempt to achieve the hydrazone substrate with R² being a bulkier benzyl or phenyl group, or chained alkyl group was unsuccessful, since the condensation reaction of the corresponding 1,1-dimethylhydrazine and β -ketonitrile did not occur at room temperature, while raising the reaction temperature only led to the formation of either an inseparable complex mixture (R² = Bn, Ph) or an unexpected 5-aminopyrazole compound **4** (R² = *n*-Pr). Although the reaction of β -ketonitrile and 1-methylhydrazine has been well known to

give the *N*-methylpyrazole compound,⁹ we did not assume that replacing 1-methylhydrazine with 1,1-dimethylhydrazine would also afford the same pyrazole compound. However, to our surprise, the reactions gave good yields, and furthermore, both the electron-withdrawing and electron-donating aromatic substituents could be tolerated (eqn (1)).



We propose the reason that condensation of β -ketonitrile **3** with 1,1-dimethylhydrazine can hardly occur at room temperature is due to the steric hindrance. Raising the reaction temperature had probably brought about the intramolecular cyclization followed by a tautomerization to give intermediate **5**, which led to the formation of the pyrazole derivative **4** with the subsequent removal of a methyl group on the quaternary nitrogen center by a nucleophile (e.g. H₂NNMe₂, EtOH or acetate anion) (Scheme 1).

**Scheme 1** Proposed mechanism for the formation of pyrazole derivatives.

Considering that the two methyl groups on the hydrazono moiety in the substrates are electron-donating in nature, we initiated further studies by replacing the methyl groups with an electron-withdrawing phthalyl group. The *N,N*-phthalyl hydrazone substrates **1o–q**, whether the R² group is a chained propyl, bulkier benzyl or phenyl group, can be conveniently prepared by the condensation of the β -ketonitriles and *N*-aminophthalimide. We postulated that the reaction difference of this condensation reaction from the previous case should be attributed to the decreased nucleophilicity of the *N*-moiety in the *N,N*-phthalyl hydrazone substrates, on which it was substituted by the electron-withdrawing phthalyl group, thus preventing the formation of the similar byproduct **5**. To our delight, *N,N*-phthalyl hydrazone substrates **1o–q** can also afford the desired cyclized products **2o–q** in even better yields, although higher reaction temperature and longer reaction time were required (Table 2, entries 15–17). Similarly, the results also demonstrate that both electron-withdrawing and electron-donating aromatic substituents can be well tolerated in the process. It is worth noting that the removal of

Table 2 Oxidative intramolecular hetero-cyclization of 2-aryl-3-substituted hydrazono-alkylnitriles **1** mediated by FeBr₃^a

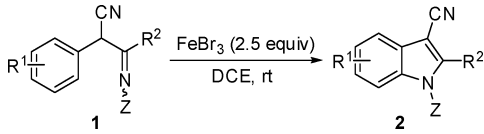
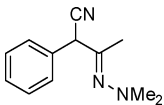
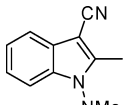
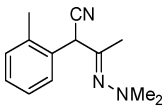
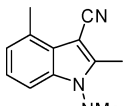
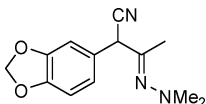
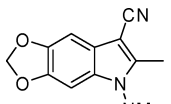
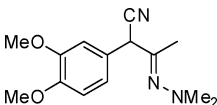
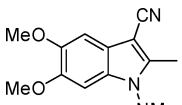
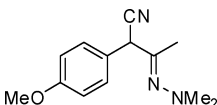
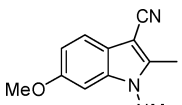
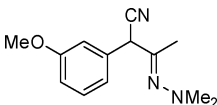
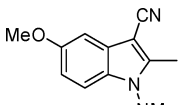
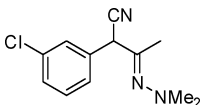
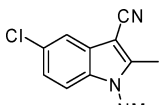
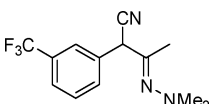
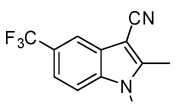
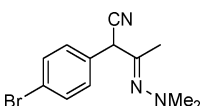
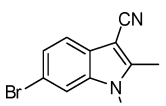
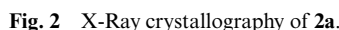
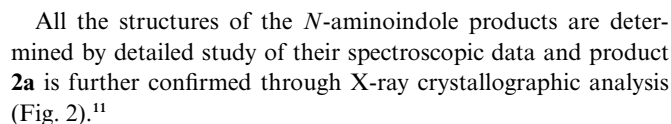
				
Entry	Substrate 1	Product 2	Time/h	Yield ^c (%)
1	 1a	 2a	0.5	60
2	 1b	 2b	0.5	49
3	 1c	 2c	0.5	61
4	 1d	 2d	0.5	63
5	 1e	 2e	0.5	57
6 ^b	 1f	 2f	0.5	51
7 ^b	 1g	 2g	0.5	43
8 ^b	 1h	 2h	0.5	46
9	 1i	 2i	0.5	47

Table 2 (Contd.)

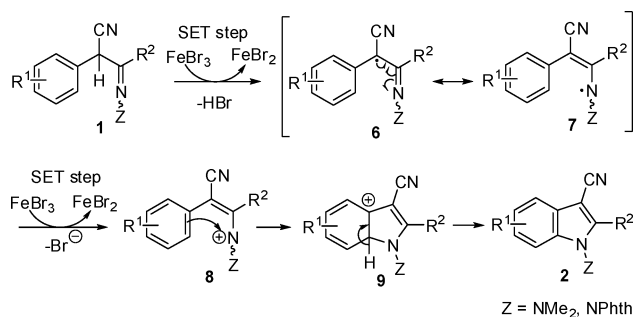
Entry	Substrate 1	Product 2	Time/h	Yield ^c (%)
10	 1j	 2j	0.5	51
11	 1k	 2k	0.5	50
12	 1l	 2l	0.75	52
13	 1m	 2m	1	48
14	 1n	 2n	1	47
15	 1o	 2o	2	79
16	 1p	 2p	3	70
17	 1q	 2q	2.5	67

^a Reaction conditions: **1** (2 mmol) and FeBr₃ (2.5 equiv.) in 20 mL of DCE at room temperature. ^b Major regioisomeric product was isolated by chromatography. ^c Yield of isolated product after chromatography.

substrates, this method provides access to a wide range of *N*-aminoindoles that could only be synthesized by a limited number of methods.^{3,4}



The mechanism of this intramolecular oxidative C–N bond formation process was postulated (Scheme 2).¹² Firstly, abstraction of the benzylic hydrogen atom from **1** by a SET (single electron transfer) process gives the carbon-based radical **6**, with resonance structure *N*-radical **7**. Secondly, mediated by iron(III) bromide, a second SET process occurs to convert the *N*-radical **7** to the nitrenium ion **8**. Finally, nucleophilic attack on the nitrenium ion by the benzene ring results in carbocation **9**, which undergoes rearomatization *via* the loss of a proton, to afford title compound **2**.^{5b}



Scheme 2 Proposed mechanistic pathway.

Conclusions

In summary, we have described an efficient synthesis of *N*-aminoindole compounds, which allows the *N*-moiety on the side-chain to be annulated to the substituted benzene ring *via* FeBr₃-mediated oxidative aromatic C–N bond formation. *Via* a protection and subsequent deprotection step of the hydrazone

¹H and ¹³C NMR spectra were recorded on a 400 MHz BRUKER AVANCE spectrometer at 25 °C. Chemical shifts values are given in ppm and referred to the internal standard TMS: 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad and dd, doublet of doublets. The coupling constants *J*, are reported in hertz (Hz). GC-MS was performed by direct inlet on a Shimadazu GCMS-QP2010 Plus instrument. IR were recorded on a Bruker Tensor 27 infrared spectrometer as KBr pellets with absorption in cm⁻¹. High-resolution mass spectra (HRMS) were obtained on a Q-TOF micro (Waters) spectrometer. Melting points were determined with a national micromelting point apparatus without corrections. TLC plates were visualized by exposure to ultraviolet light. 1,2-Dichloroethane was dried by CaH₂ before use, other reagents and solvents were purchased as reagent grade and were used without further purification. Flash column chromatography was performed over silica gel 200–300 m and the eluent was a mixture of EtOAc and petroleum ether, or a mixture of MeOH and CH₂Cl₂.

General procedure for the preparation of 17

A mixture of β -ketonitriles (10 mmol), 1,1-dimethylhydrazine or *N*-aminophthalimide (15 mmol), *p*-toluenesulfonic acid (1 mmol) with several 4 Å molecular sieves in 100 mL of toluene was stirred at room temperature (if *N*-amino phthalimide was used, the solution was heated to reflux) under nitrogen atmosphere, and TLC was used to monitor the reaction process. After completion of the reaction, it was filtered and the solvent was removed under vacuum. The residue was purified by column chromatography using a mixture of petroleum ether and EtOAc as eluent to afford the substrate.

3-(2,2-Dimethylhydrazono)-2-phenylbutanenitrile (1a)

General procedure was followed (4 h), white solid, 1.53 g (10.0 mmol, 76% yield, *cis:trans* = 2:3), R_f 0.52 (EtOAc/petroleum ether = 30/70), mp 66–68 °C; ^1H NMR (400 MHz, CDCl_3): major isomer (*trans*) δ 7.41–7.18 (m, 5H, H_{arom} , peaks of two isomers overlapped), 5.59 (s, 1H, CH), 2.43 (s, 6H, NCH_3), 2.34 (s, 3H, CH_3); minor isomer (*cis*) δ 7.41–7.18 (m, 5H, H_{arom} , peaks of two isomers overlapped), 5.73 (s, 1H, CH), 2.56 (s, 6H, NCH_3), 2.07 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): major isomer (*trans*) δ 157.0, 133.1, 129.4, 128.9, 127.2, 122.3, 78.8, 48.3, 17.3; minor isomer (*cis*) δ 158.9, 134.5, 129.6, 128.4, 126.4, 120.4, 76.9, 48.5, 15.3; IR (KBr) 2183 s, 1593vs, 1495 m, 1393 m, 1361 m, 766 m, 704 cm^{-1} ; GC-MS: R_t 4.2 min; m/z (EI) 201 (M^+ , 100%), 169 (19), 157 (52), 142 (84), 130 (37), 115 (46), 103 (13), 89 (29), 77 (16), 59 (56), 44 (81), 42 (49); HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{Na}$ 224.1158; found 224.1162.

3-(2,2-Dimethylhydrazono)-2-*o*-tolylbutanenitrile (1b)

General procedure was followed (4.5 h), white solid, 1.35 g (9.7 mmol, 65% yield, *cis*:*trans* = 1:3), R_f 0.44 (EtOAc/petroleum ether = 30/70), mp 52–54 °C; ^1H NMR (400 MHz, CDCl_3): major isomer (*trans*) δ 7.28–7.12 (m, 4H, H_{arom} , peaks of two isomers overlapped), 4.85 (s, 1H, CH), 2.37 (s, 6H, NCH_3), 2.33 (s, 3H, CH_3), 2.29 (s, 3H, CH_3); minor isomer (*cis*) δ 7.28–7.12 (m, 4H, H_{arom} , peaks of two isomers overlapped), 4.70 (s, 1H, CH), 2.56 (s, 6H, NCH_3), 2.35 (s, 3H, CH_3), 1.81 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): major isomer (*trans*) δ 157.2, 138.3, 131.8, 131.0, 128.5, 126.8, 126.0, 121.6, 77.6, 48.4, 19.5, 16.6; minor isomer (*cis*) δ 159.1, 138.3, 133.0, 131.1, 130.3, 127.9, 126.0, 119.6, 75.5, 48.5, 19.9, 15.1; IR (KBr) 2173 s, 1604 vs, 1489 m, 1394 m, 1362 w, 766 m cm^{-1} ; GC-MS: R_t 4.2 min; m/z (EI) 215 (M^+ , 100%), 185 (9), 156 (49), 130 (22), 103 (12), 77 (17), 59 (59), 44 (48), 42 (29); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{Na}$ 238.1315; found 238.1323.

(*E*)-2-(Benzo[d][1,3]dioxol-5-yl)-3-(2,2-dimethylhydrazono)-butanenitrile (1c)

General procedure was followed (3 h), light yellow solid, 1.82 g (9.8 mmol, 76% yield), R_f 0.55 (EtOAc/petroleum ether = 40/60), mp 71–73 °C; ^1H NMR (400 MHz, CDCl_3): δ 6.82 (d, J = 8.0 Hz, 1H H_{arom}), 6.77–6.74 (m, 2H, H_{arom}), 5.98 (s, 2H, CH_2), 5.45 (s, 1H, CH), 2.43 (s, 6H, NCH_3), 2.31 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.0, 148.4, 146.8, 126.4, 122.7, 122.2, 109.6, 109.0, 101.3, 78.5, 48.4, 17.1; IR (KBr) 2180 s, 1598 vs, 1500 s, 1392 s, 1359 m, 1218 s, 1039 s cm^{-1} ; GC-MS: R_t 5.4 min; m/z (EI) 245 (M^+ , 100%), 213 (8), 202 (46), 185 (22), 171 (94), 159 (39), 143 (97), 129 (17), 101 (22), 85 (53), 75 (23), 59 (20), 44 (74), 42 (50); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{NaO}_2$ 268.1056; found 268.1064.

(*E*)-2-(3,4-Dimethoxyphenyl)-3-(2,2-dimethylhydrazono)-butanenitrile (1d)

General procedure was followed (3 h), white solid, 2.14 g (10.0 mmol, 82% yield), R_f 0.45 (EtOAc/petroleum ether = 40/60), mp 148–149 °C; ^1H NMR (400 MHz, CDCl_3): δ 6.88 (d, J = 8.0 Hz, 1H, H_{arom}), 6.85–6.82 (m, 2H, H_{arom}), 5.49 (s, 1H, CH), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.43 (s, 6H, NCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 156.8, 149.5, 148.2, 125.3, 122.4, 121.4, 112.1, 110.7, 78.5, 55.9, 48.3, 17.1; IR (KBr) 2179 s, 1601 vs, 1515 s, 1391 s, 1367 m, 1244 s, 1028 s cm^{-1} ; GC-MS: R_t 5.7 min; m/z (EI) 261 (M^+ , 92%), 246 (8), 203 (42), 186 (79), 175 (35), 159 (21), 131 (20), 104 (17), 85 (100), 77 (20), 63 (11), 44 (80), 42 (52); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{NaO}_2$ 284.1369; found 284.1371.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(4-methoxyphenyl)butanenitrile (1e)

General procedure was followed (4.5 h), white solid, 1.9 g (9.5 mmol, 87% yield), R_f 0.56 (EtOAc/petroleum ether = 40/60), mp 103–104 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.20 (d, J = 8.0 Hz, 2H, H_{arom}), 6.90 (d, J = 8.0 Hz, 2H, H_{arom}), 5.49 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 2.40 (s, 6H, NCH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 158.7, 156.7, 130.3, 124.9, 122.4,

114.7, 78.2, 55.2, 48.2, 17.1; IR (KBr) 2178 s, 1601 vs, 1511 s, 1387 s, 1359 m, 1247 s, 1036 s, 832 s cm^{-1} ; GC-MS: R_t 5.1 min; m/z (EI) 231 (M^+ , 100%), 202 (1), 187 (50), 172 (69), 145 (36), 132 (14), 103 (12), 85 (34), 77 (15), 59 (16), 42 (40); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{NaO}$ 254.1264; found 254.1272.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(3-methoxyphenyl)butanenitrile (1f)

General procedure was followed (5 h), white solid, 1.76 g (10.0 mmol, 76% yield), R_f 0.50 (EtOAc/petroleum ether = 30/70), mp 79–81 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.29 (t, J = 8.0 Hz, 1H, H_{arom}), 6.89 (d, J = 8.0 Hz, 1H, H_{arom}), 6.85 (s, 1H, H_{arom}), 6.78 (d, J = 8.0 Hz, 1H, H_{arom}), 5.71 (s, 1H, CH), 3.79 (s, 3H, OCH_3), 2.44 (s, 6H, NCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 160.3, 157.1, 134.5, 130.3, 122.3, 121.0, 114.3, 112.8, 78.5, 55.2, 48.3, 17.3; IR (KBr) 2180 s, 1601 vs, 1489 m, 1392 s, 1361 m, 1243 m, 1035 m cm^{-1} ; GC-MS: R_t 5.0 min; m/z (EI) 231 (M^+ , 100%), 207 (3), 188 (33), 171 (51), 143 (33), 128 (10), 116 (24), 103 (15), 85 (96), 77 (22), 59 (36), 44 (81), 42 (68); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{NaO}$ 254.1264; found 254.1273.

(*E*)-2-(3-Chlorophenyl)-3-(2,2-dimethylhydrazono)butanenitrile (1g)

General procedure was followed (6 h), white solid, 1.99 g (10.2 mmol, 83% yield), R_f 0.53 (EtOAc/petroleum ether = 30/70), mp 62–63 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.34–7.30 (m, 2H, H_{arom}), 7.24–7.19 (m, 2H, H_{arom}), 5.56 (s, 1H, CH), 2.45 (s, 6H, NCH_3), 2.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.7, 135.1, 135.1, 130.5, 128.9, 127.3, 127.0, 121.9, 77.2, 48.3, 17.4; IR (KBr) 2180 s, 1589 s, 1483 m, 1392 m, 1360 m, 781 m, 695 m cm^{-1} ; GC-MS: R_t 4.8 min; m/z (EI) 235 (M^+ , 72%), 220 (9), 203 (5), 193 (28), 170 (9), 156 (51), 128 (12), 114 (24), 101 (7), 85 (39), 75 (12), 59 (48), 44 (100), 42 (58); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{Na}$ 258.0768; found 258.0778.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(3-(trifluoromethyl)phenyl)butanenitrile (1h)

General procedure was followed (6 h), white solid, 1.14 g (7.0 mmol, 60% yield), R_f 0.47 (EtOAc/petroleum ether = 30/70), mp 60–62 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.58 (s, 1H, H_{arom}), 7.50 (s, 3H, H_{arom}), 5.66 (s, 1H, CH), 2.45 (s, 6H, NCH_3), 2.35 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.8, 134.3, 132.2, 131.6 (q, $J_{\text{C-F}}$ = 32.1 Hz), 129.8, 125.7 (d, $J_{\text{C-F}}$ = 3.5 Hz), 123.9 (q, $J_{\text{C-F}}$ = 270.6 Hz), 123.7 (d, $J_{\text{C-F}}$ = 3.4 Hz), 77.0, 48.0, 17.4; IR (KBr) 2185 s, 1588 vs, 1492 w, 1390 m, 1362 w, 1329 s cm^{-1} ; GC-MS: R_t 3.9 min; m/z (EI) 269 (M^+ , 100%), 239 (5), 227 (29), 223 (6), 205 (44), 185 (17), 177 (7), 156 (16), 134 (9), 115 (10), 107 (2), 85 (22), 70 (11), 59 (59), 44 (79), 42 (67); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{N}_3\text{Na}$ 292.1032; found 292.1041.

2-(4-Bromophenyl)-3-(2,2-dimethylhydrazono)butanenitrile (1i)

General procedure was followed (5.5 h), yellow solid, 2.15 g (10.0 mmol, 77% yield, *cis*:*trans* = 3:4), R_f 0.52 (EtOAc/petroleum

ether = 30/70), mp 117–119 °C; ^1H NMR (400 MHz, CDCl_3): major isomer (*trans*) δ 7.44 (d, J = 8.4 Hz, 2H, H_{arom}), 7.12 (d, J = 8.4 Hz, 2H, H_{arom}), 5.58 (s, 1H, CH), 2.56 (s, 6H, NCH_3), 2.06 (s, 3H, CH_3); minor isomer (*cis*) δ 7.51 (d, J = 8.4 Hz, 2H, H_{arom}), 7.20 (d, J = 8.4 Hz, 2H, H_{arom}), 5.52 (s, 1H, CH), 2.44 (s, 6H, NCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): major isomer (*trans*) δ 157.4, 132.2, 131.6, 131.1, 120.9, 120.2, 77.6, 48.5, 17.3; minor isomer (*cis*) δ 159.1, 133.6, 132.5, 130.6, 121.9, 120.0, 75.6, 48.3, 15.3; IR (KBr) 2182 s, 1593 s, 1485 m, 1382 m, 1359 m, 826 s cm^{-1} ; GC-MS: R_f 5.2 min; m/z (EI) 279 (M^+ , 57%), 264 (4), 239 (22), 237 (25), 221 (3), 207 (13), 170 (18), 155 (94), 128 (18), 114 (39), 101 (8), 85 (51), 70 (11), 59 (44), 44 (100), 42 (77); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{BrN}_3\text{Na}$ 302.0263; found 302.0274.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(2-methoxyphenyl)butanenitrile (1j)

General procedure was followed (4.5 h), white solid, 1.96 g (11.4 mmol, 75% yield), R_f 0.47 (EtOAc/petroleum ether = 30/70), mp 94–95 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.32–7.25 (m, 2H, H_{arom}), 7.00–6.93 (m, 2H, H_{arom}), 5.17 (s, 1H, CH), 3.85 (s, 3H, OCH_3), 2.41 (s, 6H, NCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.4, 156.5, 131.7, 129.3, 122.4, 121.4, 121.2, 111.8, 74.5, 55.5, 48.4, 17.0; IR (KBr) 2171 s, 1600 vs, 1493 m, 1397 s, 1360 m, 1260 m, 1054 m, 755 s cm^{-1} ; GC-MS: R_f 4.7 min; m/z (EI) 231 (M^+ , 100%), 216 (7), 185 (14), 172 (26), 146 (30), 132 (11), 103 (13), 85 (75), 77 (16), 59 (64), 44 (94), 42 (42); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{NaO}$ 254.1264; found 254.1275.

(*E*)-2-(4-Chlorophenyl)-3-(2,2-dimethylhydrazono)butanenitrile (1k)

General procedure was followed (6 h), white solid, 1.86 g (10.0 mmol, 79% yield), R_f 0.53 (EtOAc/petroleum ether = 30/70), mp 110–112 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.36 (d, J = 8.4 Hz, 2H, H_{arom}), 7.25 (d, J = 8.4 Hz, 2H, H_{arom}), 5.50 (s, 1H, CH), 2.44 (s, 6H, NCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.4, 132.9, 131.6, 130.3, 129.5, 121.9, 77.6, 48.4, 17.3; IR (KBr) 2181 s, 1594 vs, 1489 m, 1383 m, 1359 m, 831 m cm^{-1} ; GC-MS: R_f 4.8 min; m/z (EI) 235 (M^+ , 88%), 220 (9), 203 (7), 193 (28), 170 (10), 156 (93), 149 (16), 128 (14), 114 (30), 101 (8), 85 (37), 75 (10), 59 (46), 44 (100), 42 (60); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{Na}$ 258.0768; found 258.0779.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(trimethoxyphenyl)butanenitrile (1l)

General procedure was followed (3 h), light yellow solid, 1.85 g (7.2 mmol, 88% yield), R_f 0.48 (EtOAc/petroleum ether = 50/50), mp 107–109 °C; ^1H NMR (400 MHz, CDCl_3): δ 6.53 (s, 2H, H_{arom}), 5.65 (s, 1H, CH), 3.85 (s, 9H, OCH_3), 2.47 (s, 6H, NCH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.1, 153.8, 137.0, 128.4, 122.1, 106.0, 78.6, 60.8, 56.1, 48.3, 17.1; IR (KBr) 2181 s, 1593 vs, 1508 m, 1391 s, 1365 m, 1244 s, 1023 m cm^{-1} ; GC-MS: R_f 6.1 min; m/z (EI) 291 (M^+ , 67%), 262 (3), 248 (58), 233 (80), 216 (41), 201 (22), 173 (20), 158 (10), 132 (7), 104 (7), 85 (100), 77 (10), 59 (6), 44 (77), 42 (30); HRMS-

ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{N}_3\text{NaO}_3$ 314.1475; found 314.1477.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(naphthalen-2-yl)butanenitrile (1m)

General procedure was followed (8 h), light yellow solid, 1.18 g (8.1 mmol, 58% yield), R_f 0.55 (EtOAc/petroleum ether = 30/70), mp 106–108 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.86–7.76 (m, 4H, H_{arom}), 7.50–7.24 (m, 3H, H_{arom}), 5.72 (s, 1H, CH), 2.42 (s, 6H, NCH_3), 2.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 157.3, 133.7, 132.3, 130.6, 129.2, 127.8, 127.8, 127.7, 126.8, 126.6, 126.3, 122.4, 78.8, 48.4, 17.4; IR (KBr) 2180 s, 1586 vs, 1503 m, 1434 m, 1398 m, 1363 w cm^{-1} ; GC-MS: R_f 6.2 min; m/z (EI) 251 (M^+ , 87%), 219 (8), 206 (57), 192 (73), 179 (23), 165 (61), 140 (25), 139 (37), 115 (11), 103 (3), 85 (86), 77 (8), 59 (13), 44 (100), 42 (49); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{Na}$ 274.1315; found 274.1323.

(*E*)-3-(2,2-Dimethylhydrazono)-2-(naphthalen-1-yl)butanenitrile (1n)

General procedure was followed (6.5 h), light yellow liquid, 1.74 g (11.0 mmol, 63% yield), R_f 0.42 (EtOAc/petroleum ether = 20/80); ^1H NMR (400 MHz, CDCl_3): δ 7.94–7.91 (m, 1H, H_{arom}), 7.87–7.81 (m, 2H, H_{arom}), 7.52–7.44 (m, 4H, H_{arom}), 4.92 (s, 1H, CH), 2.47 (s, 3H, CH_3), 2.28 (s, 6H, NCH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 158.1, 134.2, 131.4, 129.5, 129.1, 128.9, 128.7, 126.7, 126.4, 126.0, 125.0, 122.2, 75.6, 48.2, 16.9; IR (KBr) 2180 s, 1585 vs, 1505 m, 1432 m, 1396 m, 1360 w cm^{-1} ; GC-MS: R_f 6.3 min; m/z (EI) 251 (M^+ , 93%), 219 (11), 206 (65), 192 (75), 179 (28), 165 (63), 140 (27), 139 (39), 115 (15), 103 (4), 85 (89), 77 (6), 59 (10), 44 (100), 42 (55); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{Na}$ 274.1315; found 274.1324.

3-(1,3-Dioxoisindolin-2-ylimino)-2-phenylhexanenitrile (1o)

General procedure was followed (8 h), white solid, 2.38 g (10.0 mmol, 72% yield, *cis:trans* = 1:5), R_f 0.50 (EtOAc/petroleum ether = 40/60), mp 157–159 °C; ^1H NMR (400 MHz, CDCl_3): major isomer (*trans*) δ 7.84–7.80 (m, 2H, H_{arom} , peaks of two isomers overlapped), 7.79–7.76 (m, 2H, H_{arom}), 7.44 (d, J = 7.6 Hz, 2H, H_{arom}), 7.36–7.28 (m, 3H, H_{arom}), 6.37 (s, 1H, CH), 2.50 (t, J = 7.8 Hz, 2H, CH_2), 1.71 (sxt, J = 7.6 Hz, 2H, CH_2), 1.03 (t, J = 7.4 Hz, 3H, CH_3); minor isomer (*cis*) δ 7.96–7.94 (m, 2H, H_{arom}), 7.84–7.80 (m, 2H, H_{arom} , peaks of two isomers overlapped), 7.18–7.14 (m, 3H, H_{arom}), 6.52 (s, 1H, CH), 2.21 (t, J = 8.0 Hz, 2H, CH_2), 1.62–1.53 (sxt, J = 7.6 Hz, 2H, CH_2), 0.83 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): major isomer (*trans*) δ 165.6, 158.3, 134.9, 131.7, 129.9, 129.4, 128.8, 128.1, 124.3, 123.9, 87.5, 33.1, 21.8, 13.8; minor isomer (*cis*) δ 165.7, 158.4, 135.1, 131.7, 129.7, 129.3, 128.7, 127.9, 124.5, 120.0, 87.6, 31.3, 21.7, 13.7; IR (KBr) 2193 s, 1793 m, 1743 vs, 1613 s, 1536 s, 1422 m cm^{-1} ; GC-MS: R_f 4.3 min; m/z (EI) 331 (M^+ , 100%), 303 (40), 286 (8), 274 (20), 249 (1), 207 (5), 183 (25), 169 (2), 155 (26), 147 (3), 130 (35), 115 (15), 104 (28), 89 (9), 76 (35), 43 (5); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{NaO}_2$ 354.1213; found 354.1215.

(*E*)-2-(4-Bromophenyl)-3-(1,3-dioxoisindolin-2-ylimino)-3-phenylpropanenitrile (1p)

General procedure was followed (10 h), light yellow solid, 2.80 g (9.6 mmol, 66% yield), R_f 0.40 (EtOAc/petroleum ether = 30/70), mp 69–71 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.82–7.80 (m, 2H, H_{arom}), 7.73–7.70 (m, 4H, H_{arom}), 7.32 (d, J = 7.2 Hz, 2H, H_{arom}), 7.24–7.22 (m, 3H, H_{arom}), 7.23 (d, J = 8.8 Hz, 2H, H_{arom}), 6.88 (d, J = 8.4 Hz, 2H, H_{arom}), 6.50 (s, 1H, CH). ^{13}C NMR (100 MHz, CDCl_3): δ 165.4, 158.4, 134.8, 131.4, 131.1, 131.1, 131.0, 129.6, 129.3, 129.0, 128.8, 124.0, 123.8, 121.0, 88.9; IR (KBr) 2190 s, 1794 m, 1737 vs, 1609 m, 1517 m, 1405 cm^{-1} ; MS (ESI $^+$): m/z 332 (M^+ , 100%); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{23}\text{H}_{14}\text{BrN}_3\text{NaO}_2$ 466.0162; found 466.0170.

(*E*)-3-(1,3-Dioxoisindolin-2-ylimino)-2-(4-methoxy-phenyl)-4-phenylbutanenitrile (1q)

General procedure was followed (7 h), white solid, 2.78 g (10.6 mmol, 64% yield), R_f 0.46 (EtOAc/petroleum ether = 40/60), mp 167–169 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.69–7.67 (brd, 4H, H_{arom}), δ 7.44 (d, J = 7.6 Hz, 2H, H_{arom}), 7.13–7.12 (m, 5H, H_{arom}), 6.85 (d, J = 7.6 Hz, 2H, H_{arom}), 6.38 (s, 1H, CH), 3.95 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 165.1, 159.6, 155.6, 134.7, 134.6, 130.8, 129.2, 128.7, 128.3, 127.2, 123.6, 123.3, 120.1, 114.9, 89.4, 55.3, 37.6; IR (KBr) 2190 m, 1795 m, 1742 vs, 1599 s, 1513 s, 1356 s, 1255 s, 1031 cm^{-1} ; GC-MS: R_t 8.0 min; m/z (EI) 409 (M^+ , 100%), 394 (5), 376 (1), 355 (2), 332 (9), 281 (2), 262 (6), 234 (1), 205 (2), 176 (1), 165 (13), 147 (2), 115 (3), 91 (14), 76 (14), 65 (3), 43 (8); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{25}\text{H}_{19}\text{N}_3\text{NaO}_3$ 432.1319; found 432.1329.

General procedure for the preparation of 2 5

To a stirring solution of the 2-aryl-3-dimethylhydrazonoalkylnitriles **1** (2.0 mmol) in DCE (20 mL) was added one portion of the FeBr_3 powder (5.0 mmol) at room temperature under a N_2 atmosphere. TLC was used to monitor the reaction process until the total consumption of **1**. To the solution was then added H_2O (20 mL), and stirring was continued for an additional 5 min. The reaction mixture was extracted with CH_2Cl_2 (30 mL $\times$ 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the given residue was purified by column chromatography by using a mixture of petroleum ether and EtOAc as eluent to afford the pure compounds.

1-(Dimethylamino)-2-methyl-1*H*-indole-3-carbonitrile (2a)

General procedure was followed (0.5 h), white solid, 0.24 g (2.0 mmol, 60% yield), R_f 0.52 (EtOAc/petroleum ether = 20/80), mp 85–87 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.68–7.66 (m, 1H, H_{arom}), 7.56–7.53 (m, 1H, H_{arom}), 7.23 (d, J = 8.0 Hz, 1H, H_{arom}), 7.23 (dd, J = 4.0 Hz, 1H, H_{arom}), 3.09 (s, 6H, NCH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 146.9, 132.8, 126.1, 122.6, 121.9, 119.5, 116.3, 111.6, 82.4, 44.9, 11.7; IR (KBr) 2211 s, 1609 w, 1552 m, 1460 cm^{-1} ; GC-MS: R_t 4.5 min; m/z (EI) 199 (M^+ , 75%), 184 (100), 169 (9), 155 (47), 143 (18), 128 (29), 118 (9), 101 (20), 77 (11), 63 (5), 42 (12); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{Na}$ 222.1002; found 222.1011.

1-(Dimethylamino)-2,4-dimethyl-1*H*-indole-3-carbonitrile (2b)

General procedure was followed (0.5 h), white solid, 0.23 g (2.2 mmol, 49% yield), R_f 0.46 (EtOAc/petroleum ether = 20/80), mp 120–122 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.38 (d, J = 8.0 Hz, 1H, H_{arom}), 7.12 (t, J = 8.0 Hz, 1H, H_{arom}), 6.96 (d, J = 8.0 Hz, 1H, H_{arom}), 3.07 (s, 6H, NCH_3), 2.73 (s, 3H, CH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 147.3, 132.8, 130.9, 124.5, 122.9, 122.6, 118.0, 109.2, 81.8, 44.8, 18.5, 11.6; IR (KBr) 2213 s, 1549 m, 1497 w, 1456 cm^{-1} ; GC-MS: R_t 4.9 min; m/z (EI) 213 (M^+ , 67%), 198 (100), 183 (7), 169 (46), 157 (22), 140 (10), 115 (14), 89 (3), 77 (10), 63 (3), 42 (11); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{Na}$ 236.1158; found 236.1167.

5-(Dimethylamino)-6-methyl-5*H*-[1,3]dioxolo[4,5-*f*]-indole-7-carbonitrile (2c)

General procedure was followed (0.5 h), white solid, 0.30 g (2.0 mmol, 61% yield), R_f 0.40 (EtOAc/petroleum ether = 25/75), mp 175–176 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.03 (s, 1H, H_{arom}), 7.00 (s, 1H, H_{arom}), 6.00 (s, 2H, CH_2), 3.03 (s, 6H, NCH_3), 2.50 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 145.2, 144.8, 144.4, 127.6, 120.2, 116.4, 101.2, 98.6, 92.6, 82.8, 44.7, 11.8; IR (KBr) 2209 s, 1549 m, 1499 m, 1467 s, 1257 m, 1036 cm^{-1} ; GC-MS: R_t 6.0 min; m/z (EI) 243 (M^+ , 48%), 228 (100), 213 (12), 199 (43), 187 (10), 157 (1), 143 (16), 133 (1), 114 (15), 88 (4), 63 (4), 43 (3), 42 (14); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{NaO}_2$ 266.0900; found 266.0902.

1-(Dimethylamino)-5,6-dimethoxy-2-methyl-1*H*-indole-3-carbonitrile (2d)

General procedure was followed (0.5 h), white solid, 0.35 g (2.1 mmol, 63% yield), R_f 0.50 (EtOAc/petroleum ether = 40/60), mp 150–151 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.08 (s, 1H, H_{arom}), 6.99 (s, 1H, H_{arom}), 3.94 (s, 6H, OCH_3), 3.07 (s, 6H, NCH_3), 2.54 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 147.0, 146.6, 144.6, 127.1, 119.0, 116.7, 101.0, 95.1, 82.2, 56.5, 56.3, 44.8, 11.9; IR (KBr) 2210 s, 1551 m, 1492 s, 1268 s, 1026 cm^{-1} ; GC-MS: R_t 6.1 min; m/z (EI) 259 (M^+ , 45%), 244 (100), 229 (4), 215 (30), 200 (16), 187 (2), 171 (19), 145 (4), 116 (24), 103 (3), 63 (1), 42 (10); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{NaO}_2$ 282.1213; found 282.1222.

1-(Dimethylamino)-6-methoxy-2-methyl-1*H*-indole-3-carbonitrile (2e)

General procedure was followed (0.5 h), white solid, 0.26 g (2.0 mmol, 57% yield), R_f 0.45 (EtOAc/petroleum ether = 25/75), mp 104–105 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.53 (d, J = 8.8 Hz, 1H, H_{arom}), 7.01 (s, 1H, H_{arom}), 6.88 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H, H_{arom}), 3.87 (s, 3H, OCH_3), 3.07 (s, 6H, NCH_3), 2.53 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 156.5, 146.0, 133.8, 119.9, 119.8, 116.4, 110.7, 95.9, 82.3, 55.8, 44.6, 11.9; IR (KBr) 2209 s, 1621 s, 1557 m, 1494 s, 1460 s, 1268 s, 1037 cm^{-1} ; GC-MS: R_t 5.4 min; m/z (EI) 229 (M^+ , 70%), 214 (100), 199 (8), 185 (64), 171 (18), 157 (4), 142 (36), 127 (4), 115 (13), 89 (5), 75 (5), 63 (3), 43 (5), 42 (14); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{NaO}$ 252.1107; found 252.1116.

1-(Dimethylamino)-5-methoxy-2-methyl-1*H*-indole-3-carbonitrile (2f)

General procedure was followed (0.5 h), white solid, 0.22 g (1.9 mmol, 51% yield), R_f 0.44 (EtOAc/petroleum ether = 25/75), mp 105–106 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.42 (d, J = 8.8 Hz, 1H, H_{arom}), 7.11 (s, 1H, H_{arom}), 6.86 (dd, J = 8.8 Hz, 1H, H_{arom}), 3.86 (s, 3H, OCH_3), 3.06 (s, 6H, NCH_3), 2.53 (m, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 155.7, 146.7, 127.4, 127.1, 116.5, 112.7, 112.4, 101.3, 82.0, 55.7, 45.0, 11.7; IR (KBr) 2213 s, 1617 m, 1581 m, 1545 m, 1467 s, 1238 s, 1025 m cm^{-1} ; GC-MS: R_t 5.5 min; m/z (EI) 229 (M^+ , 52%), 214 (100), 199 (9), 171 (17), 158 (5), 142 (27), 127 (3), 115 (12), 89 (4), 75 (4), 63 (3), 42 (8); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{NaO}$ 252.1107; found 252.1115.

5-Chloro-1-(dimethylamino)-2-methyl-1*H*-indole-3-carbonitrile (2g)

General procedure was followed (0.5 h), white solid, 0.20 g (2.0 mmol, 43% yield), R_f 0.43 (EtOAc/petroleum ether = 20/80), mp 134–136 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.63 (s, 1H, H_{arom}), 7.45 (d, J = 8.8 Hz, 1H, H_{arom}), 7.19 (dd, J = 8.8 Hz, 1H, H_{arom}), 3.07 (s, 6H, NCH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 148.1, 131.2, 127.9, 127.1, 123.0, 119.0, 115.5, 112.4, 82.4, 44.9, 11.8; IR (KBr) 2217 s, 1608 w, 1571 m, 1555 m, 1446 s cm^{-1} ; GC-MS: R_t 5.4 min; m/z (EI) 233 (M^+ , 65%), 218 (100), 203 (5), 189 (29), 177 (13), 153 (14), 127 (22), 114 (7), 99 (7), 87 (5), 75 (8), 63 (4), 44 (9), 42 (19); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{ClN}_3\text{Na}$ 256.0612; found 256.0613.

1-(Dimethylamino)-2-methyl-5-(trifluoromethyl)-1*H*-indole-3-carbonitrile (2h)

General procedure was followed (0.5 h), white solid, 0.26 g (2.1 mmol, 46% yield), R_f 0.50 (EtOAc/petroleum ether = 25/75), mp 119–120 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.96 (s, 1H, H_{arom}), 7.64 (d, J = 8.4 Hz, 1H, H_{arom}), 7.48 (d, J = 8.8 Hz, 1H, H_{arom}), 3.10 (s, 6H, NCH_3), 2.60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 148.9, 134.5, 125.5, 124.7 (q, $J_{\text{C-F}}$ = 270.1 Hz), 124.4 (q, $J_{\text{C-F}}$ = 2.2 Hz), 119.5 (q, $J_{\text{C-F}}$ = 3.3 Hz), 117.0 (q, $J_{\text{C-F}}$ = 3.9 Hz), 115.2, 111.8, 83.7, 44.9, 11.9; IR (KBr) 2213 s, 1621 w, 1556 m, 1465 m cm^{-1} ; GC-MS: R_t 4.6 min; m/z (EI) 267 (M^+ , 79%), 266 (86), 252 (100), 225 (30), 223 (40), 203 (10), 176 (12), 157 (13), 133 (9), 112 (3), 87 (2), 75 (4), 45 (12), 42 (24); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{N}_3\text{Na}$ 290.0876; found 290.0886.

6-Bromo-1-(dimethylamino)-2-methyl-1*H*-indole-3-carbonitrile (2i)

General procedure was followed (0.5 h), white solid, 0.26 g (2.0 mmol, 47% yield), R_f 0.53 (EtOAc/petroleum ether = 20/80), mp 167–168 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.70 (s, 1H, H_{arom}), 7.51 (d, J = 8.4 Hz, 1H, H_{arom}), 7.33 (d, J = 8.4 Hz, 1H, H_{arom}), 3.07 (s, 6H, NCH_3), 2.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 147.6, 133.7, 125.2, 124.8, 120.7, 116.2, 115.6, 114.3, 83.1, 44.9, 11.9; IR (KBr) 2210 s, 1607 w, 1550 m, 1466 s cm^{-1} ; GC-MS: R_t 5.6 min; m/z (EI) 277 (M^+ , 66%), 262 (100), 247 (4), 235 (46), 221 (11), 198 (14), 183 (27), 169 (4), 154 (60), 153 (15), 127 (66), 113

(14), 87 (10), 75 (9), 63 (7), 44 (21), 42 (44); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{BrN}_3\text{Na}$ 300.0107; found 300.0118.

1-(Dimethylamino)-4-methoxy-2-methyl-1*H*-indole-3-carbonitrile (2j)

General procedure was followed (0.5 h), white solid, 0.22 g (1.9 mmol, 51% yield), R_f 0.52 (EtOAc/petroleum ether = 25/75), mp 118–120 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.14 (d, J = 4.4 Hz, 2H, H_{arom}), 6.61 (t, J = 4.2 Hz, 1H, H_{arom}), 3.98 (s, 3H, OCH_3), 3.08 (s, 6H, NCH_3), 2.55 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 153.4, 146.3, 134.2, 123.5, 117.2, 115.6, 104.5, 101.9, 80.7, 55.6, 44.8, 11.5; IR (KBr) 2217 s, 1615 w, 1589 m, 1548 m, 1505 m, 1459 m, 1270 s, 1048 m cm^{-1} ; GC-MS: R_t 5.6 min; m/z (EI) 229 (M^+ , 100%), 214 (91), 199 (18), 185 (38), 171 (19), 142 (24), 116 (15), 89 (11), 63 (4), 42 (16); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{NaO}$ 252.1107; found 252.1118.

6-Chloro-1-(dimethylamino)-2-methyl-1*H*-indole-3-carbonitrile (2k)

General procedure was followed (0.5 h), white solid, 0.23 g (2.0 mmol, 50% yield), R_f 0.52 (EtOAc/petroleum ether = 20/80), mp 158–160 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.56 (d, J = 8.4 Hz, 1H, H_{arom}), 7.54 (s, 1H, H_{arom}), 7.20 (dd, J = 8.4 Hz, 1H, H_{arom}), 3.07 (s, 6H, NCH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 147.7, 133.3, 128.6, 124.4, 122.6, 120.4, 115.7, 111.4, 83.0, 44.9, 11.9; IR (KBr) 2211 s, 1610 w, 1553 m, 1469 s cm^{-1} ; GC-MS: R_t 5.2 min; m/z (EI) 233 (M^+ , 67%), 218 (100), 203 (6), 189 (42), 177 (16), 153 (18), 127 (22), 114 (7), 87 (4), 75 (8), 45 (10), 42 (20); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{ClN}_3\text{Na}$ 256.0612; found 256.0621.

1-(Dimethylamino)-5,6,7-trimethoxy-2-methyl-1*H*-indole-3-carbonitrile (2l)

General procedure was followed (0.75 h), light yellow solid, 0.32 g (2.1 mmol, 52% yield), R_f 0.44 (EtOAc/petroleum ether = 20/80), mp 93–95 °C; ^1H NMR (400 MHz, CDCl_3): δ 6.83 (s, 1H, H_{arom}), 4.15 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.93 (s, 6H, NCH_3), 2.49 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 150.9, 147.8, 139.4, 139.0, 123.4, 120.3, 116.7, 95.6, 81.6, 61.1, 60.5, 56.3, 45.2, 11.9; IR (KBr) 2212 s, 1577 m, 1486 s, 1462 s, 1253 s, 1058 s cm^{-1} ; GC-MS: R_t 6.2 min; m/z (EI) 289 (M^+ , 37%), 274 (100), 258 (4), 244 (15), 230 (30), 200 (5), 172 (8), 149 (4), 117 (10), 89 (2), 75 (3), 58 (3), 42 (11); HRMS-ESI (m/z): [$\text{M} + \text{Na}$] $^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_3\text{NaO}_3$ 312.1319; found 312.1321.

1-(Dimethylamino)-2-methyl-1*H*-benzo[*g*]indole-3-carbonitrile (2m)

General procedure was followed (1 h), light yellow liquid, 0.25 g (2.0 mmol, 48% yield), R_f 0.53 (EtOAc/petroleum ether = 30/70); ^1H NMR (400 MHz, CDCl_3): δ 9.15 (d, J = 8.4 Hz, 1H, H_{arom}), 7.95 (d, J = 8.0 Hz, 1H, H_{arom}), 7.70 (d, J = 8.4 Hz, 1H, H_{arom}), 7.65–7.60 (m, 2H, H_{arom}), 7.52 (t, J = 7.8 Hz, 1H, H_{arom}), 3.19 (s, 6H, NCH_3), 2.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 143.8, 131.8, 128.9, 128.3, 126.2, 124.6, 123.6, 122.5, 121.5, 121.5, 117.8, 116.0, 86.8, 44.5, 13.3; IR (KBr) 2211 s, 1529 m, 1451 m cm^{-1} ; GC-MS: R_t 6.7 min; m/z (EI) 249 (M^+ , 46%), 234 (100), 219 (10), 205 (40),

193 (10), 164 (7), 151 (20), 125 (4), 103 (1), 87 (2), 75 (2), 63 (2), 42 (7); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}N_3Na$ 272.1158; found 272.1169.

3-(Dimethylamino)-2-methyl-3*H*-benzo[e]indole-1-carbonitrile (2n)

General procedure was followed (1 h), light yellow liquid, 0.24 g (2.0 mmol, 47% yield), R_f 0.45 (EtOAc/petroleum ether = 20/80); 1H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, J = 8.4 Hz, 1H, H_{arom}), 7.90 (d, J = 8.0 Hz, 1H, H_{arom}), 7.65 (dd, J = 21.2 Hz, 2H, H_{arom}), 7.61 (t, J = 7.6 Hz, 1H, H_{arom}), 7.48 (t, J = 7.4 Hz, 1H, H_{arom}), 3.190 (s, 6H), 2.815 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 130.1, 129.7, 128.6, 127.3, 126.6, 124.7, 123.8, 122.5, 119.8, 118.1, 111.9, 82.9, 45.3, 11.7; IR (KBr) 2213 s, 1527 m, 1454 m cm^{-1} ; GC-MS: R_t 6.8 min; m/z (EI) 249 (M^+ , 61%), 234 (100), 219 (19), 205 (60), 177 (18), 164 (8), 151 (27), 125 (5), 96 (1), 75 (3), 56 (3), 42 (41); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{16}H_{15}N_3Na$ 272.1158; found 272.1166.

1-(1,3-Dioxoisindolin-2-yl)-2-propyl-1*H*-indole-3-carbonitrile (2o)

General procedure was followed (2 h), white solid, 0.55 g (2.1 mmol, 79% yield), R_f 0.58 (EtOAc/petroleum ether = 40/60), mp 132–133 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.08–8.05 (m, 2H, H_{arom}), 8.00–7.98 (m, 1H, H_{arom}), 8.08–8.05 (m, 2H, H_{arom}), 8.00–7.98 (m, 1H, H_{arom}), 7.97–7.94 (m, 2H, H_{arom}), 7.87–7.85 (m, 1H, H_{arom}), 7.75 (d, J = 8.0 Hz, 1H, H_{arom}), 7.04 (d, J = 8.0 Hz, 1H, H_{arom}), 2.77 (t, J = 7.6 Hz, 2H, CH_2), 1.73 (sxt, J = 7.6 Hz, 2H, CH_2), 0.98 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 149.7, 135.8, 135.0, 129.2, 125.3, 124.9, 124.8, 123.6, 119.7, 115.1, 108.8, 87.0, 27.5, 21.8, 13.7; IR (KBr) 2222 s, 1799 m, 1744 vs, 1607 w, 1553 m, 1467 m, 1396 m, 1322 s cm^{-1} ; GC-MS: R_t 4.1 min; m/z (EI) 329 (M^+ , 100%), 314 (10), 300 (87), 273 (6), 254 (4), 229 (2), 207 (1), 183 (61), 182 (88), 155 (47), 154 (19), 130 (53), 114 (7), 104 (20), 90 (7), 76 (26), 63 (6), 42 (1); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{20}H_{15}N_3NaO_2$ 352.1056; found 352.1065.

6-Bromo-1-(1,3-dioxoisindolin-2-yl)-2-phenyl-1*H*-indole-3-carbonitrile (2p)

General procedure was followed (3 h), light yellow solid, 0.62 g (2.0 mmol, 70% yield), R_f 0.39 (EtOAc/petroleum ether = 30/70), mp 131–133 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.97–7.95 (m, 2H, H_{arom}), 7.89–7.87 (m, 2H, H_{arom}), 7.72 (d, J = 8.4 Hz, 1H, H_{arom}), 7.58–7.55 (m, 2H, H_{arom}), 7.52 (dd, J = 8.4 Hz, 1H, H_{arom}), 7.44–7.42 (m, 3H, H_{arom}), 7.32 (s, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 148.8, 136.8, 135.7, 130.8, 129.3, 129.0, 128.8, 127.6, 126.2, 124.8, 124.7, 121.5, 119.2, 114.4, 112.7, 88.1; IR (KBr) 2224 s, 1799 m, 1751 vs, 1612 m, 1549 w, 1467 s, 1379 m, 1301 s cm^{-1} ; GC-MS: R_t 6.4 min; m/z (EI) 441 (M^+ , 100%), 398 (3), 363 (4), 334 (1), 317 (6), 297 (14), 294 (14), 268 (6), 249 (1), 230 (1), 216 (39), 201 (4), 189 (19), 181 (4), 153 (3), 130 (17), 113 (5), 104 (38), 90 (5), 76 (24), 63 (3), 45 (6); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{23}H_{12}BrN_3NaO_2$ 464.0005; found 464.0016.

2-Benzyl-1-(1,3-dioxoisindolin-2-yl)-6-methoxy-1*H*-indole-3-carbonitrile (2q)

General procedure was followed (2.5 h), white solid, 0.54 g (2.0 mmol, 67% yield), R_f 0.42 (EtOAc/petroleum ether = 40/60), mp 265–267 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.90 (brd, s, 4H, H_{arom}), 7.65 (d, J = 8.8 Hz, 1H, H_{arom}), 7.05–6.96 (m, 6H, H_{arom}), 4.19 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 159.5, 146.1, 138.2, 136.5, 135.3, 134.6, 129.2, 128.7, 127.3, 124.4, 120.7, 118.7, 116.4, 115.0, 113.0, 88.0, 55.3, 32.3; IR (KBr) 2219 s, 1799 m, 1754 vs, 1625 m, 1561 m, 1498 m, 1317 m, 1234 m, 1037 m cm^{-1} ; GC-MS: R_t 6.7 min; m/z (EI) 407 (M^+ , 96%), 392 (2), 364 (1), 330 (2), 287 (1), 269 (1), 261 (100), 245 (68), 229 (18), 217 (33), 190 (11), 165 (3), 147 (2), 115 (3), 91 (7), 65 (3), 42 (1); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{25}H_{17}N_3NaO_3$ 430.1162; found 430.1173.

General procedure for the preparation of 2o¹⁰

A solution of phthalimidoindole compound **2o** (1 mmol) in 10 mL of absolute EtOH was treated with vigorous stirring with 1.1 equiv. of hydrazine monohydrate at room temperature. After the mixture was stirred for 2 h, the precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O , and the aqueous phase was extracted with 50 mL of CH_2Cl_2 three times. The combined organic phase was dried over anhydrous Na_2SO_4 , concentrated under reduced pressure, and chromatographed to afford the desired compound **2o'**.

1-Amino-2-propyl-1*H*-indole-3-carbonitrile (2o')

General procedure was followed (8 h), light yellow solid, 0.18 g (1.0 mmol, 88% yield), R_f 0.54 (EtOAc/petroleum ether = 30/70), mp 51–53 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.2 Hz, 1H, H_{arom}), 7.41 (d, J = 8 Hz, 1H, H_{arom}), 7.34–7.25 (m, 2H, H_{arom}), 4.61 (s, 2H, NH_2), 3.02 (t, J = 7.6 Hz, 2H, CH_2), 1.81 (sxt, J = 7.6 Hz, 2H, CH_2), 1.04 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 136.3, 125.2, 123.2, 122.3, 119.1, 116.5, 108.9, 82.1, 27.3, 22.6, 13.8; IR (KBr) 3325 s, 3221 m, 2207 s, 1633 m, 1533 m, 1478 m, 1462 w cm^{-1} ; GC-MS: R_t 5.6 min; m/z (EI) 199 (M^+ , 78%), 184 (53), 170 (88), 155 (100), 143 (34), 116 (26), 103 (17), 89 (8), 77 (12), 63 (6), 43 (2); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $C_{12}H_{13}N_3Na$ 222.1002; found 222.1012.

General procedure for the preparation of 4⁹

To a stirring solution of β -ketonitriles (10 mmol), 1,1-dimethylhydrazine (20 mmol) in anhydrous ethanol (50 mL) was added acetic acid (1 mmol). The mixture was heated to reflux with a condenser under nitrogen atmosphere until TLC indicated the total consumption of the β -ketonitriles. The solvent was removed under vacuum and the residue was purified by column chromatography using a mixture of CH_2Cl_2 and MeOH as eluent to afford the substrate.

1-Methyl-4-phenyl-3-propyl-1*H*-pyrazol-5-amine (4a)

General procedure was followed (8 h), light yellow solid, 1.34 g (10.4 mmol, 60% yield), R_f 0.55 (MeOH/ CH_2Cl_2 = 2.5/97.5), mp 139–141 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.42–7.38 (m, 2H,

H_{arom}), 7.29–7.23 (m, 3H, H_{arom}), 3.67 (s, 3H, NCH_3), 3.55 (s, 2H, NH), 2.56 (t, $J = 7.9$ Hz, 2H, CH_2), 1.57 (sxt, $J = 7.6$ Hz, 2H, CH_2), 0.89 (t, $J = 7.4$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 149.2, 142.0, 134.0, 128.9, 128.1, 126.0, 104.9, 34.2, 29.3, 22.7, 14.2; IR (KBr) 3316 s, 3190 s, 1641 s, 1601 s, 1561 s, 1543 s, 1500 m, 1452 m cm^{-1} ; GC-MS: R_f 4.7 min; m/z (EI) 215 (M^+ , 55%), 200 (13), 187 (100), 169 (7), 145 (13), 115 (19), 103 (4), 89 (7), 77 (8), 57 (6), 42 (2); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{Na}$ 238.1315; found 238.1317.

4-(4-Methoxyphenyl)-1-methyl-3-propyl-1H-pyrazol-5-amine (4b)

General procedure was followed (6 h), light yellow solid, 1.66 g (10.1 mmol, 67% yield), R_f 0.54 ($\text{MeOH}/\text{CH}_2\text{Cl}_2 = 4/96$), mp 138–139 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.19 (d, $J = 8.0$ Hz, 2H, H_{arom}), 6.95 (d, $J = 8.0$ Hz, 2H, H_{arom}), 3.83 (s, 3H, OCH_3), 3.67 (s, 3H, NCH_3), 3.49 (s, 2H, NH), 2.53 (t, $J = 8.0$ Hz, 2H, CH_2), 1.56 (sxt, $J = 7.6$ Hz, 2H, CH_2), 0.88 (t, $J = 7.2$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 158.0, 149.3, 141.8, 130.1, 126.1, 114.3, 104.7, 55.3, 34.2, 29.3, 22.7, 14.1; IR (KBr) 3320 s, 3192 s, 1640 m, 1566 s, 1540 s, 1513 s, 1464 m, 1249 s, 1019 m cm^{-1} ; GC-MS: R_f 5.6 min; m/z (EI) 245 (M^+ , 74%), 230 (13), 217 (100), 202 (8), 175 (8), 158 (6), 130 (5), 107 (4), 91 (3), 77 (5), 57 (4), 42 (2); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{NaO}$ 268.1420; found 268.1429.

4-(4-Chlorophenyl)-1-methyl-3-propyl-1H-pyrazol-5-amine (4c)

General procedure was followed (10 h), white solid, 1.34 g (10.0 mmol, 54% yield), R_f 0.48 ($\text{MeOH}/\text{CH}_2\text{Cl}_2 = 4/96$), mp 162–164 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.37 (d, $J = 8.4$ Hz, 2H, H_{arom}), 7.21 (d, $J = 8.0$ Hz, 2H, H_{arom}), 3.68 (s, 3H, NCH_3), 3.55 (s, 2H, NH), 2.53 (t, $J = 8.0$ Hz, 2H, CH_2), 1.56 (sxt, $J = 7.6$ Hz, 2H, CH_2), 0.88 (t, $J = 7.4$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 149.1, 142.0, 132.4, 131.8, 130.1, 129.1, 103.9, 34.3, 29.3, 22.6, 14.1; IR (KBr) 3316 s, 3193 s, 1642 m, 1599 w, 1569 s, 1540 s, 1494 s, 1452 m cm^{-1} ; GC-MS: R_f 5.5 min; m/z (EI) 249 (M^+ , 48%), 234 (11), 221 (100), 198 (4), 179 (7), 149 (7), 128 (5), 115 (14), 92 (8), 77 (3), 57 (6), 42 (4); HRMS-ESI (m/z): $[M + Na]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{ClN}_3\text{Na}$ 272.0925; found 272.0934.

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- 11 **Compound 2a**: Crystallized in the triclinic space group $P\bar{1}$ with cell dimensions: $a = 8.8268(18)$ Å, $b = 8.9764(18)$ Å, $c = 16.501(3)$ Å, $\alpha = 99.27(3)^\circ$, $\beta = 96.72(3)^\circ$, $\gamma = 118.09(3)^\circ$, $V = 1110.1(4)$ Å³, $D_c = 1.192$ g cm⁻³, $Z = 4$. CCDC: 772745†.
- 12 One reviewer has proposed a following alternative mechanism, which features: (i) FeBr_3 plays a role of Lewis acid to coordinate with the cyano group, which assists the tautomerization of imine **1'** into enamine **A**; (ii) the formation of a N–Fe bond between **A** and FeBr_3 , with the release of HBr, will give imine intermediate **B**; (iii) the abstraction of $[\text{FeBr}]$ from **B** will give ammonium intermediate **C**, which will undergo the same cyclization and aromatization process we have described; (iv) the released $[\text{FeBr}]$ species will be oxidized by FeBr_3 to give FeBr_2 .

