Tetrahedron 67 (2011) 6944–6952

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of *N*,*N*-dialkylaminobenzonitriles and halo-(*N*,*N*-dialkyl)benzamidines by reaction of halobenzonitriles with lithium amides

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ARTICLE INFO

Article history:
Received 20 April 2011
Received in revised form 7 June 2011
Accepted 20 June 2011
Available online 25 June 2011

Keywords:
N,*N*-Dialkylaminobenzonitriles
Lithium amides
Benzyne mechanism
Thermodynamic and kinetic control
N,*N*-Dialkylbenzamidines

ABSTRACT

3- and 4-*N*,*N*-Dialkylaminobenzonitriles and 4-chloro-(*N*,*N*-dialkyl)benzamidines were isolated by reacting 4-chlorobenzonitrile with hindered lithium amides under thermodynamic (0 °C) and kinetic control conditions (−78 °C), respectively. As previously reported, a benzyne mechanism seems to be confirmed since *N*,*N*-dialkylaminobenzonitriles are formed. Only benzamidines were isolated in fair to high yields at both 0 °C and −78 °C with non-hindered lithium amides. Exploitation and mechanistic rationale of the reaction of different halobenzonitriles are also reported.

1. Introduction

Aminobenzonitriles are important targets in organic synthesis, due to their potential applications as electron donor–acceptor (EDA) molecules, as probes to study materials properties,[1] for the development of optical switches, and for the potential conversion of photon energy into electricity. The photodynamics of some 4-(dialkylamino)benzonitriles have been studied by time-resolved X-ray diffraction,[2–4] femtosecond UV/Vis, and mid-IR absorption spectroscopy, both on single crystal or solubilized in polar/non polar solvents,[5,6] because these compounds (Fig. 1) often undergo dual fluorescence and fast intramolecular charge transfer (ICT) reactions.

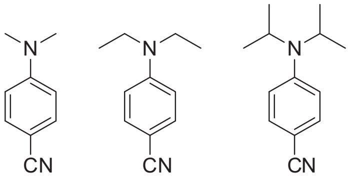
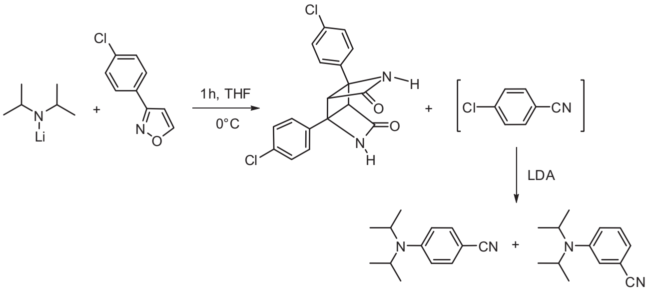


Fig. 1. 4-(Dialkylamino)benzonitriles

Various starting materials and synthetic strategies, mainly based on transition-metal catalytic processes,[7] are used to prepare these compounds. Herein, we report a simple approach to *N*,*N*-dialkylaminobenzonitriles by reacting halobenzonitriles with hindered lithium amides. This reaction was first observed by us[8] during a study of the reactivity of 3-(4-chlorophenyl)isoxazole and 3-(2-chlorophenyl)isoxazole in the presence of LDA, in which some chlorobenzonitriles were formed by partial fragmentation of isoxazoles,[9] as depicted in Scheme 1 for 3-(4-chlorophenyl)isoxazole.



Scheme 1. Isolation of 3- and 4-diisopropylaminobenzonitrile from the reaction of 3-(4-chlorophenyl)isoxazole with LDA.

Accordingly, similar results were also obtained directly starting from the commercially available 4- and 2-chlorobenzonitrile under the same experimental conditions. On the other hand, concerning the mechanism of substitution of chlorine by LDA, a benzyne mechanism was postulated, as both normal- (NS) and cine-substitution (CS) products were observed.

This mechanistic hypothesis is also in accord with the reported conversion of chlorobenzonitriles into arylboronic derivatives by

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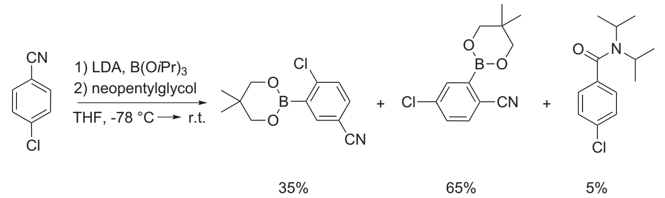
doi:10.1016/j.tet.2011.06.066

reaction with LDA and $B(OiPr)_3$ at −78 °C.[10] The first step of this reaction, in fact, consists only of the removal of the protons *ortho* to chlorine and cyano-group (Scheme 2), the former reaction being also the first step in the benzyne formation.



Scheme 2. Synthesis of arylboronic derivatives from the reaction of 4-chlorobenzonitrile with LDA.

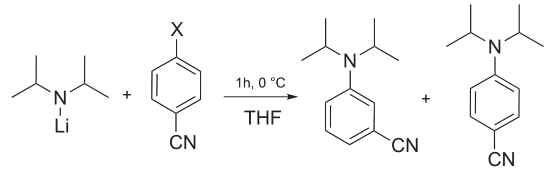
However, no nucleophilic substitution of chlorine is observed at −78 °C,[10] possibly because the elimination of Cl^- (rate determining step in the benzyne formation from chlorobenzenes)[11] is too slow at this temperature.

Clearly, the temperature plays a very important role in determining the course of this reaction. Besides, an important role is expected to be played also by the nature of the halogen, as well as by the structure of the lithium amide.

Thus, with the aim of a deeper elucidation of such a complex behaviour, particularly important in order to optimize the conditions for the formation of the aminobenzonitriles, we decided to deepen and extend the study of such a reaction using various halobenzonitriles and lithium amides, as well as different reaction conditions.

2. Results and discussion

As reported above,[8] the formation of 3- and 4-(diisopropylamino) benzonitrile (DIABN) was the only reaction observed by reacting 4-chlorobenzonitrile with an excess of LDA at 0 °C, in accordance with a benzyne mechanism of substitution. In order to confirm such a mechanism, we investigated the same reaction starting from other different 4-halobenzonitriles (Scheme 3 and Table 1). As expected, a similar behaviour was observed in the case of 4-chloro and 4-bromobenzonitrile, both able to react via a benzyne intermediate, while a completely different behaviour was observed for 4-fluorobenzonitrile, conceivably not able to undergo dehydrofluorination under these experimental conditions,[12] and so to react by the same mechanism.



1

2a
(26% X=Cl)
(29% X=Br)

3a
(73% X=Cl)
(71% X=Br)

Scheme 3. Synthesis of 3-DIABN and 4-DIABN from the reaction of 4-halobenzonitriles with 1.5 equiv of LDA at 0 °C.

Table 1
Percentages (%) of products isolated by reacting 4-halobenzonitriles with 1.5 equiv of LDA at 0 °C[a]

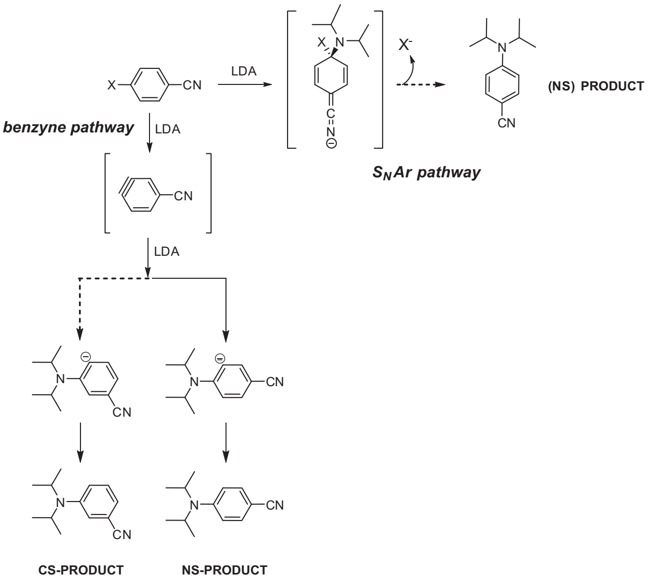
Entry	X	**2a** (%)	**3a** (%)
1	Cl	26[b]	73[b]
2	Br	29	71
3	F	—[c]	—[c]

[a] Percentages determined by GC on reaction crude.

[b] In a few experiments the formation of 4-chloro-3-[(4-chlorophenyl)(imino) methyl]benzonitrile (**4**) was observed (see Experimental section).

[c] An unidentified complex fluorinated products mixture was obtained.

On the other hand, the benzyne mechanism is generally expected when good electron withdrawing groups are absent and the nucleophile is a very strong base. However, this is not the case of 4-chlorobenzonitrile and 4-bromobenzonitrile, provided with C≡N group with electronic effects not very different from those of classical EWGs (e.g., $\sigma_p NO_2 = 0.81 \cong \sigma_p CN = 0.70$).[13] So, in principle, a S_NAr mechanism[14] could be expected, at least as a competitive mechanism of reaction (Scheme 4).



Scheme 4. Reaction of 4-halobenzonitriles and LDA: hypothesis of both S_NAr and benzyne mechanisms.

In contrast, the formation of both NS and CS products in similar relative amounts starting from chloro- and bromo-derivatives suggests the occurrence of only the benzyne mechanism. This is also in agreement with the absence of nucleophilic substitution of the halogen in the case of the 4-fluorobenzonitrile, unfavoured towards a benzyne mechanism but hypothetically favoured towards the S_NAr mechanism. Hence, this may constitute an example of benzyne mechanism induced only (or mainly) by the large steric hindrance of the nucleophile, and not by the absence of one activating group on the aromatic ring.

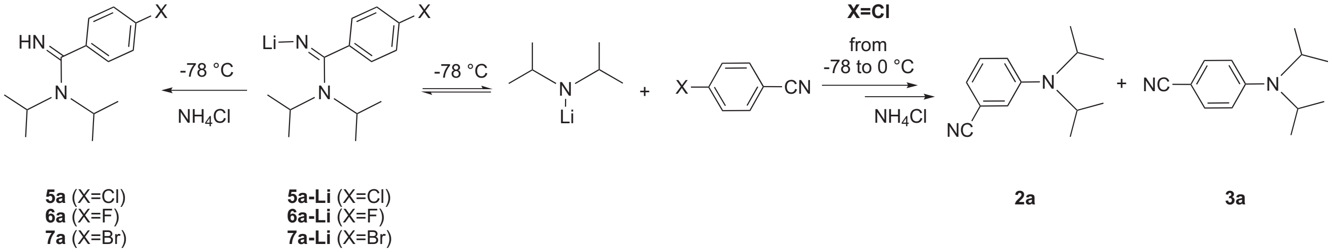
However, as said above, no halogen substitution is observed when the reaction is carried out at −78 °C instead of 0 °C. In this case the addition of LDA onto the cyano-group is found for all halobenzonitriles, affording benzamidines **5a**–**7a** (Scheme 5, Table 2).[15] Furthermore, when the reaction mixture of 4-chlorobenzonitrile and LDA at −78 °C is allowed to reach 0 °C, NS and CS substitution products were obtained in the same relative amounts observed by performing the reaction directly at 0 °C (Scheme 5, Table 2, entry 4: comparison with Table 1, entry 1).

Finally, when 4-chloro-*N*,*N*-diisopropylbenzimidamide **5a** was lithiated at 0 °C, formation of *N*,*N*-diisopropylaminobenzonitriles **2a** and **3a** in the same relative amounts was observed after 1 h (Scheme 6).

All of the above data clearly indicates that the reaction is subjected to both kinetic and thermodynamic control, giving different products depending on the temperature used.

At this point, to better define the scope of this synthetic methodology for the synthesis of *N*,*N*-dialkylaminobenzonitriles **2** and **3**, the behaviour of 4-chlorobenzonitrile with a wide number of different lithium amides at both 0 and −78 °C was investigated.

The obtained results are summarized in Scheme 7 and Table 3.



Scheme 5. Reaction of 4-halobenzonitriles with LDA under thermodynamic and kinetic control conditions.

Table 2
Percentages (%) of products isolated by reacting 4-halobenzonitriles with LDA at −78 °C[a]

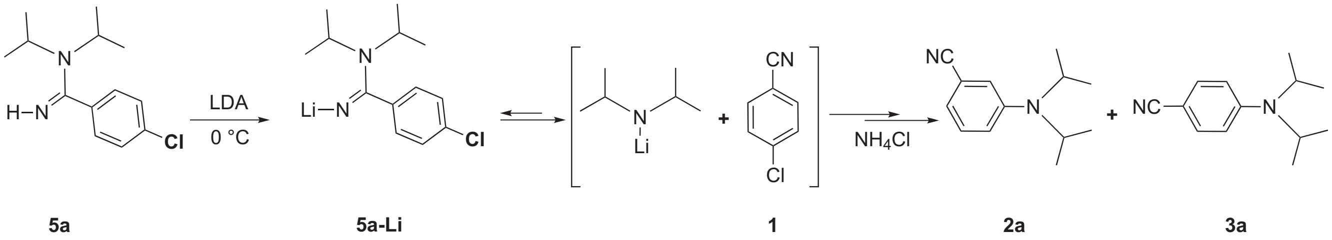
Entry	BASE/S	X	*T* (°C)	4-Halobenzonitrile (%)	**2a** (%)	**3a** (%)	Benzamidine (%)
1	1.5:1	Cl	−78	77	—	—	22 (**5a**)
2	3:1	Cl	−78	40	—	—	60 (**5a**)
3	1.5:1	Cl	−78	60 (79% D)[b]	—	—	40 (**5a**)
4	1.5:1	Cl	From −78 to 0	—	70	29	—
5	1.5:1	F	−78	8	—	—	76 (**6a**)[c]
6	1.5:1	Br	−78	74 (62% D)[d]	—	—	23 (**7a**)

[a] Percentages (%) determined by GC on reaction crude.

[b] Quenched with CD_3OD; percentages determined by GC–MS and ^1H NMR on reaction crude [2-deutero-/3-deutero-4-chlorobenzonitrile (**1-2D**/**1-3D**) ratio=40:60]: see Experimental section.

[c] 4-Fluoro-2-[(4-fluorophenyl)iminomethyl]benzonitrile (**8**) (16%) was also detected.

[d] Quenched with CD_3OD; percentages determined by GC–MS and ^1H NMR on reaction crude.



Scheme 6. 3-DIABN and 4-DIABN formation in the reaction of 4-chloro-*N*,*N*-diisopropylbenzimidamide (**5a**) with LDA at 0 °C.

As it can be observed, in the presence of hindered lithium amides with one or both bulky substituent on the amide nitrogen atom, the formation of both aminobenzonitriles **2a**–**o** and **3a**–**o** was observed at 0 °C. On the other hand, the nucleophilic addition to C≡N giving benzamidines **5a**–**o** was obtained at −78 °C, with the exception of the reaction of 4-chlorobenzonitrile and LTMP, where just lithiation was observed, as previously reported for the synthesis of arylboronic derivatives,[10] and confirmed by us through a deuteration experiment (Table 3, entry 18).

In contrast, only benzamidines were obtained at both −78 and 0 °C in the case of non-hindered lithium amides. This different behaviour is plausibly due to the higher stability of **5-Li** adducts formed from non-hindered lithium amides, so that the latter are at the same time the kinetic and thermodynamic products.

Afterwards, if required, benzamidines could be easily further functionalized as indicated by the ‘one pot’ *N*-methylation of **5d-Li**, accomplished simply by adding iodomethane at −78 °C (Scheme 8).

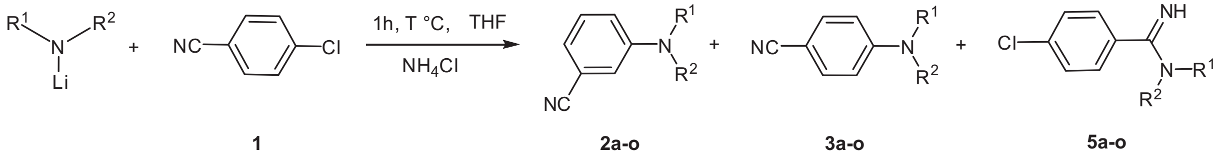
On the other hand, with reference to the reaction with LDA, we extended our investigation also to 2-chlorobenzonitrile both at 0 °C and −78 °C, observing a behaviour quite similar to 4-chlorobenzonitrile (Scheme 9, Table 4). In fact, at −78 °C the formation of benzamidine **12a** (entry 3, Table 4) was observed together with unreacted 2-chlorobenzonitrile (recovered largely deuterated at both 3 and 6 positions when the reaction was quenched with CD_3OD: see Experimental section). In contrast, when the reaction was performed at −78 °C for 1 h, and then allowed to warm up to 0 °C, we observed the formation of NS and CS products, the same as performing the reaction directly at 0 °C (Table 4, entries 1 and 2).

Again a different behaviour was observed by reacting 2-chlorobenzonitrile (**10**) with $(n\text{-Pr})_2NLi$. In the presence of this less hindered base, in fact, benzamidine formation was again observed both at −78 and 0 °C (Table 4, entry 4), just as previously observed in the case of 4-chlorobenzonitrile.

Further studies are in progress to exploit the use of these reactions to synthesize benzamidines endowed with unexplored properties. Some fluorescence emission spectra of some aminobenzonitriles in different solvents were also recorded,[17] to explore potential interesting properties as EDA molecules or new dual-fluorescence probes.[18] Although, deeper investigations are also in progress regarding the photophysical properties of selected novel dual fluorescent compounds, prepared by our above described methodology, since ratiometric fluorescent probes and sensors are powerful analytical tools, especially in studies using biological samples, such as living cells and tissues.

3. Conclusions

In conclusion, a number of *N*,*N*-dialkylaminobenzonitriles were prepared by reacting *o*- and *p*-chlorobenzonitrile with bulky lithium amides at 0 °C, whereas halo-(*N*,*N*-disubstituted) benzamidines were isolated in fair to high yields at low temperatures (−78 °C) starting from the same reagents. Based on the



Scheme 7. Reaction of 4-chlorobenzonitrile and lithium amides.

Table 3
Yields of products isolated from reaction of 4-chlorobenzonitrile and lithium amides (substrate/base ratio=1:1.5), under thermodynamic (0 °C) or kinetic control conditions (−78 °C)[a]

Entry	*T* (°C)	R^1	R^2	**1** (%)	**2a**–**o** (%)	**3a**–**o** (%)	**5a**–**o** (%)
1	0	*i*-Pr	*i*-Pr	—	**2a** (26)	**3a** (73)	—
2	0	Cy	Cy	16	**2b** (32)	**3b** (51)	—
3	0	*n*-Bu	*n*-Bu	—	—	—	**5c** (>98)
4	0	Bn	α-CH_3Bn	—	—	—	**5d** (97)
5	0	TMP		—	**2e** (33)[b,c]	**3e** (49)[b]	—
6	0	*i*-Pr	Et	18	—	—	**5f** (79)
7	0	*i*-Pr	Cy	—	**2g** (16)	**3g** (83)	—
8	0	*i*-Pr	Bn	35[d]	—	—	**5h** (49)
9	0	*t*-Bu	Bn	8[e]	**2i** (11)	**3i** (11)	—
10	0	*t*-Bu	Et	—	**2l** (32)[f]	**3l** (46)[f]	—
11	0	*n*-Pr	*n*-Pr	20	—	—	**5m** (80)
12	0	$-CH_2CH_2-O-CH_2CH_2-$		13	—	—	**5n** (87)
13	0	*cis*-2,6-DMP		—	**2o** (24)	**3o** (57)	**5o** (1)
14	−78	*i*-Pr	*i*-Pr	60	—	—	**5a** (40)
15	−78	Cy	Cy	83	—	—	**5b** (17)
16	−78	*n*-Bu	*n*-Bu	—	—	—	**5c** (>98)
17	−78	Bn	(*S*)α-CH_3Bn	43	—	—	**5d** (56)
18	−78	TMP		100[g]	—	—	—
19	−78	*i*-Pr	Et	17	—	—	**5f** (83)
20	−78	*i*-Pr	Cy	89	—	—	**5g** (11)
21	−78	*i*-Pr	Bn	19	—	—	**5h** (81)
22	−78	*t*-Bu	Bn	—	—	—	**5i** (>95)
23	−78	*t*-Bu	Et	80	—	—	**5l** (20)
24	−78	*n*-Pr	*n*-Pr	6	—	—	**5m** (94)
25	−78	$-CH_2CH_2-O-CH_2CH_2-$		—	—	—	**5n** (>95)
26	−78	*cis*-2,6-DMP		—	—	—	**5o** (>95)

[a] Percentages determined by ^{1}H NMR spectra recorded on reaction crudes.

[b] Percentages determined by GC on reaction crude.

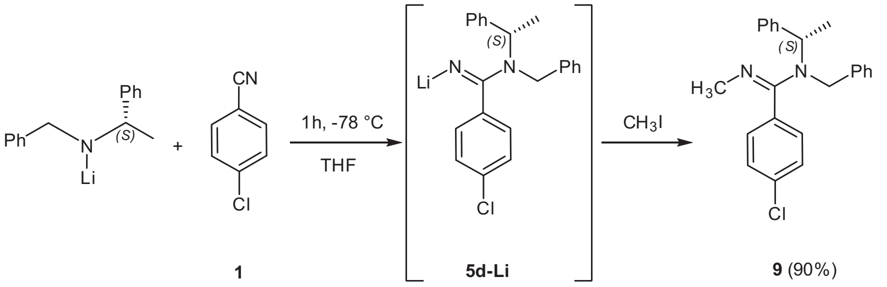
[c] An unidentified compound (18%) was detected by GC in reaction crude.

[d] An unidentified compound (16%) was detected by GC in reaction crude.

[e] Low yields of products **2i** and **3i** were obtained when benzyl was one of the nitrogen substituents, probably due to a complex mixture of lithiated intermediates formed in this reaction. *N*-benzylidene-2-methylpropan-2-amine formation (18%) was detected in the complex reaction mixture crude by GC, probably due to the base-decomposition, and through the LiH elimination.[16]

[f] 4-Chloro-3-[(4-chlorophenyl)(imino)methyl]benzonitrile (**4**) (11%) was also observed in the reaction crude.

[g] Deuterated 4-chlorobenzonitrile (93%) was isolated by quenching the reaction mixture with CD_3OD; the product percentages were determined by GC–MS and ^{1}H NMR in reaction crude and revealed a 2-deutero-/3-deutero-4-chlorobenzonitrile (**1-2D**/**1-3D**) ratio=83:17; see Experimental section.

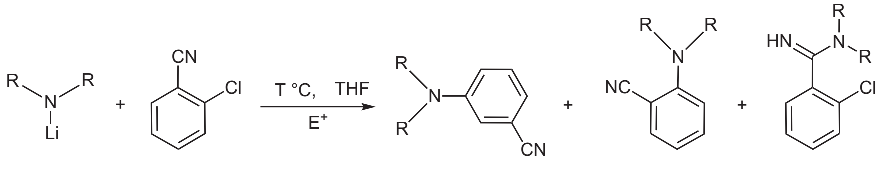


Scheme 8. Synthesis of (*S*)-*N*-benzyl-4-chloro-*N*′-methyl-*N*-(1-phenylethyl)benzimidamide (**9**).

isolation of both the normal- and cine-substitution products from *o*- and *p*-chlorobenzonitriles, and on other experimental evidences, a benzyne mechanism seems to be confirmed for the reaction outcome at 0 °C. Conversely, 4-chloro-(*N*,*N*-disubstituted)benzamidines were always isolated in the presence of less hindered lithium amides, regardless of the temperature of the reaction. So, by this investigation we uncovered a new synthetic approach for the synthesis of a number of *N*,*N*-dialkylaminobenzonitriles, and a deeper insight of the reaction mechanism was gained.

Further studies are in progress with regard to *N*,*N*-disubstituted benzamidines, that could be useful synthons in different synthetic[19–21] and pharmaceutical[22,23] applications.

Moreover, deeper investigations are ongoing about *N*,*N*-dialkylaminobenzonitriles and their photophysical properties, since ratiometric fluorescent probes and sensors are powerful



10 **2a** **11** **12** (**a**: R=*i*Pr)
(**b**: R=*n*Pr)

Scheme 9. Reaction of 2-chlorobenzonitrile with lithium amides.

Table 4
Percentages (%) of products isolated by reacting 2-chlorobenzonitrile with lithium amides[a]

Entry	*T* (°C)	*E*$^+$	R	**10** (%)	**2a** (%)	**11** (%)	Benzamidine (%)
1	0	NH_4Cl	*i*-Pr	—	57[b]	16[b]	—
2	−78→0	NH_4Cl	*i*-Pr	6	61[b]	13[b]	—
3	−78	CD_3OD	*i*-Pr	65 (87% D)[c]	—	—	35 (**12a**)
4	−78→0	NH_4Cl	*n*-Pr	6	—	—	92 (**12b**)

[a] Percentages determined by GC on reaction crude.
[b] 2-Chloro-6-[(2-chlorophenyl)(imino)methyl]benzonitrile or 2-chloro-3-[(2-chlorophenyl)(imino)methyl] benzonitrile (20%) was detected in reaction crudes by GC.
[c] Quenched with CD_3OD; percentages determined by GC–MS and ^1H NMR on reaction crude [3-deutero-/6-deutero-2-chlorobenzonitrile (**10-3D**/**10-6D**) ratio=46:54].

analytical tools, especially in bio-pharmacological studies *in vitro* and in *ex-vivo*.

4. Experimental section

4.1. General methods

Melting points were taken on an electrothermal apparatus. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian-Mercury 300 MHz, on a Varian Inova 400 MHz spectrometer, or on a Bruker-Aspect 3000 console-500 MHz spectrometer and chemical shifts are reported in parts per million (δ). ^{19}F NMR spectra were recorded by using $CFCl_3$ as an internal standard. Absolute values of the coupling constants are reported. FT-IR spectra were recorded on a Perkin–Elmer 681 spectrometer. GC analyses were performed on an HP 6890 model, Series II by using an HP1 column (methyl siloxane; 30 m×0.32 mm×0.25 μm film thickness). Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator; TLC spots were observed under ultraviolet light or were visualized by I_2 vapour exposure. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 ASTM. GC–MS analyses were performed on HP 5995C model and elemental analyses on an Elemental Analyzer 1106-Carlo Erba-instrument. ESI–MS analyses were performed on Agilent 1100 LC/MSD trap system VL.

Tetrahydrofuran (THF) from a commercial source was purified by distillation (twice) from sodium wire under nitrogen. *n*-Butyllithium (2.5 M) in hexanes was purchased from Aldrich Chemical Co. Titration of *n*-butyllithium was performed by using *N*-pivaloyl-*o*-toluidine.[24] Dialkylamines were purified by distillation from CaH_2. All other chemicals and solvents were commercial grade further purified by distillation or crystallization prior to use.

4.2. Reaction of halobenzonitriles with lithium amides: general procedure (Tables 1–4)

The amount of base indicated below refer to the reaction of 4-chlorobenzonitrile with LDA. See Table 1 for other substrate/base ratios and conditions.

A 2.5 M solution of *n*-BuLi in hexanes (1.61 mL, 4.01 mmol) was added to a solution of the dialkylamine (0.670 mL, 4.82 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen atmosphere, using a nitrogen-flushed three necked flask equipped with a magnetic stirrer and a nitrogen inlet. After 15 min, to such a solution kept at the temperature indicated in Tables 2–4, a solution of halobenzonitrile (500 mg, 3.650 mmol) in anhydrous THF (10 mL) was dropwise added and the obtained brown reaction mixture was stirred for 1 h and then quenched by adding aq NH_4Cl (or CD_3OD and then aq NH_4Cl). The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. GC analysis or ^1H NMR spectra were recorded on reaction crudes for the determination of the percentages of substrate/products conversions.

After crude characterization, acid/base extraction was performed for the separation of neutral and basic compounds. From the work-up procedure of reactions performed at −78 °C the neutral extract afforded halobenzonitriles, while basic extract afforded the benzamidines **5a**–**o** in the yields indicated in Tables 2–4. At variance, for the reactions performed at 0 °C, column chromatography (alumina or silica gel, petroleum ether/ethyl acetate=19:1) of the basic fraction residue afforded the *N*,*N*-dialkylaminobenzonitriles indicated in Schemes 3, 5, 7, 9 and Tables 1–4.

*4.2.1. 3-(Diisopropylamino)benzonitrile (**2a**).* Yield[8] 20% (29.0 mg). Yellow semi-solid. [Found: C, 76.56; H, 8.71; N, 13.74. $C_{13}H_{18}N_2$ requires C, 77.18; H, 8.97; N, 13.85%]; R_f (5% EtOAc/petroleum ether) 0.75; ν_{max} (liquid film) 2971, 2932, 2875, 2228, 1591, 1569, 1496, 1370, 1334, 1301, 1196, 1181, 1149, 1126, 1000, 776, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23–7.19 (1H, m, Ar*H*); 7.03–7.00 (2H, m, Ar*H*); 6.95–6.91 (1H, m, Ar*H*); 3.82 (2H, heptet, *J* 6.8 Hz, 2C*H*Me$_2$); 1.25 (12H, d, *J* 6.8 Hz, CH*Me*$_2$); δ_C (100 MHz, $CDCl_3$) 148.3, 129.2, 120.8, 119.8, 119.23, 112.3, 47.4, 21.0; *m*/*z* (70 eV, rel Int.) 202 (13, M$^+$), 187 (49), 159 (4), 146 (11), 145 (100), 129 (6), 117 (3), 102 (12), 43 (6), 41 (6).

*4.2.2. 4-(Diisopropylamino)benzonitrile (**3a**)*[8,25]. Yield 70% (103.0 mg). White crystals. Mp 85–86 °C (lit. 81–84 °C).[25] R_f (5% EtOAc/petroleum ether) 0.73; ν_{max} (KBr) 2969, 2925, 2851, 2206, 1598, 1515, 1428, 1334, 1303, 1180, 1156, 1119, 821 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.41–7.39 (2H, m, Ar*H*); 6.78–6.75 (m, 2H, Ar*H*); 3.92 (2H, septuplet, *J* 6.8 Hz, C*H*Me$_2$); 1.30 (12H, d, *J* 6.8 Hz, CH*Me*$_2$); δ_C (100 MHz, $CDCl_3$) 150.9, 132.9, 120.8, 114.5, 96.7, 47.4, 20.7; *m*/*z* (70 eV, rel Int.) 202 (15, M$^+$), 187 (55), 159 (5), 146 (10), 145 (100), 129 (7), 102 (14), 43 (7), 41 (6).

*4.2.3. 4-Chloro-3-[(4-chlorophenyl)(imino)methyl] benzonitrile (**4**)*[26]. Yield 45% (45.0 mg). Pale semi-solid. R_f (5% EtOAc/petroleum ether)

0.6; δ_H (400 MHz, $CDCl_3$) 9.8 (1H, br s, *NH*: exchanges with D_2O), 7.86–7.24 (7H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 172.2, 140.5, 138.0, 136.4, 134.7, 133.6, 132.3, 131.3, 129.4, 128.9, 127.7, 117.1, 111.6; *m*/*z* (70 eV, rel Int.) 276 (16, M^++2), 275 (18), 274 (25, M^+), 273 (23), 241 (34), 240 (16), 139 (100), 165 (5), 163 (14), 140 (11), 138 (33), 111 (10), 100 (7), 75 (10); this product was fully characterized after conversion in the corresponding 4-*chloro*-3-(4-*chlorobenzoyl*) *benzonitrile* (**13**). This isomer was identified by one proton coupled ^{13}C NMR experiment, where the C≡N carbon was a triplet (*J* 4.6 Hz) and the C_{ipso}(CN) a doublet (^3J 9.0 Hz); [Found: C, 60.49; H, 2.53; N, 5.03. $C_{14}H_7Cl_2NO$ requires C, 60.90; H, 2.56; N, 5.07%]; ν_{max}(liquid film) 3065, 2961, 2918, 2850, 2233, 1729, 1672, 1586, 1463, 1401, 1259, 1088, 1049, 1014, 798, 755 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.76–7.65 (4H, m, Ar*H*), 7.62 (1H, d, *J* 8.4 Hz, Ar*H*), 7.49 (2H, d, *J* 8.4 Hz, Ar*H*); δ_C (100 MHz, $CDCl_3$) 191.8, 141.4, 139.7, 136.6, 134.6, 134.0, 132.7, 131.55, 131.51, 129.6, 117.3, 111.7; *m*/*z* (70 eV, rel Int.) 277 (15, M^++2), 275 (24, M^+), 240 (2), 177 (3), 166 (6), 164 (18), 141 (33), 139 (100), 136 (10), 113 (9), 111 (27), 100 (9), 85 (3), 75 (17), 51 (2), 50 (5).

4.2.4. 4-Chloro-N,N-diisopropylbenzimidamide (***5a***). Yield 22% (38.0 mg). Pale yellow semi-solid. Mp 82–85 °C; [Found: C, 65.81; H, 8.06; N, 11.77. $C_{13}H_{19}ClN_2$ requires C, 65.40; H, 8.02; N, 11.73%]; ν_{max} (liquid film) 3310, 3036, 3017, 2973, 2932, 1578, 1446, 1382, 1366, 1219, 1171, 1077, 1027, 1010, 856, 824, 770, 729 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32–7.28 (2H, m, Ar*H*), 7.18–7.14 (2H, m, Ar*H*), 5.40–5.0 (1H, br s, *NH*: exchanges with D_2O), 3.56 (2H, septuplet, *J* 6.8 Hz, C*H*Me$_2$), 1.27 (12H, d, *J* 6.8 Hz, CH*Me*$_2$); δ_C ($CDCl_3$, 125 MHz) 166.7, 139.6, 133.9, 128.6, 127.3, 48.3, 20.7; *m*/*z* (70 eV, rel Int.) 240 (3, M^++2), 239 (5), 238 (8, M^+), 237 (11), 197 (33), 195 (100), 183 (20), 181 (58), 140 (21), 139 (8), 138 (61), 137 (8), 111 (14), 102 (10), 86 (9), 75 (7), 58 (19), 44 (14), 43 (12).

4.2.5. 4-Fluoro-N,N-diisopropylbenzimidamide (***6a***). Yield 76% (139 mg). Pale yellow oil. [Found: C, 70.22; H, 8.71; N, 12.40. $C_{13}H_{19}FN_2$ requires C, 70.24; H, 8.61; N, 12.60%]; ν_{max} (liquid film) 3313, 2967, 2928, 1669, 1598, 1575, 1511, 1446, 1367, 1222, 1180, 1155, 1082, 1029, 841, 792 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.19 (2H, m, Ar*H*), 7.08–6.98 (2H, m, Ar*H*), 5.2–4.6 (1H, br s, *NH*: exchanges with D_2O), 3.6 (2H, septuplet, *J* 6.8 Hz, C*H*Me$_2$), 1.3 (12H, d, *J* 6.8 Hz, CH*Me*$_2$); δ_C ($CDCl_3$, 100 MHz) 166.9, 162.4 (d, $^1J_{C-F}$ 246 Hz), 137.1 (d, $^4J_{C-F}$ 3.2 Hz), 127.8 (d, $^3J_{C-F}$ 8 Hz), 115.4 (d, $^2J_{C-F}$ 21.5 Hz), 48.3, 20.8; δ_F (376 MHz, $CDCl_3$) −117.3; *m*/*z* (70 eV, rel Int.) 222 (M^+, 9), 221 (11), 180 (12), 179 (100), 165 (57), 122 (78), 121 (30), 95 (22), 94 (10), 86 (17), 75 (8), 58 (25), 44 (34).

4.2.6. 4-Bromo-N,N-diisopropylbenzimidamide (***7a***). Yield 23% (36 mg). Pale yellow semi-solid. Mp 84–86 °C. [Found: C, 55.10; H, 6.48; N, 9.67. $C_{13}H_{19}BrN_2$ requires C, 55.13; H, 6.76; N, 9.89%]; ν_{max}(KBr) 3306, 2970, 2929, 2867, 1579, 1559, 1557, 1449, 1385, 1366, 1221, 1174, 1128, 1082, 1063, 1029, 1009, 824, 785, 723, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8.4 Hz, Ar*H*), 7.14 (2H, d, *J* 8.4 Hz, Ar*H*), 3.60 (2H, septuplet, *J* 6.8 Hz, C*H*Me$_2$), 1.31 (12H, d, *J* 6.8 Hz, CH*Me*$_2$); δ_C ($CDCl_3$, 125 MHz) 166.4, 139.0, 131.8, 127.7, 122.6, 48.7, 20.8; *m*/*z* (70 eV, rel Int.) 284 (M^++2, 6), 283 (10), 282 (6, M^+), 281 (10), 241 (99), 239 (100), 227 (51), 225 (52), 184 (58), 182 (59), 157 (11), 155 (12), 103 (25), 102 (34), 86 (27), 76 (20), 75 (18), 58 (43), 50 (11), 44 (55), 43 (16), 41 (16).

4.2.7. 4-Fluoro-3-[(4-fluorophenyl)(imino)methy] benzonitrile (***8***). Compound (**8**): *m*/*z* (70 eV, rel Int.) 242 (31, M^+), 240 (100), 223 (3), 147 (8), 122 (32), 95 (5), 75 (6), 40 (7).

The product, obtained in 16% yield, was fully characterized after conversion in the corresponding 4-*fluoro*-3-(4-*fluorobenzoyl*)*benzonitrile* (**14**). Yield 16 mg [Found: C, 69.10; H, 2.85; N, 5.70. $C_{14}H_7F_2NO$ requires C, 69.14; H, 2.90; N, 5.76%]; ν_{max} (neat): 2925, 2854, 2233, 1738, 1710, 1673, 1600, 1464, 1410, 1380, 1261, 1237, 1157, 1108, 853, 802, 723 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.88–7.82 (4H, m, Ar*H*), 7.32 (1H, d, *J* 8.4 Hz, Ar*H*), 7.21–7.16 (2H, m, Ar*H*); δ_F (376 MHz, $CDCl_3$) −105.6 (m); −105.8 (m); *m*/*z* (70 eV, rel Int.) 243 (43, M^+), 148 (19), 123 (100), 120 (11), 95 (33), 75 (13).

4.2.8. 3-(Dicyclohexylamino)benzonitrile (***2b***). Yield 32% (66 mg). Pale yellow powder. Mp 78–80 °C. R_f (1% EtOAc/petroleum ether) 0.78; [Found: C, 80.71; H, 9.35; N, 9.66. $C_{19}H_{26}N_2$ requires C, 80.80; H, 9.28; N, 9.92%]; ν_{max} (neat) 2930, 2854, 2227, 1590, 1568, 1493, 1451, 1345, 1296, 1262, 1242, 1166, 1121, 1050, 894, 776, 690 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.16–7.10 (1H, m, Ar*H*), 7.08–7.06 (2H, m, Ar*H*), 6.96–6.92 (1H, m, Ar*H*), 3.31–3.22 (2H, m, 2C*H*N), 1.84–1.47 (10H, m), 1.39–1.10 (10H, m); δ_C ($CDCl_3$, 125 MHz) 149.1, 129.0, 122.2, 120.5, 120.4, 119.9, 112.2, 57.9, 31.6, 26.3, 25.7; *m*/*z* (70 eV, rel Int.) 282 (28, M^+), 239 (100), 157 (74), 144 (40), 129 (17), 102 (13), 55 (27), 41 (14).

4.2.9. 4-(Dicyclohexylamino)benzonitrile (***3b***). Yield 51% (105 mg). Brown powder. Mp 69–71 °C. R_f (5% EtOAc/petroleum ether) 0.75; [Found: C, 81.06; H, 9.40; N, 10.02. $C_{19}H_{26}N_2$ requires C, 80.80; H, 9.28; N, 9.92%]; ν_{max} (KBr) 2930, 2854, 2212, 1606, 1515, 1449, 1346, 1296, 1176, 1108, 894, 823, 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37 (2H, m, *J* 9.0 Hz, Ar*H*); 6.80 (2H, m, *J* 9.0 Hz, Ar*H*); 3.41–3.33 (2H, m, 2C*H*N); 1.87–1.60 (16H, m); 1.42–1.10 (4H, m); δ_C ($CDCl_3$, 125 MHz) 151.7, 132.8, 120.8, 115.2, 125.6, 97.0, 58.0, 31.2, 26.4, 25.6; *m*/*z* (70 eV, rel Int.) 282 (30, M^+), 240 (15), 239 (100), 157 (62), 144 (39), 129 (14), 102 (20), 55 (31), 41(19).

4.2.10. 4-Chloro-N,N-dicyclohexylbenzimidamide (***5b***). Yield 17% (39 mg). Pale yellow semi-solid. [Found: C, 71.43; H, 8.20; N, 8.49. $C_{19}H_{27}ClN_2$ requires C, 71.56; H, 8.53; N, 8.78%]; ν_{max} (neat) 3348, 2918, 2850, 1567, 1447, 1417, 1261, 1153, 1081, 1022, 873, 801 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.32–7.28 (2H, m, Ar*H*), 7.17–7.14 (2H, m, Ar*H*), 3.14–3.05 (2H, m, 2C*H*N), 2.62–2.49 (4H, m); 2.1–1.9 (2H, m); 1.84–1.80 (2H, m), 1.75–1.52 (4H, m); 1.29–0.95 (8H, m); δ_C ($CDCl_3$, 125 MHz) 167.5, 139.7, 133.8, 128.6, 127.2, 58.2, 31.0, 26.1, 25.3; *m*/*z* (70 eV, rel Int.) 318 (8, M^+), 238 (11), 237 (37), 236 (34), 235 (100), 207 (9), 195 (11), 194 (19), 193 (23), 181 (21), 179 (17), 155 (16), 140 (16), 139 (21), 138 (79), 137 (20), 98 (12), 56 (18), 55 (19), 41 (13).

4.2.11. N,N-Dibutyl-4-chlorobenzimidamide (***5c***). Yield 98% (190 mg). Colourless semi-solid. [Found: C, 67.43; H, 8.55; N, 8.42. $C_{15}H_{23}ClN_2$ requires C, 67.52; H, 8.69; N, 10.50%]; ν_{max}(neat) 3312, 2959, 2925, 2853, 1580, 1455, 1380, 1367, 1221, 1178, 1092, 1029, 1015, 824, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.29–7.25 (2H, m, Ar*H*), 7.19–7.15 (2H, m, Ar*H*), 5.45–4.85 (1H, br s, *NH*, exchanges with D_2O), 3.16 (4H, triplet, *J* 7.3 Hz, 2C*H*$_2$N), 1.47 (4H, quintet, *J* 7.3 Hz, 2CH$_2$C*H*$_2$CH$_2$), 1.17 (4H, sextet, *J* 7.3 Hz, 2CH$_2$C*H*$_2$CH$_3$), 0.80 (6H, triplet, *J* 7.3 Hz, 2CH$_2$C*H*$_3$); δ_C ($CDCl_3$, 125 MHz) 167.8, 137.7, 134.3, 128.5, 127.9, 47.6, 29.9, 20.0, 13.8; *m*/*z* (70 eV, rel Int.) 268 (10, M^++2), 267 (27), 266 (30, M^+), 265 (74), 237 (11), 225 (15), 224 (12), 223 (46), 211 (10), 209 (29), 183 (77), 182 (16), 181 (88), 169 (31), 168 (20), 167 (88), 140 (32), 139 (26), 138 (100), 111 (22), 102 (24), 86 (36), 75 (13), 72 (12), 57 (10), 44 (30), 41 (12).

4.2.12. (S)-N-Benzyl-4-chloro-N-(1-phenylethyl)benzimidamide (***5d***). Yield 56–97% (142 mg). Pale yellow semi-solid. [Found: C, 75.33; H, 5.95; N, 7.74. $C_{22}H_{21}ClN_2$ requires C, 75.74; H, 6.07; N, 8.03%]; $[\alpha]_D^{20}$ −123.2 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 3317, 3086, 3062, 3029, 2977, 2934, 1582, 1494, 1447, 1416, 1349, 1179, 1090, 1028, 1015, 836, 729, 697, cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.4–7.1 (m, 14H, ArH), 5.16–5.15 (1H, br q, C*H*Me), 4.67 (1H, d, *J* 16.2 Hz, PhC*H*$_a$N), 4.5–3.5 (1H, br s, N*H*, exchanges with D_2O); 4.09 (1H, d, *J* 16.2 Hz, PhC*H*$_b$N), 1.52 (d, 3H, *J* 7.1 Hz, CHC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 168.4, 141.3, 139.3, 137.1, 135.0, 128.9, 128.5, 128.2, 127.9, 127.3, 126.9, 126.6, 126.5, 56.7, 46.8, 17.9; *m*/*z* (70 eV, rel Int.) 350 (7, M^++2), 349 (10), 348 (19, M^+), 347 (16), 259 (32), 257 (96), 245 (19), 243 (54), 216 (22), 214 (68), 140 (18), 138 (56), 120 (60), 106 (91), 105 (43), 103 (27), 91 (100), 79 (58), 77 (67), 65 (30), 51 (31).

An inseparable mixture of 3-(2,2,6,6-*tetramethylpiperidin*-1-*yl*) *benzonitrile* (**2e**) and 4-(2,2,6,6-*tetramethylpiperidin*-1-*yl*)*benzonitrile* (**3e**)=40:60 was obtained as a pale yellow solid. R_f (1% EtOAc/petroleum ether) 0.81 (145 mg).

*4.2.13. 3-(2,2,6,6-Tetramethylpiperidin-1-yl)benzonitrile (**2e**).* Yield 33%. δ_H (500 MHz, $CDCl_3$) 7.52–7.44 (3H, m, Ar*H*); 7.36 (t, 1H, *J* 7.9 Hz, Ar*H*); 1.76–1.66 (2H, m); 1.56 (4H, t, *J* 5.9 Hz); 0.98 (s, 12H); *m*/*z* (70 eV, rel Int.) 242 (2, M$^+$), 228 (11), 227 (68), 171 (13), 159 (13), 143 (16), 102 (19), 69 (48), 56 (15), 55 (14), 43 (10), 42 (15).

*4.2.14. 4-(2,2,6,6-Tetramethylpiperidin-1-yl)benzonitrile (**3e**).* Analytical data for (**3e**) are identical to those previously reported.[27] Yield 49%. δ_H (500 MHz, $CDCl_3$) 7.56 (2H, d, *J* 7.9 Hz, Ar*H*), 7.30 (2H, d, *J* 7.9 Hz, Ar*H*), 1.76–1.66 (2H, m), 1.56 (4H, t, *J* 5.9 Hz), 1.00 (s, 12H); *m*/*z* (70 eV, rel Int.) 242 (M$^+$, 3), 228 (16), 227 (91), 171(15), 159 (23), 143 (19), 109 (10), 102 (21), 69 (55), 56 (13), 55 (14), 42 (17).

δ_C ($CDCl_3$, 125 MHz) (**2e**)+(**3e**): 152.2, 139.3, 137.7, 135.0 (major isomer), 131.8 (major isomer), 129.4, 128.8, 119.3 (major isomer), 110.5, 109.3 (major isomer), 108.7, 54.5 (major isomer), 54.4 (minor isomer), 42.1 (major isomer), 42.08 (minor isomer), 29.8 (minor isomer), 18.2.

*4.2.15. 4-Chloro-(N-ethyl-N-isopropyl)benzimidamide (**5f**).* Yield 79–83% (129 mg). Yellow oil. [Found: C, 64.27; H, 7.55; N, 12.15. $C_{12}H_{17}ClN_2$ requires C, 64.13; H, 7.62; N, 12.47%]; ν_{max} (neat) 3317, 2972, 2932, 2873, 1576, 1455, 1426, 1369, 1350, 1223, 1090, 1015, 834, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33–7.29 (2H, m, Ar*H*), 7.22–7.18 (m, 2H, Ar*H*), 5.50–5.20 (1H, br s, *NH*, exchanges with D_2O), 3.90–3.70 (1H, m, $CHCH_3$), 3.30 (2H, q, *J* 6.7 Hz, CH_2CH_3), 1.16 (3H, t, *J* 6.7 Hz, CH_2CH_3), 1.07 (3H, d, *J* 6.7 Hz, $CHCH_3$); δ_C ($CDCl_3$, 100 MHz) 167.4, 138.3, 134.5, 128.9, 127.8, 49.7, 36.2, 21.1, 15.0; *m*/*z* (70 eV, rel Int.) 226 (10, M$^+$+2), 225 (33), 224 (28, M$^+$), 223 (89), 197 (31), 196 (11), 195 (91), 183 (18), 181 (55), 169 (15), 167 (45), 140 (33), 138 (100), 137 (14), 111 (26), 102 (16), 75 (14), 72 (21), 58 (20), 44 (19).

*4.2.16. 3-(N-Cyclohexyl-N-isopropylamino)benzonitrile (**2g**).* Yield 16% (28 mg). Colourless oil; R_f (1% EtOAc/petroleum ether) 0.80; [Found: C, 79.21; H, 9.10; N, 11.59. $C_{16}H_{22}N_2$ requires C, 79.29; H, 9.15; N, 11.56%]; ν_{max} (neat) 2964, 2930, 2854, 2227, 1733, 1591, 1568, 1494, 1451, 1260, 1179, 1094, 1057, 1019, 798, 686 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23–7.16 (1H, m, Ar*H*), 7.07–7.00 (2H, m, Ar*H*), 6.96–6.90 (1H, m, Ar*H*), 3.80 (1H, heptet, *J* 7.0 Hz, $CH(CH_3)_2$), 3.34–3.24 (1H, m, $CH(CH_2)_2$), 1.90–1.78 (2H, m), 1.78–1.53 (6H, m), 1.44–1.06 (8H, m, $CH(CH_3)_2$+$2CH_2$); δ_C (100 MHz, $CDCl_3$) 148.6, 132.9, 129.1, 121.4, 120.0, 119.8, 114.8, 57.7, 47.6, 31.4, 26.3, 25.7, 21.2; *m*/*z* (70 eV, rel Int.) 242 (20, M$^+$), 227 (24), 199 (73), 185 (2), 171 (2), 157 (43), 145 (45), 129 (18), 116 (4), 102 (21), 83 (5), 75 (5), 55 (44), 43 (55).

*4.2.17. 4-(N-Cyclohexyl-N-isopropylamino)benzonitrile (**3g**).* Yield 83% (147 mg). Yellow oil. R_f (1% EtOAc/petroleum ether) 0.78; [Found: C, 79.15; H, 9.09; N, 11.51. $C_{16}H_{22}N_2$ requires C, 79.29; H, 9.15; N, 11.56%]; ν_{max} (neat) 2920, 2850, 2212, 1602, 1515, 1446, 1419, 1298, 1176, 1150, 1124, 1091, 1026, 873, 821 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 7.39 (2H, d, *J* 9.0 Hz, Ar*H*), 6.78 (2H, d, *J* 9.0 Hz, Ar*H*), 3.91 (1H, heptet, *J* 7.0 Hz, $CH(CH_3)_2$), 3.47–3.35 (m, 1H, $CH(CH_2)_2$), 1.92–1.82 (m, 2H), 1.78–1.63 (m, 6H), 1.45–1.08 (m, 2H), 1.31 (d, 6H, *J* 7.0 Hz, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 151.2, 132.8, 120.8, 114.8, 96.9, 57.8, 47.6, 31.0, 26.3, 25.6, 21.0; *m*/*z* (70 eV, rel Int.) 242 (25, M$^+$), 227 (26), 200 (12), 199 (78), 171 (3), 157 (40), 145 (41), 144 (10), 143 (11), 129 (17), 102 (24), 83 (5), 75 (5), 55 (47), 43(55).

*4.2.18. 4-Chloro-N-cyclohexyl-N-isopropylbenzamidine (**5g**).* Yield 11% (22 mg). Yellow oil. [Found: C, 68.10; H, 7.99; N, 10.14. $C_{16}H_{23}ClN_2$ requires C, 68.92; H, 8.31; N, 10.05%]; ν_{max} (neat) 2928, 2854, 1580, 1444, 1385, 1368, 1264, 1208, 1174, 1119, 1090, 1015, 825, 799 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d, *J* 8.2 Hz, Ar*H*), 7.18 (2H, d, *J* 8.2 Hz, Ar*H*), 5.25–5.00 (1H, br s, *NH*, exchanges with D_2O), 3.64 (1H, heptet, *J* 6.8 Hz, $CH(CH_3)_2$), 3.15–3.00 (m, 1H), 2.10–1.9 (2H, m), 1.80–1.70 (2H, m), 1.70–1.60 (2H, m), 1.60–1.50 (1H, m), 1.20 (1H, m), 1.31 (6H, d, *J* 6.8 Hz, $CH(CH_3)_2$), 1.17–1.00 (m, 3H); δ_C ($CDCl_3$, 100 MHz) 166.9, 139.1, 134.1, 128.7, 127.3, 58.2, 48.8, 31.0, 26.2, 25.3, 20.8; *m*/*z* (70 eV, rel Int.) 280 (2, M$^+$+2), 279 (2), 278 (5, M$^+$), 235 (20), 197 (8), 196 (9), 195 (23), 183 (18), 181 (55), 140 (13), 138 (38), 98 (20), 58 (27), 56 (28), 55 (23), 43 (50).

*4.2.19. 4-Chloro-N-benzyl-N-isopropylbenzamidine (**5h**).* Yield 49–81% (102 mg). Yellow oil. [Found: C, 71.15; H, 6.61; N, 9.69. $C_{17}H_{19}ClN_2$ requires C, 71.19; H, 6.68; N, 9.77%]; ν_{max} (neat) 3086, 3060, 3029, 2969, 2928, 2872, 2854, 1579, 1560, 1493, 1451, 1413, 1368, 1352, 1182, 1089, 1054, 1015, 963, 837, 799, 728, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37–7.34 (2H, m, Ar*H*), 7.32–7.28 (5H, m, Ar*H*), 7.26–7.21 (2H, m, Ar*H*), 5.1–4.70 (1H, br s, *NH*, exchanges with D_2O), 4.55 (2H, s, $PhCH_2$), 4.12–3.92 (1H, m, $CH(CH_3)_2$), 1.13 (6H, d, *J* 6.6 Hz, $CH(CH_3)_2$); δ_C ($CDCl_3$, 100 MHz) 167.8, 139.3, 136.8, 135.0, 128.9, 128.3, 127.8, 126.6, 126.5, 50.4, 45.1, 20.9; *m*/*z* (70 eV, rel Int.) 288 (19, M$^+$+2), 287 (14), 286 (19, M$^+$), 285 (31), 245 (18), 243 (54), 214 (12), 197 (10), 195 (31), 140 (19), 139 (11), 138 (56), 111 (16), 106 (95), 102 (15), 91 (100), 79 (28), 77 (18), 65 (28), 58 (97), 51 (18), 43 (19).

*4.2.20. 3-(N-tert-Butyl-N-benzylamino)benzonitrile (**2i**).* Yield 11% (21 mg). Yellow semi-solid. R_f (1% EtOAc/petroleum ether) 0.76; [Found: C, 81.73; H, 7.32; N, 10.52. $C_{18}H_{20}N_2$ requires C, 81.78; H, 7.63; N, 10.60%]; ν_{max} (neat) 3063, 3028, 2960, 2924, 2853, 2228, 1727, 1592, 1453, 1363, 1261, 1193, 1096, 1027, 801, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.45–7.38 (1H, m, Ar*H*), 7.37.7.30 (1H, m, Ar*H*), 7.29–7.15 (6H, m, Ar*H*), 7.12–7.08 (1H, m, Ar*H*), 4.34 (2H, s, $PhCH_2$), 1.22 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 149.9, 140.2, 135.2, 133.5, 132.1, 128.8, 128.0, 127.9, 127.5, 126.5, 125.0, 119.1, 111.9, 55.9, 52.8, 28.4; *m*/*z* (70 eV, rel Int.) 264 (M$^+$, 4), 250 (10), 249 (56), 208 (9), 207 (6), 205 (4), 179 (1), 143 (5), 131 (3), 129 (4), 102 (15), 92 (8), 91 (100), 77 (4), 76 (2), 75 (3), 65 (10), 57 (9), 41 (8).

*4.2.21. 4-(N-tert-Butyl-N-benzylamino)benzonitrile (**3i**).* Yield 11% (21 mg). Yellow oil. R_f (1% EtOAc/petroleum ether) 0.73; [Found: C, 81.41; H, 7.39; N, 10.45. $C_{18}H_{20}N_2$ requires C, 81.78; H, 7.63; N, 10.60%]; ν_{max} (neat) 3061, 3027, 2964, 2923, 2851, 2215, 1641, 1602, 1509, 1347, 1194, 1174, 1092, 1071, 1027, 828, 801, 744, 730, 698 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* 8.8 Hz, Ar*H*), 7.30–7.16 (5H, m, Ar*H*), 7.04 (2H, d, *J* 8.8 Hz, Ar*H*), 4.50 (2H, s, $PhCH_2$), 1.38 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 153.5, 140.4, 132.2, 128.4, 126.7, 126.6, 122.9, 119.8, 102.5, 56.4, 53.3, 28.8; *m*/*z* (70 eV, rel Int.) 264 (6, M$^+$), 250 (9), 249 (47), 208 (16), 207 (6), 143 (4), 129 (4), 102 (13), 91 (100), 77 (4), 65 (9), 57 (8), 41 (8).

*4.2.22. N-tert-Butyl-N-benzyl-4-chlorobenzamidine (**5i**).* Yield 95% (208 mg). Yellow oil. [Found: C, 71.51; H, 7.08; N, 9.39. $C_{18}H_{21}ClN_2$ requires C, 71.87; H, 7.04; N, 9.31%]; ν_{max} (neat) 3088, 3063, 3028, 2964, 2925, 2871, 2856, 1580, 1565, 1484, 1454, 1406, 1359, 1205, 1179, 1089, 1014, 958, 836, 733, 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.32–7.16 (9H, m, Ar*H*), 5.00–4.60 (1H, br s, *NH*, exchanges with D_2O), 4.38 (s, 2H, $PhCH_2$), 1.47 (9H, s, $(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 140.9, 139.7, 134.7, 128.6, 128.3, 128.0, 126.9, 126.7, 57.5, 51.6, 28.9; *m*/*z* (70 eV, rel Int.) 302 (2, M$^+$+2), 301 (2), 300 (5, M$^+$), 245 (25), 244 (12), 243 (69), 214 (10), 148 (10), 140 (11), 139 (17), 132 (30), 111 (11), 106 (57), 91 (100), 79 (11), 57 (22), 55 (20).

*4.2.23. 3-(tert-Butyl(ethyl)amino)benzonitrile (**2l**).* Yield 32% (47 mg). Yellow oil. R_f (1% EtOAc/petroleum ether, alumina) 0.40; [Found: C, 77.22; H, 8.51; N, 13.73. $C_{13}H_{18}N_2$ requires C, 77.18; H, 8.97; N, 13.85%]; ν_{max} (neat) 2923, 2851, 2230, 1736, 1593, 1464, 1380, 1360, 1262, 1101, 800, 703 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.44–7.33 (4H, m, Ar*H*), 3.11 (2H, q, *J* 7.0 Hz), 1.10 (9H, s), 0.82 (3H, t, *J* 7.0 Hz); δ_C (125 MHz, CDCl$_3$) 149.7, 134.7, 133.1, 128.1, 119.1, 112.1, 55.6, 41.6, 28.1, 15.1; *m/z* (70 eV, rel Int.) 202 (M$^+$, 6), 188 (13), 187 (100), 159 (14), 143 (8), 131 (38), 102 (11), 57 (10), 41 (6).

*4.2.24. 4-(tert-Butyl(ethyl)amino)benzonitrile (**3l**).* Yield 46% (68 mg). Yellow oil. R_f (1% EtOAc/petroleum ether, alumina) 0.38; [Found: C, 77.22; H, 8.51; N, 13.73. $C_{13}H_{18}N_2$ requires C, 77.18; H, 8.97; N, 13.85%]; ν_{max} (neat) 2967, 2927, 2854, 2225, 1734, 1602, 1501, 1466, 1452, 1363, 1264, 1200, 1177, 1096, 1022, 846, 800, 739 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.51 (2H, d, *J* 8.4 Hz, Ar*H*), 7.13 (d, 2H, *J* 8.4 Hz, Ar*H*), 3.25 (2H, q, *J* 7.0 Hz), 1.22 (9H, s), 0.85 (3H, t, *J* 7.0 Hz); δ_C (100 MHz, CDCl$_3$) 153.2, 132.1, 126.4, 119.7, 104.7, 56.0, 41.7, 28.6, 15.4; *m/z* (70 eV, rel Int.) 202 (M$^+$, 8), 188 (14), 187 (100), 159 (16), 143 (10), 131 (46), 102 (14), 57 (12), 41 (6).

*4.2.25. N-tert-Butyl-N-ethyl-4-chlorobenzamidine (**5l**).* Yield 20% (20 mg). Yellow oil; [Found: C, 65.21; H, 7.77; N, 11.51. $C_{13}H_{19}ClN$ requires C, 65.40; H, 8.02; N, 11.73%]; ν_{max} (neat) 3303, 2964, 2926, 2872, 2855, 1584, 1407, 1360, 1209, 1186, 1089, 1042, 1014, 837, 796, 687 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.34–7.26 (4H, m, Ar*H*), 4.60–3.90 (1H, br s, *NH*, exchanges with D$_2$O), 3.17 (2H, q, *J* 7.1 Hz), 1.5 (9H, s), 0.98 (3H, t, *J* 7.1 Hz); δ_C (100 MHz, CDCl$_3$) 168.8, 139.8, 134.6, 128.5, 128.0, 56.7, 42.0, 29.0, 16.5; *m/z* (70 eV, rel Int.) 240 (1, M$^+$+2), 239 (2), 238 (2, M$^+$), 237 (6), 223 (1), 195 (2), 184 (4), 183 (20), 182 (24), 181 (48), 169 (32), 168 (11), 167 (89), 140 (22), 139 (37), 138 (68), 137 (96), 111 (18), 102 (30), 86 (100), 75 (22), 58 (31), 57 (13), 50 (14), 44 (12), 41 (18).

*4.2.26. 4-Chloro-N,N-dipropylbenzamidine (**5m**).* Yield 80–94% (139 mg). Yellow oil. [Found: C, 65.28; H, 7.68; N, 11.52. $C_{13}H_{19}ClN$ requires C, 65.40; H, 8.02; N, 11.73%]; ν_{max} (neat) 3318, 3045, 2964, 2932, 2873, 1679, 1582, 1459, 1425, 1380, 1211, 1173, 1090, 1015, 928, 893, 836, 785, 743, 682 cm^{-1}. δ_H (400 MHz, CDCl$_3$) 7.35–7.32 (2H, m, Ar*H*), 7.24–7.22 (2H, m, Ar*H*), 4.8 (s, 1H), 3.20 (2H, t, *J* 7.5 Hz), 1.58 (s, 2H, *J* 7.5 Hz), 0.84 (3H, t, *J* 7.5 Hz); δ_C (100 MHz, CDCl$_3$) 168.0, 137.8, 134.4, 128.6, 128.0, 49.6, 21.0, 11.2; *m/z* (70 eV, rel Int.) 240 (10, M$^+$+2), 239 (32), 238 (28, M$^+$), 237 (83), 223 (2), 211 (4), 209 (13), 197 (8), 195 (25), 181 (3), 169 (34), 168 (21), 167 (100), 153 (4), 140 (26), 139 (12), 138 (79), 137 (14), 125 (4), 113 (7), 111 (19), 102 (14), 86 (3), 75 (10), 72 (18), 58 (13), 41 (9).

*4.2.27. (4-Chlorophenyl)-1-morpholinomethanimine (**5n**).* Yield 87–95% (142 mg). Yellow oil. [Found: C, 58.56; H, 5.40; N, 12.11. $C_{11}H_{13}ClN_2O$ requires C, 58.80; H, 5.83; N, 12.4%]; ν_{max} (neat) 3305, 2963, 2917, 2896, 2852, 1590, 1563, 1455, 1428, 1367, 1176, 1142, 1115, 1089, 1008, 877, 831, 747 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.27 (2H, d, *J* 8.4 Hz, Ar*H*), 7.19 (2H, d, *J* 8.4 Hz, Ar*H*), 6.12–5.64 (1H, br s, *NH*, exchanges with D$_2$O), 3.62–3.58 (4H, m, 2C*H*$_2$O), 3.24–3.21 (4H, m, 2C*H*$_2$N); δ_C (100 MHz, CDCl$_3$) 168.6, 135.8, 135.3, 128.9, 128.3, 66.5, 46.5; *m/z* (70 eV, rel Int.) 226 (7, M$^+$+2), 225 (34), 224 (17, M$^+$) (17), 223 (100), 195 (17), 193 (44), 181 (4), 179 (4), 169 (3), 168 (3), 167 (10), 166 (6), 140 (21), 139 (19), 138 (63), 137 (24), 113 (7), 111 (21), 102 (17), 86 (11), 76 (10), 75 (20), 57 (21), 56 (13), 51 (5), 50 (8), 42 (5).

*4.2.28. 3-[(2R,6S)-2,6-Dimethylpiperidin-1-yl]benzonitrile (**2o**).* Yield 24% (37 mg). Purified just in little amount from 4-[(2*R*,6*S*)-2,6-*dimethylpiperidin*-1-*yl*]*benzonitrile* (**3o**) as a yellow oil; R_f (1% EtOAc/petroleum ether) 0.72; diagnostic analytical data for *meta* isomer: ν_{max} (neat) 2927, 2857, 2229, 1602, 1591, 1512, 1494, 1454, 1363, 1314, 1065, 1005, 699 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.36–7.32 (1H, m, Ar*H*), 7.28–7.22 (3H, m, Ar*H*), 3.35–3.25 (2H, m, 2C*H*(CH$_3$)), 1.92–1.44 (6H, m), 0.88 (6H, d, *J* 6.6 Hz, 2CH(C*H*$_3$)); δ_C (100 MHz, CDCl$_3$) 150.7, 126.4, 119.3, 112.8, 97.9, 53.4, 31.9, 29.3, 22.6, 20.2, 14.1; *m/z* (70 eV, rel Int.) 214 (6, M$^+$), 200 (15), 199 (100), 145 (11), 144 (5), 143 (9), 129 (14), 102 (20), 90 (1), 77 (2) 75 (43), 55 (6) 41 (4).

*4.2.29. 4-[(2R,6S)-2,6-Dimethylpiperidin-1-yl]benzonitrile (**3o**).* Yield 57% (89 mg). Yellow oil. R_f (1% EtOAc/petroleum ether, alumina) 0.71; [Found: C, 78.51; H, 8.33; N, 13.01. $C_{14}H_{18}N_2$ requires C, C, 78.46; H, 8.47; N, 13.07%]; ν_{max} (neat): 2949, 2925, 2858, 2211, 1604, 1513, 1458, 1365, 1316, 1234, 1160, 1123, 1090, 982, 909, 817, 734 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.46 (2H, d, *J* 9.0 Hz, Ar*H*), 6.80 (2H, d, *J* 9.0 Hz, Ar*H*), 4.10–3.97 (2H, m, 2C*H*(CH$_3$)), 1.92–1.64 (4H, m), 1.60–1.44 (2H, m), 1.14 (6H, d, *J* 7.0 Hz, 2CH(C*H*$_3$)); δ_C (100 MHz, CDCl$_3$) 151.2, 133.5, 129.7, 125.0, 120.5, 113.4, 47.5, 33.4, 31.0, 20.3, 18.5, 14.7; *m/z* (70 eV, rel Int.) 214 (10, M$^+$), 200 (15), 199 (100), 157 (6), 145 (11), 144 (6), 143 (8), 129 (17), 102 (20), 81 (1), 75 (3), 55 (6).

*4.2.30. (4-Chlorophenyl)[(2R,6S)-2,6-dimethylpiperidin-1-yl]methanimine (**5o**).* Yield 95% (173 mg). Yellow semi-solid. [Found: C, 67.36; H, 7.77; N, 11.19. $C_{14}H_{19}ClN_2$ requires C, 67.05; H, 7.64; N, 11.17%]; ν_{max} (neat) 3313, 2966, 2934, 2869, 2854, 1574, 1558, 1425, 1248, 1184, 1117, 1090, 1052, 1015, 902, 836, 790, 734, 683cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.32 (d, 2H, *J* 7.7 Hz, Ar*H*), 7.21 (d, 2H, *J* 7.7 Hz, Ar*H*), 5.60–5.30 (1H, br s, *NH*, exchanges with D$_2$O), 4.23–4.07 (2H, m, 2C*H*(CH$_3$)), 1.90–1.75 (1H, m), 1.73–1.58 (2H, m), 1.58–1.45 (3H, m), 1.20 (6H, d, *J* 7.0 Hz, 2CH(C*H*$_3$)); δ_C (100 MHz, CDCl$_3$) 168.0, 137.9, 134.3, 128.7, 127.7, 47.4, 30.3, 20.3, 14.0; *m/z* (70 eV, rel Int.) 252 (12, M$^+$+2), 251 (29), 250 (37, M$^+$), 249 (71), 237 (2), 235 (6), 223 (6), 221 (16), 210 (9), 209 (37), 208 (28), 207 (100), 196 (5), 195 (19), 194 (14), 193 (40), 181 (10), 168 (9), 167 (5), 166 (28), 141 (11), 140 (30), 139 (51), 138 (82), 137 (49), 132 (8), 113 (11), 112 (14), 111 (26), 103 (6), 102 (29), 98 (52), 76 (10), 75 (25), 70 (28), 56 (12), 55(13), 50 (11), 44 (12), 42 (21), 41 (17).

*4.2.31. (S)-N-Benzyl-4-chloro-N′-methyl-N-(1-phenylethyl)benzimidamide (**9**).* Yield 90% (237 mg). Yellow oil. [Found: C, 76.20; H, 6.29; N, 7.66. $C_{23}H_{23}ClN_2$ requires C, 76.12; H, 6.39; N, 7.72%]; $[\alpha]_D^{20}$ −87.8 (*c* 0.5, CHCl$_3$); ν_{max} 3087, 3060, 3028, 2972, 2928, 2863, 1617, 1609, 1490, 1449, 1394, 1307, 1089, 831, 727, 697 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.40–7.20 (9H, m, Ar*H*), 7.19–7.10 (4H, m, Ar*H*), 5.16–4.95 (1H, br q, C*H*Me), 4.62 (br d, 1H, *J* 16.0 Hz, PhC*H*$_a$N), 4.02 (d, 1H, *J* 16.0 Hz, PhC*H*$_a$N), 2.77 (s, 3H), 1.43 (d, 3H, *J* 6.9 Hz); δ_C (100 MHz, CDCl$_3$) 161.7, 142.3, 140.7, 134.3, 133.0, 129.0, 128.9, 128.4, 127.9, 127.1, 127.0, 126.8, 126.1, 55.3, 46.3, 38.1, 18.1; *m/z* (70 eV, rel Int.) 364 (0.4, M$^+$+2), 362 (2, M$^+$), 273 (16), 271 (43), 259 (13), 257 (41), 214 (3), 166 (2), 154 (33), 152 (100), 138 (7), 113 (3), 111 (10), 105 (13), 91 (22), 77 (10), 65 (5), 51 (2).

*4.2.32. 2-(Diisopropylamino)benzonitrile (**11**).* Yield 13–16% (19 mg). Yellow semi-solid. [Found: C, 77.41; H, 9.22; N, 13.74. $C_{13}H_{18}N_2$ requires C, 77.18; H, 8.97; N, 13.98%]; R_f (5% EtOAc/petroleum ether) 0.78; ν_{max} (neat): 2963, 2920, 2850, 2228, 1592, 1486, 1463, 1382, 1261, 1097, 1018, 799 cm^{-1}; δ_H (400 MHz, CDCl$_3$) 7.61 (1H, dd, *J* 7.7, 1.8 Hz, Ar*H*), 7.51–7.46 (1H, m, Ar*H*), 7.32 (1H, dd, *J* 8.8, 0.7 Hz, Ar*H*), 3.60 (2H, heptet, *J* 6.2 Hz, C*H*(CH$_3$)$_2$), 1.05 (d, 6H, *J* 6.2 Hz, CH(C*H*$_3$)$_2$); δ_C (100 MHz, CDCl$_3$) 151.8, 133.2, 132.2, 129.5, 125.0, 118.9, 116.5, 50.0, 21.3; *m/z* (70 eV, rel Int.) 202 (6, M$^+$), 188 (5), 187 (36), 159 (3), 146 (11), 145 (100), 129 (6), 118 (4), 117 (3), 102 (8), 91 (2), 77 (4), 75 (2), 43 (3).

*4.2.33. 2-Chloro-N,N-diisopropylbenzimidamide (**12a**).* Yield 35%. Pale yellow powder. Mp 81–83 °C. [Found: C, 65.79; H, 8.19; N, 11.94. $C_{13}H_{19}ClN_2$ requires C, 65.40; H, 8.02; N, 11.73%]; ν_{max} (KBr) 3304, 3056, 2972, 2930, 1578, 1445, 1367, 1221, 1090, 1025, 870, 831, 777, 751, 741 cm^{-1}; δ_H (60 °C, 400 MHz, CD$_3$OD) 7.49–7.29 (4H, m, Ar*H*), 3.90–3.40 (2H, br m, 2C*H*Me$_2$), 1.43–1.23 (12H, br m, 2CH*Me*$_2$); δ_C (25 °C, 100 MHz, CDCl$_3$) 163.4, 138.7, 130.5, 129.7, 129.3, 127.7, 127.0, 53.0–45.0 (br), 20.1 (br); *m*/*z* (70 eV, rel Int.) 240 (4, M^++2), 239 (8), 238 (12, M^+), 237 (15), 203 (36), 197 (33), 195 (100), 183 (34), 181 (100), 140 (25), 138 (78), 102 (42), 75 (10), 58 (25), 44 (19), 41 (9).

*4.2.34. 2-Chloro-N,N-dipropylbenzimidamide (**12b**).* Yield 92%. Yellow oil; [Found: C, 65.21; H, 7.99; N, 11.70. $C_{13}H_{19}ClN_2$ requires C, 65.40; H, 8.02; N, 11.73%]; ν_{max} (KBr) 3323, 3058, 2964, 2874, 1582, 1487, 1460, 1435, 1381, 1335, 1214, 1178, 1092, 1052, 1032, 931, 894, 771, 743, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.35 (1H, m, Ar*H*), 7.32–7.26 (1H, m, Ar*H*), 3.47–3.30 (1H, br s, *NH*, exchanges with D_2O), 3.30–3.10 (4H, br s, 2CH_2N), 1.70–1.50 (4H, br s, 2CH_2CH_3), 0.90–0.80 (6H, br t, 2CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 164.9, 138.2, 130.7, 129.5, 129.3, 128.6, 126.7, 50–48.5 (br s), 21.3–20.3 (br s), 11.2; *m*/*z* (70 eV, rel Int.) 240 (3, M^++2), 239 (12), 238 (9, M^+), 237 (32),211 (3), 209 (11), 204 (11), 203 (80), 197 (3), 195 (8), 181 (3), 175 (6), 169 (34), 168 (16), 167 (100), 161 (12), 153 (4), 140 (24), 139 (17), 138 (71), 137 (29), 125 (3), 111 (3), 102 (49), 86 (5), 77 (4), 75 (13), 72 (31), 58 (20), 51 (4), 43 (11), 41 (11).

4.3. Deuteration of halobenzonitriles with lithium amides: general procedure (Tables 1–4)

A 2.5 M solution of *n*-BuLi in hexanes (0.438 mL, 1.095 mmol) was added to a solution of the diisopropylamine (0.184 mL, 1.314 mmol) in anhydrous THF (9 mL) at 0 °C under nitrogen atmosphere, using a nitrogen-flushed three necked flask equipped with a magnetic stirrer and a nitrogen inlet. After 15 min, to such a solution kept at −78 °C, a solution of chlorobenzonitrile (100 mg, 0.730 mmol) in anhydrous THF (9 mL) was dropwise added and the obtained brown reaction mixture was stirred for 1 h and then quenched by adding CD_3OD all at once. Then aq NH_4Cl was added and the two phases were separated. The aqueous layer was extracted three times with ethyl acetate, the combined organic extracts were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. The deuterium incorporation was detected by ^1H NMR and GC–MS on reaction crudes. After crude characterization, acid/base extraction was performed for the separation of neutral and basic compounds. Just, for example, the analytical data for the mixture of 7% of 4-chlorobenzonitrile (**1**) (D) with 93% of **1-D** are here reported.

[*2-Deutero-/3-deutero-4-chlorobenzonitrile* (**1-2D**/**1-3D**) in 83:17 ratio, Table 3, entry 18]: ν_{max} (KBr) 2962, 2927, 2856, 2220, 1684, 1587, 1465, 1260, 1091, 1018, 799 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63–7.57 (m, 2H of **1-2D**+1H of **1-3D**+2H of **1**); 7.03–7.00 (m, 1H of **1-2D**+2H of **1-3D**+2H of **1**); *m*/*z* (70 eV, rel Int.) 140 (27, M^++2), 139 (11), 138 (100, M^+), 137 (7), 103 (26), 102 (4), 77 (4), 76 (10), 75 (8), 52 (5), 51 (7), 50 (5).

Acknowledgements

This work was financially supported by National Project PRIN ‘Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni’ MiUR (Rome), and by the University of Bari. Thanks are due to Istituto di Chimica dei Composti OrganoMetallici (ICCOM-CNR, Bari) for NMR facilities. The authors would like to acknowledge Dr. Davide Nardi, Dr. Emanuele Petruzzella and Dr. Domenico Rizzitelli for their contribution to the Experimental section.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.06.066. These data include MOL files and InChIKeys of the most important compounds described in this article.

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