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Reactions of some *ortho* and *para* halogenated aromatic nitriles with ethylenediamine: selective synthesis of imidazolines☆

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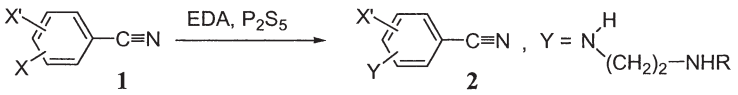
Abstract—The reaction of ethylenediamine (EDA) with *ortho* and/or *para* halogenated benzonitriles did not lead to the imidazolines expected: a competitive aromatic nucleophilic substitution (S_NAr) was observed instead. The selective synthesis of these imidazolines was performed by nucleophilic addition of EDA to thiobenzamide derivatives. The difference in reactivity between the nitrile and thioamide derivatives was estimated by a frontier orbital approach at the RHF/6-31G** level which predicted a greater reactivity of substituted thiobenzamides towards the nucleophilic addition of EDA.

1. Introduction

Imidazoline derivatives exhibit significant biological and pharmacological activities, including antihypertensive,[1,2] antihyperglycemic,[3–8] antidepressive,[9] antihypercholesterolemic[10] and anti-inflammatory[11] activities. Due to these practical applications, we have expended considerable effort in the preparation of new imidazoline derivatives.

In a previous paper,[12] we synthesized imidazolines by the nucleophilic addition of ethylenediamine (EDA) to the corresponding nitriles in the presence of catalytic amounts of a sulfur reagent: P_2S_5,[13] CS_2[14] or S.[15] The preparation of 3-aromatic halogenated imidazolines was easily accomplished by this method[16] with yields of up to 80%. However, the formation of the imidazoline moiety does not take place with the 2- and/or 4-aromatic halogenated nitriles. The



1 **2**

	X	X'		Y	X'	R
1a	2-F	H	**2a**	2-	H	H
1c	4-F	H	**2c**	4-	H	H
1h	3-F	4-F	**2h**	4-	3-F	H
			2h'[a]	4-	3-F	CH_3CO
1i	3-Cl	4-F	**2i**	4-	3-Cl	H
1j	2-Cl	6-F	**2j**	6-	2-Cl	H
1k	2-Cl	6-Cl	**2k**	6-	2-Cl	H

[a] **2h** was converted to **2h'** by the action of Ac_2O

Scheme 1. Synthesis of 2-aminoethylamino-benzonitriles **2**.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.04.075

Keywords: Aromatic nucleophilic substitution; Nucleophilic addition; Phenylimidazolines; Benzonitriles; Thiobenzamides.
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reaction observed is an aromatic nucleophilic substitution (S_NAr): the nitrile is electron-withdrawing thus favoring the displacement of the halogen[17] by EDA and resulting in a S_NAr.[18,19]

The aim of the present study was to selectively synthesize *ortho* and *para* halogenated aromatic imidazolines from the corresponding nitriles by avoiding a S_NAr and favoring nucleophilic addition of EDA.

2. Results and discussion

The addition of EDA in stoichiometric or excess amounts, to different benzonitriles, mono or disubstituted by fluorine and/or chlorine atoms (**1a**, **1c**, **1h**–**1k**), with or without catalytic amounts of P_2S_5 (Scheme 1), at 50 °C or under reflux, gave the 2-aminoethylamino-benzonitriles **2** (Table 1) resulting from the S_NAr of the EDA and not the expected imidazolines. Compound **2h** was not amenable to direct purification and identification because it was hygroscopic and sensitive to carbonation. In order to establish its structure, the free-amino group was acylated using acetic anhydride to give compound **2h′**.

Table 1. Physical data of compounds **2**

	Yield[a] (%)	Mp[b] (°C)	Molecular formula[c] (MW)
2a	90	97	$C_9H_{11}N_3$ (161)
2c	99	80	$C_9H_{11}N_3$ (161)
2h	99	112	$C_9H_{10}FN_3$ (179)
2h′	82	144	$C_{11}H_{12}FN_3O$ (221)
2i	41	109	$C_9H_{10}ClN_3$ (195,5)
2j	40	70	$C_9H_{10}ClN_3$ (195,5)
2k	38	70	$C_9H_{10}ClN_3$ (195,5)

[a] Yield of analytically pure product.
[b] Mp of analytically pure material.
[c] All products gave satisfactory microanalyses.

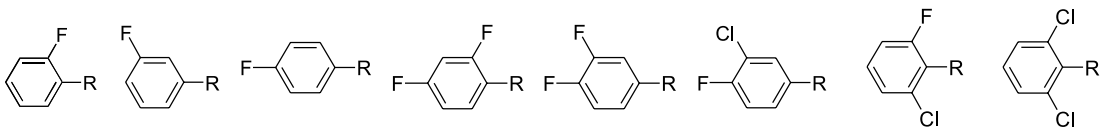
Only the displacement of the fluorine by EDA occurs in the disubstituted compounds **1i** and **1j**. Therefore, fluorine is the best leaving group among the halogens in S_NAr.

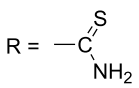
Aromatic nitriles are not a very reactive group because of resonance that stabilizes the reactant molecule. This explains why the number of aromatic halogenated imidazolines obtained by the addition of EDA to benzonitrile derivatives still remains limited. However, these compounds may be obtained by addition of EDA to the corresponding esters in the presence of trimethylaluminium[12] with moderate yields.

To avoid S_NAr of EDA on the aromatic ring, we decided to activate the cyano group by transforming it into a thioamide group. It is noteworthy that regardless of the choice of sulfur reagent used, the reaction occurring was always the same. All the current catalysts (P_2S_5, CS_2, S) generated H_2S in situ and led, in the presence of a nitrile, to the formation of a thioamide intermediate, a principal functional group in imidazoline preparation.[20,21]

The variability of reactivity between the nitrile and the

Table 2. Calculated properties of selected structures **1** and **3** optimized at the RHF/6-31G** theory level



R=–C≡N	**1a**	**1b**	**1c**	**1g**	**1h**	**1i**	**1j**	**1k**
LUMO (eV)	2.19	2.11	2.46	2.21	2.11	2.11	1.83	1.75
Atomic charges								
C_{ar}[a]	0.49	0.45	0.47	0.49 (*p*) 0.51 (*o*)	0.41 (*p*) 0.39 (*m*)	0.52 (*p*) −0.26 (*m*)	0.51 (F) −0.13 (Cl)	−0.14 −0.14
C_{CN}[b]	0.3	0.272	0.269	0.3	0.272	0.27	0.31	0.29
LUMO coefficients								
C_{ar}[a]	0.17	0.10	0.38	0.37 (*p*) 0.14 (*o*)	0.36 (*p*) 0.06 (*m*)	0.38 (*p*) 0.11 (*m*)	0.16 (F) 0.32 (Cl)	0.25 0.25
C_{CN}[b]	0.13	0.15	0.15	0.13	0.14	0.14	0.12	0.12
R = 	**3a**	**3b**	**3c**	**3g**	**3h**	**3i**	**3j**	**3k**
LUMO (eV)	1.71	1.92	2.05	1.79	1.80	1.81	2.71	2.76
Atomic charges								
C_{ar}[a]	0.47	0.45	0.46	0.49 (*p*) 0.49 (*o*)	0.40 (*p*) 0.39 (*m*)	0.51 (*p*) −0.26 (*m*)	0.50 (F) −0.15 (Cl)	−0.15 −0.15
C_{thio}[b]	0.259	0.213	0.22	0.25	0.218	0.216	0.213	0.19
LUMO coefficients								
C_{ar}[a]	0.21	0.09	0.27	0.3 (*p*) 0.21 (*o*)	0.27 (*p*) 0.02 (*m*)	0.28 (*p*) 0.1 (*m*)	0.08 (F) 0.29 (Cl)	0.23 0.22
C_{thio}[b]	0.34	0.33	0.37	0.35	0.34	0.34	0.27[c]	0.04
Torsion[d] (°)	2	38	34	19	35	36	83	89.5

[a] Mulliken atomic charges or LUMO coefficients of the halogen-bonded carbons.
[b] Mulliken atomic charges or LUMO coefficients of the nitrile or thioamide carbon atoms.
[c] Pointed perpendicular to the aromatic plane.
[d] Torsion angle defined by the aromatic and thioamide planes.

thioamide functions could actually be estimated from the empirical Hammet σ constants[22] which reflect the total electronic effects of compounds containing substituted phenyl groups. The average substituent constant σ_p is 0.62 for the nitrile group and 0.30 for the thioamide one. The nitrile function exhibits a stronger electron-withdrawing effect than the thioamide one. Thus S_NAr is facilitated by the nitrile function as it decreases the electronic density on the aromatic ring.

However, the Hammet equation is not applicable to *ortho* substituents and also some of the compounds studied were disubstituted. Because our aim was to include the effect of all substituents on the aromatic ring, we considered the reactivity of nitriles and thioamides using molecular-orbital theory. In the present case (nucleophilic attack of EDA) the frontier orbital treatment was based upon the interaction of the HOMO of EDA with LUMO of nitriles or thioamides. As the nucleophile was always the same (EDA), the lower the energy of the LUMO of aromatic derivatives, the greater the propensity to give a specific reaction.

2.1. Computational methods

Ab initio calculations were achieved using PC GAMESS version 6.2[23] of the GAMESS (US) quantum chemistry package.[24] The geometries of selected compounds were fully optimized at the RHF/6-31G** level[25] utilizing gradient techniques and default thresholds for convergence.

The energies of the LUMO of compounds **1** (nitriles) and **3** (thioamides) are shown in Table 2. This table also gives the molecular orbital coefficients (LU_{π^*}) and the charges of the carbons bonded to halogens, as well as those of the carbon of the function nitrile or thioamide.

For thioamides **3**, the torsion angles defined by the phenyl and thioamide planes are also included.

The ab initio calculations show that:

1. The thioamide group adopts an angle of approximately 35° with the aromatic ring or is nearly coplanar in the case of **3a** and **3g**; this can be explained by a favorable interaction between the *ortho* fluorine and the NH_2 group. On the other hand, the thioamide and the aromatic moieties are perpendiculars in **3j** and **3k**; this torsion may be explained by a strong steric hindrance between the bulky thioamide sulfur atom and the *ortho* halogens, which makes it impossible for the molecule to remain coplanar. It can be noticed that we observed the same phenomenon with **3a** and **3g** compounds: when calculations were performed with sulfur and *o*-fluorine atoms pointed on the same side, in both cases the resulting conformation exhibited a dihedral angle value of 62° and was energetically unfavorable compared with the latter described in Table 2.
2. The LUMO energy of thioamides **3a**–**3i** is lower than that of the nitriles **1**. The energy difference between the two series varies between 0.41 and 0.48 eV when the ring is *ortho* or *para* substituted (**a**, **c**, **g**) and between 0.19 and 0.31 eV when *meta* substituted (**b**, **h**, **i**). The **3j** and **3k** derivatives remain exceptions, as their orbital energy is respectively 0.88 and 1 eV greater than that of nitriles **1j** and **1k**. This fact reflects a loss of resonance between the aromatic and thioamide planes. These results suggest that thioamides **3a**–**3i** have a high potential to be attacked by EDA even when **3j** and **3k**, on the contrary, should not exhibit much reactivity towards nucleophilic addition.
3. For the benzonitrile derivatives, with the exception of the *meta* positions, the LUMO orbital coefficients of the halogen-bonded carbons are greater than the coefficient of the nitrile carbon. This is in agreement with the experimental data: with the exception of the *meta* derivative **1b** which gave the expected imidazoline, all the other nitriles reacted with EDA via a S_NAr mechanism. However, one can observe that for the disubstituted compound **1j**, the highest orbital coefficient is on the C_2–Cl carbon (0.32), and not on the C_6–F one (0.16). This would suggest a stronger reactivity at the C_2-position, which is not actually observed; the S_NAr occurs at the C_6-position. Both the small size of the fluorine atom compared with chlorine, and the strong positive charge of the C_6 carbon direct the reaction.
4. On the contrary, for the thioamide series, the orbital coefficient of the carbon on the thioamide function is highest than those found on the aromatic carbons. The compound **3j** is still an exception insofar as the C_2 and the thioamide carbon coefficients are equivalent (0.29 vs. 0.27). As for **3k**, the thioamide coefficient is insignificant. One might expect that the condensation of EDA on thiobenzamides would yield more easily to the related imidazolines.

However, an examination of the atomic charges does not enable us to differentiate a priori the reactivity of compounds **1** and **3**.

2.2. Imidazoline synthesis from thioamides

In an attempt to validate the theoretical results, we synthesized a series of thiobenzamides which were mono (**3a**–**3f**) or disubstituted (**3g**–**3k**) by fluorine and/or chlorine atoms (Table 3) by reaction of the related nitriles **1** with triethylamine (TEA) and an aqueous solution of ammonium sulfide[26,27] in pyridine. The choice of ammonium sulfide as an in situ H_2S generator was determined by the fact that

Table 3. Preparation of thioamides **3** from nitriles

	X	X′	Yield[a] (%)	Mp[b] (Mp lit.) (°C)	Molecular formula[c] (MW)
3a	2-F	H	65	83 (83)[33]	C_7H_6FNS (155)
3b	3-F	H	95	110 (110–111)[34]	C_7H_6FNS (155)
3c	4-F	H	85	148 (145–147)[35]	C_7H_6FNS (155)
3d	2-Cl	H	73	68 (65)[28]	C_7H_6ClNS (171,5)
3e	3-Cl	H	83	115 (121–122)[34]	C_7H_6ClNS (171,5)
3f	4-Cl	H	83	130 (130)[36]	C_7H_6ClNS (171,5)
3g	2-F	4-F	85	133	$C_7H_5F_2NS$ (173)
3h	3-F	4-F	55	105	$C_7H_5F_2NS$ (173)
3i	3-Cl	4-F	76	130	C_7H_5ClFNS (189,5)
3j	2-Cl	6-F	75	164 (161–162)[30]	C_7H_5ClFNS (189,5)
3k	2-Cl	6-Cl	73	152 (152)[37]	$C_7H_5Cl_2NS$ (206)

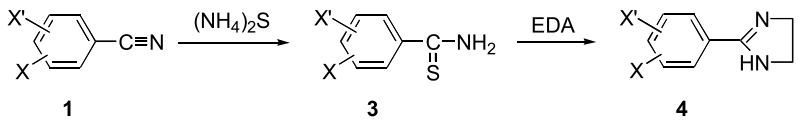
[a] Yield of analytically pure product.
[b] Mp of analytically pure material.
[c] All products gave satisfactory microanalyses.

Table 4. Preparation of imidazolines **4** from thioamides

	X	X′	Yield[a] (%)	Mp[b] (Mp lit.) (°C)	Molecular formula[c] (MW)
4a	2-F	H	65	83 (83)[12]	$C_9H_9FN_2$ (164)
4b	3-F	H	99	92 (92)[38]	$C_9H_9FN_2$ (164)
4c	4-F	H	72	153 (152–153)[39]	$C_9H_9FN_2$ (164)
4d	2-Cl	H	76	69 (69–70)[40]	$C_9H_9ClN_2$ (180,5)
4e	3-Cl	H	99	138 (136–137)[40]	$C_9H_9ClN_2$ (180,5)
4f	4-Cl	H	85	188 (186–187)[41]	$C_9H_9ClN_2$ (180,5)
4g	2-F	4-F	40	96	$C_9H_8F_2N_2$ (182)
4h	3-F	4-F	45	155	$C_9H_8F_2N_2$ (182)
4i	3-Cl	4-F	60	160 (160)[12]	$C_9H_8ClFN_2$ (198,5)
4j	2-Cl	6-F	–	–	$C_9H_8ClFN_2$ (198,5)
4k	2-Cl	6-Cl	–	–	$C_9H_8Cl_2N_2$ (215)

[a] Yield of analytically pure product.
[b] Mp of analytically pure material.
[c] All products gave satisfactory microanalyses.

hydrogen sulfide H_2S[28–31] is a particularly toxic agent.[32] The thiobenzamides were obtained with high yields, whether the aromatic nitrile was mono or disubstituted. The imidazolines **4** (Table 4) were synthesized by treating the thiobenzamides with a slight excess of EDA. The mixture was stirred under reflux for 3 days (Scheme 2).



1 **3** **4**

Scheme 2. Synthesis of imidazolines **4**.

All the thioamides, with the exception of the 2,6-disubstituted compounds (**3j** and **3k**), produced the corresponding imidazolines. The lack of nucleophilic addition with compounds **3j** and **3k** could be explained by the results of the theoretical study; particularly the high energy level of LUMO's and the perpendicular torsion of the thioamide group with regard to the aromatic moiety, associated with the strong steric hindrance of the chlorine atoms would prevent the addition to proceed.

3. Concluding remarks

The experimental results confirmed our analysis. The expected imidazolines were obtained with yields higher than 90%. The two-step protocol used thus favored the nucleophilic addition compared with nucleophilic substitution and produced high yields of the expected imidazolines.

4. Experimental

4.1. General

Melting points were determined by differential scanning calorimetry using a Shimadzu DSC-50 calorimeter. Infrared spectra were recorded on a Perkin–Elmer 983G spectrophotometer. All the imidazoline compounds gave the same IR absorption bands at approximately 3000 cm^{-1} (ν CH, CH_2, CH_3) and 3150 cm^{-1} (ν NH). ^1H NMR spectra were determined in the indicated solvent with a 250 MHz spectrometer, and peak positions given as s (singlet), d (doublet), t (triplet), q (quadruplet) or m (multiplet). The microanalyses were performed in the Microanalytical Laboratory of the Ecole Nationale Superieure de Chimie de Toulouse in Toulouse and the results obtained are within ±0.4% of the theoretical values. Reactions were monitored by thin-layer chromatography (TLC) and product mixtures were purified by column chromatography using silica gel 60 F-254, 70–200 mesh.

4.1.1. 2-(2-Aminoethylamino)-benzonitrile (2a).[20] A stirred mixture of 2-fluorobenzonitrile (2.64 g, 0.02 mol), EDA, in excess or in stoichiometric quantity, freshly distilled on KOH, and 0.15 g of P_2S_5 was heated at 120 °C in an oil bath for 4 h. The reaction mixture was then cooled, poured into cold water and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude solid was collected and purified by recrystallization from cyclohexane. ^1H NMR ($CDCl_3$) δ: 1.76 (s, 2H, NH_2), 2.85 (m, 2H, CH_2NH_2), 3.14 (m, 2H, $CH_2CH_2NH_2$), 5.02 (s, 1H, NH), 6.60–7.26 (m, 4H, ArH). IR (KBr, cm^{-1}) 2250 (νCN), 2958 (νCH_2), 3076 (νCH), 3203 and 3400 (νNH). Elemental analysis calculated for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07; found: C, 67.22; H, 6.69; N, 26.17.

Compounds **2c**, **2h**, **2i**, **2j** and **2k** were prepared from the appropriate nitriles in the same way.

4.1.2. 4-(2-Aminoethylamino)-benzonitrile (2c). ^1H NMR ($CDCl_3$) δ: 1.31 (s, 2H, NH_2), 2.93 (m, 2H, CH_2NH_2), 3.14 (m, 2H, $CH_2CH_2NH_2$), 4.76 (s, 1H, NH), 6.53–7.36 (m, 4H, ArH) IR (KBr, cm^{-1}) 2252 (νCN), 2943 (νCH_2), 3084 (νCH), 3205 and 3407 (νNH). Elemental analysis calculated for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07; found: C, 67.15; H, 6.76; N, 25.89.

4.1.3. 3-Fluoro-4-(2-aminoethylamino)-benzonitrile (2h). The crude product obtained was acylated to produce compound **2h′** as described below.

4.1.4. 3-Chloro-4-(2-aminoethylamino)-benzonitrile (2i). ^1H NMR ($CDCl_3$) δ: 1.38 (s, 2H, NH_2), 3.28 (t, 2H, CH_2NH_2), 3.01 (t, 2H, $CH_2CH_2NH_2$), 4.95 (s, 1H, NH), 6.75–7.72 (m, 3H, ArH) IR (KBr, cm^{-1}) 2250 (νCN), 2901 (νCH_2), 3079 (νCH), 3205 and 3401 (νNH). Elemental analysis calculated for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48; found: C, 55.19; H, 5.21; N, 21.32.

4.1.5. 3-Chloro-6-(2-aminoethylamino)-benzonitrile (2j). ^1H NMR ($CDCl_3$) δ: 2.81 (t, 2H, CH_2NH_2), 3.10 (s, 2H, NH_2), 3.24 (m, 2H, $CH_2CH_2NH_2$), 6.45 (t, 1H, NH), 6.85–7.46 (m, 3H, ArH) IR (KBr, cm^{-1}) 2253 (νCN), 2933 (νCH_2), 3074 (νCH), 3203 and 3405 (νNH).). Elemental analysis calculated for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48; found: C, 55.32; H, 5.24; N, 21.40 for **2j**; C, 55.12; H, 5.17; N, 21.52 for **2k**.

4.1.6. 3-Fluoro-4-(2-acetamidoethylamino)-benzonitrile (2h′). 3-Fluoro-4-(2-aminoethylamino)-benzonitrile **2h** (3.22 g, 0.02 mol) in acetic anhydride (25 mL) was heated under reflux with stirring in an oil bath for 5 h. The reaction mixture was then cooled, and the anhydride was removed under reduced pressure. The crude product was washed with water, collected by filtration and purified on silica gel column using as eluent AcOEt/CH_2Cl_2 (1:1). ^{1}H NMR (DMSO-d_6) δ: 1.90 (s, 3H, CH_3), 3.31–3.48 (m, 4H, $2CH_2$), 6.73 (s, 1H, PhNH), 6.92–7.67 (m, 3H, ArH), 8.15 (s, 1H, CONH). IR (KBr, cm^{-1}) 1635 (νCO), 2247 (νCN), 2975 (νCH_2CH_3), 3081 (νCH), 3251 and 3395 (νNH). Elemental analysis calculated for $C_{11}H_{12}FN_3O$: C, 59.72; H, 5.47; N, 18.99; found: C, 59.53; H, 5.54; N, 19.06.

4.2. General procedure for thioamides 3

An appropriate aromatic halogenated nitrile **1** (about 0.03 mol) was dissolved in pyridine (20 mL), then triethylamine (0.033 mol, 5 mL) and ammonium sulfide 20 % wt solution in water (0.033 mol, 10 mL) were added into the mixture at 50 °C for 3–6 h. After cooling, the mixture was diluted with cold water (50 mL). The precipitated solid was filtered off, washed with cold water and crystallized from cyclohexane or purified by column chromatography with dichloromethane as eluent.

NMR data of compounds **3a**,[33] **3b**,[34] **3c**,[35] **3d**,[28] **3e**,[34] **3f**,[36] **3j**[30] and **3k**[37] are in agreement with literature data.

4.2.1. 2,4-Difluorothiobenzamide (3g). ^{1}H NMR ($CDCl_3$) δ: 6.86 (m, 1H, H_5), 6.99 (m, 1H, H_3), 7.76 and 8.04 (2s broad, 2H, NH_2), 8.46 (m, 1H, H_6) IR (KBr, cm^{-1}): 3366, 3292 (νNH_2), 3167 (νCH), 1630, 1602 (νC=C), 1283 (νC=S). Elemental analysis calculated for $C_7H_5F_2NS$: C, 48.55; H, 2.91; N, 8.09; S, 18.51; found: C, 48.52; H, 3.09; N, 7.92; S, 18.23

4.2.2. 3,4-Difluorothiobenzamide (3h). ^{1}H NMR ($CDCl_3$) δ: 7.11 (s broad, 2H, NH_2), 7.19 (m, 1H, H_5), 7.62 (m, 1H, H_6), 7.81 (m, 1H, H_2) IR (KBr, cm^{-1}): 3402, 3270 (νNH_2), 3155 (νCH), 1627, 1600 (νC=C), 1261 (νC=S). Elemental analysis calculated for $C_7H_5F_2NS$: C, 48.55; H, 2.91; N, 8.09; S, 18.51; found: C, 48.36; H, 2.85; N, 8.17; S, 18.62.

4.2.3. 3-Chloro-4-fluoro-thiobenzamide (3i). ^{1}H NMR ($CDCl_3$) δ: 7.19 (m, 1H, H_2), 7.64 (s, 2H, NH_2), 7.78 (m, 1H, H_5), 7.99 (dd, 1H, H_6) IR (KBr, cm^{-1}): 3442, 3206 (νNH_2), 3101, 3129 (νCH), 1618 (νC=C), 1262 (νC=S). Elemental analysis calculated for C_7H_5ClFNS: C, 44.34; H, 2.66; N, 7.39; S, 16.91; found: C, 44.41; H, 2.53; N, 7.21; S, 16.88.

4.3. General procedure for imidazolines 4

A stirred mixture of aromatic halogenated thiobenzamides **3** (0.02 mol) and EDA in stoichiometric quantity, freshly distilled on KOH was heated at 120 °C in an oil bath for several days. The reaction mixture was then cooled, poured into cold water and extracted with CH_2Cl_2. The organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude free base was collected and purified by recrystallization from cyclohexane or by column chromatography with ethyl acetate/ethanol (1:1) as eluent. All imidazoline compounds present the same IR absorption bands towards 3000 cm^{-1} (νCH, CH_2) and 3150 cm^{-1} (νNH).

NMR data of compounds **4a**[12], **4b**[38], **4c**[39], **4d**[40], **4e**[40], **4f**[41] and **4i**[12] are in agreement with literature data.

4.3.1. 2-(2′,4′-Difluorophenyl)-4,5-dihydro-1*H*-imidazole (4g). ^{1}H NMR ($CDCl_3$) δ: 3.76 (s, 4H, CH_2CH_2), 5.03 (s, 1H, NH), 6.89 (m, 2H, H_5, H_6), 8.08 (m, 1H, H_3). Elemental analysis calculated for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38; found: C, 59.28; H, 4.55; N, 15.23.

4.3.2. 2-(3′,4′-Difluorophenyl)-4,5-dihydro-1*H*-imidazole (4h). ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 5H, CH_2CH_2 and NH), 7.17 (m, 1H, H_5), 7.49 (m, 1H, H_6), 7.61 (m, 1H, H_2). Elemental analysis calculated for $C_9H_8F_2N_2$: C, 59.34; H, 4.43; N, 15.38; found: C, 59.31; H, 4.38; N, 15.52.

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Appendix A

Supporting information

Computed total energies and Cartesian coordinates of optimized structures of series **1** and **3**.