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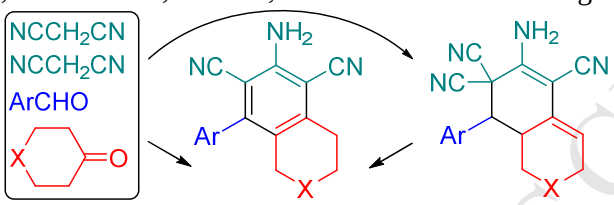

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Facile one-pot synthesis of novel *ortho*-aminocarbonitriles and dicyanoanilines fused to heterocycles via *pseudo* four-component reactions

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ABSTRACT

1-Methylpiperidin-4-one and its sulfur and oxygen analogues undergo individual facile *pseudo* four-component reactions with two folds of malononitrile and various aldehydes by using ultrasonic irradiation and deficient quantities of pyrrolidine. As a consequence, *ortho*-aminocarbonitrile products are formed efficiently in the mixture within 1-2 minutes of irradiation. Alternatively, the same mixtures of the reactants would lead to direct high-yield formation of dicyanoanilines, a group of products which are also attainable in a stepwise manner starting from the respective *ortho*-aminocarbonitriles.

1. Introduction

Derivatives of *ortho*-aminocarbonitrile are considered as an important group of organic intermediates[1] due to having many applications in the synthesis of heterocyclic compounds.[2] Moreover, these compounds are useful precursors for the preparation of their respective dicyanoanilines[3] which are important for their optical properties.[4] These features make the preparation of *ortho*-aminocarbonitriles very attractive to synthetic chemists and consequently several methods are introduced in recent years for their synthesis.[5]

Despite these developments, still many of these methods have limitations such as the use of commercially unavailable reactants or catalysts,[6] involve relatively harsh conditions,[7] go through multistep procedures,[8] or require specific solvents or workup precausions.[9] In addition, this chemistry is mainly limited to the synthesis of the products with cyclohexanone **1a** and its homologues as the central ring, and only scattered reports are available for the same processes for heterocyclic analogues.[2a]

1-Methylpiperidin-4-one **1b** is a key six-membered ring among the nitrogen containing heterocyclic structures,[10] and is highly utilized as an intermediate in the synthesis of other heterocycles[11] and more complex molecules.[12] Alternatively, the sulfur and oxygen analogues of **1b** (e.g., thiopyran-4-one **1c** and pyran-4-one **1d**, respectively) are also useful substrates for the synthesis of various compounds[13] having unique biological properties[14] and being part of the structure of several natural products.[15] Therefore, it is always of great demand to develop new methods for the synthesis of molecules involving these three heterocyclic ketones **1b-d**.

We are interested in heterocyclic chemistry[16] and so far have used ketones **1b-d** as building blocks in aldol condensations,[17] Diels-Alder cycloadditions,[18] and Baylis-Hillman reactions.[19] In continuation, here we report a general and convenient procedure for the one-pot combination of ketones **1b-d** with various aldehydes **2a-j** and malononitrile **3** under aqueous/sonochemical conditions.[20] Thus, we succeeded to conveniently access novel *ortho*-aminocarbonitrile derivatives of tetrahydroisoquinoline, isothiochromene, and isochromene skeletons via a *pseudo* four-component approach. The study is further developed by both direct and indirect synthesis of the dicyanoanilines of the tetrahydroisoquinoline system which are fluorescent due to having strong conjugated acceptor-donor-acceptor (A-D-A) functionalities (Figure 1).[21] As far as we know, there are very limited procedures on the synthesis of *ortho*-aminocarbonitrile compounds having the tetrahydroisoquinoline, isothiochromene, and isochromene units as the core rings in their structure,[22] which proceed via the stepwise treatment of the respective Knoevenagel intermediates at high temperature.

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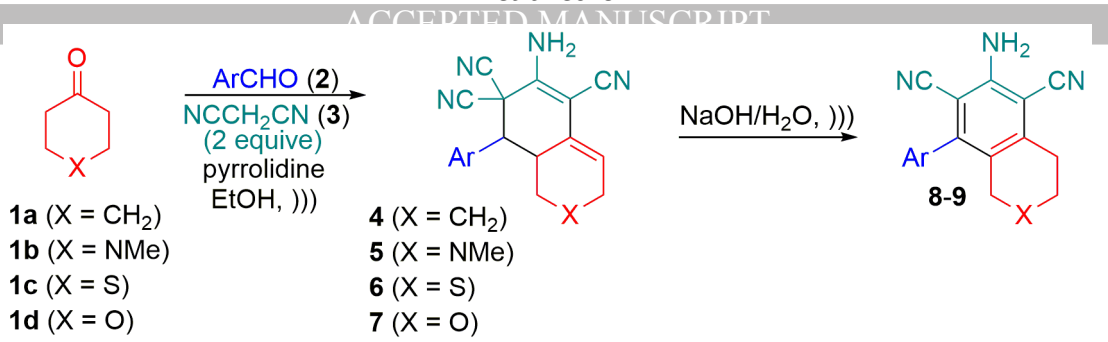

Fig. 1. One-pot synthesis of **4**-**7** and stepwise synthesis of **8**-**9**.

2. Results and discussion

First, we found optimized conditions by studying a model reaction between cyclohexanone **1a**, benzaldehyde **2a**, and malononitrile **3** (Table 1). A 1.0:1.0:2.0 mixture of the reactants and 10 mol% of pyrrolidine in EtOH gave **4a** after 90 seconds of ultrasound irradiation (US) (entry 1). The product precipitated spontaneously in the mixture allowing an easy separation by a simple filtration. The use of no base led to complete recovery of the reactants (entry 2), while with other bases (entries 3-6) or other solvents (7-8) lower yields of the same product were obtained. The use of greater amounts of pyrrolidine (entries 9-10) or prolonged reaction time under conventional heating did not cause any improvement (entry 11).

Table 1. Optimization of the conditions

Entry	Base (mol%)/solvent	Yield (%)[a]
1	pyrrolidine (10)/EtOH	78
2	none/EtOH	0
3	DABCO (10)/EtOH	38
4	Et_2NH (10)/EtOH	47
5	Et_3N (10)/EtOH	23
6	NaOH (10)/EtOH	20
7	pyrrolidine (30)/MeOH	48
8	pyrrolidine (30)/H_2O	31
9	pyrrolidine (20)/EtOH	78
10	pyrrolidine (30)/EtOH	69
11	pyrrolidine (10)/EtOH[b]	65

[a] Isolated yields.

[b] Reflux (no US), 2 h.

The applicability of the optimum conditions (US, EtOH, and 10 mol% of pyrrolidine) to other starting ketones was examined by evaluating the reactions of 1-methylpiperidin-4-one **1b** with **3** and several derivatives of **2** (Table 2). Thus, the reaction of **1b** with **2a** and malononitrile gave 76% of **5a** after 120 seconds (entry 1). Similarly electron releasing- (entries 2) and electron withdrawing substituted aldehydes (entries 3-6) gave their respective products in high yields and comparable time periods.

Table 2. Synthesis of derivatives of **5**

Entry	Aldehyde	Product	Ar	Time (s)	Yield (%)[a]
1	**2a**	**5a**	C_6H_5	120	76
2	**2b**	**5b**	4-$MeOC_6H_4$	60	78
3	**2c**	**5c**	3,4,5-$(MeO)_3C_6H_2$	90	82
4	**2d**	**5d**	4-ClC_6H_4	90	86
5	**2e**	**5e**	4-$NO_2C_6H_4$	60	77
6	**2f**	**5f**	4-NCC_6H_4	120	81

[a] Isolated yields.

The generality of the method was further expanded by replacing **1b** with thiopyran-4-one**1c** (Table 3), a very important six-membered heterocyclic compound in organic synthesis. Consequently, **1c** reacted conveniently with various aldehydes in 60-90 seconds to produce the respective tricarbonitrile compounds efficiently (entries 1-10).

Table 3. Synthesis of derivatives of **6**

Entry	Aldehyde	Product	Ar	Time (s)	Yield (%)[a]
1	**2a**	**6a**	C_6H_5	90	89
2	**2g**	**6g**	4-MeC_6H_4	90	75
3	**2b**	**6b**	4-$MeOC_6H_4$	60	80
4	**2c**	**6c**	3,4,5-$(MeO)_3C_6H_2$	90	79
5	**2d**	**6d**	4-ClC_6H_4	60	81
6	**2h**	**6h**	4-BrC_6H_4	90	73
7	**2e**	**6e**	4-$NO_2C_6H_4$	90	85
8	**2f**	**6f**	4-NCC_6H_4	60	77
9	**2i**	**6i**	2-furanyl	90	80
10	**2j**	**6j**	2-thienyl	90	81

[a] Isolated yields.

Similarly, pyran-4-one **1d** (Figure 2) behaved equally well under the optimized conditions. Therefore, three representative products **7a**, **7b**, and **7d** were synthesized using the procedure in 89, 92, and 87%, respectively within 90 s.

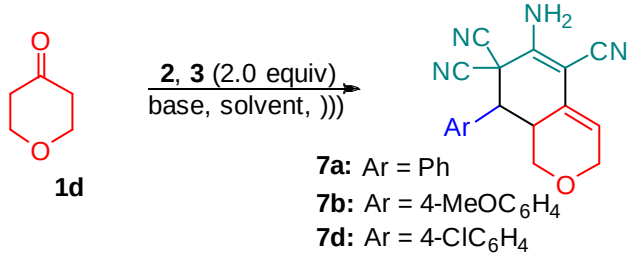

Fig. 2. Synthesis of derivatives of **7**.

In all cases, products precipitated in the reaction mixtures spontaneously. This allowed easy purification of the products by a simple filtration to avoid time consuming and expensive column chromatography separations. The structure of the products was assigned based on their spectral properties. In the IR spectra, the peaks at about 2200 and 3330 cm^{-1} were indicative of the presence of the nitrile and the NH_2 moieties, respectively. More importantly, in the ^1H NMR spectra, the dd signal at about 5.9 ppm suggested that the C=C band in the heterocyclic ring is *exo* and is adjacent to the CH_2X (X = S, O, NMe) group, while the doublet peak with a large $^3J_{H\text{-}H}$ at around 3.5 ppm showed that the two neighboring stereogenic centers exist in a *trans* relationship. To further confirm this, a single crystal of **6e** was prepared and subjected to X-ray analysis (Figure 3), where the outcome is clearly in agreement with the proposed structure.

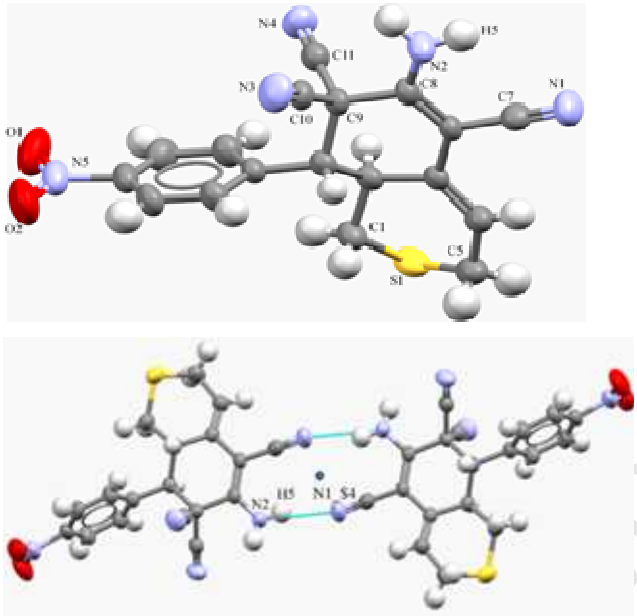

Fig. 3. (top) Structure of the formula unit of **6e** (thermal ellipsoids set at the 40% probability level).[23]

The study was further developed by converting **4**-**5** to **8**-**9** to prepare the respective dicyanoanilines which are important for their fluorescence activities. As shown in Table 4, this conversion could be achieved in both indirect and direct manners starting from either a derivative of **4** or a mixture of **1**, **2**, and **3**, respectively. In practice, the respective products could be obtained efficiently by treating **4** with a NaOH solution under US conditions. Alternatively, the same products were synthesized via a one-pot operation starting from a 1.0:1.0:2.0 mixture of the three reactants under $NaOH/H_2O$/US conditions.

Table 4. Stepwise and one-pot synthesis of **8**-**9**

Entry	Ar	X	Product	Time (s)	Yield (%)[a]
1	C_6H_5	CH_2	**8a**	150	87[b]
2	C_6H_5	CH_2	**8a**	90	90[c]
3	4-ClC_6H_4	CH_2	**8d**	120	93[b]
4	4-ClC_6H_4	CH_2	**8d**	60	98[c]
5	C_6H_5	NMe	**9a**	150	88[b]
6	C_6H_5	NMe	**9a**	90	90[c]
7	4-ClC_6H_4	NMe	**9d**	120	89[b]
8	4-ClC_6H_4	NMe	**9d**	90	95[c]

[a] Isolated yields.

[b] Stepwise reaction: (i) Pyrrolidine (10 mol%)/EtOH/US, (ii) $NaOH/H_2O$/US.

[c] $NaOH/H_2O$/US.

3. Conclusion

In summary, we presented a facile one-pot method for high yield and rapid synthesis of various series of *ortho*-aminocarbonitrile derivatives. The method is useful for the preparation of both carbocyclic and heterocyclic analogues and is particularly interesting from environmental point of view since products are directly obtained at the end of the reactions due to spontaneous precipitation. This helped us avoid cumbersome and expensive chromatographic separations and obtain pure products by a simple filtration and recrystallization of the precipitated solids. A comparison of the present method with some other related reports is summarized in the Table 5.

Based on the comparison of the one-pot and stepwise routes, we propose a mechanism in which both the starting ketones and the aldehyde undergo separate Knoevenagel condensations with **3**, as exemplified in Figure 4 (route A) for the synthesis of **4a**. In the first step, the respective olefinic intermediates **13** and **23** are formed. Apparently, nucleophilic addition of **13** to **23** proceeds highly stereoselectively so that sole formation of *exo* **4a'** occurs. The intermediate **4a'** further isomerizes *in situ* to the more stable product **4a**. Although similar hypothesis is suggested by Zhang et al,[6a] an alternative pathway with different order of addition of the reactants is also possible (route B). In this way, initial formation of aldol condensation intermediate **12** is followed by Michael addition and Knoevenagel condensation steps to form **123'**.[25] This intermediate can continue the process to rich to the same product **4a**. In control experiments, we prepared Knoevenagel (**13** and **23**) and aldol condensation (**12**) intermediates and separately subjected them to the reaction conditions. In practice, both experiments led to efficient synthesis of **4a** within the expected time period. However, TLC observations of the reaction mixtures are in favor of route A, where formation of **13** and **23** is clearly spotted. Ultimately, **4a** itself would aromatize conveniently under mild basic conditions to form the expected product **8a**. This difference in the behavior of the reactants under the two sets of conditions would be attributed to the basic strength of pyrrolidine and sodium hydroxide, where with the latter base the final aromatization step does also occur.

Table 5. Comparison of the present method with previous studies

Product	Conditions	Time/Yield (%)	Reference

4a	pyrrolidine (10 mol%)/EtOH/US	90 s/78	This work
4a	[BPy]BF_4, 60 ^oC	5 h/83	Wan et al.,[6b]
6h	pyrrolidine (10 mol%)/EtOH/US	90 s/85	This work
6h	[Bmim]BF_4, 90 ^oC (2-step process)	9 h/89	Wang et al.,[22a]
7a	pyrrolidine (10 mol%)/EtOH/US	90 s/89	This work
7a	piperidine (cat.), US (2-step process)	45 min/82	Saleh et al.,[22c]
8a	NaOH/H_2O/US	90 s/90	This work
8a	MW, Et_3N	2 min/54	Cui et al.,[4b]
8a	(i) pyrrolidine (10 mol%)/EtOH/US, (ii) NaOH/H_2O/US	150 s/87	This work
8a	(i) piperidine/EtOH (ii) morpholine, EtOH, reflux	not given /85	Sharanin et al.,[24]
9a	(i) pyrrolidine (10 mol%)/EtOH/US, (ii) NaOH/H_2O/US	150 s/88	This work
9a	(i) MeOH, (ii) MeOH/KOH, heat	not given/33	Andresen et al.,[22d]

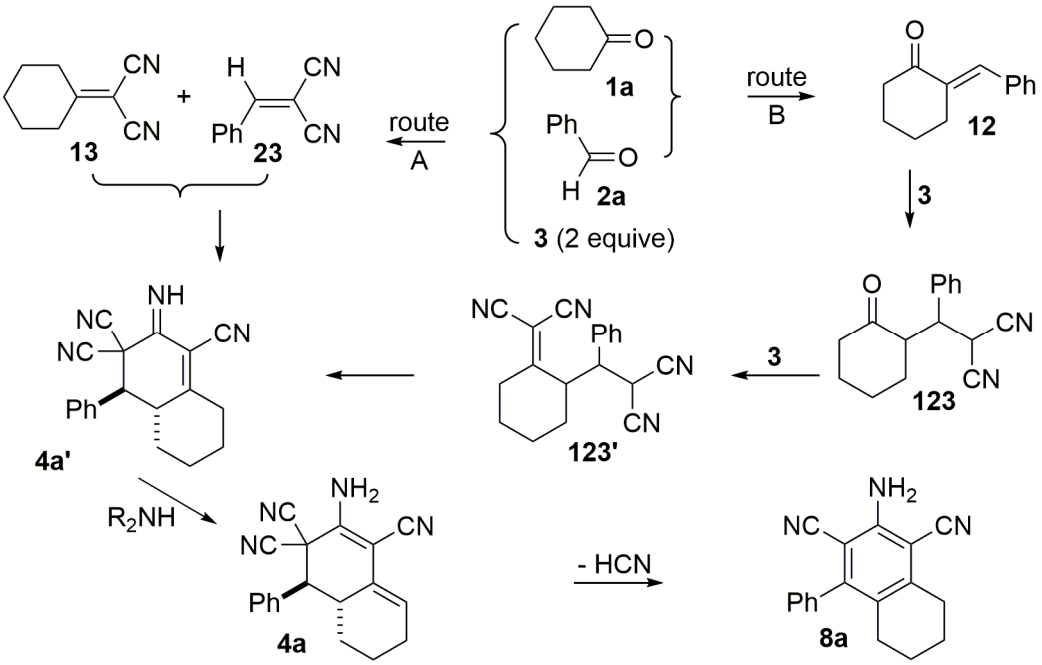

Fig. 4. The proposed mechanism.

4. Experimental

4.1. General information

Reactions were monitored by TLC using a mixture of petroleum ether/EtOAc (4:1) as the eluent. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions were reported as wave numbers (cm^{-1}). NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz for ^1H and 125 MHz for ^{13}C) or Bruker DRX-400 AVANCE (400 MHz for ^1H and 100 MHz for ^{13}C) instruments as $CDCl_3$ or DMSO-d_6 solutions and the chemical shifts were expressed as δ units with Me_4Si as the internal standard. Mass spectra were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analyses were performed by a Thermo Finnigan Flash EA 1112 instrument. All chemicals and reagents were purchased from commercial sources and were purified by standard procedures prior to use. Sonication was performed using a Sartorius Ultrasonic-homogenizer LABSONIC®P 230V/50 Hz instrument with a frequency of 24 KHz and nominal power of 460 W/cm^2. The intensity level of irradiation was adjusted at 80% level for the synthesis of the products. In all reactions the tip of the sonotrode was located in the same position just under the liquid surface in order to obtain optimal sonication and reproducible results.

4.2. General procedure for one-pot synthesis of ortho-aminocarbonitriles

A mixture of ketone **1c** (116 mg, 1.0 mmol), malononitrile (132 mg, 2.0 mmol), and pyrrolidine (8.5 μL, 10 mol%) in EtOH (2.0 mL) was sonicated in a 10 mL test tube for 30 s. At this point, 4-nitrobenzaldehyde (151 mg, 1.0 mmol) was added to the mixture and sonication was continued for another 60 s until TLC showed completion of the reaction. The product which precipitated in the mixture was filtered and recrystallized from MeCN to obtain the final product **6e** (309 mg, 85%) as a white solid.

*4.2.1. 6-Amino-2-methyl-8-(3,4,5-trimethoxyphenyl)-2,3,8,8a-tetrahydroisoquinoline-5,7,7(1H)-tricarbonitrile **5c**.* White solid, 82%; m.p. 205−207 ^oC: [Found: C, 65.27; H, 5.79; N, 16.99. $C_{22}H_{23}N_5O_3$ requires C, 65.17; H, 5.72; N, 17.27%]; ν_{max} (KBr) 3338, 2211, 1672, 1596 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.45 (2H, s, NH_2), 6.83 (1H, s, Ar), 6.78 (1H, s, Ar), 5.62−5.61 (1H, m,

=CH), 3.77 (3H, s, OMe), 3.71 (3H, s, OMe), 3.67 (3H, s, OMe), 3.49 (1H, d, *J* 12.5 Hz, CHAr), 3.31 (1H, dd, *J* 18.0, 2.0 Hz, =CHC$\underline{H}_a$H$_b$N), 3.00−2.97 (1H, m, C$\underline{H}$CH$_2$N), 2.60 (1H, ddd, *J* 18.0, 2.0, 2.0 Hz, =CHCH$_a\underline{H}_b$N), 2.49 (1H, dd, *J* 11.0, 5.0 Hz, CHC$\underline{H}_a$H$_b$N), 2.11 (3H, s, NMe), 1.65 (1H, dd, *J* 10.5, 10.5 Hz, CHCH$_a\underline{H}_b$N); δ_C (125 MHz, DMSO-d$_6$) 154.0, 153.4, 145.1, 138.8, 130.1, 128.0, 118.5, 116.8, 113.5, 113.0, 110.8, 104.7, 81.1, 60.9, 57.0, 56.9, 55.6, 55.0, 49.7, 46.0, 43.8, 35.2; MS (EI) *m/z* (%) 405 (100, M$^+$), 390 (20), 340 (41), 305 (24), 181 (78).

4.2.2. 6-Amino-2-methyl-8-(4-nitrophenyl)-2,3,8,8a-tetrahydroisoquinoline-5,7,7(1H)-tricarbonitrile ***5e***. White solid, 77%; m.p. 181−184 ^{o}C: [Found: C, 63.51; H, 4.58; N, 23.39. $C_{19}H_{16}N_6O_2$ requires C, 63.32; H, 4.48; N, 23.32%]; ν_{max} (KBr) 3354, 3084, 2212, 1726 cm^{-1}; δ_H (500 MHz, DMSO-d$_6$) 8.34 (1H, d, *J* 8.0 Hz, Ar), 8.30 (1H, d, *J* 8.0 Hz, Ar), 7.92 (1H, d, *J* 8.0 Hz, Ar), 7.70 (1H, d, *J* 8.0 Hz, Ar), 7.53 (2H, s, NH$_2$), 5.66−5.65 (1H, m, =CH), 3.94 (1H, d, *J* 12.5 Hz, CHAr), 3.33−3.29 (1H, m, =CHC$\underline{H}_a$H$_b$N), 3.06−3.03 (1H, m, C$\underline{H}$CH$_2$N), 2.61 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHCH$_a\underline{H}_b$N), 2.35 (1H, dd, *J* 11.0, 5.0 Hz, CHC$\underline{H}_a$H$_b$N), 2.09 (3H, s, NMe), 1.62 (1H, dd, *J* 10.5, 10.5 Hz, CHCH$_a\underline{H}_b$N); δ_C (125 MHz, DMSO-d$_6$) 148.9, 144.6, 141.9, 134.5, 129.3, 127.5, 124.8, 124.6, 118.9, 116.6, 112.8, 112.7, 81.3, 55.5, 54.9, 48.4, 45.8, 43.0, 34.9; MS (EI) *m/z* (%) 360 (72, M$^+$), 332 (100), 201 (39), 159 (60), 136 (89).

4.2.3. 6-Amino-8-(4-cyanophenyl)-2-methyl-2,3,8,8a-tetrahydroisoquinoline-5,7,7(1H)-tricarbonitrile ***5f***. White solid, 77%; m.p. 211−214 ^{o}C: [Found: C, 70.68; H, 4.68; N, 24.52. $C_{20}H_{16}N_6$ requires C, 70.57; H, 4.74; N, 24.69%]; ν_{max} (KBr) 3383, 3127, 2244, 2206, 1661 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$) 8.02 (1H, d, *J* 8.0 Hz, Ar), 7.96 (1H, d, *J* 8.0 Hz, Ar), 7.85 (1H, d, *J* 8.0 Hz, Ar), 7.65 (1H, d, *J* 8.0 Hz, Ar), 7.56 (2H, s, NH$_2$), 5.68−5.67 (1H, m, =CH), 3.86 (1H, d, *J* 12.0 Hz, CHAr), 3.33−3.29 (1H, m, =CHC$\underline{H}_a$H$_b$N), 3.09−3.04 (1H, m, C$\underline{H}$CH$_2$N), 2.64 (1H, ddd, *J* 18.5, 3.0, 3.0 Hz, =CHCH$_a\underline{H}_b$N), 2.35 (1H, dd, *J* 11.0, 5.0 Hz, CHC$\underline{H}_a$H$_b$N), 2.12 (3H, s, NMe), 1.63 (1H, dd, *J* 10.5, 10.5 Hz, CHCH$_a\underline{H}_b$N); δ_C (100 MHz, DMSO-d$_6$) 144.2, 139.7, 133.6, 133.3, 133.1, 128.5, 127.1, 118.8, 118.4, 116.3, 112.7, 112.5, 112.3, 80.8, 55.1, 54.5, 48.2, 45.5, 42.6, 34.4; MS (EI) *m/z* (%) 342 (100), 340 (16, M$^+$), 307 (42), 279 (57), 244 (37).

4.2.4. 6-Amino-8-phenyl-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6a***. White solid, 78%; m.p. 281−283 ^{o}C: [C, 67.81; H, 4.52; N, 17.81; S, 9.93. $C_{18}H_{14}N_4S$ requires C, 67.90; H, 4.43; N, 17.60; S, 10.07%]; ν_{max} (KBr) 3331, 3164, 2208, 1668, 1604 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$) 7.66−7.44 (7H, m, Ph, NH$_2$), 5.96−5.93 (1H, m, =CH), 3.66 (1H, d, *J* 12.0 Hz, CHPh), 3.44 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.17 (1H, ddd, *J* 18.0, 6.0, 1.0 Hz, =CHCH$_a\underline{H}_b$S), 3.02−3.00 (1H, m, C$\underline{H}$CH$_2$S), 2.27−2.25 (2H, m, CH$_2$S); δ_C (100 MHz, DMSO-d$_6$) 144.6, 134.3, 130.1, 129.7, 129.4, 118.1, 116.5, 112.7, 112.5, 82.0, 49.9, 43.3, 35.6, 28.2, 25.5; MS (EI) *m/z* (%) 318 (22, M$^+$), 314 (32), 300 (21), 273 (8), 210 (28), 105 (100).

4.2.5. 6-Amino-8-(p-tolyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6g***. White solid, 75%; m.p. 272−273 ^{o}C: [Found: C, 68.49; H, 4.78; N, 17.09; S, 9.90. $C_{19}H_{16}N_4S$ requires C, 68.65; H, 4.85; N, 16.85; S, 9.65%]; ν_{max} (KBr) 3340, 3230, 2211, 1642 cm^{-1}; δ_H (500 MHz, DMSO-d$_6$) 7.48 (4H, ap s, Ar), 7.26 (2H, s, NH$_2$), 5.90 (1H, ap s, =CH), 3.57 (1H, d, *J* 12.0 Hz, CHAr), 3.42−3.38 (1H, m, =CHC$\underline{H}_a$H$_b$S), 3.14−3.11 (1H, m, =CHCH$_a\underline{H}_b$S), 2.95−2.91 (1H, m, C$\underline{H}$CH$_2$S), 2.31 (3H, s, Me), 2.23−2.20 (2H, m, CH$_2$S); δ_C (125 MHz, DMSO-d$_6$) 145.1, 139.6, 131.7, 130.6, 130.4, 118.9, 118.4, 116.9, 113.2, 113.0, 82.4, 50.1, 43.9, 36.1, 28.6, 25.9, 21.6; MS (EI) *m/z* (%) 332 (100, M$^+$), 299 (20), 274 (40), 131 (57), 105 (82).

4.2.6. 6-Amino-8-(4-methoxyphenyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6b***. White solid, 80%; m.p. 252−254 ^{o}C: [Found: C, 65.39; H, 4.72; N, 16.22; S, 9.34. $C_{19}H_{16}N_4OS$ requires C, 65.50; H, 4.63; N, 16.08; S, 9.20%]; ν_{max} (KBr) 3344, 2214, 1640, 1597 cm^{-1}; δ_H (500 MHz, DMSO-d$_6$) 7.51 (2H, ap s, Ar), 7.37 (2H, br s, NH$_2$), 7.04 (2H, ap s, Ar), 5.95−5.93 (1H, m, =CH), 3.80 (3H, s, OMe), 3.61 (1H, d, *J* 12.0 Hz, CHAr), 3.45 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.16 (1H, dd, *J* 18.5, 5.5 Hz, =CHCH$_a\underline{H}_b$S), 2.97 (1H, ddd, *J* 12.0, 10.5, 4.5 Hz, C$\underline{H}$CH$_2$S), 2.31 (1H, dd, *J* 13.5, 4.5 Hz, C$\underline{H}_a$H$_b$S), 2.22 (1H, dd, *J* 13.5, 10.5 Hz, CH$_a\underline{H}_b$S); δ_C (125 MHz, DMSO-d$_6$) 160.6, 144.9, 130.6, 126.4, 118.3, 116.9, 115.3, 113.2, 113.0, 82.4, 56.0, 49.8, 44.0, 36.2, 28.6, 25.9; MS (EI) *m/z* (%) 348 (6, M$^+$), 301 (82), 161 (78), 146 (47), 118 (100).

4.2.7. 6-Amino-8-(3,4,5-trimethoxyphenyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6c***. White solid, 79%; m.p. 232−233 ^{o}C: [Found: C, 61.79; H, 5.12; N, 13.91; S, 7.62. $C_{21}H_{20}N_4O_3S$ requires C, 61.75; H, 4.94; N, 13.72; S, 7.85%]; ν_{max} (KBr) 3338, 2211, 1650, 1594 cm^{-1}; δ_H (500 MHz, DMSO-d$_6$) 7.50 (2H, s, NH$_2$), 6.87 (1H, s, Ar), 6.77 (1H, s, Ar), 5.92−5.91 (1H, m, =CH), 3.82 (3H, s, OMe), 3.78 (3H, s, OMe), 3.68 (3H, s, OMe), 3.52 (1H, d, *J* 12.0 Hz, CHAr), 3.38 (1H, ddd, *J* 18.5, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.12 (1H, dd, *J* 18.5, 5.5 Hz, =CHCH$_a\underline{H}_b$S), 2.97 (1H, ddd, *J* 12.0, 10.5, 3.0 Hz, C$\underline{H}$CH$_2$S), 2.38 (1H, dd, *J* 13.5, 3.0 Hz, CHC$\underline{H}_a$H$_b$S), 2.24 (1H, dd, *J* 13.5, 10.5 Hz, CHCH$_a\underline{H}_b$S); δ_C (125 MHz, DMSO-d$_6$) 145.1, 138.8, 130.6, 130.2, 118.5, 116.9, 113.5, 112.9, 104.8, 82.3, 60.9, 56.9, 51.0, 43.8, 36.0, 28.6, 25.8; MS (EI) *m/z* (%) 408 (100, M$^+$), 391 (16), 360 (17), 212 (79), 181 (34), 164 (18).

4.2.8. 6-Amino-8-(4-chlorophenyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6d***. White solid, 81%; m.p. 289−292 ^{o}C: [Found: C, 61.39; H, 3.92; N, 16.01; S, 8.93. $C_{18}H_{13}ClN_4S$ requires C, 61.27; H, 3.71; N, 15.88; S, 9.09%]; ν_{max} (KBr) 3346, 2210, 1640, 1598 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$) 7.68−7.47 (6H, m, Ar, NH$_2$), 5.96−5.94 (1H, m, =CH), 3.75 (1H, d, *J* 12.0 Hz, CHAr), 3.44 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.15 (1H, dd, *J* 18.0, 6.0 Hz, =CHCH$_a\underline{H}_b$S), 3.03−2.94 (1H, m, C$\underline{H}$CH$_2$S), 2.31−2.23 (2H, m, CH$_2$S); δ_C (100 MHz, DMSO-d$_6$) 144.4, 134.6, 133.3, 129.9, 129.5, 118.2, 116.4, 112.6, 112.4, 82.0, 49.2, 43.1, 35.4, 28.1, 25.4; (EI) *m/z* (%) 354 (30, M+2), 352 (93, M$^+$), 294 (49), 227 (43), 151 (71), 125 (95).

4.2.9. 6-Amino-8-(4-bromophenyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6h***. White solid, 73%; m.p. 294−297 ^{o}C: [Found: C, 54.55; H, 3.43; N, 14.01; S, 8.21. $C_{18}H_{13}BrN_4S$ requires C, 54.42; H, 3.30; N, 14.10; S, 8.07%]; ν_{max} (KBr) 3346, 2210, 1641, 1598 cm^{-1}; δ_H (400 MHz, DMSO-d$_6$) 7.70 (2H, d, *J* 8.0 Hz, Ar), 7.56 (2H, ap s, Ar), 7.41 (2H, br s, NH$_2$), 5.96−5.94 (1H, m, =CH), 3.76 (1H, d, *J* 12.0 Hz, CHAr), 3.45 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.16 (1H, dd, *J* 18.0, 6.0 Hz, =CHCH$_a\underline{H}_b$S), 3.02−2.99 (1H, m, C$\underline{H}$CH$_2$S), 2.31−2.20 (2H, m, CH$_2$S); δ_C (100 MHz, DMSO-d$_6$) 144.4, 133.7, 132.4, 129.9, 123.3, 118.2, 116.4, 112.6, 112.4, 82.0, 49.2, 43.1, 35.4, 28.1, 25.5; MS (EI) *m/z* (%) 398 (16, M+2), 396 (18, M$^+$), 244 (29), 227 (18), 69 (100).

4.2.10. 6-Amino-8-(4-nitrophenyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6e***. White solid, 85%; m.p. 255−258 ^{o}C: [Found: C, 59.61; H, 3.75; N, 19.40; S, 8.71. $C_{18}H_{13}N_5O_2S$ requires C, 59.49; H, 3.61; N, 19.27; S, 8.82%]; ν_{max} (KBr) 3341, 2212, 1600, 1515 cm^{-1}; δ_H (500 MHz, DMSO-d$_6$) 8.32 (2H, d, *J* 8.5 Hz, Ar), 7.91 (1H, br s, Ar), 7.72 (1H, br s, Ar), 7.55 (2H, s, NH$_2$) 5.95−5.94 (1H, m, =CH), 3.96 (1H, d, *J* 12.0 Hz, CHAr), 3.40 (1H, ddd, *J* 18.5, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.14 (1H, dd, *J* 18.5, 6.0 Hz, =CHCH$_a\underline{H}_b$S), 3.06−3.05 (1H, m, C$\underline{H}$CH$_2$S), 2.23−2.22 (2H, m, CH$_2$S); δ_C (125

MHz, DMSO-d_6) 149.0, 144.6, 142.0, 130.0, 124.8, 118.9, 116.8, 112.8, 112.6, 82.5, 49.6, 43.1, 35.7, 28.4, 25.8; MS (EI) *m/z* (%) 363 (100, M^+), 336 (35), 305 (75), 115 (38), 91 (45).

4.2.11. 6-Amino-8-(4-cyanophenyl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6f***. White solid, 77%; m.p. 292−295 °C: [Found: C, 66.39; H, 3.92; N, 20.50; S, 9.27. $C_{19}H_{13}N_5S$ requires C, 66.45; H, 3.82; N, 20.39; S, 9.34%]; ν_{max} (KBr) 3394, 2231, 2210, 1655, 1601 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.96 (2H, d, *J* 8.5 Hz, Ar), 7.85 (1H, ap s, Ar), 7.65 (1H, ap s, Ar), 7.54 (2H, br s, NH_2), 5.94−5.93 (1H, m, =CH), 3.87 (1H, d, *J* 12.0 Hz, CHAr), 3.40 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.13 (1H, dd, *J* 18.0, 6.0 Hz, =CHCH$_a\underline{H}_b$S), 3.04−3.02 (1H, m, C$\underline{H}$CH$_2$S), 2.22−2.20 (2H, m, CH$_2$S); δ_C (125 MHz, DMSO-d_6) 144.6, 140.1, 133.7, 130.1, 119.2, 118.8, 116.8, 113.1, 112.8, 112.6, 82.5, 49.9, 43.1, 35.6, 28.4, 25.8,; MS (EI) *m/z* (%) 343 (11, M^+), 227 (10), 140 (18), 115 (33), 43 (100).

4.2.12. 6-Amino-8-(furan-2-yl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6i***. White solid, 80%; m.p. 243−246 °C: [Found: C, 62.23; H, 3.99; N, 18.09; S, 10.55. $C_{16}H_{12}N_4OS$ requires C, 62.32; H, 3.92; N, 18.17; S, 10.40%]; ν_{max} (KBr) 3341, 2212, 1644, 1602 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.79 (1H, d, *J* 1.5 Hz, Ar), 7.50 (2H, s, NH_2), 6.58 (1H, d, *J* 3.0 Hz, Ar), 6.52 (1H, dd, *J* 3.0, 1.5 Hz, Ar), 5.87−5.85 (1H, m, =CH), 3.93 (1H, d, *J* 12.0 Hz, CHAr), 3.42 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.12 (1H, dd, *J* 18.0, 6.0 Hz, =CHCH$_a\underline{H}_b$S), 2.88−2.84 (1H, m, C$\underline{H}$CH$_2$S), 2.35 (1H, dd, *J* 13.0, 11.0 Hz, CHC$\underline{H}_a$H$_b$S), 2.10 (1H, dd, *J* 13.0, 4.0 Hz, CHCH$_a\underline{H}_b$S); δ_C (125 MHz, DMSO-d_6) 148.4, 145.6, 144.7, 129.9, 118.2, 116.7, 113.0, 112.9, 112.8, 111.7, 82.2, 45.3, 42.0, 36.3, 28.0, 25.8; MS (EI) *m/z* (%) 308 (100, M^+), 261 (36), 233 (44), 195 (20).

4.2.13. 6-Amino-8-(thiophen-2-yl)-8,8a-dihydro-1H-isothiochromene-5,7,7(3H)-tricarbonitrile ***6j***. White solid, 81%; m.p. 251−254 °C: [Found: C, 59.38; H, 3.89; N, 17.44; S, 19.92. $C_{16}H_{12}N_4S_2$ requires C, 59.23; H, 3.73; N, 17.27; S, 19.77%]; ν_{max} (KBr) 3342, 2213, 1647, 1603 cm^{-1} δ_H (500 MHz, DMSO-d_6) 7.65 (1H, d, *J* 5.0 Hz, Ar), 7.50 (2H, s, NH_2), 7.29 (1H, d, *J* 3.5 Hz, Ar), 7.13 (1H, dd, *J* 5.0, 3.5 Hz, Ar), 5.89−5.88 (1H, m, =CH), 4.12 (1H, d, *J* 12.0 Hz, CHAr), 3.43 (1H, ddd, *J* 18.0, 3.0, 3.0 Hz, =CHC$\underline{H}_a$H$_b$S), 3.13 (1H, dd, *J* 18.0, 6.0 Hz, =CHCH$_a\underline{H}_b$S), 2.80 (1H, ddd, *J* 11.0, 11.0, 1.0 Hz, C$\underline{H}$CH$_2$S), 2.33 (1H, dd, *J* 13.0, 11.0 Hz, CHC$\underline{H}_a$H$_b$S), 2.25 (1H, dd, *J* 4.0, 13.5 Hz, CHCH$_a\underline{H}_b$S); δ_C (125 MHz, DMSO-d_6) 144.8, 136.8, 130.3, 130.1, 128.7, 128.2, 118.4, 116.8, 113.4, 112.8, 82.3, 46.7, 44.2, 38.4, 28.4, 25.9; MS (EI) *m/z* (%) 324 (100, M^+), 291 (20), 277 (40), 123 (55), 97 (92).

4.2.14. 6-Amino-8-(4-methoxyphenyl)-8,8a-dihydro-1H-isochromene-5,7,7(3H)-tricarbonitrile ***7b***. White solid, 87%; m.p. 248−252 °C: [Found: C, 68.81; H, 5.01; N, 16.73. $C_{19}H_{16}N_4O_2$ requires C, 68.66; H, 4.85; N, 16.86%]; ν_{max} (KBr) 3339, 2217, 1645, 1515 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.54 (1H, d, *J* 8.0 Hz, Ar), 7.53 (2H, s, NH_2), 7.27 (1H, d, *J* 8.0 Hz, Ar), 7.02 (1H, d, *J* 8.0 Hz, Ar), 6.94 (1H, d, *J* 8.0 Hz, Ar), 5.65−5.64 (1H, m, =CH), 4.23 (1H, ddd, *J* 17.5, 1.5, 1.5 Hz, =CHC$\underline{H}_a$H$_b$O), 4.07 (1H, ddd, *J* 17.5, 1.5, 1.5 Hz, =CHCH$_a\underline{H}_b$O), 3.75 (3H, s, OMe), 3.55 (1H, d, *J* 12.0 Hz, CHAr), 3.45 (1H, dd, *J* 10.0, 4.0 Hz, CHC$\underline{H}_a$H$_b$O), 2.98−2.94 (1H, m, C$\underline{H}$CH$_2$O), 2.92 (1H, dd, *J* 10.0, 10.0 Hz, CHCH$_a\underline{H}_b$O); δ_C (125 MHz, DMSO-d_6) 160.7, 145.4, 134.2, 128.7, 128.0, 125.8, 118.0, 116.6, 115.4, 114.7, 113.1, 113.0, 80.6, 66.8, 66.2, 56.0, 47.2, 43.9, 33.5; MS (EI) *m/z* (%) 332 (47, M^+), 235 (24), 147 (64), 121 (100).

4.2.15. 6-Amino-8-(4-chlorophenyl)-8,8a-dihydro-1H-isochromene-5,7,7(3H)-tricarbonitrile ***7d***. White solid, 92%; m.p. 271−273 °C: [Found: C, 64.29; H, 3.97; N, 16.54. $C_{18}H_{13}ClN_4O$ requires C, 64.19; H, 3.89; N, 16.64%]; ν_{max} (KBr) 3234, 2233, 1631, 1596 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 7.69 (1H, d, *J* 7.0 Hz, Ar), 7.59 (2H, s, NH_2), 7.55 (1H, d, *J* 7.0 Hz, Ar), 7.50 (1H, d, *J* 7.0 Hz, Ar), 7.40 (1H, d, *J* 7.0 Hz, Ar), 5.71−5.68 (1H, m, =CH), 4.24 (1H, dd, *J* 17.5, 1.5 Hz, =CHC$\underline{H}_a$H$_b$O), 4.09 (1H, dd, *J* 17.5, 1.5 Hz, =CHCH$_a\underline{H}_b$O), 3.73 (1H, d, *J* 13.0 Hz, CHAr), 3.45 (1H, dd, *J* 5.0, 11.0 Hz, CHC$\underline{H}_a$H$_b$O), 3.04−3.02 (1H, m, C$\underline{H}$CH$_2$O), 2.94 (1H, dd, *J* 10.5, 9.5 Hz, CHCH$_a\underline{H}_b$O); δ_C (125 MHz, DMSO-d_6) 145.1, 135.1, 133.1, 129.7, 127.7, 118.2, 116.5, 112.9, 112.8, 80.7, 66.6, 66.2, 47.0, 43.4, 33.3; MS (EI) *m/z* (%) 336 (100, M^+), 307 (28), 244 (50), 151 (75), 125 (93).

4.3. General procedure for indirect synthesis of dicyanoanilines

A mixture of **4a** (300 mg, 1.0 mmol) and aqueous NaOH (200 μL, 10% w/v) was sonicated for 150 s until TLC showed completion of the reaction. The product precipitated in the mixture as a yellow solid by adding drops of water to the mixture. The solid was filtered and recrystallized from ethanol to obtain the final product (238 mg, 87%).

4.4. General procedure for direct synthesis of dicyanoanilines

A mixture of **1a** (103.5 μL, 1.0 mmol), malononitrile (132 mg, 2.0 mmol), benzaldehyde (102 μL, 1.0 mmol) and NaOH (200 μL, 10% w/v) in water (2.0 mL) was sonicated for 90 s until TLC showed completion of the reaction. The product precipitated in the mixture as a yellow solid. The solid was filtered and recrystallized from ethanol to obtain the final product (246 mg, 90%).

4.5. Crystal structure of ***6e***

Single Crystals of compound **6e** suitable for SCXRD measurement were grown by slow evaporation of an MeCN/MeOH solution. The unit cell dimensions were determined from 1500 reflections. The structure was solved by direct method and refined by full matrix least-squares calculations based on F^2 to final R1 = 0.032 and wR2 (all data) = 0.064, using SHELXL-2014 and WinGX-2013.3 programs.[26] Compound is crystallized at Monoclinic system and P21/c Space group. One independent molecules with molecular formula of $C_{20}H_{16}N_6O_2S$ and a molecule of solvent (MeCN) were found in the asymmetric unit giving a total Z=4 for the unit cell; *a* = 13.856(3), *b* = 9.059(1), *c* = 15.837(3), beta= 94.91(3), cell volume V= 1980.7(7)Å^3, crystal dimensions: 0.6 × 0.5 × 0.2 mm, measurement range: 2.58 <Θ<24.99, 3480 independent reflections and max/min residual electron density [e Å^3].: 0.11/ -0.16. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. A view of the structure is depicted in Figure 2 (top). As it revealed by X-ray crystallography,[27] solid state structure of compound **6e** exhibits an interesting twofold R2,2(12) intermolecular hydrogen-bonding motif [(N2-H5⋯N1_$4 d(D⋯A = 3.084(3)Å and < DHA=162.4°(5)] locking two molecules of the compound around a lattice center of symmetry Figure 2 (bottom). The crystal structure of **6e** reveals another hydrogen bonding between the nitrogen atom of a solvent molecule (acetonitrile) and the amino hydrogen atom [(N2-H4...N6_$3 d(D⋯A = 3.019(3) Å and < DHA= 159.4°(5)] in an intermolecular fashion.

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23. Solvent molecule is omitted for clarity. Selected bond lengths [Å] and angles [°]:C5-S1 1.798(2), C1-S1 1.797(2), C11-N4 1.134(2), C9-C10 1.490(3), C2-C1-S1 112.77(14), N2-C8-C9 115.47(16). (bottom) Depiction of an intercellular R2,2(12) hydrogen-bonding with [(N2-H5···N1_$4 d(D···A = 3.084(3)Å and < DHA = 162.4°(5)]. The dark spot in the middle of the motif indicates the location of a lattice center of symmetry. $4 is generated by -x, -y, -z.
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27. CCDC-1431272 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Supplementary data (copies of ^{1}H and ^{13}C NMR spectra for all new products) associated with this article can be found in the online version, at …

- *Ortho*-aminocarbonitriles are synthesized efficiently by ultrasound irradiation.
- Products based on various heterocyclic ketones are synthesized.
- Reactions rapidly give the corresponding products.
- *Ortho*-aminocarbonitriles give dicyanoanilines in direct or stepwise modes.