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Ultrasound promoted synthesis of some novel fused pyrans

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ABSTRACT

Novel fused pyrans were synthesized from the reaction of the tetrahydropyran-4-one with arylidine malononitriles. Different fused pyran derivatives were obtained from the mentioned reaction depending on type of catalyst used and type of energy used. Reactions were carried out under silent and ultrasonic conditions. In general, it was found that sometimes ultrasound irradiations change the reaction path in comparing with silent condition. In addition to improvement in reaction times, the products were obtained in high yields and their structures were determined by elemental analyses, spectral data.

1. Introduction

The pyran ring system and fused pyrans are widely present in the animal and plant kingdom, they possess diverse pharmacological activities [1–5], like cromakalim (Fig. 1), which is pyran derivative used to treat hypertension as it will relax vascular smooth muscle to lower blood pressure [6,7].

Pyrano pyran presents in many natural marine products such as brevetoxin B (Fig. 2) [8,9], which contains repeating units of the pyrano[3,2-*b*]pyran ring system (shown in red,[1] Fig. 2).

In addition, the presence of pyranopyridine scaffold in the frame work of several biologically active naturally occurring alkaloids of plant origin [10–12] has enthused researchers to synthesize and study their potential biological activities. They are known to possess antiallergic, anti-inflammatory, and estrogenic properties [13,14].

The structural complexity of natural products, such as intricate ring systems and numerous chiral centers, may lead to limited supplies and hamper mechanism of action studies and clinical development [15]. For this reason, structural simplification of natural products is a powerful and highly productive tool for lead development and analog design [16].

In the last few years, the application of ultrasound in synthetic organic chemistry became more and more interesting. "Sonochemistry" is a new trend in organic chemistry, offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation in high yields, short reaction times and mild conditions [17–21].

Motivated by the afore-mentioned findings, and in a continuation of our interest in synthesis of a wide range of heterocyclic systems, for biological screening programme in our laboratory [22–27], and as a part of our growing interest in sonochemistry [28–31]. We describe here a facile sonochemical synthesis of some novel fused pyrans.

2. Results and discussion

The reaction of tetrahydropyran-4-one (**1**) with arylidine malononitrile derivatives (**2a–c**) in ethanol in presence of catalytic amount of piperidine under ultrasonic irradiation at room temperature afforded a product in each time identified as isochromene derivatives in good yields and shorter reaction time in comparing with conventional condition (silent reactions), the products formed may be formulated as (**6a–c**) or its isomer (**7a–c**) (Scheme 1).

Each steroisomers **6** or **7** present as pair of enantiomers as in Fig. 3, a pair of enantiomers **6a–c** was formed [(8*R*, 8a*S*) and (8*S*, 8a*R*)]. The obtained spectra do not show any hints for diastereomeric

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[1] For interpretation of color in Fig. 2, the reader is referred to the web version of this article.

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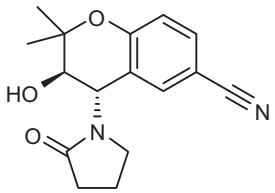


Fig. 1. Structure of cromakalim.

pair of enantiomers **7a–c** (8*R*) and (8*S*). The ^{1}H NMR of the formed product show that the hydrogen atoms on C-8 and C-8a are *trans* and have both *axial* position (J = 12.3 Hz). Thus the structure **7a–c** was easily ruled out on basis of spectral data.

All efforts to separate the mixture of two enantiomers $\mathbf{6_A}$ and $\mathbf{6_B}$ by chromatographic methods failed due to their equal R_f values.

Moreover, structure **6** seems more likely based on its similarity to the well established behavior of cyclic ketones towards arylidine-malononitrile derivatives as reported previously [32,33].

The structures of compounds **6a–c** were established on the basis of their elemental analyses and spectral data. The IR spectrum revealed the absence of any band due to carbonyl function, in addition to appearance of absorption bands of amino group in the region 3380–3249 cm^{-1} and absorption band of cyano groups in the region 2224–2215 cm^{-1}. Taken compound **6b** as representative example, its mass spectrum revealed a molecular ion peak at m/z 327. The nature of these compounds makes the proton NMR study particularly interesting due to the non-equivalence of the methylene protons. H_a and H_b appear as two doublets of doublets with different chemical shifts. The shift at down field can be assigned to the proton H_a. The proton H_c appears as doublet of triplets, due to its coupling with the protons H_a, H_b, and H_d was located upfield. The proton H_d is coupled with H_c to form a doublet at lower field to H_c [34]. Time of reaction and yields are shown in Table 1.

Table 1 shows that ultrasound technique reduced the time of reactions from several hours to minutes and improved the yields from 52–56% (under conventional conditions) to 82–87%.

The formation of the products **6a–c** is assumed to take place *via* first condensation of tetrahydropyran-4-one with malononitrile, produced as result of hydrolysis of **2** to yield **3** (This observation is further evidenced for the existence of **1** in its solutions in equilibrium with its constituents as has been suggested earlier [35]), which on reaction with further molecule of **2** gives products **6a–c** *via* an initial Michael adduct **4** followed by an intermolecular cyclization (intermediate **5**) and subsequent tautomerism to be the final product (Scheme 1).

A further evidence for the formation of the products **6a–c** with above mechanism stems from the synthesis of the same products **6a–c** by condensing **1** with malononitrile to afford **3** [36] which reacted with **2a–c** to afford products identical in all respects (m.p., mixed m.p. and IR) with those corresponding **6** (Scheme 2).

In contrast to the above mentioned behavior, when we doing the reaction of tetrahydropyran-4-one (**1**) with arylidine malononitrile derivatives **2a–c** in ethanol in presence of 2–3 drops of 5% sodium hydroxide solution as catalyst instead of piperdine under both ultrasonic irradiation at room temperature or conventional condition (reflux) as shown in Scheme 3. There is only one isolable product formed in each case (as examined by TLC) but it was found that the product formed under conventional condition differing from that formed under ultrasonic irradiation.

The product formed under conventional condition identified as 2-amino-4-aryl-4,5,7,8-tetrahydropyrano[4,3-b]pyran-3-carbonitrile **8a–c**. The structure of compounds **8a–c** was established on the basis of their elemental analyses and spectral data. For example its mass spectrum of compound **8a** revealed a molecular ion peak at m/z 254, IR spectrum of the compound **8a** revealed no carbonyl absorption band, two absorption bands at 3350, 3249 cm^{-1} due to amino group, one absorption band at 2213 cm^{-1} due to cyano group. Its ^{1}H NMR revealed the presence of two triplet signals due to two adjacent methylene group at 2.71, 3.04 and two singlet signals at δ 4.00 and 4.15 due to CH_2, CH, respectively, a D_2O exchangeable proton due to NH_2 group in addition to multiplet due to aromatic protons. Formation of the products **8a–c** may proceed *via* cyclization of intermediate A (Scheme 3).

On the other hand, the products formed under ultrasonic condition from the same reaction identified as 4-amino-3,3-dicyano-2,5-diaryl-2,3,5,6,8,9-hexahydropyrano[3″,4″:5′,6′]pyrano[2,3-b]pyridine **10a–c**. The ^{1}H NMR of the products **10a–c** revealed three singlet signals due to methylene group of pyran, CH (pyran) and CH (pyridine), respectively, and that two triplet signals due to two adjacent methylene group, a D_2O exchangeable proton due to NH_2 group in addition to multiplet due to aromatic protons (*cf.* Section 4). The latter spectroscopic data of the reaction products formed under ultrasonic irradiation and their satisfactory elemental analyses supported the structure **10a–c** as postulated in Scheme 3 which suggest the reaction proceed *via* formation of 1:2 adduct. Although the latter spectral data fits better structure **10**, an independent chemical proof seemed mandatory. Thus, compound **8a** on reaction with further one molecule of **2a** in ethanol and catalytic amount of piperidine under ultrasonic irradiation, gave the 1:2 adduct product **10a** in 52% yield. A plausible mechanism for the formation of compound **10a–c** is outlined in Scheme 3. Compound **10a–c** are formed *via* initial Michael adduct **9a–c** followed by intramolecular cyclization. It is obvious that in this reaction, ultrasonic change path of reaction in comparing with conventional condition.

Also, we extended the study to find out the reactivity tetrahydropyran-4-one (**1**) with arylidine malononitrile derivatives **2a–c** in ethanol in presence of ammonium acetate under both ultrasonic irradiation at room temperature or conventional condition (reflux) only one product obtained in each time (as evidenced by TLC) identified as 2-amino-4-aryl-7,8-dihydro-5*H*-pyrano[4,3-b]pyridine-3-carbonitrile **14a–c** in excellent yields and shorter reaction time under ultrasonic irradiation in comparing with conventional condition (silent reactions) Scheme 4.

The isolated products **14a–c** gave satisfactory elemental analyses and spectroscopic data (IR, ^{1}H NMR, MS) consistent with their assigned structures for example its IR spectra of the **14a** revealed no absorption bands due to carbonyl group and two absorption bands at 3219, 3158 due to amino group and a band at 2214 due to cyano group. Their ^{1}H NMR of the same compound revealed the presence of two triplet signals due to two adjacent methylene group at 2.71, 3.04 and two singlet signals at δ 3.65, 5.57 due to methylene group and a D_2O exchangeable proton due to NH_2 group respectively in addition to multiplet due to aromatic protons.

The formation of pyrano[4,3-b]pyridine derivatives **14a–c** from the reaction of tetrahydropyran-4-one (**1**) with arylidine malononitrile derivatives **2a–c** seems to follow the sequence outlined in Scheme 4, which shows that the reaction starts with initial Michael addition to form Michael adduct **11** followed by intramolecular cyclization and spontaneous autooxidation (intermediates **12** and **13**) to give pyrano[4,3-b]pyridine derivatives **14a–c** as end products.

Table 2 shows that ultrasound technique reduced the time of reactions from several hours to minutes and improved the yields from 79–83% (under conventional conditions) to 90–95%.

Generally, ultrasound showed beneficial effect on synthesis of some novel fused pyrans in which decreases time of the above reaction from several hours in conventional procedure to few minutes with high yield under ultrasound irradiation. The improvement induced by ultrasound can be attributed to the well established theory of ultrasonic irradiation in which it differs from

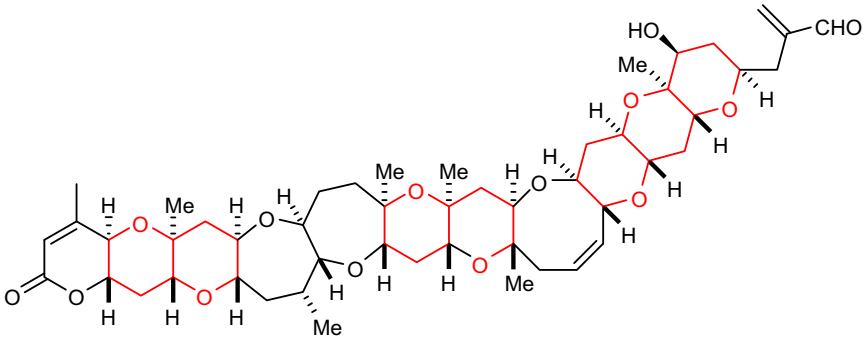


Fig. 2. Structure of brevetoxin B.

Table 1
Synthesis of isochromene derivative **6a–c** under both ultrasonic irradiation and conventional method.

Compound	Ar	Ultrasonic irradiation		Conventional	
		Time (min.)	Yield (%)	Time (h)	Yield (%)
6a	C_6H_5	45	82	9	52
6b	C_6H_4CN-*p*	30	87	6	56
6c	C_6H_4F-*p*	30	85	7	56

traditional energy sources (such as heat) in duration, pressure, and energy per molecule. Because of the immense temperatures and pressures and the extraordinary heating rate generated by cavitation bubble collapse, ultrasound provides an unusual mechanism [37,38] so reaction time decreases clearly and high yield obtained.

In addition, according to sonochemical reactions classification of Luche [39–41], we have both types false and true sonochemistry, in which some of the above mentioned reactions are considered false sonochemistry type in which cavitation effect provides the mechanical energy for all subsequent chemical reactions, including bond scission induced by viscous frictional forces and same products produced under both silent and ultrasonic conditions, and the other mentioned reactions considered true sonochemistry type which occur due to the effects derived directly from the "hotspots" of cavitational collapse energy, which cause in our case what is called "sonochemical switching" means the products obtained under conventional conditions are different from those obtained under the influence of ultrasound [41].

3. Conclusion

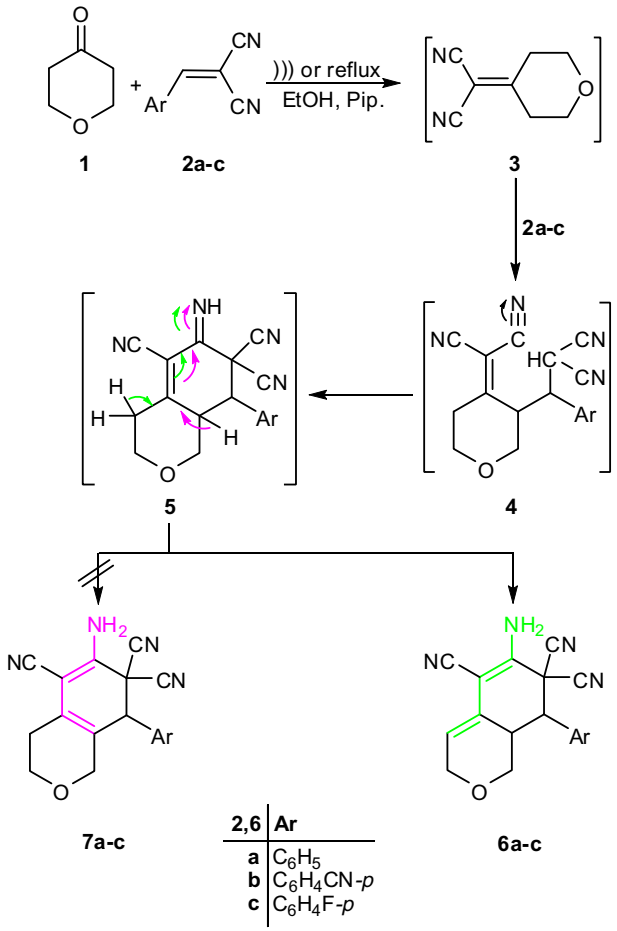
Tetrahydropyran-4-one was found to be a good precursor for synthesis of novel fused pyrans in reaction with arylidine malononitriles which afforded of isochromene, tetrahydropyrano [4,3-b]pyran, hexahydro-pyrano[3″,4″:5′,6′]pyrano[2,3-b]pyridine and pyrano[4,3-b]pyridine derivatives respectively depending on type of catalyst used and type of energy used for this reaction. Moreover, the present work evidences that sometimes ultrasound irradiations change the reaction path in comparing with silent condition. In general, improvements in rates and yield of reactions are observed when reactions were carried out under sonication compared with classical condition.

4. Experimental

4.1. General

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out on Elmentar instrument C, H, N, S analyzer Vario EL III. Sonication was performed by Fischer sonicator (with a frequency of 25 kHz and a nominal power 150 W).

Arylidine malononitriles were prepared according to literature procedure [42].



Scheme 1.

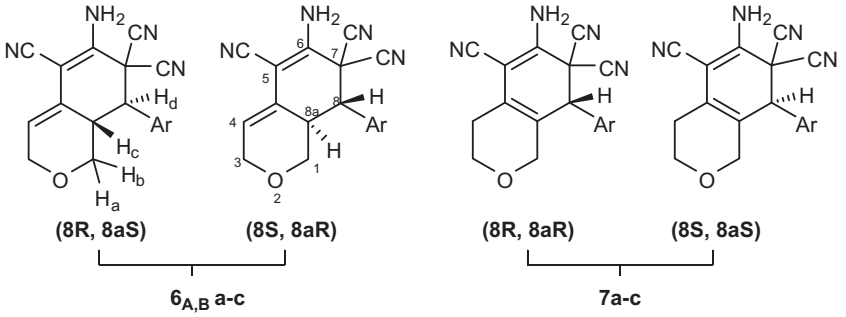


Fig. 3. Enantiomers of stereoisomer **6** and **7**.

4.2. Typical procedure for the reactions

4.2.1. Synthesis of isochromene derivative ***6a–c***

4.2.1.1. Method A: silent reactions. A mixture of tetrahydropyran-4-one (10 mmol) (**1**) and arylidine malononitrile **2a–c** (10 mmol) was heated under reflux in 25 mL ethanol in the presence of catalytic amount of piperidine for a suitable time (untill disappearance of starting materials as examined by TLC). The crude product, soformed, was collected by filtration and recrystallized from ethanol to afford the corresponding 6-amino-8-aryl-*1H*-isochromene-5,7,7(3*H*,8*H*,8a*H*)-tricarbonitrile (**6$_{A,B}$a–c**).

4.2.1.2. Method B: sonicated reactions. To a solution of tetrahydropyran-4-one (10 mmol) (**1**) in ethanol (20 mL), and the appropriate arylidine malononitrile **2a–c** (10 mmol), catalytic amount of piperidine (3–4 drops) were added in 50 mL Erlenmeyer flask. The mixture was subjected to ultrasound irradiation for suitable time (*cf.* Table 1) until the starting materials were no longer detectable by TLC. All The reactions were kept at room temperature 25–30 °C which attained by addition or removal of water in ultrasonic bath (the temperature inside reaction vessel was 28–30 °C). The precipitate was filtered off, washed with ethanol and recrystallized from ethanol to afford the corresponding 6-amino-8-aryl-*1H*-isochromene-5,7,7(3*H*,8*H*,8a*H*)-tricarbonitrile (**6$_{A,B}$a–c**).

4.2.1.3. Method C. A mixture of 2-(2*H*-pyran-4(3*H*,5*H*,6*H*)-ylidene)malononitrile (**3**) (10 mmol) and the appropriate arylidine malononitrile **2a–c** (10 mmol) in presence of catalytic amount of piperidine (3–4 drops) in ethanol (20 mL) was heated under reflux condition for 3 h. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure and the formed solid was collected, washed with ethanol and recrystallized from the mixture of ethanol to give the corresponding **6$_{A,B}$a–c**.

4.2.1.4. Method D. To a solution of 2-(2*H*-pyran-4(3*H*,5*H*,6*H*)-ylidene)malononitrile (**3**) (10 mmol) in ethanol (20 mL), and the appropriate arylidine malononitrile **2a–c** (10 mmol), catalytic amount of piperidine (3–4 drops) were added in 50 mL Erlenmeyer flask. The mixture was subjected to ultrasound irradiation for 15 min (until the starting materials were no longer detectable by TLC). All The reactions were kept at room temperature 25–30 °C which attained by addition or removal of water in ultrasonic bath (the temperature inside reaction vessel was 28–30 °C). The precipitate was filtered off, washed with ethanol and recrystallized from ethanol to afford the corresponding (**6$_{A,B}$a–c**).

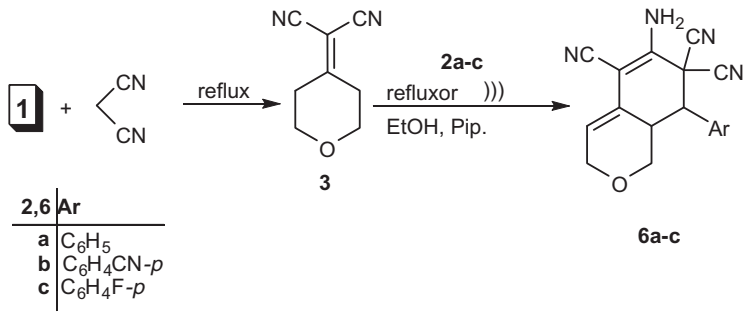
The synthesized compounds (**6$_{A,B}$a–c**) with their physical data are listed below:

6-Amino-8-phenyl-1H-isochromene-5,7,7(3H,8H,8aH)-tri-carbonitrile (***6$_{A,B}$a***)

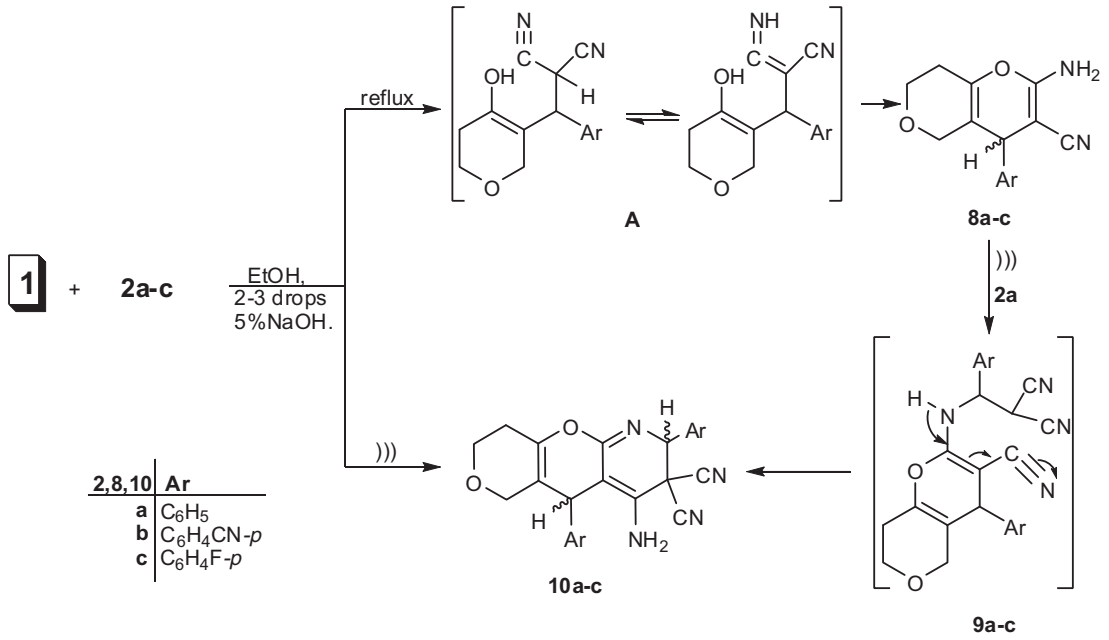
IR (KBr): 3359, 3229 (NH_2), 2254 (C≡N), 2213 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.88 (dt, J_{HcHa} = 10.5 Hz, J_{HcHb} = 4.2 Hz, J_{HcHd} = 12.3 Hz, H_c), 3.03 (dd, J_{HbHa} = 8.8 Hz, J_{HbHc} = 4.2 Hz, H_b), 3.11 (dd, J_{HaHb} = 8.8 Hz, J_{HaHc} = 10.5 Hz, H_a), 3.34 (m, 2H,CH_2), 4.03 (d, J_{HdHc} = 12.3 Hz, H_d), 5.55 (dd, J = 4.3 Hz, J = 3.8 Hz, =CH), 6.55 (s, 2H, NH_2, D_2O exchangeable), 7.32–7.62 (m, 5H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 26.21, 31.58, 36.47, 65.89, 69.98, 88.65, 108.97, 114.52, 118.45, 118.49, 125.06, 127.11, 127.13, 136.95, 147.45, 166.01; MS (*m*/*z*): 302 M^+. (Found: C, 71.73; H, 4.58; N, 18.40. $C_{18}H_{14}N_4O$ requires C, 71.51; H, 4.67; N, 18.53.)

6-Amino-8-(4-cyanophenyl)-1H-isochromene-5,7,7(3H,8H,8aH)-tri-carbonitrile (***6$_{A,B}$b***)

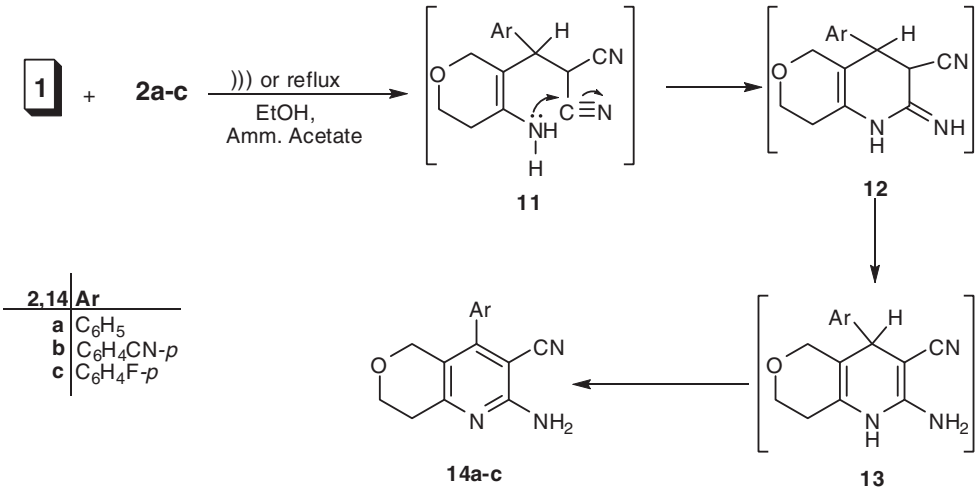
IR (KBr): 3319, 3222 (NH_2), 2249 (C≡N), 2213 (C≡N), 2192 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.74 (dt, J_{HcHa} = 10 Hz, J_{HcHb} = 3.9 Hz, J_{HcHd} = 12.3 Hz, H_c), 3.22(dd, J_{HbHa} = 9.2 Hz, J_{HbHc} = 3.9 Hz, H_b), 3.31 (dd, J_{HaHb} = 9.2 Hz, J_{HaHc} = 10 Hz, H_a), 3.54 (m, 2H,CH_2), 4.22 (d, J_{HdHc} = 12.3 Hz, H_d), 5.16 (dd, J = 4.3 Hz, J = 3.9 Hz, =CH), 6.24 (s, 2H, NH_2, D_2O exchangeable), 7.45–7.89 (m, 4H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 26.87, 32.05, 35.17, 65.87, 68.99, 88.58, 106.54, 109.08, 114.11, 114.52, 118.15, 125.88, 125.95, 132.11, 132.23, 139.87, 146.05, 168.01; MS (*m*/*z*): 327 M^+. (Found: C, 69.82; H, 3.91; N, 21.27. $C_{19}H_{13}N_5O$ requires C, 69.71; H, 4.00; N, 21.93.)



Scheme 2.



Scheme 3.



Scheme 4.

Table 2
Synthesis of pyrano[4,3-b]pyridine derivative **14a–c** under both ultrasonic irradiation and conventional method.

Compound	Ar	Ultrasonic irradiation		Conventional	
		Time (min.)	Yield (%)	Time (h)	Yield (%)
14a	C_6H_5	30	90	9	79
14b	C_6H_4CN-*p*	15	95	5	83
14c	C_6H_4F-*p*	30	95	7	83

*6-Amino-8-(4-florophenyl)-1H-isochromene-5,7,7(3H,8H,8aH)-tri-carbonitrile (**6$_{A,B}$c**)*

IR (KBr): 3374, 3215 (NH_2), 2249 (C≡N), 2217 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.65 (dt, J_{HcHa} = 10.8 Hz, J_{HcHb} = 4.2 Hz, J_{HcHd} = 12.6 Hz, H_c), 3.15 (dd, J_{HbHa} = 9.2 Hz, J_{HbHc} = 4.2 Hz, H_b), 3.28 (dd, J_{HaHb} = 9.2 Hz, J_{HaHc} = 10.8 Hz, H_a), 3.47 (m, 2H, CH_2), 4.36 (d, J_{HdHc} = 12.6 Hz, H_d), 5.27 (dd, *J* = 4.2 Hz, *J* = 3.9 Hz, =CH), 6.16 (s, 2H, NH_2, D_2O exchangeable), 7.26–7.78 (m, 4H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 27.01, 31.98, 35.02, 66.14, 67.87, 88.13, 109.24, 116.11, 116.14, 131.12, 131.19, 134.23, 144.19, 149.85, 168.00; MS (*m*/*z*): 320 M^+. (Found: C, 67.64; H, 4.03; N, 17.40. $C_{18}H_{13}FN_4O$ requires C, 67.49; H, 4.09; N, 17.49.)

*4.2.2. Synthesis of 2-amino-4-aryl-4,5,7,8-tetrahydropyrano[4,3-b] pyran-3-carbonitrile **8a–c***

A mixture of tetrahydropyran-4-one (10 mmol) (**1**) and arylidine malononitrile **2a–c** (10 mmol) was heated under reflux in 25 mL ethanol in the presence of catalytic amount of 5% sodium hydroxide for 10 h (as examined by TLC). The crude product, so-formed, was collected by filtration and recrystallized from ethanol to afford the corresponding 2-amino-4-aryl-4,5,7,8-tetrahydropyrano[4,3-b]pyran-3-carbonitrile **8a–c** in 70–79% yield.

*2-Amino-4-phenyl-4,5,7,8-tetrahydropyrano[4,3-b]pyran-3-carbonitrile (**8a**)*

Yield 70%, m.p. 254 °C; IR (KBr): 3315, 3229 (NH_2), 2219 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.67 (m, 2H, CH_2), 3.65 (m, 2H, CH_2), 3.87 (s, 2H, CH_2), 4.12 (s, 1H,CH), 5.55 (s, 2H, NH_2, D_2O exchangeable), 6.89–7.33 (m, 5H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 26.44, 38.21, 55.32, 63.44, 65.89, 104.87, 116.25, 121.08, 124.58, 124.89, 126.55, 126.97, 138.95, 140.25, 155.29; MS (*m*/*z*): 254 M^+. (Found: C, 70.62; H, 5.42; N, 10.90. $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.02.)

*2-Amino-4-(4-cyanophenyl)-4,5,7,8-tetrahydropyrano[4,3-b]pyran-3-carbonitrile (**8b**)*

Yield 79%, m.p. 280–282 °C; IR (KBr): 3342, 3216 (NH_2), 2226 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.57 (m, 2H, CH_2), 3.45 (m, 2H, CH_2), 3.77 (s, 2H, CH_2), 4.39 (s, 1H,CH), 5.94 (s, 2H, NH_2, D_2O exchangeable), 7.22–7.79 (m, 4H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 25.98, 37.59, 54.28, 63.23, 65.87, 103.52, 108.27, 116.54, 120.00, 125.47, 126.48, 126.55, 132.01, 140.57, 143.12, 157.89; MS (*m*/*z*): 279 M^+. (Found: C, 68.56; H, 4.59; N, 14.90. $C_{16}H_{13}N_3O_2$ requires C, 68.81; H, 4.69; N, 15.05.)

*2-Amino-4-(4-florophenyl)-4,5,7,8-tetrahydropyrano[4,3-b]pyran-3-carbonitrile (**8c**)*

Yield 76%, m.p. 272 °C; IR (KBr): 3342, 3218 (NH_2), 2212 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.56 (m, 2H, CH_2), 3.54 (m, 2H, CH_2), 3.91 (s, 2H, CH_2), 4.59 (s, 1H,CH), 6.01 (s, 2H, NH_2, D_2O exchangeable), 6.92–7.48 (m, 4H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 25.97, 36.78, 52.19, 63.44, 65.49, 105.11, 115.14, 120.08, 129.54, 129.84, 138.00, 142.14, 154.23, 155.10; MS (*m*/*z*): 272 M^+. (Found: C, 66.42; H, 4.66; N, 10.19. $C_{15}H_{13}FN_2O_2$ requires C, 66.17; H, 4.81; N, 10.29.)

4.2.3. Synthesis of 4-amino-3,3-dicyano-2,5-diaryl-2,3,5,6,8,9-hexahydropyrano [3″,4″:5′,6′] pyrano[2,3-b]pyridine **10a–c**

4.2.3.1. Method A: sonicated reactions. To a solution of tetrahydropyran-4-one (10 mmol) (**1**) in ethanol (20 mL), and the appropriate arylidine malononitrile **2a–c** (10 mmol), catalytic amount of 5% sodium hydroxide (0.25 mL) were added in 50 mL Erlenmeyer flask. The mixture was subjected to ultrasound irradiation for 30 min until the starting materials were no longer detectable by TLC. All the reactions were kept at room temperature 25–30 °C which attained by addition or removal of water in ultrasonic bath (the temperature inside reaction vessel was 28–30 °C). The precipitate was filtered off, washed with ethanol and recrystallized from ethanol/DMF (3:1) to afford the corresponding 4-amino-3,3-dicyano-2,5-diaryl-2,3,5,6,8,9-hexahydro-pyrano[3″,4″:5′,6′]pyrano [2,3-b]pyridine **10a–c** in 45–52% yield.

4.2.3.2. Method B. To a solution of 2-amino-4-phenyl-4,5,7,8-tetrahydropyrano[4,3-b]pyran-3-carbonitrile **8a** (10 mmol) in ethanol (25 mL), and the appropriate benzylidine malononitrile **2a** (10 mmol), catalytic amount of 5% sodium hydroxide (0.25 mL) were added in 50 mL Erlenmeyer flask. The mixture was subjected to ultrasound irradiation for 15 min (until the starting materials were no longer detectable by TLC). All the reactions were kept at room temperature 25–30 °C bath (the temperature inside reaction vessel was 28–30 °C). The precipitate was filtered off, washed with ethanol and recrystallized from ethanol/DMF to afford the corresponding **10a**.

*4-Amino-3,3-dicyano-2,5-diphenyl-2,3,5,6,8,9-hexahydropyrano [3″,4″:5′,6′] pyrano[2,3-b]pyridine (**10a**)*

Yield 49%; IR (KBr): 3312, 3190 (NH_2), 2195 (C≡N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.75 (t, J = 5.1 Hz, 2H, CH_2), 3.64 (t, J = 5.1 Hz, 2H, CH_2), 3.89 (s, 2H, CH_2), 4.59 (s,1H,CH), 4.87 (s,1H,CH), 6.00 (s, 2H, NH_2, D_2O exchangeable), 7.02–7.91 (m, 10H, ArH's); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 25.69, 29.54, 42.01, 53.14, 63.85, 65.44, 102.11, 105.53, 118.25, 123.41, 123.65, 126.02, 126.13, 127.11, 140.89, 145.84, 159.41, 165.08, 169.10; MS (*m*/*z*): 408 M^+. (Found: C, 73.77; H, 4.83; N, 13.57. $C_{25}H_{20}N_4O_2$ requires C, 73.51; H, 4.94; N, 13.72.)

*4-Amino-3,3-dicyano-2,5-di(4-cyanophenyl)-2,3,5,6,8,9-hexahydropyrano[3″,4″:5′,6′]pyrano[2,3-b]pyridine (**10b**)*

Yield 55%; IR (KBr): 3298, 3162 (NH_2), 2198 (C≡N), 2113(C≡N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.52 (t, J = 4.5 Hz, 2H, CH_2), 3.88 (t, J = 4.5 Hz, 2H, CH_2), 4.08 (s, 2H, CH_2), 4.65 (s,1H,CH), 4.92 (s,1H,CH), 5.89 (s, 2H, NH_2, D_2O exchangeable), 7.12–7.91 (m, 8H, ArH's); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 24.09, 27.47, 40.89, 51.85, 63.84, 66.00, 103.12, 106.01, 114.49, 119.00, 121.11, 122.01, 126.56, 126.98, 129.17, 129.23, 131.47, 131.99, 142.58, 145.78, 154.23, 162.00, 167.85; MS (*m*/*z*): 458 M^+. (Found: C, 71.01; H, 3.83; N, 18.18. $C_{27}H_{18}N_6O_2$ requires C, 70.73; H, 3.96; N, 18.33.)

*4-Amino-3,3-dicyano-2,5-di(4-flurophenyl)-2,3,5,6,8,9-hexahydropyrano [3″,4″:5′,6′] pyrano[2,3-b]pyridine (**16a**)*

Yield 52%; IR (KBr): 3313, 3189 (NH_2), 2208 (C≡N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.79 (t, J = 5.1 Hz, 2H, CH_2), 3.59 (t, J = 5.1 Hz, 2H, CH_2), 4.02 (s, 2H, CH_2), 4.89 (s,1H,CH), 5.14 (s,1H,CH), 6.24 (s, 2H, NH_2, D_2O exchangeable), 7.19–8.06 (m, 8H, ArH's); ^{13}C NMR (75.46 MHz, DMSO-d_6) δ: 24.54, 29.04, 41.98, 49.28, 63.54, 66.00, 103.44, 105.01, 116.45, 116.89, 119.25, 119.48, 120.01, 127.15, 127.59, 131.45, 131.56, 139.02, 141.08, 155.12, 159.49, 166.74, 167.89; MS (*m*/*z*): 444 M^+. (Found: C, 67.85; H, 3.95; N, 12.46. $C_{25}H_{18}FN_4O_2$ requires C, 67.56; H, 4.08; N, 12.61.)

4.2.4. Synthesis of 2-amino-4-aryl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile **14a–c**

4.2.4.1. Method A: silent reactions. A mixture of tetrahydropyran-4-one (10 mmol) (**1**) and arylidine malononitrile **2a–c** (10 mmol) in 30 mL absolute ethanol containing excess amount of ammonium acetate was heated under reflux for suitable time (as examined by TLC) (*cf.* Table 2). The crude product, so-formed, was collected by filtration and recrystallized from ethanol/DMF to afford the corresponding 2-amino-4-aryl-7,8-dihydro-5*H*-pyrano[4,3-b]pyridine-3-carbonitrile (**14a–c**).

4.2.4.2. Method B: sonicated reactions. To a solution of tetrahydropyran-4-one (10 mmol) (**1**) in absolute ethanol (30 mL), and the appropriate arylidine malononitrile **2a–c** (10 mmol), excess amount of ammonium acetate (25 mmol) was added in 50 mL Erlenmeyer flask. The mixture was subjected to ultrasound irradiation for suitable time (*cf.* Table 2) at room temperature (the temperature inside reaction vessel was 28–30 °C), until the starting materials were no longer detectable by TLC. All the reactions were kept at room temperature 25–30 °C which attained by addition or removal of water in ultrasonic bath. The precipitate formed was filtered off, washed with ethanol and recrystallized from ethanol/DMF to afford the corresponding 2-amino-4-aryl-7,8-dihydro-5*H*-pyrano[4,3-b]pyridine-3-carbonitrile (**14a–c**).

*2-Amino-4-phenyl-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (**14a**)*

Yield 90%, m.p. 225 °C; IR (KBr): 3219, 3158 (NH_2), 2214 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.78 (t, J = 4.2, 2H, CH_2), 3.21 (t, J = 4.2, 2H, CH_2), 3.65 (s, 2H, CH_2), 5.57 (s, 2H, NH_2, D_2O exchangeable), 7.12–7.58 (m, 5H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 26.78, 54.87, 57.47, 79.25, 111.54, 116.00, 125.14, 125.26, 129.25,129.47,131.78, 152.31, 159.45, 163.20; MS (*m*/*z*): 251 M^+. (Found: C, 71.96; H, 5.11; N, 16.56. $C_{15}H_{13}N_3O$ requires C, 71.70; H, 5.21; N, 16.72.)

*2-Amino-4-(4-cyanophenyl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (**14b**)*

Yield 95%, m.p. 254 °C; IR (KBr): 3358, 3210 (NH_2), 2249 (C≡N), 2212 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.83 (t, J = 4.8, 2H, CH_2), 3.19 (t, J = 4.8, 2H, CH_2), 3.55 (s, 2H, CH_2), 5.48 (s, 2H, NH_2,

D_2O exchangeable), 7.22–7.33 (m, 4H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 28.36, 58.22, 60.21, 77.25, 111.89, 113.25 116.10, 117.85, 126.87, 130.02, 130.54, 135.09, 150.01, 157.45, 161.12; MS (*m*/*z*): 276 M^+. (Found: C, 69.78; H, 4.26; N, 20.12. $C_{16}H_{12}N_4O$ requires C, 69.55; H, 4.38; N, 20.28.)

*2-Amino-4-(4-flurophenyl)-7,8-dihydro-5H-pyrano[4,3-b]pyridine-3-carbonitrile (**14c**)*

Yield 95%, m.p. 229–231 °C; IR (KBr): 3392, 3257 (NH_2), 2221 (C≡N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.58 (t, J = 4.2, 2H, CH_2), 3.02 (t, J = 4.2, 2H, CH_2), 3.36 (s, 2H, CH_2), 6.01 (s, 2H, NH_2, D_2O exchangeable), 7.23–7.39 (m, 4H, ArH's); ^{13}C NMR (75.46 MHz, $CDCl_3$) δ: 30.25, 58.00, 59.98, 81.28, 112.25, 116.00, 116.09, 117.89, 125.80, 130.55, 130.62, 151.24, 158.00, 161.87, 166.19; MS (*m*/*z*): 269 M^+. (Found: C, 67.16; H, 4.39; N, 15.44. $C_{15}H_{12}FN_3O$ requires C, 66.90; H, 4.49; N, 15.60.)

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