Facile one-pot synthesis of novel dicyanoanilines fused to tetrahydro-4H-thiopyran-4-one ring via Et$_3$N/H$_2$O catalyzed pseudo four-component reaction

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Dedicated to Professor MM Heravi

ABSTRACT

A facile procedure is developed for one-pot synthesis of a new group of dicyanoanilines. Tetrahydro-4H-thiopyran-4-one, 1, undergoes a pseudo four-component reaction with various aldehydes bearing different groups and two equivalents of malononitrile in aqueous media in the presence of triethylamine (Et$_3$N). As a result, novel thiopyran-fused dicyanoanilines 4 are formed efficiently in the reaction mixtures in 90–97% yield within 9–12 h mixing at 40°C. Due to the polarity of the medium, products precipitate in the mixture spontaneously allowing for easy purification by recrystallization avoiding cumbersome chromatographic separations. Characterization of the products was performed by spectroscopic methods and, in one case, was further supported by X-ray crystallographic experiments.

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1. Introduction

Multicomponent reactions (MCRs) are among the most practiced strategies to combine several reactants in a single operation and directly access diverse libraries of products. [1–3] Dicyanoanilines constitute an important group of acceptor–donor–acceptor (A–D–A) species and the best methods for their synthesis go through MCR routes [4,5] proceeding
more efficiently than the available stepwise protocols.[6–8] In addition, optical studies show that dicyanoanilines possess fluorescence activity with high quantum yields.[9,10] These features make the synthesis of dicyanoanilines very attractive to organic chemists and consequently several methods are introduced in recent years for the synthesis of different groups of dicyanoanilines.[11–16]

Tetrahydro-4H-thiopyran-4-one 1 is a key structure among the sulfur-containing heterocycles.[17] Moreover, 1 is a versatile building block for the synthesis of other heterocycles [18] and complex molecules.[19] Thus, it is always interesting to develop new methods to access various molecules containing the thiopyran unit in their structures.

In the framework of our studies in heterocyclic chemistry,[20,21] we have demonstrated the application of 1 in Mannich reaction,[22] Diels–Alder cycloaddition,[23] aldol condensation,[24,25] and Baylis–Hillman reactions.[26] On this track, we would like to introduce a general and facile method for the one-pot reactions of 1 with aldehydes 2 and malononitrile 3. This versatility is due to the fact that 3 is a very useful participant in MCRs because of having reactive methylene and cyano functionalities.[27] As a result, convenient pseudo four-component synthesis of novel thiopyran-fused dicyanoanilines 4 is achieved (Scheme 1). Due to the presence of the A–D–A functionalities in the structures of 4, the products are expected to demonstrate fluorescence activity, and could be explored in continuation of our studies for this feature in the near future. Although few reports exist on the synthesis of dicyanoanilines involving benzothiopyran ketone,[28,29] to the best of our knowledge the present report is the first work on the synthesis of isothiochroman derivatives starting from tetrahydro-4H-thiopyran-4-one 1.

2. Results and discussion

The process was optimized by evaluating the combination of 1 with benzaldehyde 2a and 3 under various conditions (Table 1). In a H2O/Et3N medium, a 1.0:1.0:2.0 mixture of

\[ \text{Scheme 1. One-pot synthesis of 4.} \]
the reactants gave \( 4a \) in 95% yield after 10 h at 40°C (Entry 1). Without the amine (Entry 2) or water (Entry 3), reaction either halted completely or proceeded with much lower efficiency after the same time period. At room temperature (Entry 4), the process gave

| Entry | Aldehyde | Product | Yield (%)\textsuperscript{a} |
|-------|----------|---------|-----------------------------|
| 1     |          | ![Structure 4a](image) | 95                          |
| 2     |          | ![Structure 4b](image) | 94                          |
| 3     |          | ![Structure 4c](image) | 91                          |
| 4     |          | ![Structure 4d](image) | 90                          |
| 5     |          | ![Structure 4e](image) | 96                          |
| 6     |          | ![Structure 4f](image) | 97                          |

(continued).
Table 2. Continued.

| Entry | Aldehyde | Product | Yield (%)$^a$ |
|-------|----------|---------|--------------|
| 7     |          | ![Image](image1.png) | 90           |
| 8     | ![Image](image2.png) | ![Image](image3.png) | 91           |

$^a$Isolated yield.

lower quantities of 4a after 24 h. Alternatively, use of less equivalents of the amine did not cause the completion of the reaction after the same time period (Entries 5–7). This was also the case when Et$_3$N was replaced with other amines (Entries 8–9).

The best conditions (Table 1, Entry 1, synthesis of 4a) were used to evaluate the generality of the method by examining the reactions of 1 with other aldehydes (Table 2). Consequently, in addition to the model reaction (Entry 1), combination of 1 and 3 with electron releasing- (Entries 2–4) and electron-withdrawing aldehydes (Entries 5–6) produced more than 90% of the respective products within 9–12 h time period. This was also the case for thiophene-2-carbaldehyde (Entry 7) and formaldehyde (Entry 8) to produce the expected products efficiently.

The structure of the products was elucidated based on their physical and spectral properties. The peaks at about 2200 and 3300 cm$^{-1}$ in IR spectra supported the presence of nitrile and amine moieties in the final products, respectively. In addition, the signals corresponding to three methylene groups in both $^1$H and $^{13}$C NMR spectra confirmed the participation of the heterocyclic ring in the structure of the products 4. More importantly, a single crystal was prepared in the case of 4c and subjected to X-ray crystallography. The depiction in Figure 1 clearly supports the formation of the proposed structure.

Based on the observations, we propose an organocatalyzed mechanism exemplified in Figure 2 for the reaction of 1 with benzaldehyde 2a and 3. First both the ketone and the aldehyde undergo parallel Knoevenagel condensations with $^{13}$C to produce their olefinic intermediates 13 and 23, respectively. This is easily caused due to the basic nature of Et$_3$N in aqueous medium.[30] These basic conditions can further cause combination of the two intermediates into the final product via two consecutive Michael additions to produce 4a'. Finally, the amine furnishes an imine-enamine tautomerization to 4a'', HCN elimination, and an aromatization process to give the final product 4a. We supported this hypothesis by separate preparation of 13 and 23 and subjecting them to H$_2$O/Et$_3$N reaction conditions, where they could efficiently convert to 4a within the expected time period.
3. Conclusion

In summary, we have presented an efficient one-pot method for the synthesis of novel series of dicyanoanilines fused to a heterocyclic ring. To the best of our knowledge, this work presents the first general method for successful synthesis of several novel isothiochroman derivatives. Reactions take place rapidly and high yields of the products are obtained under very mild conditions. The extension of the method to other heterocyclic systems and the study of the optical properties of these compounds in the near future are underway in our laboratory.

4. Experimental

All reactions are carried out in a fume hood. Melting points are uncorrected. FT–IR spectra were recorded using KBr disks on a Shimadzu Prestige-21 spectrometer. NMR spectra were obtained on a FT-NMR Bruker Ultra Shield™ (500 MHz) as CDCl₃ solutions using TMS as internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. MS spectra were obtained on a Fisons 8000 Trio instrument.
at ionization potential of 70 eV. TLC experiments were carried out on pre-coated silica gel plates using petroleum ether/EtOAc (4:1) as the eluent. Ketone 1 was prepared using an available procedure.[31] All other reagents and starting materials were purchased from the Merck company. Aldehydes were redistilled or recrystallized before being used. Products 13 and 14 are known.[32] All other products are new and were identified based on their physical and spectral properties.

4.1. Typical procedure for the synthesis of 4

A mixture of 1 (232 mg, 2.0 mmol), 2a (203 μL, 2.0 mmol), 3 (264 mg, 4.0 mmol), and Et₃N (557 μL, 4.0 mmol) in H₂O (5.0 mL) was stirred at 40°C for 10 h until TLC showed complete disappearance of the starting materials. The product which precipitated at the end of the reaction spontaneously was separated by filtration and recrystallized using the EtOAc/hexane mixture (1:4). Product 4a was obtained in 95% yield (552 mg). The product was identified based on its physical and spectral characteristics.

4.2. Spectral data of new products

4.2.1. 6-Amino-8-phenylisothiochroman-5,7-dicarbonitrile (4a)

Mp 205–206°C; IR (KBr, cm⁻¹) 3423, 3340, 3226, 2210, 1600;¹HNMR (CDCl₃, 500 MHz) δ 7.52–7.56 (m, 3H), 7.29–7.31 (m, 2H), 5.19 (s, 2H), 3.4 (s, 2H), 3.28 (t, J = 6.3 Hz, 2H), 2.96 (t, J = 6.3 Hz, 2H);¹³C NMR (CDCl₃, 125 MHz) δ 150.7, 148.7, 147.2, 136.4, 129.8, 129.4, 128.9, 125.9, 115.7, 115.4, 97.3, 96.7, 30.7, 26.8, 25.5 ppm; MS (70 eV): m/z 291 (M⁺), 257, 244, 231, 190; Anal. Calcd for C₁₇H₁₃N₃S: C, 70.08; H, 4.50; N, 14.42. Found: C, 70.11; H, 4.27; N, 14.67.

4.2.2. 6-Amino-8-p-tolylisothiochroman-5,7-dicarbonitrile (4b)

Mp 215–216°C; IR (KBr, cm⁻¹) 3336, 2214, 1598;¹HNMR (CDCl₃, 500 MHz) δ 7.33 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 5.18 (s, 2H), 3.40 (s, 2H), 3.26 (t, J = 6.5 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H);¹³C NMR (CDCl₃, 125 MHz) δ 150.7, 149.1, 147.1, 139.8, 133.4, 130.1, 128.8, 125.7, 115.9, 115.5, 97.3, 97.1, 30.7, 26.8, 25.5, 21.8 ppm; MS (70 eV): m/z 305 (M⁺), 290, 244, 131, 105; Anal. Calcd for C₁₈H₁₅N₃S: C, 70.79; H, 4.95; N, 13.76. Found: C, 71.00; H, 4.96; N, 13.91.

4.2.3. 6-Amino-8-(4-methoxyphenyl)isothiochroman-5,7-dicarbonitrile (4c)

Mp 198–199°C; IR (KBr, cm⁻¹) 3346, 2214, 1284;¹HNMR (CDCl₃, 500 MHz) δ 7.12 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H), 5.40 (s, 2H), 3.79 (s, 3H), 3.30 (s, 2H), 3.14 (t, J = 6.3 Hz, 2H), 2.83 (t, J = 6.3 Hz, 2H);¹³C NMR (CDCl₃, 125 MHz) δ 160.5, 151.1, 148.7, 147.1, 130.3, 128.5, 125.4, 120.1, 116.1, 115.6, 112.4, 55.7, 30.6, 26.7, 25.4 ppm; MS (70 eV): m/z 321 (M⁺), 235, 147, 121; Anal. Calcd for C₁₈H₁₅N₃OS: C, 67.27; H, 4.70; N, 13.07. Found: C, 67.57; H, 4.70; N, 13.21; HRMS Calcd for C₁₈H₁₅N₃OS: 321.09371, found: 321.09360.

4.2.4. 6-Amino-8-(2,4,6-trimethoxyphenyl)isothiochroman-5,7-dicarbonitrile (4d)

Mp 216–217°C; IR (KBr, cm⁻¹) 3344, 2200, 1549;¹HNMR (CDCl₃, 500 MHz) δ 6.21 (s, 2H), 5.07 (s, 2H), 3.96 (s, 3H), 3.93 (s, 6H), 3.35 (s, 2H), 3.12 (t, J = 5.7 Hz, 2H), 2.80
(t, J = 5.7 Hz, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 162.8, 160.9, 160.5, 143.2, 130.9, 120.6, 115.7, 112.8, 101.4, 91.6, 91.5, 88.4, 42.1, 41.9, 35.4, 28.7, 26.3 ppm; MS (70 ev): m/z 381 (M$^+$), 322, 181; Anal. Calcd for C$_{20}$H$_{19}$N$_3$O$_3$S: C, 62.98; H, 5.02; N, 11.02. found: C, 63.11; H, 4.97; N, 11.21.

4.2.5. 6-Amino-8-(4-chlorophenyl)isothiochroman-5,7-dicarbonitrile (4e)
Mp 196–197°C; IR (KBr, cm$^{-1}$) 3334, 2210, 1562; $^1$HNMR (CDCl$_3$, 500MHz) $\delta$ 7.47 (dd, J = 6.5, 1.6 Hz, 2H), 7.20 (dd, J = 6.5, 1.6 Hz, 2H), 5.36 (s, 2H), 3.31 (s, 2H), 3.22 (t, J = 6.5 Hz, 2H), 2.90 (t, J = 6.5 Hz, 2H); $^{13}$CN M R (CDCl$_3$, 125MHz) $\delta$ 150.9, 147.4, 135.9, 134.8, 130.4, 129.7, 125.2, 115.7, 115.3, 97.7, 96.7, 30.7, 26.7, 25.4 ppm; MS (70 ev): m/z 325 (M$^+$), 290, 244, 213, 190; Anal. Calcd for C$_{17}$H$_{12}$ClN$_3$S: C, 62.67; H, 3.71; N, 12.90. found: C, 62.87; H, 3.70; N, 12.93; HRMS Calcd for C$_{17}$H$_{12}$ClN$_3$S: 325.04395, found: 325.04404.

4.2.6. 6-Amino-8-(4-nitrophenyl)isothiochroman-5,7-dicarbonitrile (4f)
Mp 218–219°C; IR (KBr, cm$^{-1}$) 3361, 2210, 1519; $^1$HNMR (CDCl$_3$, 500MHz) $\delta$ 8.43 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 5.25 (s, 2H), 3.33 (s, 2H), 3.31 (t, J = 6.5 Hz, 2H), 2.98 (t, J = 6.5 Hz, 2H); $^{13}$CN M R (CDCl$_3$, 125MHz) $\delta$ 150.8, 147.0, 141.6, 135.8, 129.5, 128.6, 128.1, 126.7, 115.6, 115.3, 98.3, 98.1, 30.7, 26.9, 25.4 ppm; MS (70 ev): m/z 335 (M$^+$), 305, 244, 131, 105; HRMS Calcd for C$_{17}$H$_{12}$N$_4$O$_2$S: 336.06800. Found: 336.06808.

4.2.7. 6-Amino-8-(thiophen-2-yl)isothiochroman-5,7-dicarbonitrile (4g)
Mp 184–185°C; IR (KBr, cm$^{-1}$) 3344, 2218, 1562; $^1$HNMR (CDCl$_3$, 500MHz) $\delta$ 7.51 (d, J = 5.0 Hz, 1H), 7.15 (t, J = 3.5 Hz, 1H), 7.07 (d, J = 3.5 Hz, 1H), 5.36 (s, 2H), 3.47 (s, 2H), 3.21 (t, J = 6.5 Hz, 2H), 2.90 (t, J = 6.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 151.1, 146.9, 141.4, 135.8, 129.3, 128.5, 128.0, 126.3, 115.6, 115.3, 98.1, 97.9, 30.6, 26.8, 25.3 ppm; MS (70 ev): m/z 297 (M$^+$), 264, 249, 164; Anal. Calcd for C$_{15}$H$_{11}$N$_3$S$_2$: C, 60.58; H, 3.73; N, 14.13. found: C, 60.59; H, 3.69; N, 14.41; HRMS Calcd for C$_{15}$H$_{11}$N$_3$S$_2$: 297.03941. Found: 297.03943.

4.2.8. 6-Aminoisothiochroman-5,7-dicarbonitrile (4h)
Mp 165–166°C; IR (KBr, cm$^{-1}$) 3342, 2216, 1747; $^1$HNMR (CDCl$_3$, 500MHz) $\delta$ 7.39 (s, 1H), 5.12 (s, 2H), 3.67 (s, 2H), 3.22 (t, J = 6.1 Hz, 2H), 2.97 (t, J = 6.1 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 150.8, 146.9, 136.2, 125.8, 116.1, 115.1, 98.8, 95.4, 30.4, 29.2, 25.8 ppm; MS (70 ev): m/z 215 (M$^+$), 182, 168, 45; Anal. Calcd for C$_{11}$H$_9$N$_3$S: C, 61.37; H, 4.21; N, 19.52; found: C, 61.43; H, 4.28; N, 19.87; HRMS Calcd for C$_{11}$H$_9$N$_3$S: 215.05170. Found: 215.05171.

4.3. X-ray data for 4c
Crystallographic data for 4c have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1419462. Copies of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. Code +44(1223)336-033; E-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/retrieving.html].
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No potential conflict of interest was reported by the authors.

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