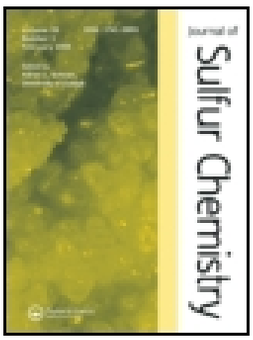

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A convenient one-pot synthesis of thiopyrano[4,3-*b*]pyran derivatives under LiOH·H_2O/EtOH/ultrasonic conditions

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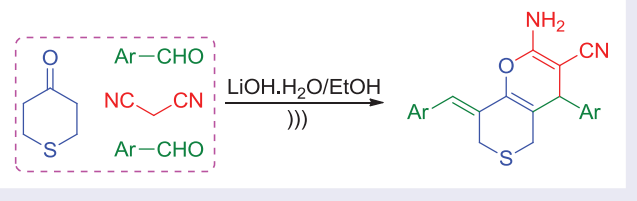
ABSTRACT

Various derivatives of thiopyrano[4,3-*b*]pyran structure are synthesized via a multicomponent procedure starting from tetrahydro-4*H*-thiopyran-4-one, aromatic aldehydes, and malononitrile. Reactions take place by the use of catalytic quantities of LiOH·H_2O in one pot under ultrasonic conditions and in an ethanolic medium. Isolation of products occurs by spontaneous precipitation in reaction mixtures and no cumbersome and expensive chromatographic separations are needed.



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Thiopyranopyran; thiopyran; ethanolic medium; multicomponent reaction; lithium hydroxide

1. Introduction

The tetrahydro-4*H*-thiopyran-4-one (**1**) is an important six-membered heterocyclic structure among the sulfur-containing molecules.[1] Compound **1** has served to build the central heterocyclic ring of many important target compounds [2] and complex multicyclic systems.[3] In this context, we have extended the thiopyran chemistry by presenting the use of **1** in several named reactions, such as Diels-Alder,[4] Mannich,[5] and Baylis–Hillman reactions.[6] On another front, due to the increase in the popularity of multicomponent reactions (MCRs),[7–9] many MCR procedures are developed in recent years starting from **1** for the synthesis of isothiochroman,[10] azabicycloalkanes,[3] thiopyrano-pyrimidines,[11] and multicyclic hydantoins.[12]

Bis(arylmethylidene)thiopyranones **2** are a group of products which can be further manipulated because of having reactive functionalities in their structures. Ghashang et al. conducted a MgO-catalyzed synthesis of thiopyrano[4,3-*b*]pyran derivatives **3**

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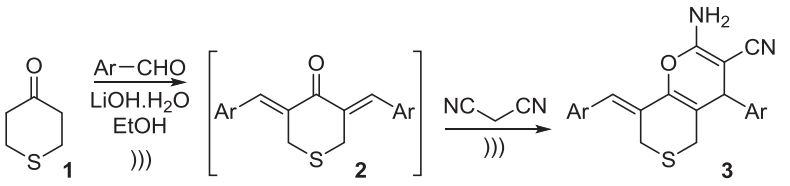


Scheme 1. Multicomponent synthesis of **3**.

starting from **2**.[13] Similarly, a few other derivatives of **3** have been synthesized by others via stepwise reactions.[14–16] In continuation of our studies on the preparation and synthetic applications of **2**,[17,18] we would like here to introduce a one-pot procedure for the synthesis of **3** starting from **1**, aldehydes, and malononitrile under $LiOH{\cdot}H_2O$/EtOH/ultrasonic conditions. To the best of our knowledge, this would be the first general multicomponent procedure for the synthesis of **3** starting from simple and commercially available reactants (Scheme 1).

Table 1. Selection of the catalyst for the synthesis of **3a**.

Entry	Conditions	Yield (%)[a]
1	$LiOH{\cdot}H_2O$/EtOH	85
2	LiBr/EtOH	< 10
3	$LiClO_4$/EtOH	< 10
4	NaOH/EtOH	63
5	KOH/EtOH	52
6	$KHCO_3$/EtOH	25
7	EtOH	0
8	Et_2NH/EtOH	< 10
9	Et_3N/EtOH	23
10	Bu_2NH/EtOH	41
11	pyrrolidine/EtOH	38
12	morpholine/EtOH	45
13	$LiOH{\cdot}H_2O$/EtOH[b]	< 10

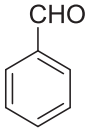
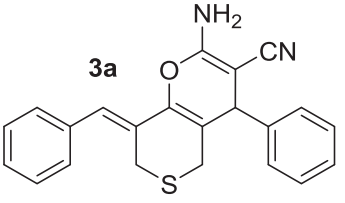
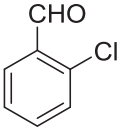
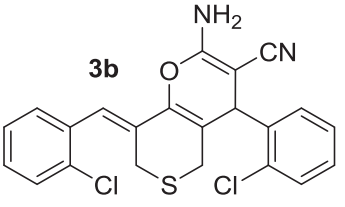
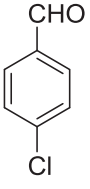
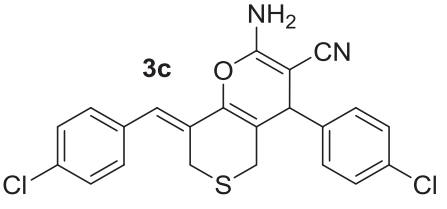
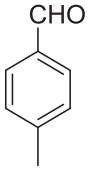
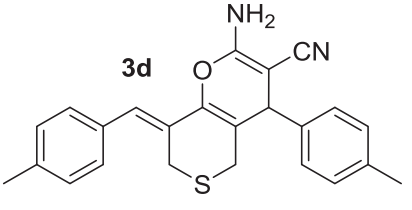
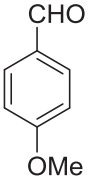
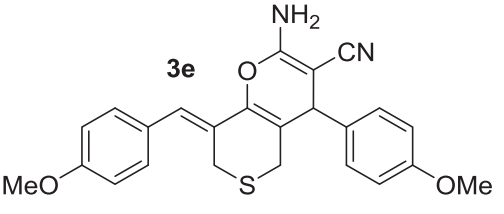
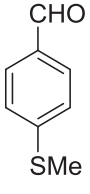
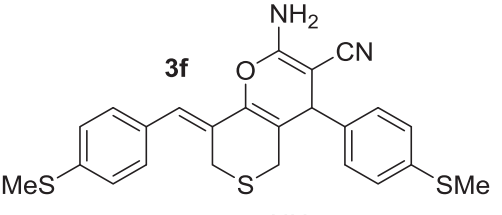
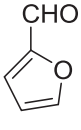
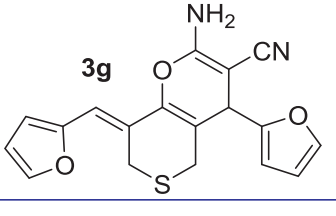
[a]Isolated yield.
[b]No sonication.

Table 2. Optimization of the conditions for the synthesis of **3a**.

Entry	Solvent	$LiOH{\cdot}H_2O$ (mol%)	$NCCH_2CN$ (Equiv)	Yield (%)[a]
1	EtOH	0	1.25	0
2	EtOH	10	1.25	23
3	EtOH	20	1.25	48
4	EtOH	30	1.25	74
5	EtOH	41	1.25	85
6	EtOH	51	1.25	85
7	EtOH	51	1.00	78
8	EtOH	51	1.50	85
9	–	41	1.25	31
10	H_2O	41	1.25	< 10
11	H_2O/EtOH	41	1.25	50
12	PhMe	41	1.25	< 10
13	CH_2Cl_2	41	1.25	< 10

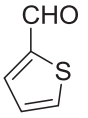
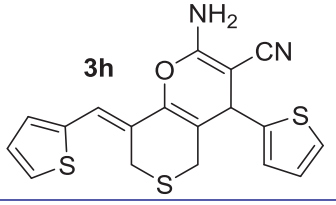
[a]Isolated yield.

Table 3. Synthesis of various derivatives of **3**.

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	Reference
1			30	85	[15]
2			25	82	–
3			20	95	–
4			30	70	[13]
5			30	72	[13]
6			30	78	–
7			20	94	–

(*continued*).

Table 3. Continued.

Entry	Aldehyde	Product	Time (min)	Yield (%)[a]	Reference
8		 **3h**	20	90	–

[a]Isolated yield.

2. Results and discussion

We first evaluated the role of various bases in the progress of the reaction of **1** with benzaldehyde and malononitrile (Table 1). In an ultrasound bath, when an ethanolic mixture of **1**, benzaldehyde, and malononitrile was treated with $LiOH{\cdot}H_2O$, **3a** was obtained in 85% after 30 min sonication (entry 1). To see the effect of other lithium salts, LiBr (entry 2) and $LiClO_4$ (entry 3) were used, where low yields of **3a** were obtained. Use of other alkaline (entries 4–5) or bicarbonate bases (entry 6) did not improve the outcome, while in the absence of any base (entry 7) no conversion was observed. Alternatively, the use of some amine organocatalysts gave no better results (entries 8–12), suggesting that $LiOH{\cdot}H_2O$/EtOH provides the best conversion of the reactants to **3a** under ultrasonic conditions. Similarly, conducting the reaction under silent conditions led to negligible formation of **3a** (entry 13), illustrating the crucial role of the sonication in the progress of the reaction.

More experiments were carried out to further improve the conditions (Table 2). Variation of the amount of the base in EtOH (entries 1–5) showed that 41 mol% $LiOH{\cdot}H_2O$ and 1.25 equivalents of malononitrile are enough for the reaction to complete and lead to 85% yield of **3a**. Use of more quantities of the base (entries 6–7) or even excessive amounts of malononitrile (entry 8) did not give better results. Alternatively, in the absence of a solvent (entry 9) or in other media (entries 10–13) no improvement was observed.

Finally, optimum conditions were employed to evaluate the generality of the process. Therefore, in addition to the model reaction (Table 3, entry 1), when other derivatives of benzaldehyde bearing electron- withdrawing (entries 2–3) or electron-donating groups (entries 4–6) were used, products **3b**–**3f** were synthesized in good yields. Additionally, heterocyclic aromatic aldehydes behaved equally well and gave the corresponding products in short time periods (entries 7–8). In all reactions, a derivative of **3** was formed solely or as the major product. The structure of the products was elucidated based on their spectroscopic characters. In FT-IR spectra, the amine and nitrile bands support the formation of the pyran ring. ^{1}H NMR analysis spots the presence of four doublet signals with high $^2J_{H-H}$ coupling constants at about 3.0 and 3.5 ppm corresponding to CH_2–S–CH_2 protons. An additional singlet proton in high field at $\sim$4.0 ppm correlates to the CHAr moiety in the pyran ring.

Monitoring of the reactions by thin-layer chromatography (TLC) suggests that an initial double-aldol condensation process gives the corresponding bisarylmethylidene intermediates **2**. Then, these intermediates undergo a subsequent *in situ* Michael addition with

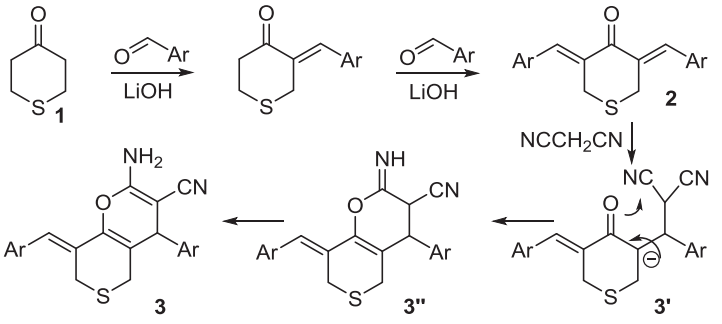


Figure 1. Feasible reaction mechanism.

malononitrile followed by a nucleophilic cyclization to form derivatives **3** after only a few minutes sonication. Control experiments supported this pathway, where derivatives of **2** were synthesized separately and treated with malononitrile to give the expected product **3** after 5 min sonication (Figure 1).

3. Conclusion

In summary, the first multicomponent synthesis of the target compounds is introduced in the present work. Reactions are rapid and take place under relatively inexpensive conditions. Products precipitate spontaneously in the reaction mixtures. This allows an easy separation and purification process which is important from an environmental point of view. We plan to extend the results to similar multicomponent syntheses starting from other analogues of **1**.

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 Bruker Vector-22. Nuclear magnetic resonance (NMR) spectra were obtained on an FT-NMR Bruker Ultra Shield^{TM} (500 MHz) as DMSO-d_6 solutions using TMS as the internal standard reference. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. MS spectra were obtained on a Finnigan Mat 8430 apparatus at an 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.[19] All other reagents and starting materials were purchased from Merck company. Aldehydes were redistilled or recrystallized before being used. Products **3a, d, e** are known.[13,15] All other products are new and were identified based on their physical and spectral properties. The yield values are averages of two independent runs.

4.1. Typical procedure for the synthesis of 3

A suspension of LiOH·H_2O (17 mg) in EtOH (1.0 mL) was added to a solution of **1** (116 mg, 1.0 mmol) and benzaldehyde (204 µL, 2.0 mmol) in EtOH (2.0 mL). The resulting mixture was irradiated in an ultrasonic bath (Sono Swiss SW3-H, 38 kHz, Switzerland) for

25 min until the formation of a yellowish precipitate of the intermediate **2a** was observed. At this point, malononitrile (83 mg, 1.25 mmol) was added and the mixture was irradiated for another 5 min. TLC showed complete disappearance of the starting materials and the intermediate **2a**. The product precipitated spontaneously in the reaction mixture and was separated by filtration and recrystallized using EtOH.

4.2. Spectral data of new products

4.2.1. (Z)-2-Amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3b)

Mp 238–239°C; infrared (IR) (KBr, cm^{-1}) 3454, 3350, 2882, 2190 (C≡N), 1669 (C=C), 1467; ^{1}HNMR (DMSO-d_6, 500 MHz) δ 2.83 (d, J = 17.0 Hz, 1H, CHS), 3.27 (d, J = 17.0 Hz, 1H, CHS), 3.45 (d, J = 15.0 Hz, 1H, CHS), 3.50 (d, J = 15.0 Hz, 1H, CHS), 4.66 (s, 1H, CHAr), 7.00 (s, 2H, NH_2), 7.15 (s, 1H,=CH), 7.29–7.32 (m, 2H, 2 arom. H), 7.35–7.38 (m, 3H, 3 arom. H), 7.41 (d, J = 8.0 Hz, 1H, 1 arom. H), 7.45 (d, J = 8.0 Hz, 1H, 1 arom. H), 7.54 (d, J = 8.0 Hz, 1H, 1 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 27.2 (CH_2S), 28.0 (CH_2S), 55.6, 114.7, 120.7, 122.6, 128.0, 128.9, 129.0, 129.9, 130.3, 130.4, 130.5, 131.3, 132.0, 133.2, 133.8, 134.9, 141.1, 142.5, 160.8 ppm; MS (70 eV): m/z 426 (M^+), 315, 300, 185; Anal. Calcd. for $C_{22}H_{16}Cl_2N_2OS$: C, 61.83; H, 3.77; N, 6.56. found: C, 61.69; H, 3.67; N, 6.65.

4.2.2. (Z)-2-Amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3c)

Mp 245–246°C; IR (KBr, cm^{-1}) 3451, 3321, 2198 (C≡N), 1674 (C=C), 1642; ^{1}HNMR (DMSO-d_6, 500 MHz) δ 2.91 (d, J = 17.0 Hz, 1H, CHS), 3.24 (d, J = 17.0 Hz, 1H, CHS), 3.59 (d, J = 15.0 Hz, 1H, CHS), 3.64 (d, J = 15.0 Hz, 1H, CHS), 4.14 (s, 1H, CHAr), 6.93 (s, 2H, NH_2), 7.13 (s, 1H,=CH), 7.26 (d, J = 8.0 Hz, 2H, 2 arom. H), 7.35 (d, J = 8.0 Hz, 2H, 2 arom. H), 7.43 (d, J = 8.0 Hz, 2H, 2 arom. H), 7.46 (d, J = 8.0 Hz, 2H, 2 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 27.0 (CH_2S), 28.0 (CH_2S), 43.4, 56.5, 115.0, 120.9, 124.2, 127.9, 129.4, 129.6, 130.3, 131.8, 132.7, 132.9, 135.6, 142.3, 143.2, 160.5 ppm; MS (70 eV): m/z 426 (M^+), 379, 315, 301, 115; Anal. Calcd. for $C_{22}H_{16}Cl_2N_2OS$: C, 61.83; H, 3.77; N, 6.56. found: C, 61.61; H, 3.88; N, 6.67.

4.2.3. (Z)-2-Amino-8-(4-methylbenzylidene)-4-(p-tolyl)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3d)

Mp 208–209°C; IR (KBr, cm^{-1}) 3473, 3319, 2201 (C≡N), 1677 (C=C), 1407; ^{1}HNMR (DMSO-d_6, 500 MHz) δ 2.29 (s, 3H, Me), 2.32 (s, 3H, Me), 2.89 (d, J = 17.0 Hz, 1H, CHS), 3.22 (d, J = 17.0 Hz, 1H, CHS), 3.58 (d, J = 15.0 Hz, 1H, CHS), 3.66 (d, J = 15.0 Hz, 1H, CHS), 4.02 (s, 1H, CHAr), 6.84 (s, 2H, NH_2), 7.11 (d, J = 8.0 Hz, 2H, 2 arom. H), 7.15–7.18 (m, 3H, 2 arom. H & =CH), 7.21–7.23 (m, 4H, 4 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 21.5 (Me), 21.7 (Me), 27.1 (CH_2S), 28.1 (CH_2S), 43.8, 57.0, 114.7, 121.2, 125.2, 126.6, 128.3, 130.0, 130.2, 133.9, 137.2, 137.7, 141.4, 142.2, 160.5 ppm; MS (70 eV): m/z 386 (M^+), 368, 325, 295, 191; Anal. Calcd. for $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25. found: C, 74.51; H, 5.51; N, 7.39.

4.2.4. (Z)-2-Amino-8-(4-methoxybenzylidene)-4-(4-methoxyphenyl)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3e)

Mp 192–193°C; IR (KBr, cm^{-1}) 3403, 3321, 2191 (C≡N), 1670 (C=C), 1414; ^{1}HNMR (DMSO-d_6, 500 MHz) δ 2.84 (d, J = 17.0 Hz, 1H, CHS), 3.17 (d, J = 17.0 Hz, 1H, CHS), 3.55 (d, J = 15.0 Hz, 1H, CHS), 3.62 (d, J = 15.0 Hz, 1H, CHS), 3.70 (s, 3H, Me), 3.73 (s, 3H, Me), 3.96 (s, 1H, CHAr), 6.75 (s, 2H, NH_2), 6.88 (d, J = 8.5 Hz, 2H, 2 arom. H), 6.94 (d, J = 8.5 Hz, 2H, 2 arom. H), 7.04 (s, 1H,=CH), 7.09 (d, J = 8.5 Hz, 2H, 2 arom. H), 7.23 (d, J = 8.5 Hz, 2H, 2 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 27.2 (CH_2S), 28.1 (CH_2S), 43.3, 55.9 (Me), 56.0 (Me), 57.2, 114.4, 114.9, 115.0, 121.2, 125.0, 125.6, 129.1, 129.5, 131.5, 136.4, 142.2, 159.3, 159.4, 160.4 ppm; MS (70 eV): m/z 418 (M^+), 368, 311, 238, 111; Anal. Calcd for $C_{24}H_{22}N_2O_3S$: C, 68.88; H, 5.30; N, 6.69. found: C, 69.01; H, 5.45; N, 6.72.

4.2.5. (Z)-2-Amino-8-(4-(methylthio)benzylidene)-4-(4-(methylthio)phenyl)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3f)

Mp 222–223°C; IR (KBr, cm^{-1}) 3472, 3325, 2183 (C≡N), 1665 (C=C), 1406; ^{1}HNMR (DMSO-d_6, 500 MHz) δ 2.48 (s, 3H, Me), 2.50 (s, 3H, Me), 2.91 (d, J = 17.0 Hz, 1H, CHS), 3.24 (d, J = 17.0 Hz, 1H, CHS), 3.61 (d, J = 15.0 Hz, 1H, CHS), 3.66 (d, J = 15.0 Hz, 1H, CHS), 4.05 (s, 1H, CHAr), 6.87 (s, 2H, NH_2), 7.10 (s, 1H,=CH), 7.17 (d, J = 8.0 Hz, 2H, 2 arom. H), 7.26 (d, J = 8.0 Hz, 2H, 2 arom. H), 7.28–7.29 (m, 4H, 4 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 27.0 (CH_2S), 28.0 (CH_2S), 43.4, 55.9, 115.0, 120.9, 124.2, 127.9, 129.4, 129.6, 130.3, 131.8, 132.7, 132.9, 135.6, 142.3, 143.2, 160.5 ppm; MS (70 eV): m/z 450 (M^+), 368, 311, 238, 137; Anal. Calcd. for $C_{24}H_{22}N_2OS_3$: C, 63.97; H, 4.92; N, 6.22. found: C, 64.14; H, 4.76; N, 6.39.

4.2.6. (Z)-2-Amino-4-(furan-2-yl)-8-(furan-2-ylmethylene)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3g)

Mp 240–241°C; IR (KBr, cm^{-1}) 3437, 3320, 2196 (C≡N), 1667 (C=C), 1418; ^{1}HNMR (DMSO-d_6, 500 MHz) δ 3.12 (d, J = 17.0 Hz, 1H, CHS), 3.29 (d, J = 17.0 Hz, 1H, CHS), 3.80 (d, J = 15.5 Hz, 1H, CHS), 3.94 (d, J = 15.5 Hz, 1H, CHS), 4.26 (s, 1H, CHAr), 6.24 (d, J = 3.0 Hz, 1H, 1 arom. H), 6.40 (dd, J = 2.0, 3.0 Hz, 1H, 1 arom. H), 6.60 (d, J = 2.0 Hz, 1H, 1 arom. H), 6.62 (d, J = 3.0 Hz, 1H, 1 arom. H), 6.90 (s, 1H, 1 arom. H), 6.95 (s, 2H, NH_2), 7.59 (s, 1H,=CH), 7.78 (s, 1H, 1 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 27.3 (CH_2S), 27.9 (CH_2S), 37.7, 53.9, 107.5, 111.3, 112.6, 113.0, 113.1, 113.8, 120.9, 124.1, 142.9, 143.6, 144.7, 152.3, 155.5, 161.2 ppm; MS (70 eV): m/z 338 (M^+), 257, 236, 111; Anal. Calcd. for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28. found: C, 63.55; H, 4.37; N, 8.17.

4.2.7. (Z)-2-Amino-4-(thiophen-2-yl)-8-(thiophen-2-ylmethylene)-4,5,7,8-tetrahydrothiopyrano[4,3-b]pyran-3-carbonitrile (3h)

Mp 242–243°C; IR (KBr, cm^{-1}) 3427, 3311, 2191 (C≡N), 1662 (C=C); ^{1}HNMR (DMSO-d_6, 500 MHz) δ 3.12 (d, J = 17.0 Hz, 1H, CHS), 3.31 (d, J = 17.0 Hz, 1H, CHS), 3.72 (d, J = 15.0 Hz, 1H, CHS), 3.82 (d, J = 15.0 Hz, 1H, CHS), 4.46 (s, 1H, CHAr), 6.96–6.99 (m, 4H, 2 arom. H & NH_2), 7.16 (dd, J = 4.0, 4.5 Hz, 1H, 1 arom. H), 7.22 (d, J = 3.0 Hz, 1H, 1 arom. H), 7.29 (s, 1H,=CH), 7.44 (d, J = 5.0 Hz, 1H, 1 arom. H), 7.66 (d, J = 5.0 Hz, 1H, 1 arom. H) ppm; ^{13}CNMR (DMSO-d_6, 125 MHz) δ 27.3 (CH_2S), 27.9 (CH_2S), 39.3,

57.2, 114.9, 118.1, 118.2, 120.9, 124.6, 125.9, 126.4, 127.8, 128.8, 130.6, 139.5, 142.2, 149.2, 160.6 ppm; MS (70 eV): m/z 370 (M^+), 286, 236, 111; Anal. Calcd. for $C_{18}H_{14}N_2OS_3$: C, 58.35; H, 3.81; N, 7.56. found: C, 58.49; H, 3.97; N, 7.44.

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