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Facile construction of densely functionalized thiopyrano[2,3-*b*]quinolines *via* three-component reactions catalyzed by L-proline†

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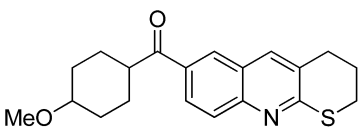
L-Proline catalyzed, three-component reactions of 2-mercaptoquinoline-3-carbaldehyde, malononitrile and thiol-based nucleophiles were developed for the first time, for the synthesis of various 4*H*-substituted thiopyrano[2,3-*b*]quinolines derivatives *via* a Knoevenagel condensation followed by inter-intramolecular double Michael addition reaction. This transformation leads to the generation of a 4-substituted thiopyran ring, together with one C–C and two C–S bonds in a single operation.

The importance of quinoline annulated thiopyran derivatives is well recognized by synthetic and medicinal chemists. Compounds possessing this ring system have attracted much attention in recent years because this key moiety emerged in a large number of bioactive natural products and pharmaceutical agents.[1] Recently a wide range of biological activities associated with the sulphur-heterocycles scaffolds have been identified.[2] Likewise thiopyran and fused-thiopyran derivatives show anti-inflammatory,[3a] anti-bacterial,[3b] anti-hyperplasia,[3c] anti-psychotic,[3d] analgesic, and anti-cancer[4] activities. Thiopyrano-quinoline annulated heterocycles are also distinguished by their biological properties. In addition to the biological importance, their structural similitude to (i) MT477 is reported as a potential anticancer drug with a high activity against protein kinase C (PKC) isoforms 2, (ii) metabotropic glutamate receptor antagonistic activity that is, mGlu1 receptor activity of thiopyranoquinoline[4] is an added attraction for the interest in the synthesis of thiopyrano-quinoline.

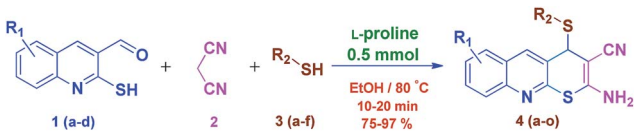
Despite the fact that the chemistry of biological significance thiopyrano-quinoline has been much less explored than that of their pyrano-quinoline analogous. Thus the development of facile synthetic strategies to access such heterocycles provided the impetus to investigate the three-component reactions for the synthesis of novel 4*H*-thiopyrano[2,3-*b*]quinolines (Scheme 1) employing the green organocatalyst, L-proline.

L-Proline is an efficient bifunctional abundant organocatalyst which is inexpensive and facilitates chemical transformations by acting as an acid or base. Further, L-proline have shown considerable catalytic efficiency in diverse organic transformations, such as aldol, Mannich, Michael, Hantzsch, Diels–Alder/Knoevenagel and other domino process.[5] L-Proline, has also been used as a catalyst in different multicomponent reactions (MCRs), and the studies have shown that this catalyst efficiently promoted these protocols.[6]

MCRs assemble three or more substrates in one pot operations with high synthetic efficiency[7] and hence are important from a green chemistry perspective.[8] As a one-pot, MCRs permit rapid access to combinatorial libraries of densely functionalized complex molecules in a single synthetic operation especially in drug discovery.[9]



The synthetic protocols reported earlier for thiopyran fused-quinoline includes, multi-component reactions involving aromatic aldehydes, naphthalen-2-amine and tetrahydrothiopyran-4-one have been reported by Wang *et al.*[10] Similarly, Mahadevan and co-workers have reported the microwave-assisted synthesis from 3-formyl-quinoline-2-thiones with active methylene esters.[11] Recently, Singh *et al.*[12] have reported the synthesis of fused thiopyrans *via* domino Michael addition followed by cyclization



Scheme 1

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reactions on 2-thione analogs of 3-formylquinolines using acrylonitrile thus demonstrating for the first time the potential of 3-formyl-quinoline-2-thiones to undergo nucleophilic additions. All these methods have some limitations such as high temperature, longer reaction time, tedious work-up and poor yield.

In our previous studies, we reported a series of new 3,5-dicyanopyridines starting from various aldehydes, malononitrile and thiols.[13] Also we have reported the synthesis of bioactive fused heterocycles *via* one-pot reaction.[14] We now report first time a facile route for the synthesis of densely functionalized thiopyrano[2,3-*b*]quinolines from the Knoevenagel condensation followed by intra/inter molecular double Michael addition reaction of 3-formyl-quinoline-2-thiones with malononitrile and thiophenols in ethanol in the presence of L-proline in a very short duration of time in good yields (Scheme 1).

Our initial attempts to convert 2-chloro-3-formylquinoline to 4*H*-thiopyrano[2,3-*b*]quinolines using 1.5 equivalent of Na_2S, malononitrile, thiophenol and base mixed together at same time and also by sequential addition of the reagents with and without base at room temperature/heating the reactions proceeded to access 2-((2-chloroquinolin-3-yl)methylene)malononitrile but failed to afford the desired cyclized product 2-amino-4-(phenylthio)-4*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile **4a**.

Next, we turn our attention to the Knoevenagel condensation followed by Michael addition/cyclization reactions to the synthesis of **4a**, using 3-formyl-quinoline-2-thione derivatives **1a** as substrates, synthesized from 2-chloro-3-formylquinoline as literature procedure.

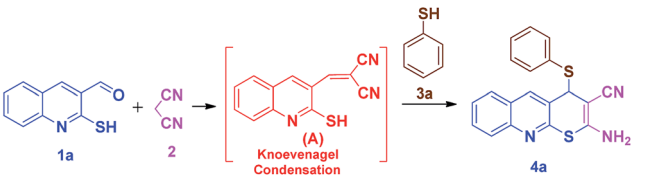
In Table 1, the reaction was performed under catalyst-free conditions, using ethanol at 80 °C although **1a** was almost consumed in 1.0 h, to form Knoevenagel adduct (**A**), no Michael addition of thiophenol **3a** took place.

To optimize the reaction conditions for the formation of the target compounds, we started this study by treating 3-formyl-quinoline-2-thione **1a** with malononitrile **2** and thiophenol **4a**.

Various reaction conditions were investigated, including bases, solvents, and temperatures. Initially, we employed various bases such as Et_3N, K_2CO_3, NaOH, piperidine and Cs_2CO_3 separately, to determine one which can give the best results. These results showed that the properties of the employed catalyst have remarkable effect in controlling the reaction selectivity in terms of addition of thiol group of the Knoevenagel adduct (**A**) towards the carbon atom of the nitrile group (**B**). This gave us force to further explore the feasibility of synthesizing **4a** from **1a**, **2** and **3a** by mean of changing the catalyst. We envisaged that L-proline might be good catalyst for our model three-component reaction because the reaction of **1a** with nucleophiles, **2** and **3a**, needed a definite compounding in order to obtain **4a**. By using L-proline as catalyst yield of **4a** significantly improved. The unique catalytic activity of L-proline from its amphoteric nature and the amino group might result in the formation of imine and the carboxylic group could stabilize the charge generated on the nitrogen atom (**C**).[15]

The results show that L-proline was the best organocatalyst for the three component reaction of 3-formyl-quinoline-2-thione, malononitrile and sulfide. We than repeated the same

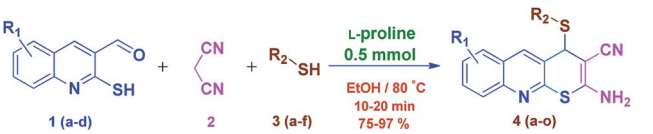
Table 1 Three component reaction of (**1a**), malononitrile (**2**) and thiophenol (**3a**) under different conditions[a]



Entry	Base	Temp (°C)	Solvent	Yields of **4a** (%)
1	—	80	EtOH	00
2	K_2CO_3	80	EtOH	25
3	Cs_2CO_3	80	EtOH	20
4	Piperidine	80	EtOH	35
5	NaOH	80	EtOH	00
6	Et_3N	80	EtOH	30
7[b]	L-Proline	Rt	EtOH	—
8[c]	L-Proline	60	EtOH	50
9[d]	L-Proline	80	EtOH	94
10	L-Proline	80	CH_3CN	37
11	L-Proline	110	Toluene	30
12	L-Proline	120	DMF	36
13	L-Proline	80	1,4-Dioxane	30
14	L-Proline	40	CH_2Cl_2	10
15	L-Proline	100	H_2O	10
16	L-Proline	60	MeOH	57
17[e]	Pyrrolidine : acetic acid (1 : 1)	80	EtOH	73

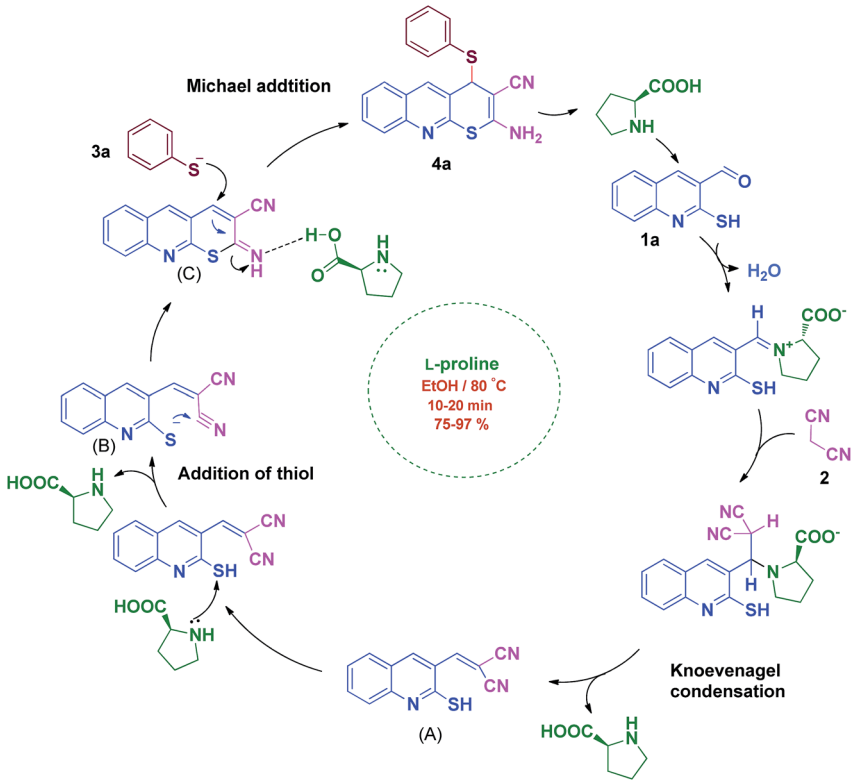
[a] **1a**: 0.5 mmol, **2a**: 0.5 mmol, **3a**: 0.5 mmol, solvent: 1.5 ml, catalyst: 0.05 mmol, 1.5–2.0 h. [b] Reaction time for 2.0 h. [c] Reaction time for 1.0 h. [d] Reaction time for 0.5 mmol, 10 min. [e] Reaction time for 45–50 min.

Table 2 Synthesis of 4*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitriles derivatives **4**(a–o)



Substrate	R_1	R_2	Product	Time (min)	Yield of **4**[a] (%)
1a	H	Phenyl	**4a**	10	94
1a	H	4-CH_3–C_6H_5	**4b**	10	97
1a	H	4-F–C_6H_5	**4c**	10	91
1a	H	Benzayl	**4d**	10	83
1a	H	Cyclopentane	**4e**	20	75
1a	H	Cyclohexane	**4f**	20	80
1b	CH_3	Phenyl	**4g**	10	93
1b	CH_3	4-CH_3–C_6H_5	**4h**	10	89
1b	CH_3	4-F–C_6H_5	**4i**	10	86
1b	CH_3	Benzayl	**4j**	10	81
1b	CH_3	Cyclopentane	**4k**	20	85
1b	CH_3	Cyclohexane	**4l**	20	88
1c	OCH_3	4-CH_3–C_6H_5	**4m**	10	90
1d	Cl	Benzayl	**4n**	20	92
1d	Cl	4-F–C_6H_5	**4o**	10	87

[a] Yield of isolated product.



Scheme 2 Proposed mechanism for the synthesis of 2-amino-4-((substituted)thio)-4*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile derivatives.

reaction in a different solvents such as acetonitrile, toluene, DMF, 1,4-dioxanedichloromethane, H_2O, MeOH are rather poor (Table 1, entry 10 to 16). Therefore, the optimal condition for L-proline (0.5 mmol) catalyst system is ethanol solvent, 80 °C, 10–20 min (Table 1, entry 9).

Mechanistically, formation of **4a** from **1a**, **2** and **3a** in the L-proline/ethanol system, a plausible mechanism was then proposed, as shown in Scheme 2. The reaction commenced with the formation of an 2-((2-mercaptoquinolin-3-yl)methylene) malononitrile (**A**) from **1a** and **2**. We realized that Knoevenagel adduct (**A**) undergo to intra-molecular thiol addition reaction to give 2-imino-2*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (**C**) stabilized by carboxylic group of L-proline, which is upon intermolecular Michael addition of thiophenol **3a** would be accessible to 2-amino-4-(phenylthio)-4*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile **4a** (Scheme 2).

With the optimized reaction condition in hand, we probe the scope of the reaction (Table 2). Thiophenols with different substituents, such as methyl, fluoro and mercaptans, like benzyl, cyclopenate and cyclohexane all smoothly reacted, producing the corresponding 4*H*-thiopyrano[2,3-*b*]quinolines in good to excellent yields. Thiophenols were proved to be more capable than mercaptane.

Experimental section

Typical experimental procedure for **4a**: a mixture of 3-formylquinoline-2-thione, **1a** (1.0 mmol), malononitrile **2** (1.0 mmol) and thiophenol **3a** in the presence of L-proline (0.5 mmol) was refluxed in ethanol for 10–20 min and cooled to room temperature. The solid formed in the reaction mixture was filtered and dried under vacuum. The crude solid product was purified by recrystallization in ethanol to obtain the pure product **4a** in good yield (94%).

2-Amino-4-(phenylthio)-4*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (**4a**). Colorless solid; yield: 94%; m.p. 143 °C; ^{1}H NMR (400 MHz, DMSO d_6): $\delta = 4.85$ (s, 1H), 7.32 (s, 2H), 7.50–7.52 (m, $J = 7.6$ Hz, 6H), 7.94–7.96 (d, $J = 7.2$ Hz, 2H), 8.12 (s, 1H), 8.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO d_6): δ = 57.0, 106.5, 117.7, 123.7, 126.9, 128.2, 128.3, 129.2, 131.8, 136.6, 140.9, 148.4, 155.7; IR (KBr): 1579, 2204 cm^{-1}. MS calcd for $C_{19}H_{13}N_3S_2$ [M$^+$] 347.06; found 348.50.

2-Amino-4-(*p*-tolylthio)-4*H*-thiopyrano[2,3-*b*]quinoline-3-carbonitrile (**4b**). Colorless solid; yield: 82%; m.p. 156 °C; ^{1}H NMR (400 MHz, DMSO d_6): δ = 2.25 (s, 3H, CH_3), 5.55 (s, 1H), 7.00–7.07 (m, 4H), 7.16–7.18 (d, $J = 8.0$ Hz, 2H), 7.39 (s, 1H), 7.71–7.77 (m, 3H), 7.88–7.93 (t, 1H); IR (KBr): 818, 1643, 2191, 3317 cm^{-1}. MS calcd for $C_{14}H_{11}N_2S$ [M$^+$] 361.07; found 361.05.

2-Amino-7-methoxy-4-(phenylthio)-4*H*-thiopyrano[2,3-*b*]-quinoline-3-carbonitrile (**4m**). Colorless solid; yield: 93%; mp 143 °C; ^{1} H NMR (400 MHz, DMSO d_6): δ = 2.26 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.65 (s, 1H), 6.93 (s, 2H, NH_2), 7.12–7.14 (t, J = 7.6 Hz, 2H), 7.34 (m, 2H), 7.97–7.99 (d, $J = 8.0$ Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (100 MHz, DMSO d_6): 19.7 (CH_3), 55.9 (OCH_3), 56.0 (CH), 99.4, 106.7, 119.9, 121.5, 122.0, 124.7, 127.1, 127.36, 128.3, 129.9, 138.4, 154.3, 156.8, 158.2, 159.4, 159.6, 162.0; IR

(KBr): 785, 1039, 2223, 2942 cm^{-1}. MS calcd for $C_{20}H_{14}FN_3S_2$ $[M^+]$ 391.06; found 391.0.

Conclusions

In conclusion, we have developed a general, practical, and environmentally benign method to construct densely functionalized 4*H*-thiopyrano[2,3-*b*]quinolines *via* the three component reaction of 3-formyl-quinoline-2-thiones, malononitrile, and thiols (nucleophile) in ethanol in the presence of green catalyst, L-proline. This one-pot transformation involves the formation of one C–C bonds and two C–S bond to attained 4-substituted thiopyran ring in a single synthetic operation. Further, investigations of the compound with the various nucleophiles to the synthesis of the present methodology are underway. Also, such type of compounds can serve as a good starting point for drug discovery.

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