MWI-promoted preparation of 4*H*-thiopyran derivatives through one-pot multi-component reactions

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One-pot reaction of aromatic aldehydes, cyanothioacetamide and malononitrile under microwave irradiation proved to be an efficient way for the synthesis of 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles without any added catalyst.

Keywords: microwave heating, thioamides, malononitrile, 4*H*-thiopyrans, multi-component reactions

Recently thiopyran derivatives have gained increasing attention due to their importance as key units in medicinal chemistry and as versatile building blocks in organic synthesis,[1] for example, thiopyrans have been used in the construction of analogues of natural products, such as tetrahydrodicranenone B,[2] serricornin,[3] thromoboxanes,[4] and cyclopentanoids.[5] In view of these points, a great deal of effort has been devoted to developing new and efficient synthetic routes to thiopyrans.[6] However, many of these reported procedures are not fully satisfactory with regard to the cost of the reagents, using of strong basic catalyst, low isolated yield, or long reaction times. Therefore, development of novel methods for the preparation of the above mentioned compounds continues to be an interesting field of research in both synthetic and medicinal chemistry.

Multi-component reactions (MCRs) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[7] In line with the increasing interest in the preparation of large heterocyclic compound libraries, the development of new and synthetically valuable multi-component reactions remains a challenge for both academic and industrial research teams.[8] Furthermore, the utility of microwave energy in synthetic organic chemistry has been increasingly recognised in recent years since microwave irradiation (MWI) promoted reactions possess advantages such as an environmentally friendly nature, improved selectivity, enhanced reaction rate and cleaner products. Therefore, MWI-mediated multi-component reactions have constituted an especially attractive synthetic strategy for rapid and efficient library generation.[9] In the past few years we have been involved in a program aimed at developing efficient and green synthetic methods for the preparation of several classes of important heterocyclic compounds from inexpensive starting materials. During this phase of our research, we recently reported an efficient preparative procedure for benzopyran derivatives from chalcones and 1,3-cyclohexanedione in the presence of $InCl_3.4H_2O$ under MWI.[10] We have also reported a multi-component reaction of aldehydes, malononitrile and 1,3-diones to give pyran derivatives in ionic liquid medium without any added catalysts.[11] In continuation of our research interests in this field, we report here results of our investigation that enable the preparation of thiopyrans (**4**) from aromatic aldehyde (**1**), malononitrile (**2**) and cyanothioacetamide (**3**) under MWI without any added catalyst (Scheme 1).

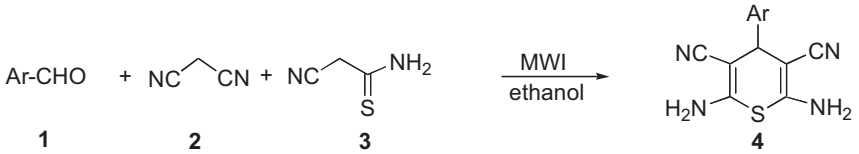
Results and discussion

Initially, the reaction of benzaldehyde (**1a**), malononitrile (**2**) and cyanothioacetamide (**3**) was examined.

A mixture of **1a** (0.5 mmol), **2** (0.5 mmol) and **3** (0.5 mmol) in 5 ml ethanol was put into a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity IR sensor for temperature control and measurement and irradiated at 250 W (internal temperature 80°C). TLC analysis showed that the reaction thus mediated under MWI came to a conclusion in 15 min. The solid formed was collected by suction. Spectra data of IR, ^{1}H NMR and ^{13}C NMR together with MS results indicated that the product was **4a** in a yield of 85%.

With the above result in hand, we then began the search for the scope of the aldehyde substrate (Scheme 1). The results shown in Table 1 indicated that aromatic aldehydes bearing either electron-donating or electron-withdrawing functional groups such as nitro, chloro, fluoro, bromo, hydroxyl or methoxy groups were able to take part in the reactions forming compounds **4**. At the same time, the electronic property and the position of the substituents on the aromatic ring of the aldehydes have obvious effects on the outcome of the condensation process. In general, shorter reaction times were needed and higher yields were obtained with substrates bearing electron-withdrawing groups on the *para*- or *meta*-position of the aromatic rings (Table 1, entries 2, 4, 7 and 9). On the other hand, while substrates bearing electron-donating groups or groups on the *ortho*-position can afford the corresponding products with good yields, a longer reaction period was necessary to complete the reaction (Table 1, entries 3, 6, 8 and 10) and the yields are somewhat lower. Aliphatic aldehydes including valeraldehyde and hexanal were also tried as substrates. However, the reactions were complicated and gave unidentified mixtures of products.

Although there are several reports of the preparation of this kind of compound, they are usually *via* the reaction of arylidenemalononitrile with 2-cyanothioacetamide in the presence of *N*-methylmorpholine or other basic promoters



1 **2** **3** **4**

Scheme 1

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Table 1 Preparation of thiopyrans under MWI

Entry	Ar	Reaction time/min)	Product	Yield/%[a]	M.p./°C
1	C_6H_5	15	**4a**	85	185–186 (181–183)[12]
2	*p*-$NO_2C_6H_4$	5	**4b**	91	198–200 (202–204)[13]
3	*o*-$NO_2C_6H_4$	10	**4c**	82	164–165
4	*m*-$NO_2C_6H_4$	8	**4d**	90	210–211
5	*p*-ClC_6H_4	12	**4e**	82	188–189 (189–190)[12]
6	*o*-ClC_6H_4	16	**4f**	75	168–170
7	*p*-BrC_6H_4	10	**4g**	85	187–188 (183) [12]
8	*o*-BrC_6H_4	16	**4h**	76	174–174.5
9	*p*-FC_6H_4	12	**4i**	88	172–172.5 (166–167)[12]
10	*o*-FC_6H_4	15	**4j**	78	181–183 (163–165)[14]
11	4-OH-3-$CH_3OC_6H_3$	18	**4k**	70	170–171

[a]Isolated yields based on aldehyde.

with reaction times of several hours. It is to say that not only are tedious preparative procedures unavoidable in that arylidenemalononitriles need to be prepared in advance from aldehydes and malononitrile, but also undesired products may be formed since the strongly basic conditions employed may be incompatible with functionalities embedded in the substrates. In contrast, with our method, thiopyrans were prepared from commercially available materials and the preparative procedure is usually complete in 5–18 minutes without any added catalysts.

In conclusion, we have developed an efficient MWI-promoted one-pot preparation of thiopyrans from aromatic aldehydes, malononitrile and cyanothioacetamide. The method has the advantages of high efficiency and preparative simplicity. Further efforts to find more applications of MWI-mediated multicomponent reactions are currently in progress in our laboratory.

Experimental

Melting points were measured by a Kofler micro-melting point apparatus. Infrared spectra were recorded on a Bruker Vector 22 spectrometer in KBr discs. ^{1}H NMR spectra were determined on a Bruker AC 400 spectrometer as DMSO-d_6 or CD_3OD solutions. Chemical shifts are reported in ppm downfield from the internal standard tetramethylsilane. Mass spectra were obtained in ESI mode using a Bruker Esquire 3000 mass spectrometer. Elemental analyses were performed on an EA-1110 instrument.

The microwave irradiations were performed in a commercially available single-mode microwave synthesis apparatus equipped with a high sensitivity infrared sensor for temperature control and measurement (MAS-I, Sineo Microwave Chemical Technology Co. Ltd., Shanghai, P.R. China).

Preparation of thiopyran derivatives **4**: *general procedure*
The aromatic aldehyde (**1**, 1 mmol), malononitrile (**2**, 0.066 g, 1 mmol) cyanothioacetamide (**3**, 0.10 g, 1 mmol) and ethanol (5 ml) were mixed in a flask and irradiated at 250 W (internal temperature 80°C) for a sufficient time as required to complete the reaction (monitored by TLC). Upon completion, the reaction mixture was allowed to cool to room temperature and the solid product was collected by filtration and washed with 95% ethanol to give the desired products **4** (Table 1). All the new products were fully characterised by IR, ^{1}H and ^{13}C NMR, MS and elemental analysis.

2,6-Diamino-4-phenyl-4H-thiopyran-3,5-dicarbonitrile (**4a**): IR: ν_{max} 3450, 3320, 2210 cm^{-1}. NMR (DMSO-d_6): δ_H 4.22 (s, 1H, CH), 6.89 (br s, 4H, 2 NH_2), 7.19–7.24 (m, 3H, ArH), 7.30–7.33 (m, 2H, ArH); δ_C 151.3, 143.55, 128.8, 127.2, 126.7, 118.9, 72.1, 43.4. MS (ESI): *m/z* 277 $[M + Na]^+$.

2,6-Diamino-4-(4-nitrophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4b**): IR: ν_{max} 3410, 3315, 2220 cm^{-1}. NMR (CD_3OD): δ_H 4.47 (s, 1H, CH), 7.53 (d, 2H, *J* = 8.0 Hz, ArH), 8.20 (d, 2H, *J* = 8.0 Hz, ArH); δ_C 152.1, 149.5, 146.8, 127.3, 123.2, 117.5, 71.65, 43.2. MS (ESI): *m/z* 322 $[M + Na]^+$.

2,6-Diamino-4-(2-nitrophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4c**): IR: ν_{max} 3400, 3320, 2210 cm^{-1}. NMR (DMSO-d_6): δ_H 4.97 (s, 1H, CH), 7.04 (br s, 4H, 2 NH_2), 7.48–7.55 (m, 2H, ArH), 7.69–7.73 (t, 1H, ArH, *J* = 7.6 Hz), 7.84–7.86 (d, 1H, ArH, *J* = 8.0 Hz); δ_C 151.7, 148.3, 137.6, 133.85, 130.0, 128.8, 124.4, 118.1, 70.7, 37.9. MS (ESI): *m/z* 322 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9N_5O_2S$: C 52.17, H 3.03, N 23.40; found: C 52.20, H 3.18, N 23.29%.

2,6-Diamino-4-(3-nitrophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4d**): IR: ν_{max} 3440, 3325, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.55 (s,1H,CH), 7.06 (br s, 4H, 2 NH_2), 7.65–7.70 (m, 2H, ArH), 8.04 (s, 1H, ArH), 8.10–8.13 (m, 2H, ArH); δ_C 152.05, 148.1, 145.8, 133.6, 130.5, 122.3, 121.1, 118.6, 71.05, 42.5. MS (ESI): *m/z* 322 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9N_5O_2S$: C 52.17, H 3.03, N 23.40; found: C 52.20, H 3.22, N 23.50%.

2,6-Diamino-4-(4-chlorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4e**): IR: ν_{max} 3460, 3320, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.28 (s, 1H, CH), 6.93 (br s, 4H, 2 NH_2), 7.21 (d, 2H, *J* = 8.4 Hz, ArH), 7.38 (d, 2H, *J* = 8.4 Hz, ArH); δ_C 151.4, 142.5, 131.8, 128.75, 128.6, 118.7, 71.7, 42.7. MS (ESI): *m/z* 311 $[M + Na]^+$.

2,6-Diamino-4-(2-chlorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4f**): IR: ν_{max} 3480, 3320, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.76 (s, 1H, CH), 6.95 (br s, 4H, 2 NH_2), 7.23–7.41 (m, 4H, ArH); δ_C 151.4, 140.9, 131.65, 129.8, 129.7, 129.1, 128.0, 118.3, 71.0, 42.65. MS (ESI): *m/z* 311 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9ClN_4S$: C 54.07, H 3.14, N 19.40; found: C 54.15, H 3.25, N 19.48%.

2,6-Diamino-4-(4-bromophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4g**): IR: ν_{max} 3460, 3330, 2210 cm^{-1}. NMR (DMSO-d_6) δ: 4.26 (s, 1H, CH), 6.49 (br s, 4H, 2 NH_2), 7.15 (d, 2H, *J* = 8.0 Hz, ArH), 7.52 (d, 2H, *J* = 8.0 Hz, ArH), ^{13}C NMR (DMSO-d_6) δ 151.4, 142.9, 131.7, 129.0, 120.3, 118.7, 71.6, 42.7. MS (ESI): m/z 355, 357 $[M + Na]^+$.

2,6-Diamino-4-(2-bromophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4h**): IR: ν_{max} 3450, 3330, 2220 cm^{-1}. NMR (DMSO-d_6): δ_H 4.78 (s, 1H, CH), 6.94 (br s, 4H, 2 NH_2), 7.15–7.19 (m, 1H, ArH), 7.34–7.37 (m, 2H, ArH), 7.55–7.59 (m,1H, ArH); δ_C 151.0, 142.9, 132.8, 129.95, 129.4, 128.7, 118.2, 71.2, 42.4. MS (ESI): *m/z* 355, 357 $[M + Na]^+$. Anal. Calcd for $C_{13}H_9BrN_4S$: C 46.86, H 2.72, N 16.81; found: C 46.98, H 2.65, N 16.88%.

2,6-Diamino-4-(4-fluorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4i**): IR: ν_{max} 3450, 3325, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.27 (s, 1H, CH), 6.91 (br s, 4H, 2 NH_2), 7.12–7.24 (m, 4H, ArH); δ_C 151.3, 139.55, 128.7, 128.6, 118.75,115.6, 115.4, 72.0, 42.4. MS (ESI): *m/z* 295 $[M + Na]^+$.

2,6-Diamino-4-(2-fluorophenyl)-4H-thiopyran-3,5-dicarbonitrile (**4j**): IR: ν_{max} 3440, 3325, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 4.52 (s, 1H, CH), 6.95 (br s, 4H, 2 NH_2), 7.14–7.32 (m, 4H, ArH); δ_C 160.8, 158.4, 152.0, 129.7, 129.6, 129.4, 129.3, 129.0, 129.0, 124.8, 118.45, 115.85, 115.6, 70.7, 37.3. MS (ESI): *m/z* 295 $[M + Na]^+$.

2,6-Diamino-4-(4-hydroxy-3-methoxyphenyl)-4H-thiopyran-3,5-dicarbonitrile (**4k**): IR: ν_{max} 3450, 3310, 2200 cm^{-1}. NMR (DMSO-d_6): δ_H 3.70 (s, 3H, OCH_3), 4.10 (s, 1H, CH), 6.58 (d, 1H, *J* = 8.0 Hz, ArH), 6.68–6.74 (m, 2H, ArH), 6.80 (br s, 4H, 2 NH_2), 8.91 (s, 1H, OH); δ_C 150.8, 147.6, 145.9, 134.5, 119.1, 118.9, 115.6, 111.2, 72.8, 55.7, 43.1. MS (ESI): *m/z* 323 $[M + Na]^+$. Anal. Calcd for $C_{14}H_{12}N_4O_2S$: C 55.99, H 4.03, N 18.65; found: C 56.10, H 4.05, N 18.78%.

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