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A concise, greener, solvent-free novel one-pot synthesis of trisubstituted thiophenes ☆

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ABSTRACT

Herein, we report a concise, greener, solvent-free, and novel one pot method for the synthesis of 2-morpholino-3-aryl-5-aroyl thiophenes using 1-morpholino-2-arylethanethione, *N,N′*-dimethyl formamide dimethyl acetal, and various phenacyl bromides. The driving force for this reaction is the removal of *N,N′*-dimethylamine from 3-(dimethylamino)-1-morpholino-2-arylprop-2-ene-1-thione resulting in various trisubstituted thiophenes (2-morpholino-3-aryl-5-aroyl thiophenes).

Syntheses of small molecules, especially five-membered ring heterocycles have always attracted the scientific community, because of their vivid therapeutic importance. In addition to this, small heterocyclic scaffolds are present in more than 50% of pharmaceutical substances and allow various interactions with the biological targets due to the presence of side chains or various polar bonds, which are not accessible in carbocyclic scaffolds. It is also revealed that the diversity of synthetic methods used by the pharmaceutical industries to generate heterocycles containing products is based on only five-membered aromatic heterocycles representing more than top 200 best selling drugs.[1]

Thiophene is an important structural motif in medicinal chemistry and it is considered as a classical bioisostere for the benzene ring and due to its small ring structure it is found in many therapeutically active substances (Fig. 1) such as Raloxifene, Olanzepine, Clopidogrel, Tiamenidine, Tiaprofenic acid, Suprofen, Raniliate strontium, potent PI3K inhibitors etc. One of the common methods for the synthesis of 2-morpholino thiophene is the Willgerodt–Kindler[2] reaction of acetophenone, sulfur, and morpholine which gives the intermediate 1-morpholino-2-arylethanethione. This 1-morpholino-2-arylethanthione intermediate on reaction with morpholine and triethyl orthoformate gives the dimorpholide compounds which on reaction with various aryl, aroyl halides result in 2-morpholino thiophenes.[3,4] In addition to this, recently, Huang et al. developed a multi-step synthesis of 2-morpholino thiophene compound known for its PI3K activity.[5] It has also been observed that the 2-aminothiophene compounds are well documented in the literature,[6,7] but the most popular Gewald method,[8] involves the multicomponent condensation of carbonyl compounds, cyanoacetates or malanonitrile, and elemental sulfur. The above mentioned processes are associated with drawbacks such as multistep reactions (except Gewald), harsh reaction conditions, complex and tedious experimental procedures, and lower yields. After a careful literature search, we realized that there is still a need to develop efficient and concise methods for the synthesis of thiophenes.

In continuation of our work on the synthesis of various bioactive heterocyclic compounds using *N,N′*-dimethyl formamide dimethyl acetal (DMF–DMA),[9,10] we were interested to explore 1-morpholino-2-arylethanethione intermediate resulting from the Willgerodt–Kindler reaction of various acetophenones, sulfur, and morpholine. We envisaged that this intermediate could be useful for the synthesis of thiophenes. We have developed an efficient, concise, greener, and novel sequential one-pot method for the synthesis of trisubstituted thiophenes from 1-morpholino-2-arylethanethione, DMF–DMA, and various phenacyl bromides resulting in various 2-morpholino-3-aryl-5-aroyl (trisubstituted) thiophenes. This method neither requires any reagent for the cyclization nor the solvents (Scheme 1) which is reported herein. To the best of our knowledge, the formation of 2-morpholino-3-aryl-5-aroyl (trisubstituted) thiophenes using *N,N′*-dimethyl formamide dimethyl acetal (DMF–DMA) has not been reported so far.

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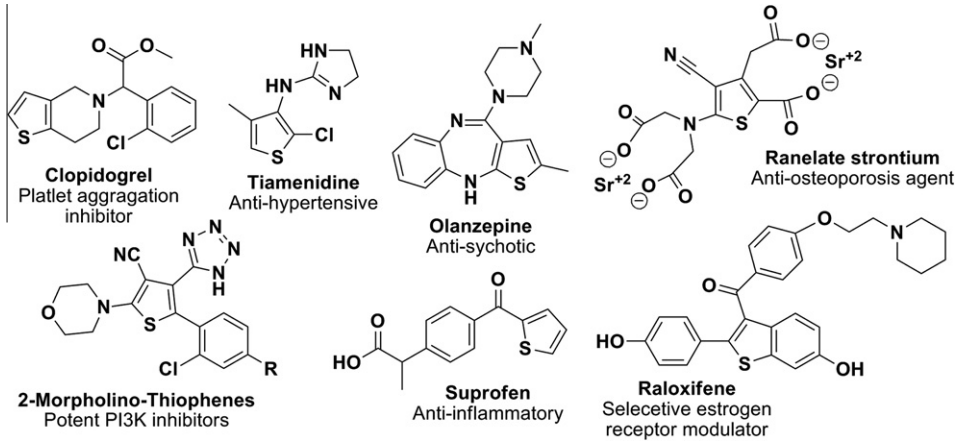
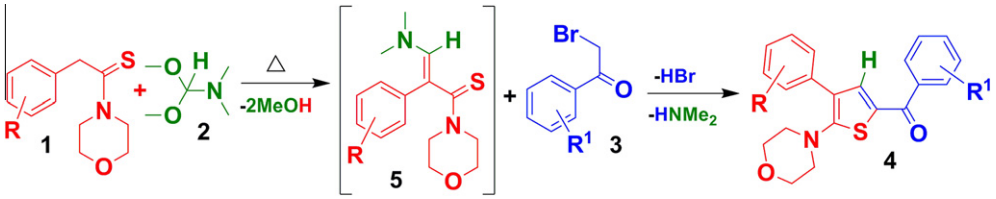


Figure 1. Select examples of biologically active thiophenes.



Scheme 1. One pot synthesis of trisubstituted thiophenes.

In order to check this hypothesis, we started our efforts by carrying out the sequential reaction of 1-morpholino-2-phenylethanethione **1a** and DMF–DMA **2** at 80–85 °C temperature which allows the removal of methanol to give the intermediate 3-(dimethylamino)-1-morpholino-2-phenylprop-2-ene-1-thione **5**. This intermediate **5** was then reacted with *p*-chloro phenacyl bromide **3a** at ambient temperature giving the desired trisubstituted thiophene **4a**, which was showing fluorescence spot in UV–visible spectroscopy. Further work-up of this reaction gave the yellowish solid.[12] The structure of this compound was confirmed by ^{1}H NMR, and Mass spectroscopy (Table 1). In addition to this, the present protocol is useful for the construction of variety of trisubstituted thiophenes with morpholine at the 2nd position of thiophene. The present protocol is novel, quite efficient (high yield), concise (one pot), and greener (no use of excess solvent as well as one of the substrate morpholines) as compared to our earlier reported method[3] in which a harsh condition (more than 130 °C temperature) is required to furnish the formation of di-morpholine compound in the second step.

The plausible reaction mechanism for the formation of these trisubstituted thiophenes is described in (Scheme 2). The synthesis of 1-morpholino-2-arylethanethione is well documented in the literature.[4] Subsequent reaction of 1-morpholino-2-arylethanethione **1** with DMF–DMA **2** at elevated temperatures resulted in the formation of intermediate **5**. The mechanism for the formation of intermediate **5** is reported in the literature.[11] The intermediate **5** is versatile in nature and has one dominant nucleophilic (C=S) site and one electrophilic (C–NMe_2) site. The highly polar C–Br bond of phenacyl bromide is facile toward the nucleophilic attack of sulfur to give species **6**. The double bond resulted from keto-enol tautomerism attacks the electron deficient imine carbon (to which electron pulling quaternary nitrogen is attached, which makes this carbon a strong electrophile) to give the intermediate **8** in a *5-exo-trig* cyclization manner. This intermediate now could be stabilized by gaining the aromatic property by the removal of dimethyl amine and hydrogen bromide resulting in the desired trisubstituted thiophenes **4**. During the course of the study, it was observed that the reaction of electron withdrawing groups present in phenacyl bromide furnished good yields (**4a**, **b**, **e**, and **m**), while the electron rich phenacyl bromide resulted in comparatively lower yields (**4d**, **j**, and **l**) and the reaction of intermediate 1-morpholino-2-arylethanethione containing electron withdrawing group with phenacyl bromide containing electron releasing groups elicited lower yields (**4h**, **j**, and **k**) as shown in Table 1.

In conclusion, we have demonstrated a novel, concise, efficient, and greener one-pot method for the synthesis of trisubstituted thiophenes from simple starting materials like 1-morpholino-2-arylethanethione, *N*,*N*′-dimethylformamide dimethyl acetal, and various phenacyl bromides to elicit the tri-substituted thiophenes in good to excellent yields. The present method is attractive due to its facile conditions suggesting this protocol could be an alternative to other protocols (harsh conditions). The product can be isolated very easily without the use of chromatography. Furthermore, the present protocol can be useful in future for the generation of compound libraries of thiophene compounds incorporating various cyclic amines like piperazine, pyrrolidine, and *N*-methyl piperazine at the 2nd position of thiophenes. Further exploration for the synthesis of thiophene compounds incorporating various halogen partners using this methodology is under development.

Acknowledgments

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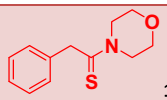
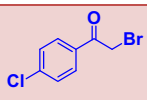
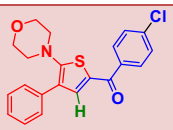
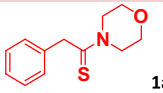
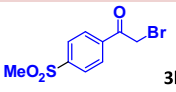
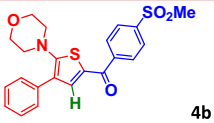
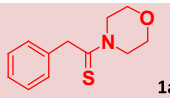
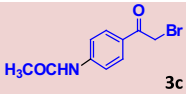
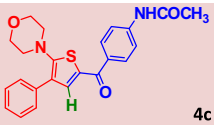
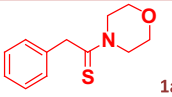
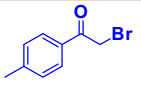
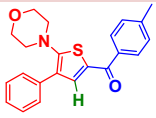
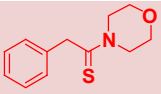
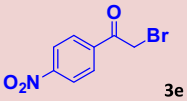
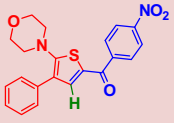
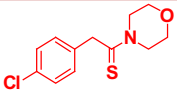
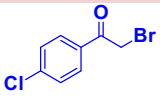
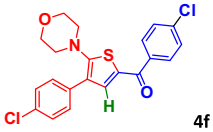
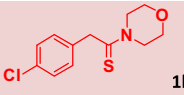
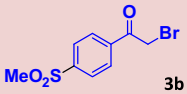
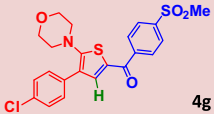
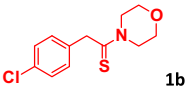
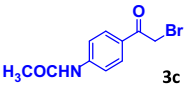
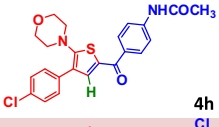
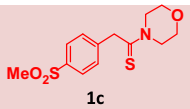
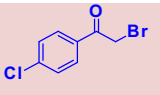
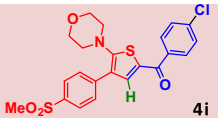
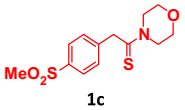
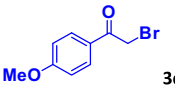
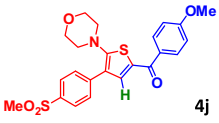
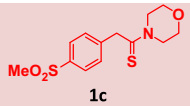
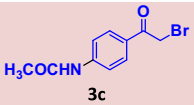
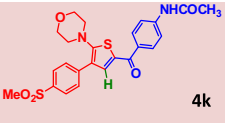
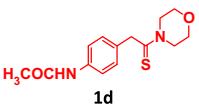
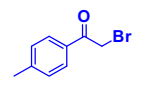
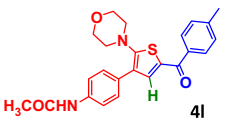
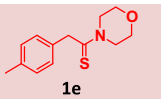
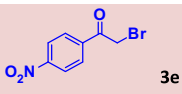
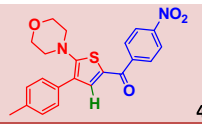
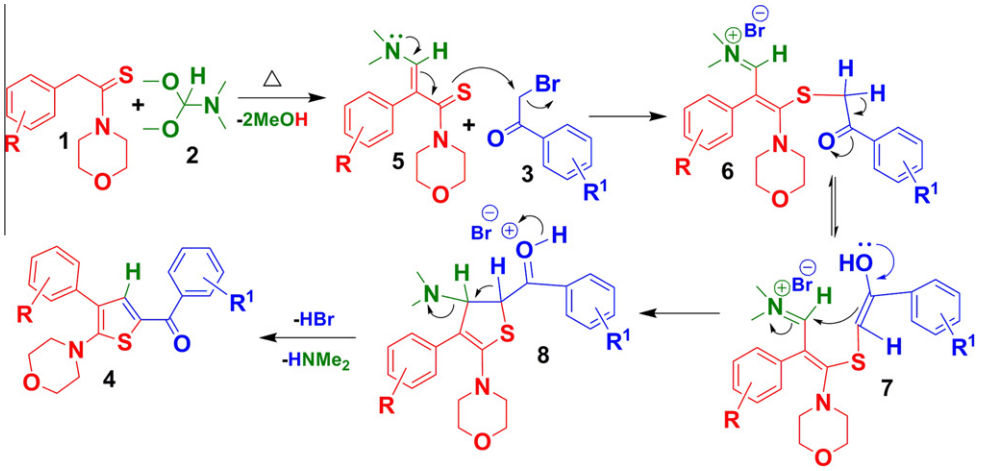
Table 1
Synthesis of trisubstituted thiophenes from 1-morpholino-2-arylethanethione, DMF–DMA, and phenacyl bromides

Entry	Thioamide (1)	Phenacyl bromide (3)	Thiophenes (4)	Yield (%)a	NMR & Mass[b] Spectral Analysis (200 MHz, $CDCl_3$, & DMSO-d_6, Chemical Shift in δ ppm)	Melting Range (°C)
1	 1a	 3a	 4a	78	**^{1}H NMR ($CDCl_3$)** = 3.0-3.1 (m, 4H), 3.73-3.77 (m, 4H), 7.24-7.78 (m, 10H). Mol. Wt. = 383.07, Found = 384.1.	152-154
2	 1a	 3b	 4b	82	**^{1}H NMR ($CDCl_3$)** = 3.1-3.13 (s, 3H and s, 3H), 3.27-3.29 (s, 1H) 3.75-3.78 (s, 3H), 4.02-4.05 (s, 1H), 7.2-7.55 (m, 6H), 7.94-7.97 (d, 2H), 8.0-8.08 (d, 2H). Mol. Wt. = 427.09, Found = 428.08.	220-222
3	 1a	 3c	 4c	79	**^{1}H NMR ($CDCl_3$)** = 2.8 (s, 3H), 3.73-3.8 (m, 4H), 3.9-4.0 (m, 4H), 7.2-7.8 (m, 10H), 9.7 (s, 1H). Mol. Wt. = 406.13, Found = 407.10.	215-216
4	 1a	 3d	 4d	67	**^{1}H NMR ($CDCl_3$) =** 2.42 (s, 3H), 3.05-3.08 (m, 4H), 3.74-3.77 (m, 4H), 7.26-7.46 (m, 5H), 7.5-7.7 (s, 5H). Mol. Wt. = 363.13, Found = 364.20.	198-200
5	 1a	 3e	 4e	82	**^{1}H NMR ($CDCl_3$)** = 3.10-3.13 (m, 4H), 3.75-3.78 (m, 4H), 7.26-7.54 (m, 6H), 7.92-7.95 (d, 2H), 8.31-8.34 (d, 2H). Mol. Wt. = 394.10, Found = 395.12.	212-214
6	 1b	 3a	 4f	73	**^{1}H NMR ($CDCl_3$)** = 3.04-3.09 (m, 4H), 3.74-3.78 (m, 4H), 7.2-7.7 (m, 9H). Mol. Wt. = 417.04 , Found = 418.10.	202-204
7	 1b	 3b	 4g	70	**^{1}H NMR ($CDCl_3$)** = 3.08-3.11 (s, 8H), 3.75-3.79 (s, 3H), 7.2-7.55 (m, 5H), 7.94-8.08 (m, 4H). Mol. Wt. = 461.05 , Found = 462.10.	222-224
8	 1b	 3c	 4h	61	**^{1}H NMR ($CDCl_3$)** =2.22(s, 3H), 3.0-3.07 (d, 4H), 3.7-3.78 (d, 4H), 7.2-7.6 (m, 9H), 7.8-7.83 (s, 1H). Mol. Wt. = 440.09, Found = 441.10.	148-149
9	 1c	 3a	 4i	66	**^{1}H NMR (DMSO-D_6):** 3.01-3.18 (m, 4H), 3.19 (s, 3H), 3.58-3.76 (m, 4H), 7.57-7.58 (d, 2Hl), 7.69 (s, 1H), 7.81-7.83 (d, 2H), 7.92 (s, 4H). Mol. Wt. = 461.05, Found = 462.10.	169-171
10	 1c	 3d	 4j	59	**^{1}H NMR (DMSO-D_6):** 3.01-3.08 (d, 4H), 3.62 (s, 3H, SO_2CH_3), 3.68 (s, 3H, OCH_3), 3.70-3.74 (d, 4H), 7.32-7.34 (m, 4H), 7.67 (s, 1H), 7.73-7.93 (s, 4H). Mol. Wt. = 457.10, Found = 458.09.	154-156
11	 1c	 3c	 4k	62	**^{1}H NMR (DMSO-D_6):** 2.07 (s, 3H, $COCH_3$), 3.00-3.02 (m, 4H), 3.21 (s, 3H, SO_2CH_3), 3.69-3.71 (m, 4H), 7.70-7.73 (m, 2H), 7.81-7.83 (d, 2H), 7.91-7.97 (m, 4H), 10.25 (s, 1H). Mol. Wt. = 484.11 , Found = 485.16.	129-131
12	 1d	 3d	 4l	67	**^{1}H NMR (DMSO-D_6):** 2.02 (s, 3H), 2.97 (m, 4H), 3.37 (s, 3H), 3.67 (m, 4H), 7.31-7.32 (d, 2H), 7.53-7.61 (m, 1H), 7.69-7.70 (m, 2H), 10.05 (1H). Mol. Wt. = 420.15, Found = 421.20.	198-200
13	 1e	 3e	 4m	83	**^{1}H NMR ($CDCl_3$)** = 2.33 (s, 3H,), 3.14-3.34 (m, 4H), 4.02(m, 4H), 7.03-8.29 (m, 9H). Mol. Wt. = 408.11, Found = 409.13.	200-201

[a] Yields refer to isolated products. Melting points of compounds are uncorrected.
[b] LC-MS analysis M^{+1} at m/z.



Scheme 2. Plausible reaction mechanism for trisubstituted thiophene formation.

References and notes

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12. *General experimental procedure for the preparation of 2-morpholino-3aryl-5aroyl thiophenes*: In a hot air dried flask, 1-morpholino-2-arylethanethione **1** (1.0 mmol) and dimethylformamide dimethyl acetal **2** (1.5 mmol) were mixed together and heated to 80–85 °C for 6–10 h. Progress of the reaction was monitored by TLC using ethyl acetate/hexane (4:6), showing the consumption of both the starting materials. The reaction was then allowed to be at ambient temperature and phenacyl bromide **3** (1.0 mmol) was added with stirring. The reaction was then again maintained at same conditions for another 3–6 h. After completion of the reaction, the reaction mixture was then evaporated (50–60 °C) on Buchi rotavapor to remove the volatiles and then poured into cold water, upon stirring precipitates were observed, which were collected on Buchner funnel (If no precipitate in case of **4d**, **4j** and **4l**, the reaction mixture was extracted with suitable solvent). These precipitates were then dissolved in either dichloromethane or ethyl acetate and dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residues were treated with hexane and/or ether to give the pure compounds (**4a**–**m**).