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ORIGINAL PAPER

Efficient synthesis of new 3-amino-4-cyanothiophene derivatives

Salwa E. M. El-Meligie[1] · Nadia A. Khalil[1] · Hala B. El-Nassan[1] · Ahmed A. M. Ibraheem[1]

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Abstract
An efficient and atom economic modification of a previously reported synthetic pathway to tetrasubstituted thiophenes is described. The previously published synthetic methodology involved a one pot procedure starting with ketene dithioacetal and an appropriate secondary amine, and subsequent reaction with Na_2S and phenacyl bromide. However, the liberated methanethiolate by-product was competed with enethiolate intermediate for phenacyl bromide, which reduced the yield and imposed the necessity to use two molar equivalents of α-haloketone reagent to increase the yield of the target thiophene products. In the present work, the proposed modification consisted in isolation of the intermediate enethiolate derivative, thereby reducing quantity of the α-haloketone to one molar equivalent. Moreover, the reaction conditions were optimized to attain optimum base/solvent combination to improve the yield of the target derivatives. Following our modified procedure, three series of new 3-amino-4-cyanothiophene derivatives were synthesized and isolated in high yields and high purity.

Keywords Thiophene · 3-Amino-4-cyanothiophene · Ketene dithioacetals · Thiophene-2-carboxamides

Introduction

Substituted and heteroannulated thiophene nucleus constitute crucial structural motifs found in a number of FDA-approved drugs of various pharmacological activities (Gramec et al. 2014) such as the antidepressant drug Duloxetine, the antihypertensive Eprosartan, and the antipsychotic Olanzapine. In addition, a number of thiophene-containing scaffolds are currently in clinical trials (Court et al. 2016; Sarker et al. 2015). The 3-amino-4-carbonitrile thiophene derivative **I** was documented as a kinase inhibitor (Cheeseright et al. 2009; Workman & Collins, 2013). The 3-aminothiophene-2-acylhydrazone derivative **II** was reported as analgesic and anti-inflammatory agent (Alves, Barreiro, Suzana, & Moreira, 2014). Whilst, the 3-amino-thiophene carbohydrazide derivative **III** was reported as inhibitor of angiogenesis (Papakyriakou et al. 2014) (Fig. 1).

On the other hand, piperazine moiety is considered as an important scaffold in a large number of biologically active candidates (Al-ghorbani et al. 2015; Singh et al. 2015; Walayat et al. 2019). Existence of piperazine moiety is known to increase the water solubility of the compounds, and piperazine ring is considered a privileged structural element in medicinal chemistry which can be used to build a library of compounds to be tested against certain receptors (Al-ghorbani et al. 2015). For example, 4-[(4-arylpiperazin-1-yl)methyl]-5-substituted-thiophenes **IV** exhibited allosteric enhancer activity at the A1 adenosine receptor (Romagnoli et al. 2012) (Fig. 1).

On the basis of the broad spectrum pharmacological profile observed by thiophene-based compounds, the development of new synthetic strategies, optimization, and greening of current synthetic routes may be beneficial to the pharmaceutical industry.

Literature has been enriched with numerous reports that describe various synthetic pathways to access thiophene derivatives with different substitution pattern (Li 2009). Particular attention has been given to ketene *N*,*S*- and *S*,*S*-acetals that have been used in the synthetic process of thiophene-containing compounds including 3-amino-4-cyanothiophenes bearing a substituted amino group at position 5. (Ahmed 2008; Farhat et al. 2016; Gompper and Töpfl 1962; Gruner et al. 2008; Thomae et al. 2009; Zhang et al. 2016).

In 2009, Thomae et al. (2009) reported a one-pot four step procedure for the synthesis of tetrasubstituted thiophenes in high yields (Scheme 1). The versatility of this method

✉ Hala B. El-Nassan
hala_bakr@hotmail.com

[1] Pharmaceutical Organic Chemistry Department, Faculty of Pharmacy, Cairo University, 33 Kasr El-Aini Street, Cairo 11562, Egypt

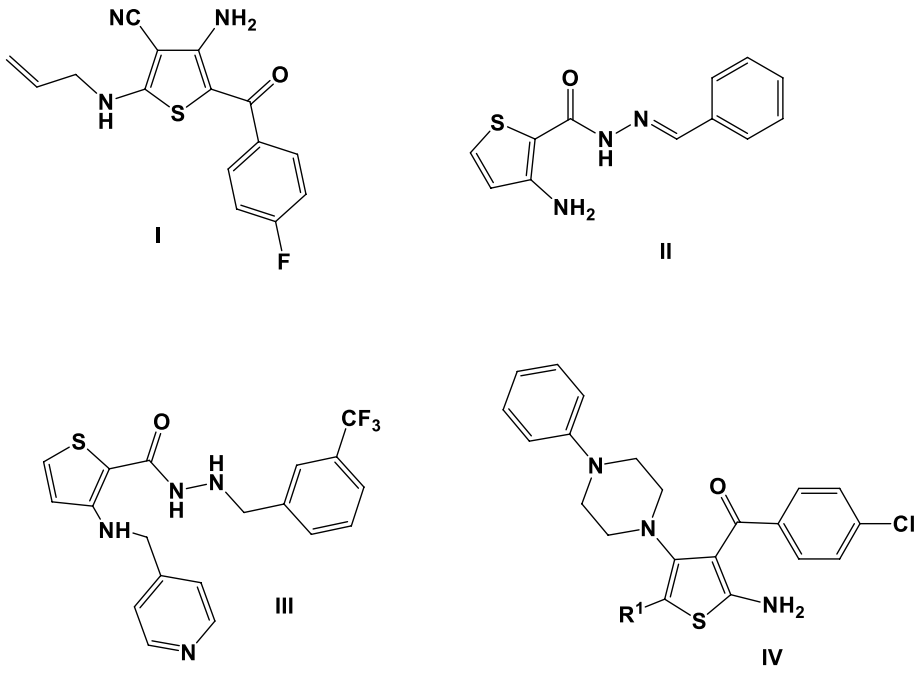
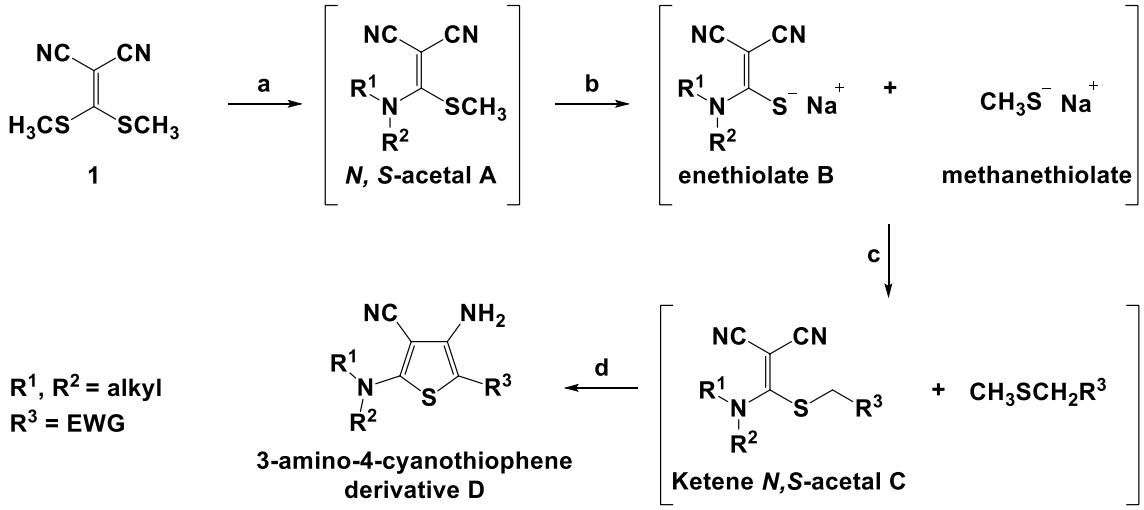


Fig. 1 A number of biologically active thiophene-containing compounds



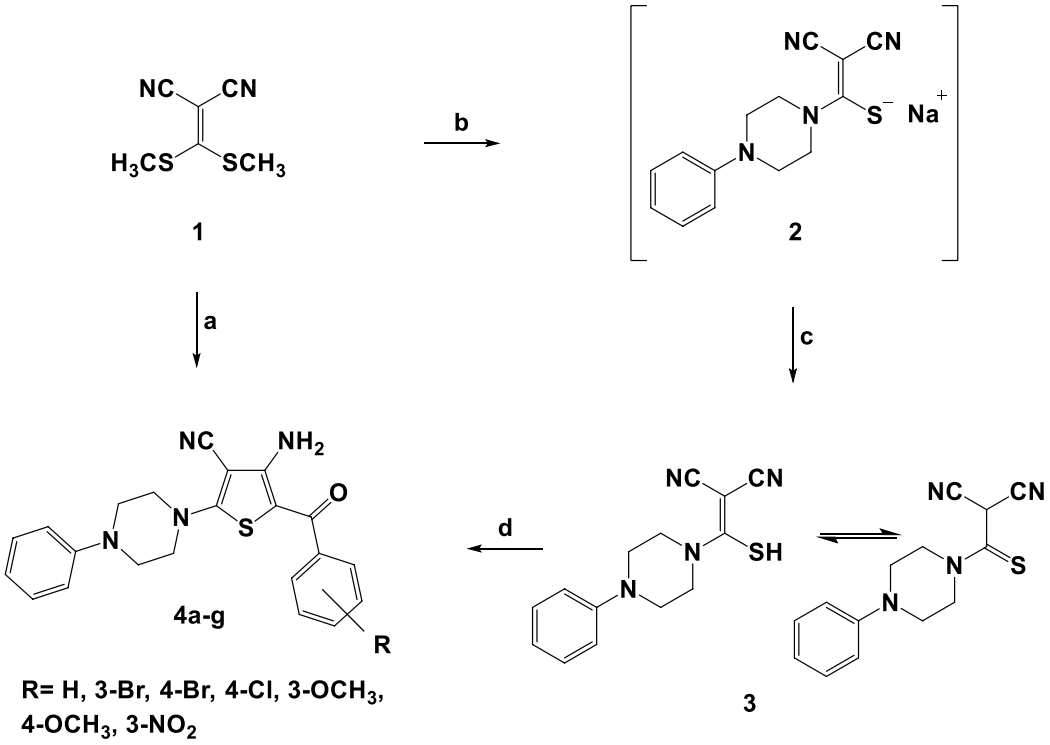
Reaction conditions: a) HNR^1R^2, 70 °C, DMF; b) $Na_2S.9H_2O$, 70 °C; c) R^3CH_2X (2 molar equiv.), 50 °C; d) K_2CO_3, 50 °C.

Scheme 1 Sequential one-pot synthesis of substituted thiophene derivatives

allowed for the access to variously substituted thiophenes, especially 3-amino-4-cyanothiophene derivatives, the synthesis of which by the common synthetic routes was found to be unsatisfactory. Motivated by these verdicts, herein we report the synthesis of novel 3-amino-4-cyanothiophenes **4a–g**, **6a–k** and **7**. Furthermore, the optimization of the reaction conditions was performed aiming to improve the yield, purity and economy of the reaction (Schemes 2, 3).

Experimental

All the chemicals were purchased from various commercial suppliers and were used without further purification. The melting points were determined using Stuart SMP20 apparatus and are uncorrected. The IR spectra were acquired using Shimadzu IR-435 spectrophotometer and



Reaction conditions:
a) i) 1-phenylpiperazine, 70 °C, DMF; ii) $Na_2S.9H_2O$, 70 °C; iii) phenacyl bromide (2 molar equiv.) 50 °C; iv) K_2CO_3, 50 °C;
b) i) 1-phenylpiperazine, DMF, 70 °C; ii) $Na_2S.9H_2O$, 70 °C;
c) saline acetic acid- sodium acetate solution;
d) different phenacyl bromides (1 molar equiv.), K_2CO_3, ethanol-water (3:1) mixture, reflux, 1h.

Scheme 2 Synthesis of substituted thiophenecarbonitrile derivatives **4a–g**

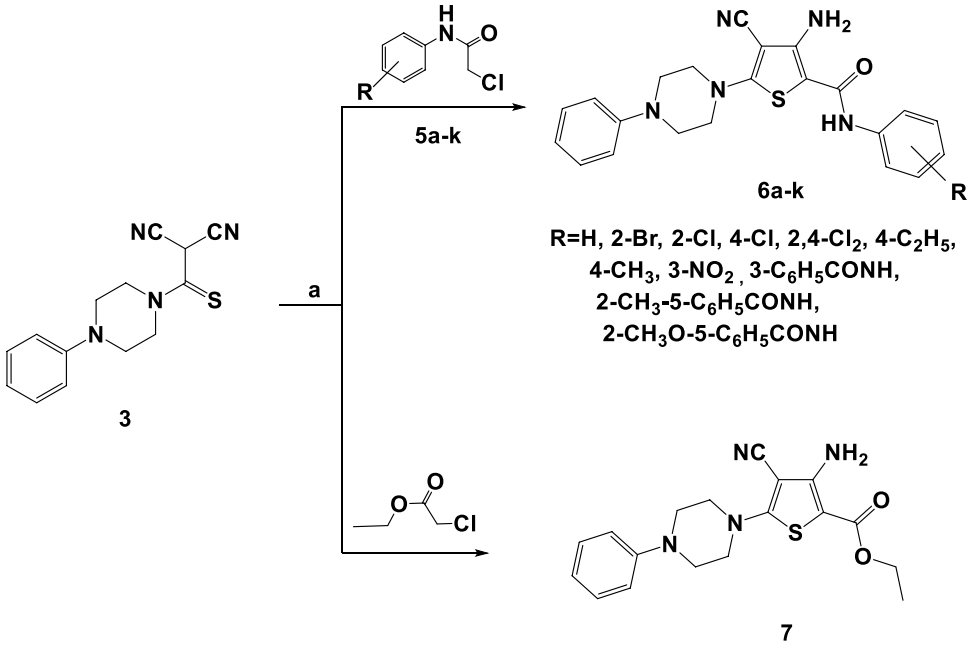
the values are represented in cm^{-1}. Bruker AVANCETM III 400 MHz spectrophotometer was used for the acquisition of ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of the new compounds using DMSO-d_6 a solvent. Nuclear magnetic resonance spectra were processed on MestreNova 11.0.4 program using residual solvent peak as the internal standard. Chemical shifts and coupling constants are presented in ppm and in Hz, respectively. Both IR and NMR spectra were carried out at Faculty of Pharmacy, Cairo University, Cairo, Egypt. Elemental analyses were carried out at The Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt. The preparation of 3,3-dimethylthio-2-cyanoacrylonitrile (Thomae et al. 2009; Yu and Cai 2003) (**1**) and 2-chloro-*N*-arylacetamides **5a–i** (Al-Nadaf et al. 2010; Kumar et al. 2014; Ma et al. 2011; Monforte et al. 2014; Rajak et al. 2012) was performed as previously reported.

2-(4-Phenylpiperazine-1-carbonothioyl)malononitrile (3)

A mixture of compound **1** (11.92 g, 70 mmol) and 1-phenylpiperazine (11.36 g, 11.0 mL, 70 mmol) in DMF (70 mL) was stirred at 70 °C for 2 h. Thereafter, $Na_2S \cdot 9H_2O$ (16.81 g, 70 mmol) was added, and the reaction mixture was stirred at 70 °C for further 2 h. The mixture was diluted with water (40 mL) and filtered. The filtrate was cooled to 0 °C, then added to a 500 mL of a stirred saline acetic acid-sodium acetate solution (NaCl: 11.69 g, 200 mmol; CH_3COONa: 12 g, 150 mmol; CH_3COOH: 75 mL, 1250 mmol). The precipitate formed was filtered, washed with water (100 mL), air-dried until a constant weight, then crystallized from water-acetic acid (1:1) mixture.

Yield: 85%. mp 130–131 °C. IR (cm^{-1}); 2194, 2164 (C≡N). ^1H NMR (ppm): 3.21 (t, 4H, $J = 4.9$ Hz, CH_2), 4.27

Scheme 3 Synthesis of substituted thiophenecarbonitrile derivatives **6a–k and 7**



Reaction conditions: a) K_2CO_3, ethanol-water (3:1) mixture, reflux.

(t, 4H, $J = 4.9$ Hz, CH_2), 6.86–7.30 (m, 6H, ArH, $CH(CN)_2$. ^{13}C NMR (ppm): 49.0, 50.5, 51.0 (piperazine Cs and $\underline{C}H(CN)_2$), 115.9, 119.5, 123.0, 129.3, 151.3 (Ar. Cs and CN), 195.4 (C=S). Anal. Calcd for $C_{14}H_{14}N_4S$: C, 62.20; H, 5.22; N, 20.72. Found: C, 62.47; H, 5.36; N, 21.04.

4-Amino-5-aroyl-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitriles 4a–g

Method A

A mixture of **1** (0.51 g, 3 mmol) and 1-phenylpiperazine (0.49 g, 0.47 mL, 3 mmol) in DMF (5 mL) was stirred at 70 °C for 75 min. Then, $Na_2S \cdot 9H_2O$ (0.72 g, 3 mmol) was added, and the stirring was continued at 70 °C for additional 2 h. The corresponding phenacyl bromide (6 mmol) was added portionwise to the reaction mixture, and the mixture was stirred at 70 °C for 2 h. Finally, the reaction was basified with K_2CO_3 (0.41 g, 3 mmol) and stirring was continued at 70 °C for 90 min. After cooling, the reaction mixture was poured onto ice water (50 mL) and stirred for 1 h. The precipitate formed was filtered, washed with ethanol (2 × 20 mL), then with diethyl ether (10 mL), dried and crystallized from a suitable solvent.

Method B

A solution of compound **3** (0.70 g, 2.6 mmol), and potassium carbonate (0.72 g, 5.2 mmol) in ethanol–water mixture (1:1, 25 mL) was added to a heated solution of the corresponding phenacyl bromide (2.6 mmol) in ethanol (25 mL). The reaction mixture was heated under reflux for 1 h. After cooling, the solid product was filtered, washed with ethanol (2 × 20 mL), oven-dried and crystallized from the suitable solvent.

4-Amino-5-benzoyl-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4a)

Yield: 74% (method B), crystallized from ethanol-ethyl acetate (1:1) mixture; mp 205–207 °C; IR (cm^{-1}): 3371, 3271 (NH_2), 2198 (C≡N), 1612 (C=O). ^1H NMR (ppm): 3.31 (t, 4H, $J = 5.2$ Hz, CH_2), 3.76 (t, 4H, $J = 5.2$ Hz, CH_2), 6.80–7.63 (m, 10H, ArH), 7.96 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (ppm): 47.2, 49.6 (piperazine Cs); 77.2, 93.6, 115.1, 115.6, 119.4, 126.8, 128.4, 129.0, 130.5, 140.8, 150.0, 158.9, 167.1 (Ar. Cs and C≡N); 184.0 (C=O). Anal. Calcd for $C_{22}H_{20}N_4OS$: C, 68.02; H, 5.19; N, 14.42. Found: C, 68.31; H, 5.27; N, 14.35.

4-Amino-5-(3-bromobenzoyl)-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4b)

Yield: 23% (method A); 71% (method B), crystallized from ethanol-ethyl acetate (1:1) mixture; mp 233–235 °C; IR (cm^{-1}): 3394, 3259 (NH_2); 2198 (C≡N); 1597 (C=O); ^1H NMR (ppm): 3.31–3.33 (m, 4H, CH_2), 3.78–3.80 (m, 4H, CH_2), 6.80–7.73 (m, 9H, ArH), 8.00 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (ppm): 47.2, 49.6 (piperazine Cs); 77.0, 93.4, 115.0, 115.6, 119.4, 121.8, 125.7, 129.0, 129.4,

130.7, 133.2, 142.9, 150.0, 159.4, 167.2 (Ar. Cs and C≡N); 181.8 (C=O). Anal. Calcd for $C_{22}H_{19}BrN_4OS$: C, 56.54; H, 4.10; N, 11.99. Found: C, 56.76; H, 3.98; N, 12.17.

4-Amino-5-(4-bromobenzoyl)-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4c)

Yield: 47% (method A); 74% (method B), crystallized from ethanol-ethyl acetate (1:1) mixture; mp 225–227 °C. IR (cm^{-1}): 3383, 3282 (NH_2); 2198 (C≡N); 1600 (C=O); ^{1}H NMR (ppm): 3.31 (t, 4H, J = 5.0 Hz, CH_2), 3.77 (t, 4H, J = 5.0 Hz, CH_2), 6.80–7.26 (m, 5H, ArH), 7.56 (d, 2H, J = 8.4 Hz, ArH), 7.68 (d, 2H, J = 8.4 Hz, ArH), 7.99 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (ppm): 47.3, 49.6 (piperazine Cs); 77.1, 93.5, 115.1, 115.7, 119.5, 124.1, 129.0, 129.0, 131.5, 139.8, 150.0, 159.3, 167.1 (Ar. Cs and C≡N); 182.6 (C=O). Anal. Calcd for $C_{22}H_{19}BrN_4OS$: C, 56.54; H, 4.10; N, 11.99. Found: C, 56.70; H, 4.17; N, 12.23.

4-Amino-5-(4-chlorobenzoyl)-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4d)

Yield: 27% (method A); 77% (method B), crystallized from ethanol-ethyl acetate (1:1) mixture; mp 218–220 °C. IR (cm^{-1}): 3383, 3286 (NH_2), 2198 (C≡N), 1600 (C=O); ^{1}H NMR (ppm): 3.31–3.33 (m, 4H, CH_2), 3.78 (t, 4H, J = 5.0 Hz, CH_2), 6.80–7.26 (m, 5H, ArH), 7.55 (d, 2H, J = 8.4 Hz, ArH), 7.64 (d, 2H, J = 8.4 Hz, ArH), 7.99 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (ppm): 47.3, 49.7 (piperazine Cs); 77.1, 93.5, 115.1, 115.7, 119.5, 128.6, 128.8, 129.1, 135.3, 139.5, 150.1, 159.3, 167.1 (Ar. Cs and C≡N); 182.6 (C=O). Anal. Calcd for $C_{22}H_{19}ClN_4OS$: C, 62.48; H, 4.53; N, 13.25. Found: C, 62.61; H, 4.70; N, 13.57.

4-Amino-5-(3-methoxybenzoyl)-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4e)

Yield: 68% (method B), crystallized from ethanol-ethyl acetate (1:1) mixture; mp 209–210 °C. IR (cm^{-1}): 3375, 3275 (NH_2), 2954, 2927, 2831 (aliphatic C–H), 2198 (C≡N), 1612 (C=O); ^{1}H NMR (ppm): 3.31 (t, 4H, J = 5.0 Hz, CH_2), 3.76 (t, 4H, J = 5.0 Hz, CH_2), 3.80 (s, 3H, OCH_3), 6.80–7.42 (m, 9H, ArH), 7.96 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (ppm): 47.3, 49.6 (piperazine Cs); 55.2 (OCH_3); 77.1, 93.7, 112.0, 115.1, 115.7, 116.3, 118.9, 119.4, 128.3, 129.0, 129.7, 142.2, 150.0, 159.1, 167.1 (Ar. Cs and C≡N); 183.7 (C=O). Anal. Calcd for $C_{23}H_{22}N_4O_2S$: C, 66.01; H, 5.30; N, 13.39. Found: C, 66.23; H, 5.39; N, 13.58.

4-Amino-5-(4-methoxybenzoyl)-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4f)

Yield: 88% (method B), crystallized from ethanol-ethyl acetate (1:1) mixture; mp 220–222 °C. IR (cm^{-1}): 3379, 3278 (NH_2), 2935, 2835 (aliphatic C–H), 2202 (C≡N), 1604 (C=O); ^{1}H NMR (ppm): 3.30–3.32 (m, 4H, CH_2), 3.75–3.77 (m, 4H, CH_2), 3.81 (s, 3H, OCH_3), 6.80–7.65 (m, 9H, ArH), 7.88 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (ppm): 47.3, 49.6 (piperazine Cs); 55.3 (OCH_3); 77.3, 93.5, 113.7, 115.2, 115.7, 119.4, 128.9, 129.0, 133.2, 150.0, 158.6, 161.1, 166.8 (Ar. Cs and C≡N); 183.4 (C=O). Anal. Calcd for $C_{23}H_{22}N_4O_2S$: C, 66.01; H, 5.30; N, 13.39. Found: C, 66.18; H, 5.28; N, 13.61.

4-Amino-5-(3-nitrobenzoyl)-2-(4-phenylpiperazin-1-yl)-3-thiophenecarbonitrile (4g)

Yield: 77% (method B), crystallized from toluene; mp 244–246 °C. IR (cm^{-1}): 3394, 3263 (NH_2), 2198 (C≡N), 1600 (C=O), 1527, 1342 (NO_2); ^{1}H NMR (ppm): 3.31–3.34 (m, 4H, CH_2), 3.79–3.81 (m, 4H, CH_2), 6.80–8.36 (m, 11H, 9 ArH and NH_2); ^{13}C NMR (ppm): 47.2, 49.7 (piperazine Cs), 76.9, 93.2, 115.0, 115.6, 119.4, 121.5, 125.1, 129.0, 130.4, 133.1, 141.9, 147.7, 150.0, 159.8, 167.2 (Ar. Cs and C≡N), 180.7 (C=O). Anal. Calcd for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16. Found: C, 61.23; H, 4.37; N, 16.40.

2-Chloro-*N*-(substituted) phenylacetamides 5j,k

Chloroacetyl chloride (5.65 g, 4 mL, 50 mmol) was added dropwise to a stirred solution of the corresponding 3-aminobenzamide derivatives (50 mmol), and TEA (5.06 g, 7 mL, 50 mmol) in DCM (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 h, then the solvent was evaporated. The residue was washed with water, air-dried until a constant weight, and recrystallized from aqueous ethanol.

N-(3-(2-Chloroacetamido)-4-methylphenyl)benzamide (5j)

Yield: 73%, mp 186–187 °C. IR (cm^{-1}): 3232, 3201 (NH), 1678, 1643 (C=O); ^{1}H NMR (ppm): 2.18 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 7.19–7.97 (m, 8H, ArH), 9.70 (s, 1H, CONH, D_2O exchangeable), 10.25 (s, 1H, CONH, D_2O exchangeable). ^{13}C NMR (ppm): 17.2 (CH_3); 43.1 (CH_2); 117.2, 117.9, 127.2, 127.6, 128.3, 130.2, 131.5, 134.8, 135.4, 137.2 (Ar. Cs); 164.8, 165.3 (2 C=O). Anal. Calcd for $C_{16}H_{15}ClN_2O_2$

(302.76): C, 63.48; H, 4.99; N, 9.25. Found: C, 63.39; H, 4.52; N, 8.96.

N-(3-(2-Chloroacetamido)-4-methoxyphenyl)benzamide (5k)

Yield: 87%, mp 178–180 °C. IR (cm^{-1}): 3379, 3271 (NH), 1697, 1643 (C=O); ^{1}H NMR (ppm): 3.85 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.05–8.38 (m, 8H, ArH), 9.52 (s, 1H, CONH, D_2O exchangeable), 10.20 (s, 1H, CONH, D_2O exchangeable). ^{13}C NMR (ppm): 43.4 (CH_2); 55.9 (CH_3); 111.0, 114.9, 117.3, 126.2, 127.5, 128.3, 131.4, 132.0, 134.9, 146.0 (Ar. Cs); 164.6, 165.1 (2 C=O). Anal. Calcd for $C_{16}H_{15}ClN_2O_3$ (318.76): C, 60.29; H, 4.74; N, 8.79. Found: C, 60.54; H, 5.01; N, 8.27.

3-Amino-4-cyano-5-(4-phenylpiperazin-1-yl)-N-(aryl)-2-thiophene-carboxamides 6a–k

A solution of compound **3** (0.81 g, 3 mmol) and K_2CO_3 (0.83 g, 6 mmol) in ethanol–water (1:1) mixture (25 mL) was added portionwise to a heated solution of an appropriate 2-chloro-*N*-phenylacetamide **5a–k** (3 mmol) in ethanol (25 mL). The reaction mixture was heated under reflux for 1 h with continuous stirring, then cooled to room temperature. The precipitated solid product was filtered, washed with ethanol (2 × 20 mL), oven-dried and crystallized from a suitable solvent.

3-Amino-4-cyano-5-(4-phenylpiperazin-1-yl)-*N*-phenyl-2-thiophenecarboxamide (6a)

Yield: 70%, crystallized from ethyl acetate, mp 188–189 °C. IR (cm^{-1}): 3441, 3387, 3325 (NH_2/NH), 2194 (C≡N), 1635 (C=O); ^{1}H NMR (ppm): 3.34–3.36 (m, 4H, CH_2), 3.73–3.75 (m, 4H, CH_2), 6.82–7.62 (m, 10H, ArH), 6.90 (s, 2H, NH_2, D_2O exchangeable), 9.10 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 47.3, 49.7 (piperazine Cs); 79.1, 85.4, 115.4, 115.7, 119.5, 120.5, 122.8, 128.3, 129.0, 139.2, 150.2, 154.8, 162.4, 164.6 (Ar. Cs, C≡N, and C=O). Anal Calcd for $C_{22}H_{21}N_5OS$: C, 65.49; H, 5.25; N, 17.36. Found: C, 65.73; H, 5.34; N, 17.61.

3-Amino-*N*-(2-bromophenyl)-4-cyano-5-(4-phenylpiperazin-1-yl)-2-thiophenecarboxamide (6b)

Yield: 68%, crystallized from ethyl acetate, mp 210–212 °C. IR (cm^{-1}): 3444, 3367, 3329 (NH_2/NH), 2198 (C≡N), 1635 (C=O); ^{1}H NMR (ppm): 3.35 (t, 4H, J = 5.0 Hz, CH_2), 3.73 (t, 4H, J = 5 Hz, CH_2), 6.82–7.67 (m, 11H, 9 ArH and NH_2), 8.69 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 47.4, 49.7 (piperazine Cs); 79.0, 85.2, 115.4, 115.7, 119.4, 119.5, 126.8, 127.5, 127.9, 129.0, 132.4, 136.6, 150.2, 154.7, 162.0, 164.7 (Ar. Cs, C≡N, and C=O). Anal Calcd for $C_{22}H_{20}BrN_5OS$: C, 54.78; H, 4.18; N, 14.52. Found: C, 54.97; H, 4.22; N, 14.67.

3-Amino-*N*-(2-chlorophenyl)-4-cyano-5-(4-phenylpiperazin-1-yl)-2-thiophenecarboxamide (6c)

Yield: 70%, crystallized from ethyl acetate, mp 214–216 °C. IR (cm^{-1}): 3448, 3390, 3336 (NH_2/NH), 2198 (C≡N), 1635 (C=O); ^{1}H NMR (ppm): 3.34–3.36 (m, 4H, CH_2), 3.72–3.75 (m, 4H, CH_2), 6.82–7.62 (m, 11H, 9ArH and NH_2), 8.75 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 47.4, 49.7 (piperazine Cs); 79.0, 85.3, 115.4, 115.7, 115.8, 119.5, 126.4, 127.3, 128.4, 129.0, 129.3, 135.2, 150.2, 154.7, 162.1, 164.7 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{22}H_{20}ClN_5OS$: C, 60.34; H, 4.60; N, 15.99. Found: C, 60.62; H, 4.73; N, 16.26.

3-Amino-*N*-(4-chlorophenyl)-4-cyano-5-(4-phenylpiperazin-1-yl)-2-thiophenecarboxamide (6d)

Yield: 77%, crystallized from ethyl acetate, mp 215–216 °C. IR (cm^{-1}): 3456, 3320, 3309 (NH_2/ NH), 2194 (C≡N), 1627 (C=O); ^{1}H NMR (ppm): 3.35–3.37 (m, 4H, CH_2), 3.73–3.75 (m, 4H, CH_2), 6.81–7.66 (m, 9H, ArH), 6.94 (s, 2H, NH_2, D_2O exchangeable), 9.22 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 47.4, 49.7 (piperazine Cs); 79.0, 85.1, 115.4, 115.8, 119.5, 121.9, 126.4, 128.2, 129.0, 138.3, 150.2, 155.1, 162.3, 164.7 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{22}H_{20}ClN_5OS$: C, 60.34; H, 4.60; N, 15.99. Found: C, 60.13; H, 4.75; N, 16.23.

3-Amino-4-cyano-*N*-(2,4-dichlorophenyl)-5-(4-phenylpiperazin-1-yl)-2-thiophene carboxamide (6e)

Yield: 68%, crystallized from ethyl acetate, mp 235–237 °C. IR (cm^{-1}): 3429, 3398, 3325 (NH_2/ NH), 2206 (C≡N), 1635 (C=O); ^{1}H NMR (ppm): 3.34–3.36 (m, 4H, CH_2), 3.74 (t, 4H, CH_2), 6.81–7.65 (m, 10H, 8 ArH and NH_2), 8.83 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 47.3, 49.7 (piperazine Cs); 78.9, 85.1, 115.3, 115.7, 119.5, 127.4, 128.4, 128.7, 129.0, 129.5, 129.6, 134.5, 150.2, 154.9, 162.0, 164.8 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{22}H_{19}Cl_2N_5OS$: C, 55.94; H, 4.05; N, 14.83. Found: C, 56.23; H, 4.01; N, 15.06.

3-Amino-4-cyano-*N*-(4-ethylphenyl)-5-(4-phenylpiperazin-1-yl)-2-thiophenecarboxamide (6f)

Yield: 80%, crystallized from ethyl acetate, mp 180–182 °C. IR (cm^{-1}): 3475, 3437, 3336 (NH_2/ NH), 2962, 2931, 2873, 2804 (aliphatic CH), 2198 (C≡N), 1635 (C=O); ^{1}H NMR (ppm): 1.15 (t, 3H, J = 7.6 Hz, CH_3), 2.54 (q, 2H, J = 7.6 Hz,

CH_2), 3.34 (t, 4H, $J = 5.0$ Hz, CH_2), 3.72 (t, 4H, $J = 5.0$ Hz, CH_2), 6.81–7.53 (m, 9H, ArH), 6.88 (s, 2H, NH_2, D_2O exchangeable), 9.03 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 15.7 (CH_3); 27.6 (CH_2); 47.4, 49.7 (piperazine Cs); 79.2, 85.6, 115.4, 115.7, 119.5, 120.7, 127.5, 129.0, 136.8, 138.2, 150.2, 154.5, 162.3, 164.5 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{24}H_{25}N_5OS$: C, 66.80; H, 5.84; N, 16.23. Found: C, 67.12; H, 5.99; N, 16.59.

3-Amino-4-cyano-*N*-(4-methylphenyl)-5-(4-phenylpiperazin-1-yl)-2-thiophenecarboxamide (6g)

Yield: 71%, crystallized from ethyl acetate, mp 194–195 °C. IR (cm^{-1}): 3441, 3421, 3313 (NH_2/ NH), 2904, 2835 (aliphatic C–H), 2194 (C≡N), 1627 (C=O); ^1H NMR (ppm): 2.24 (s, 3H, CH_3), 3.36 (t, 4H, $J = 5.0$ Hz, CH_2), 3.73 (t, 4H, $J = 5.0$ Hz, CH_2), 6.81–7.50 (m, 9H, ArH), 6.87 (s, 2H, NH_2, D_2O exchangeable), 9.02 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 20.4 (CH_3); 47.4, 49.7 (piperazine Cs); 79.2, 85.6, 115.4, 115.8, 119.5, 120.7, 128.8, 129.0, 131.8, 136.7, 150.2, 154.5, 162.3, 164.5 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{23}H_{23}N_5OS$: C, 66.16; H, 5.55; N, 16.77. Found: C, 66.47; H, 5.67; N, 16.89.

3-Amino-4-cyano-*N*-(3-nitrophenyl)-5-(4-phenylpiperazin-1-yl)-2-thiophenecarboxamide (6h)

Yield: 77%, crystallized from acetic acid, mp 238–240 °C. IR (cm^{-1}): 3429, 3352, 3321 (NH_2/NH), 2198 (C≡N), 1627 (C=O), 1530, 1346 (NO_2); ^1H NMR (ppm): 3.35–3.37 (m, 4H, CH_2), 3.74–3.76 (m, 4H, CH_2), 6.81–8.66 (m, 11H, 9 ArH and NH_2), 9.52 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (ppm): 47.4, 49.7 (piperazine Cs); 78.8, 84.8, 114.2, 115.4, 115.8, 116.9, 119.6, 126.0, 129.0, 129.5, 140.8, 147.7, 150.2, 155.8, 162.5, 164.9 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{22}H_{20}N_6O_3S$: C, 58.92; H, 4.49; N, 18.74. Found: C, 59.34; H, 4.37; N, 19.01.

3-Amino-*N*-(3-benzamidophenyl)-4-cyano-5-(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (6i)

Yield: 84%, mp 230–232 °C. IR (cm^{-1}): 3464, 3410, 3367, 3336 (NH_2/2 NH); 2191 (C≡N); 1662, 1639 (2 C=O). ^1H NMR (ppm): 3.35–3.37 (m, 4H, CH_2), 3.73–3.75 (m, 4H, CH_2), 6.81–8.20 (m, 16H, 14 ArH and NH_2), 9.20 (s, 1H, NH, D_2O exchangeable), 10.25 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 47.4, 49.7 (piperazine Cs); 79.1, 85.5, 113.2, 115.3, 115.4, 115.7, 116.3, 119.5, 127.6, 128.3, 128.3, 129.0, 131.4, 135.0, 139.1, 139.4, 150.2, 154.8, 162.4, 164.7, 165.4 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{29}H_{26}N_6O_2S$ (522.63): C, 66.65; H, 5.01; N, 16.08. Found: C, 66.23; H, 5.15; N, 15.82.

3-Amino-*N*-(5-benzamido-2-methylphenyl)-4-cyano-5-(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (6j)

Yield: 73%, mp 260–262 °C. IR (cm^{-1}): 3468, 3406, 3340, 3305 (NH_2/2 NH); 2198 (C≡N); 1662, 1635 (2 C=O). ^1H NMR (ppm): 2.16 (s, 3H, CH_3), 3.34–3.36 (m, 4H, CH_2), 3.71–3.73 (m, 4H, CH_2), 6.81–7.96 (m, 15H, 13 ArH and NH_2), 8.81 (s, 1H, NH, D_2O exchangeable), 10.21 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 17.4 (CH_3), 47.4, 49.7 (piperazine Cs), 79.2, 85.7, 115.4, 115.7, 117.7, 117.7, 118.9, 119.5, 127.6, 128.3, 129.0, 129.9, 131.4, 134.9, 136.4, 137.0, 150.2, 154.2, 162.4, 164.6, 165.3 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{30}H_{28}N_6O_2S$ (536.65): C, 67.14; H, 5.26; N, 15.66. Found: C, 67.30; H, 5.12; N, 15.87.

3-Amino-*N*-(5-benzamido-2-methoxyphenyl)-4-cyano-5-(4-phenylpiperazin-1-yl)thiophene-2-carboxamide (6 k)

Yield: 87%, mp 264–266 °C. IR (cm^{-1}): 3452, 3390, 3321 (NH_2/2 NH); 2210 (C≡N); 1666, 1635 (2 C=O). ^1H NMR (ppm): 3.35–3.37 (m, 4H, CH_2), 3.73–3.75 (m, 4H, CH_2), 3.84 (s, 3H, OCH_3), 6.82–8.08 (m, 15H, 13 ArH and NH_2), 8.25 (s, 1H, NH, D_2O exchangeable), 10.16 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (ppm): 47.3, 49.7 (piperazine Cs), 56.0 (OCH_3), 79.1, 85.7, 110.8, 115.3, 115.7, 115.7, 116.6, 119.5, 126.9, 127.5, 128.3, 129.0, 131.3, 131.9, 134.9, 146.5, 150.2, 154.2, 161.6, 164.4, 165.0 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{30}H_{28}N_6O_3S$ (552.65): C, 65.20; H, 5.11; N, 15.21. Found: C, 64.83, H, 5.35, N, 14.92.

Ethyl 3-amino-4-cyano-5-(4-phenylpiperazin-1-yl) thiophene-2-carboxylate (7)

A solution of ethyl chloroacetate (0.37 g, 0.32 mL, 3 mmol) in absolute ethanol (25 mL) was added to a solution of compound **3** (0.81 g, 3 mmol), and potassium carbonate (0.83 g, 6 mmol) in water–ethanol (1:1) mixture (25 mL). The reaction mixture was heated under reflux with continuous stirring for 1 h. After cooling, the mixture was poured onto water (50 mL). The precipitated solid was filtered, oven-dried, and crystallized from ethanol.

Yield: 62%, mp 137–139 °C. IR (cm^{-1}): 3448, 3336 (NH_2), 2974, 2893, 2831 (aliphatic C–H), 2202 (C≡N), 1647 (C=O); ^1H NMR (ppm): 1.22 (t, 3H, $J = 7.08$, CH_3), 3.32 (t, 4H, $J = 5.10$, CH_2), 3.73 (t, 4H, $J = 5.06$, CH_2), 4.15 (q, 2H, $J = 7.08$, CH_2), 6.66 (s, 2H, NH_2, D_2O exchangeable), 6.81–7.26 (m, 5H, ArH); ^{13}C NMR (ppm): 14.4 (CH_3); 47.3, 49.4 (piperazine Cs); 59.3 (CH_2); 77.9, 82.2, 115.3, 115.7, 119.4, 129.0, 150.1, 155.4, 162.7, 166.1 (Ar. Cs, C≡N, and C=O). Anal. Calcd for $C_{18}H_{20}N_4O_2S$ (356.44): C, 60.65; H, 5.66; N, 15.72. Found: C, 60.38; H, 5.78; N, 15.98.

Results and discussion

The previously reported sequential one-pot procedure developed by Thomae et al.(2009) consisted of reacting ketene dithioacetal **1** with an appropriate secondary amine to give the intermediate ketene *N,S*-acetal **A,** which upon treatment with sodium sulfide afforded the enethiolate derivative **B.** Further reaction of **B** with a number of activated halides, and subsequent base-catalyzed cyclization of the resulting intermediate **C** gave rise to the thiophene derivatives **D** (Scheme 1).

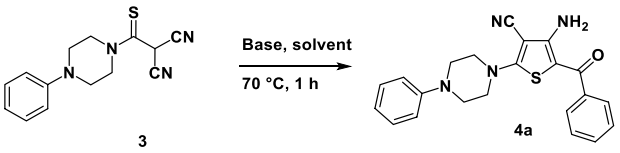
In the aforementioned method, the conversion of the ketene *N*,*S*-acetal **A** to the corresponding enethiolate intermediate **B** liberated a molar equivalent of sodium methanethiolate which competed for the activated halide in the subsequent step, thereby reducing the yield of the intended thiophene derivative **D** (Scheme 1). Although this problem has been brought under control using two molar equivalents of the activated halides (Thomae et al. 2009), this procedure suffered from a major economic drawback because of the use of excess of the expensive halides.

In an effort to optimize the reaction conditions, elimination of methanethiolate side-product from the reaction medium was supposed to be an appropriate manoeuvre. This had been achieved by isolating the enethiolate derivative **B** in its enethiol form. It was hypothesized that this extra step would improve both the reaction economy and the purity of the isolated products in the downstream reactions.

Herein, the synthetic pathway to the target thiophene derivatives **4–7** is shown in Schemes 2, 3. As a model example, the enethiolate derivative **2** was prepared via the reaction of compound **1** with 1-phenylpiperazine following previously procedure (Thomae et al. 2009). Initial attempts to isolate this intermediate in its enethiol form (compound **3**) consisted of acidification of the cooled reaction mixture with aqueous acetic acid or dil. HCl. Although this trial furnished a solid in a satisfactory yield, it suffered from lack of reproducibility from batch to batch with a sticky brown mass frequently forming during the isolation process. A product of higher purity and of higher yield (85%) has been achieved via replacement of the aqueous acidic solution by a saline acetic acid-sodium acetate buffer, Scheme 2.

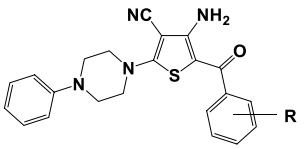
The IR spectrum of compound **3** revealed the presence of two bands at 2194 and 2164 cm^{-1} assignable to the two C≡N groups. Its ^{1}H NMR spectrum showed two triplet signals at δ 3.22 and 4.28 ppm of the piperazine ring protons; in addition to multiplet signals between δ 6.86–7.30 ppm corresponding to the five aromatic hydrogens of the phenyl ring. The presence of phenylpiperazine moiety was also confirmed by ^{13}C NMR analysis, which showed the signals of the aliphatic carbons of piperazine ring in addition to a signal at δ 195.4 ppm attributable to the C=S carbon.

Table 1 Solvent/base optimization for the synthesis of thiophene **4a** using the thioamide **3**



Solvent	Base	Yield%	Solvent	Base	Yield%
DMF	K_2CO_3	No reaction	Ethanol	TEA	64
DMF	NaOH	43	Ethanol	K_2CO_3	59
DMF	TEA	67	Ethanol/H_2O (3:1)	K_2CO_3	74

Table 2 Comparison of the yields of substituted thiophenecarbonitrile derivatives 4a–d prepared by methods A and B



Compounds	R	Method A[a] yield%	Method B[b] yield%
4a	H	No reaction	74
4b	3-Br	23	71
4c	4-Br	47	74
4d	4-Cl	27	77

[a]Reaction conditions: (a) compound **1**, phenylpiperazine, 70 °C, DMF; (b) $Na_2S.9H_2O$, 70 °C; (c) different phenacyl bromides (2 molar equiv.), 50 °C; (d) K_2CO_3, 50 °C

[b]Reaction conditions: compound **3**, different phenacyl bromides (1 molar equiv.), K_2CO_3, ethanol-H_2O (3:1) mixture, reflux

With the aim to explore the most suitable reaction conditions for the synthesis of the target thiophene derivatives **4a–g**, we tried to synthesize the derivative **4a** by reacting compound **3** with only 1 molar equivalent of phenacyl bromide in DMF using potassium carbonate as a base. However, this trial was unsuccessful, imposing further optimization of the reaction conditions using different solvent/base combinations (Table 1). The results revealed that when the reaction was carried out in DMF as a solvent in presence of a strong base such as NaOH, **4a** was obtained in about 43% yield, however, the use of TEA as a base was found to be more reproducing (67% yield). Switching the solvent to ethanol gave a comparable yield (64%). Surprisingly, ethanol/K_2CO_3 combination yielded compound **4a** in 59% yield. The

optimum solvent/base combination for the preparation of **4a** was found to be ethanol–water (3:1) mixture and K_2CO_3 as a base (74% yield).

In this work, the new compounds **4a–d** were prepared following the procedure reported by Thomae et al. (2009) (method A) as well as by our optimized procedure (method B). The yields obtained by the two methods were compared and presented in Table 2. The results showed that compounds **4a–d** prepared following method B were obtained in higher yields ranging from 71 to 77%. Accordingly, compounds **4e–g** were prepared following method B and were isolated in high purity and high yields.

The structure of compounds **4a–g** was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectroscopic analyses. Their IR spectra showed two bands in the range of 3394–3259 cm^{-1} indicating NH_2 function. In addition, bands indicating C≡N group were observed in the range of 2202–2198 cm^{-1}. It is worth to mention that, the bands corresponding to C=O group were observed at a relatively low wavenumber (1612–1581 cm^{-1}), which might be attributed to the high conjugation of C=O with the neighbouring aromatic ring systems as well as the possibility of hydrogen bonding formation with the adjacent NH_2 protons (Naguib and El-Nassan 2016). The ^{1}H NMR spectra of compounds **4a–g** showed a broad exchangeable singlet signal at δ 7.88–8.00 ppm corresponding to NH_2 protons. In the ^{13}C NMR spectra of these compounds, the C=O carbons appeared at δ 180.7–184 ppm.

Similarly, the thiophene-2-carboxamide derivatives **6a–k** were synthesized according to the modified procedure (method B) from compound **3** and 2-chloro-(*N*-aroyl)-acetamides **5a–k** (Al-Nadaf et al. 2010; Kumar et al. 2014; Ma et al. 2011; Monforte et al. 2014; Rajak et al. 2012; Yu and Cai 2003) and were isolated in moderate to high yields (68–87%). It is noteworthy that compounds **6a–k** were not reported earlier and were not accessible via the reported procedures (Scheme 3).

The IR spectra of compounds **6a–k** showed NH_2/NH bands in the range 3475–3305 cm^{-1}. Moreover, the C≡N and amidic C=O functions appeared at 2210–2191 cm^{-1} and 1639–1627 cm^{-1}, respectively. The ^{1}H NMR spectra of these compounds showed two exchangeable singlet signals at δ 6.81–7.02 ppm and 8.25–9.52 ppm corresponding to NH_2 and NH protons, respectively. The ^{13}C NMR spectra of the compounds showed the expected number of signals for all compounds. Aliphatic CH_2 carbons of the piperazine ring gave two signals between δ_C 47.3–49.7 ppm.

Likewise, the ester derivative **7** was prepared in 62% yield from compound **3** and ethyl chloroacetate following method B. The IR spectrum of compound **7** revealed two bands of NH_2 at 3448 and 3336 cm^{-1}, in addition to C≡N and C=O bands at 2202 and 1647 cm^{-1}, respectively. Its ^{1}H NMR spectrum showed triplet and quartet signals at δ 1.22 and 4.15 ppm corresponding to CH_3CH_2 protons, along with an exchangeable NH_2 singlet signal at δ 6.66 ppm. Besides, its ^{13}C NMR spectrum showed two signals at δ 14.4 and 59.3 ppm assignable to CH_3CH_2 carbons and a signal corresponding to C=O carbon at δ 166.1 ppm.

Conclusion

In summary, a modification of the procedure reported by Thomae et al. for the synthesis of tetrasubstituted thiophenes **4a–g, 6a–k** and **7** was reported. Optimization of the reaction conditions comprises the isolation of the enethiol derivative **3**, the use of K_2CO_3 or TEA as a base, and the use of ethanol, water, or a mixture of them as a solvent. The described modification eliminated the need for the use of two molar equivalents of the active halide, making it an atom economic procedure. Besides, the desired products were obtained in higher yields and in purer form.

Compliance with ethical standards

Conflict of interest No conflict of interest.

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