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Synthesis of Some Novel Methyl- and Ethyl-2-aminothiophene-3-carboxylate and Related Schiff-Bases

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Methyl- and ethyl-2-amino thiophene-3-carboxylate derivatives **1(a-h)** were synthesized by a simple one-pot condensation reaction of the ketone, elemental sulphur and methyl- or ethylcyanoacetate in the presence of morpholine as a catalyst. Further reaction of these compounds with salicylaldehyde gave related Schiff-bases, **2(a-e)**. Yields of products following recrystallization from ethanol were in the range of 70-85 %. ^{1}H NMR and IR spectra and elemental analysis data were used to identification of these compounds.

Key Words: 2-Aminothiophene, One-pot, Schiff-bases, Carboxylate.

INTRODUCTION

Thiophene derivatives exert broad applications such as functional materials in dyes[1,2], liquid crystals, molecular wires[3], organic light-emitting diodes[4], field-effect transistors[5] and agrochemicals[6]. The thiophene core of these heterocycles forms an internal part of numerous natural products[7]. They can also be used as selective site-directed inhibitors of various biological targets[8-10]. On the other hand, Schiff bases derived from aromatic amines and aromatic aldehydes are also very important class of organic compounds because of their applications in many fields including biological[11,12], inorganic[13,14] and analytical chemistry[15]. Therefore, the hybrid molecules composed of the combination of part of a heterocyclic ring, like thiophene and part of the Schiff-base may exert potential biological activities.

In continuation of our studies on the synthesis of heterocyclic compounds[16-18] and because of the versatile biological properties of thiophene derivatives, we now report the synthesis of some novel 2-aminothiophene by reaction of a ketone and elemental sulphur with methyl- or ethylcyanoacetate in the presence of morpholine, which followed by reaction with salicylaldehyde to prepare related Schiff-bases.

EXPERIMENTAL

Melting points were determined using an electro thermal digital melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Tetramethyl silane was used as an internal standard. The IR

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spectra were recorded on a Galaxy series FTIR 5000 spectrometer using KBr discs. Elemental analyses were performed on a Vario EL III elemental analyzer. Reaction courses and product mixtures were monitored by thin layer chromatography.

Preparation of methyl- and ethyl-2-amino-thiophene-3-carboxylat 1(a-h): To a mixture of appropriate ketone (0.05 mol), methyl- or ethylcyanoacetate ester (0.05 mol) and elemental sulphur (0.05 mol) in methanol (30 mL) morpholine (5 mL) was added slowly over a period of 0.5 h at 35-40 ºC with stirring. The reaction mixture was stirred at 45 ºC for 3 h and then allowed to cool to room temperature. The precipitate was filtered off and washed with ethanol. The crude product was recrystallized from ethanol.

Methyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (1a): White crystal, m.p. 136-137 ºC. IR (KBr, ν_{max}, cm^{-1}): 3414, 3308 (NH), 2931 (CH), 1656 (C=O), 1577, 1446, 1492 (C=C), 1269 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.65-1.67 (m, 4H, H-cyclohexane), 2.40-2.56 (m, 4H, H-cyclohexane), 3.66 (s, 3H, OMe), 7.20 (s, 2H, NH) ppm. The NH protons disappeared upon D_2O addition. Anal. calcd. (%) for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.18. Found. (%): C, 56.70; H, 6.11; N, 6.59; S, 15.18.

Ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (1b): Cream crystal, m.p. 118-119 ºC. IR (KBr, ν_{max}, cm^{-1}): 3400, 3298 (NH), 2987, 2939 (CH), 1649 (C=O), 1575, 1493, 1411, 1296 (C=C), 1265 (C-O). ^{1}H NMR ($CDCl_3$): δ: 1.35 (t, *J* = 7.1Hz, 3H, H-ester), 1.74-1.80 (m, 4H, H-cyclohexane), 2.49-2.71 (m, 4H, H-cyclohexane), 4.23 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.95 (s, 2H, NH) ppm. Anal. calcd (%). for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found. (%): C, 58.71; H, 6.63; N, 6.24; S, 14.27.

Methyl-2-amino-4-phenylthiophene-3-carboxylate (1c): Yellow crystal, m.p. 145-147 ºC. IR (KBr, ν_{max}, cm^{-1}): 3460, 3321 (NH), 2947 (CH), 1666 (C=O), 1593, 1496, 1438 (C=C), 1224 (C-O). ^{1}H NMR (DMSO-d_6): δ: 3.45 (s, 3H, OMe), 6.16 (s, 1H, H-thiophene), 7.25 (m, 5H, H-ph), 7.38 (s, 2H, NH) ppm. The NH protons disappeared upon D_2O addition. Anal. calcd. (%) for $C_{12}H_{11}NO_2S$: C, 61.78; H, 4.75; N, 6.00; S, 13.74. Found. (%): C, 61.53; H, 4.77; N, 5.96; S, 13.69.

2-Ethyl-4-methyl 5-amino-3-methylthiophene-2,4-dicarboxylate (1d): White crystal, m.p. 117-119 ºC. IR (KBr, ν_{max}, cm^{-1}): 3408, 3310 (NH), 2993 (CH), 1705, 1659 (C=O), 1604, 1531, 1444 (C=C), 1254, 1192 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.22 (t, *J* = 7.1 Hz, 3H, H-ester), 2.58 (s, 3H, CH_3), 3.73 (s, 3H, OMe), 4.11 (q, *J* = 7.1 Hz, 2H, OCH_2), 7.93 (s, 2H, NH) ppm. Anal. calcd. (%) for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found. (%): C, 49.22; H, 5.41; N, 5.72; S, 13.14.

Ethyl-2-amino-4-phenylthiophene-3-carboxylate (1e): Cream crystal, m.p. 148-149 ºC. IR (KBr, ν_{max}, cm^{-1}): 3460, 3319 (NH), 3056, 2947 (CH), 1666 (C=O), 1593, 1496, 1438 (C=C), 1107 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.31 (t, *J* = 7.1 Hz, 3H, H-ester), 4.19 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.1 (s, 1H, H-thiophene), 7.27 (m, 5H, H-ph), 7.38 (s, 2H, NH) ppm. Anal. calcd. (%) for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66; S, 12.97. Found. (%): C, 63.37; H, 5.28; N, 5.66; S, 13.01.

Ethyl-5-acetyl-2-amino-4-methylthiophene-3-carboxylate (1f): Brown crystal, m.p. 165-167 ºC. IR (KBr, ν_{max}, cm^{-1}): 3408, 3298 (NH), 2991 (CH), 1670, 1609 (C=O), 1587, 1510, 1440, 1336 (C=C), 1253 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.27 (t, J = 7.1 Hz, 3H, H-ester), 2.27 (s, 3H, CH_3), 2.59 (s, 3H, H-acetyl), 4.19 (q, J = 7.0 Hz, 2H, OCH_2), 8.00 (s, 2H, NH) ppm. Anal. calcd. (%) for $C_{10}H_{13}NO_4S$: C, 52.85; H, 5.77; N, 6.16; S, 14.11. Found. (%): C, 53.08; H, 5.79; N, 6.13; S, 13.97.

Ethyl-2-amino-5,6-dihydro-4*H*-cyclopenta[b]thiophene-3-carboxylate (1g): Brown crystal, m.p. 148-150 ºC. IR (KBr, ν_{max}, cm^{-1}): 3416, 3294 (NH), 2986, 2856 (CH), 1645 (C=O), 1601, 1493 (C=C), 1263 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.23 (t, J = 7.1 Hz, 3H, H-ester), 2.12 (m, 2H, H-cyclopentane), 2.62 (m, 4H, H-cyclopentane), 4.13 (q, J = 7.0 Hz, 2H, OCH_2), 7.19 (s, 2H, NH) ppm. Anal. calcd. (%) for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.18. Found. (%): C, 56.64; H, 6.26; N, 6.65; S, 15.18.

Diethyl-5-amino-3-methylthiophene-2,4-dicarboxylate (1h): White crystal, m.p. 110-112 ºC. IR (KBr, ν_{max}, cm^{-1}): 3423, 3306 (NH), 2986 (CH), 1676, 1593 (C=O), 1529, 1440 (C=C), 1238 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.25 (m, 6H, H-ester), 2.58 (s, 3H, CH_3), 4.16 (m, 4H, OCH_2), 7.90 (s, 2H, NH) ppm. Anal. calcd. (%) for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found. (%): C, 51.56; H, 5.53; N, 5.42; S, 12.50.

General procedure of preparation of Schiff-base 2(a-e): A solution of salicylaldehyde (1 mmol), corresponding 2-aminothiophenes (1 mmol), **1(a-e)** and 2-3 drops of concentrated H_2SO_4 in ethanol (10 mL) was refluxed for 3-4 h. The reaction mixture was cooled in an ice bath to give the precipitate. The crude product was collected, washed with water (5 mL) and then recrystallized from ethanol to give the pure Schiff-bases **2(a-e)**.

Methyl-2-(2-hydroxybenzylideneamino)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (2a): Yellow crystal, m.p. 141.5-143.5 ºC. IR (KBr, ν_{max}, cm^{-1}): 3074, 2928 (CH), 1701 (C=O), 1601 (C=N), 1566, 1496, 1448 (C=C), 1282, 1213 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.74 (m, 4H, H-cyclohexane), 2.69 (m, 4H, H-cyclohexane), 3.80 (s, 3H, OMe), 6.94 (t, J = 8.1 Hz, 2H, H-Ar), 7.40-7.67 (m, 2H, H-Ar), 8.77 (s, 1H, H-C=N), 12.68 (s, 1H, OH) ppm. Anal. calcd. (%) for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found. (%): C, 65.00; H, 5.40; N, 4.43; S, 10.21 %.

Ethyl-2-(2-hydroxybenzylideneamino)-4,5,6,7-tetrahydrobenzo[b]-thiophene-3-carboxylate (2b): Yellow crystal, m.p. 132-134 ºC. IR (KBr, ν_{max}, cm^{-1}): 2941, 2974 (CH), 1699 (C=O), 1604 (C=N), 1572, 1500, 1454, 1323 (C=C), 1286, 1217 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.31 (t, J = 7.1 Hz, 3H, H-ester), 1.75 (m, 4H, H-cyclohexane), 2.69 (m, 4H, H-cyclohexane), 4.25 (q, J = 7.1 Hz, 2H, OCH_2), 6.94-6.99 (m, 2H, H-Ar), 7.39-7.45 (m, 1H, H-Ar), 7.65 (d, J = 7.6 Hz, 1H, H-Ar), 8.77 (s, 1H, H-C=N), 12.58 (s, 1H, OH) ppm. Anal. calcd. (%) for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25; S, 9.73. Found. (%): C, 65.56; H, 5.83; N, 4.28; S, 9.77.

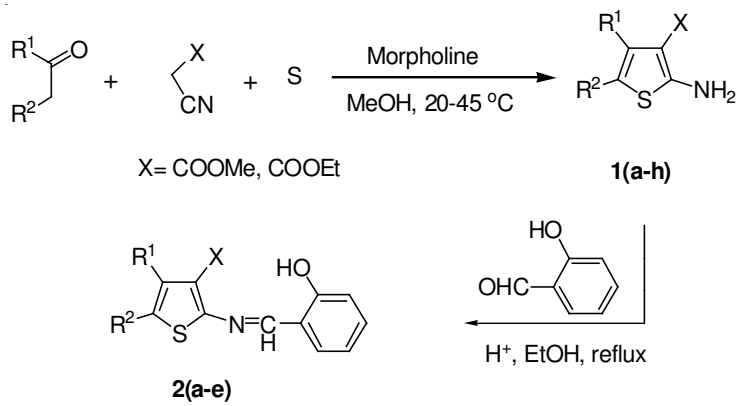
Methyl-2-(2-hydroxybenzylideneamino)-4-phenylthiophene-3-carboxylate (2c): Orange crystal, m.p. 219-221 ºC. IR (KBr, ν_{max}, cm^{-1}): 3059, 2953 (CH), 1699 (C=O), 1601 (C=N), 1566, 1505, 1446 (C=C), 1292, 1210 (C-O). ^{1}H NMR (DMSO-d_6): δ: 3.53 (s, 3H, OMe), 5.85 (s, 1H, H-thiophene), 6.69-7.29 (m, 7H, H-Ar and ph), 7.40 (d, *J* = 7.5 Hz, 1H, H-Ar), 7.68 (d, *J* = 6.8 Hz, 1H, H-Ar), 8.91 (s, 1H, H-C=N), 12.38 (s, 1H, OH) ppm. Anal. calcd. (%) for $C_{19}H_{15}NO_3S$: C, 67.64; H, 4.48; N, 4.15; S, 9.50. Found. (%): C, 67.71; H, 4.45; N, 4.15; S, 9.45.

2-Ethyl-4-methyl 5-(2-hydroxybenzylideneamino)-3-methylthiophene-2,4-dicarboxylate (2d): Yellow crystal, m.p. 142.5-144 ºC. IR (KBr, ν_{max}, cm^{-1}): 3055, 2995, 2951 (CH), 1697 (C=O), 1599 (C=N), 1560, 1444, 1384 (C=C), 1238, 1195 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.27 (t, *J* = 7.1 Hz, 3H, H-ester), 2.61 (s, 3H, CH_3), 3.85 (s, 3H, OMe), 4.29 (q, *J* = 7.1 Hz, 2H, OCH_2), 6.97-7.02 (m, 2H, H-Ar), 7.46-7.51 (m, 1H, H-Ar), 7.71 (d, *J* = 7.0 Hz, 1H, H-Ar), 9.00 (s, 1H, H-C=N), 12.35 (s, 1H, OH) ppm. Anal. calcd. (%) for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03; S, 9.23. Found. (%): C, 58.54; H, 4.95; N, 4.01; S, 9.26.

Ethyl-2-(2-hydroxybenzylideneamino)-4-phenylthiophene-3-carboxylate (2e): Yellow crystal, m.p. 218-219 ºC. IR (KBr, ν_{max}, cm^{-1}): 3180 (OH), 3055, 2951 (CH), 1714 (C=O), 1599 (C=N), 1566, 1500, 1448 (C=C), 1290, 1210 (C-O). ^{1}H NMR (DMSO-d_6): δ: 1.11 (t, *J* = 7.1Hz, 3H, H-ester), 4.13 (q, *J* = 7.1 Hz, 2H, OCH_2), 5.85 (s, 1H, H-thiophene), 6.71-7.28 (m, 7H, H-Ar and ph), 7.40 (t, *J* = 7.6 Hz, 1H, H-Ar), 7.68 (d, *J* = 7.9 Hz, 1H, H-Ar), 8.91 (s, 1H, H-C=N), 12.38 (s, 1H, OH) ppm. Anal. calcd. (%) for $C_{20}H_{17}NO_3S$: C, 63.36; H, 4.88; N, 3.99; S, 9.12. Found. (%): C, 63.61; H, 4.86; N, 4.00; S, 9.15.

RESULTS AND DISCUSSION

First, 2-aminothiophenes, **1(a-h)** were synthesized by a multicomponent condensation of ethyl- or methylcyanoacetate with appropriate ketones and elemental sulphur in the presence of morpholine as a catalyst using low modified Gewald reaction[19] (**Scheme-I**).



Scheme-I

Then, 2-thiophene Schiff-bases **2(a-e)** were obtained by refluxing **1(a-e)** with salicylaldehyde in ethanol as shown in **Scheme-I**. The results are presented in Table-1.

TABLE-1
CHEMICAL STRUCTURES OF SYNTHESIZED COMPOUNDS **1(a-h), 2(a-e)** AND YIELD

Entry	Ketone		X	Compound	Yield (%)
	R^1	R^2			
1	$-(CH_2)_4-$		COOMe	**1a**	85
2	$-(CH_2)_4-$		COOEt	**1b**	85
3	Ph	H	COOMe	**1c**	70
4	CH_3	COOEt	COOMe	**1d**	82
5	Ph	H	COOEt	**1e**	70
6	CH_3	$COCH_3$	COOEt	**1f**	85
7	$-(CH_2)_3-$		COOEt	**1g**	75
8	CH_3	COOEt	COOEt	**1h**	80
9	$-(CH_2)_4-$		COOMe	**2a**	73
10	$(CH_2)_4-$		COOEt	**2b**	75
11	Ph	H	COOMe	**2c**	70
12	CH_3	COOEt	COOMe	**2d**	80
13	Ph	H	COOEt	**2e**	72

The structural elucidation of the synthesized compounds was assigned on the basis of their FT-IR, ^{1}H NMR spectral studies and elemental analyses. The IR spectra of **1(a-h)** showed the two strong absorption bands at 3460-3400 and 3321-3294 cm^{-1} and a strong vibrational frequency at 1670-1593 cm^{-1} related to $-NH_2$ and -C=O groups, respectively. In the ^{1}H NMR spectra of the **1(a-h)**, a broad singlet at δ = 5.95-8.00 ppm was assigned to the resonance of two -NH groups. The resonance of all other protons was appeared in the expected region.

In IR spectra of the compounds **2(a-e)** the absence of bands in the regions 3460-3400 and 3321-3294 cm^{-1}, the characteristic of NH_2 groups, is in support of the expected reaction. The NMR spectra data of all synthesized Schiff bases are consistent with their structures. The ^{1}H NMR spectra of these compounds are simple and consist of the aliphatic, aromatic protons signals and two distinct signals at δ = 12.35-12.68 and 8.77-9.00 ppm due to the resonance of OH and CH (imine) groups, respectively.

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