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Synthesis and Characterization of Novel Highly Functionalized Thiophene Heterocycles.

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ABSTRACT
A series of novel Ethyl 2-(2-chloroacetamido)-4-methyl-5-(arylcarbamoyl)thiophene-3-carboxylate derivatives have been synthesized starting from various ethyl 2-amino-5-methyl-4-(arylcarbamoyl)thiophene-3-carboxylate. Reaction of 3-oxo-*N*-arylbutanamide **1a-j** with ethyl cyanoacetate and sulphur under reflux condition afforded ethyl 2-amino-5-methyl-4-(arylcarbamoyl)thiophene-3-carboxylate **2a-j** derivatives. Further reaction of 2-amino thiophene derivatives **2a-j** with chloroacetyl chloride in acetone using K_2CO_3 as base under atmospheric condition afforded novel highly functionalized Thiophene **3a-j** heterocycles with excellent yields.

Keywords: *Aminothiophene, Acetamide, Multicomponent reaction.*

1. INTRODUCTION

Thiophene is a privileged heterocycle that contains a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S [1]. Thiophene and its derivatives are essential heterocyclic compounds and show a variety of properties and applications. Thiophene derivatives are utilized in industrial chemistry and material science as corrosion inhibitors [2]. The thiophene ring is bioisosteric replacement for the phenyl groups broadly present in active drugs and exists in many natural and synthetic pharmaceuticals [3,4]. The synthesis of substituted 2-amino thiophenes is attractive to chemical researchers as they are important intermediates in organic synthesis and frequently used as the scaffold motif of a variety of agrochemicals, dyes, and biologically active products [5–7]. Thus, wide utility and several methods have been reported in the literature for the preparation of these materials [8–11]. The most convenient method for preparing thiophenes with a high degree of functionality is by the Gewald's method [12,13], which involves multicomponent condensation of a ketone with an activated nitrile and elemental sulphur in the presence of base like morpholine and piperidine as a catalyst. We have recently reviewed the chemistry of the synthesis and application of heterocycles derived from 2-amino-3-carbethoxythiophenes [14] and described the behaviour of ethyl 2-amino-4-methyl-5-(phenylcarbamoyl) thiophene-3-carboxylate towards some appropriate chemical reagents as a possible synthetic route to attain polyfunctionally substituted thieno[2,3-d] pyrimidine-4-ones and thieno[2,3-b]pyridine-4-ones. Encouraged by these findings, and as continuation of our effort [15–20] to identify new candidates that may be value in designing new, potent, selective, and less toxic antimicrobial agents, we report herein an efficient synthesis of novel biodynamic heterocycles bearing thiophene moiety starting from ethyl 2-amino-4-methyl-5-(phenylcarbamoyl) thiophene-3-carboxylate, by virtue of its vicinal amino function. The results of screening of their biological activity will be reported in due course.

2. EXPERIMENTAL

2.1. General

Melting points were determined on an electrothermal apparatus using open capillaries and are uncorrected. Thin-layer chromatography was performed on 0.2-mm precoated plates of silica gel G60 F254 (Merck). Visualization was made

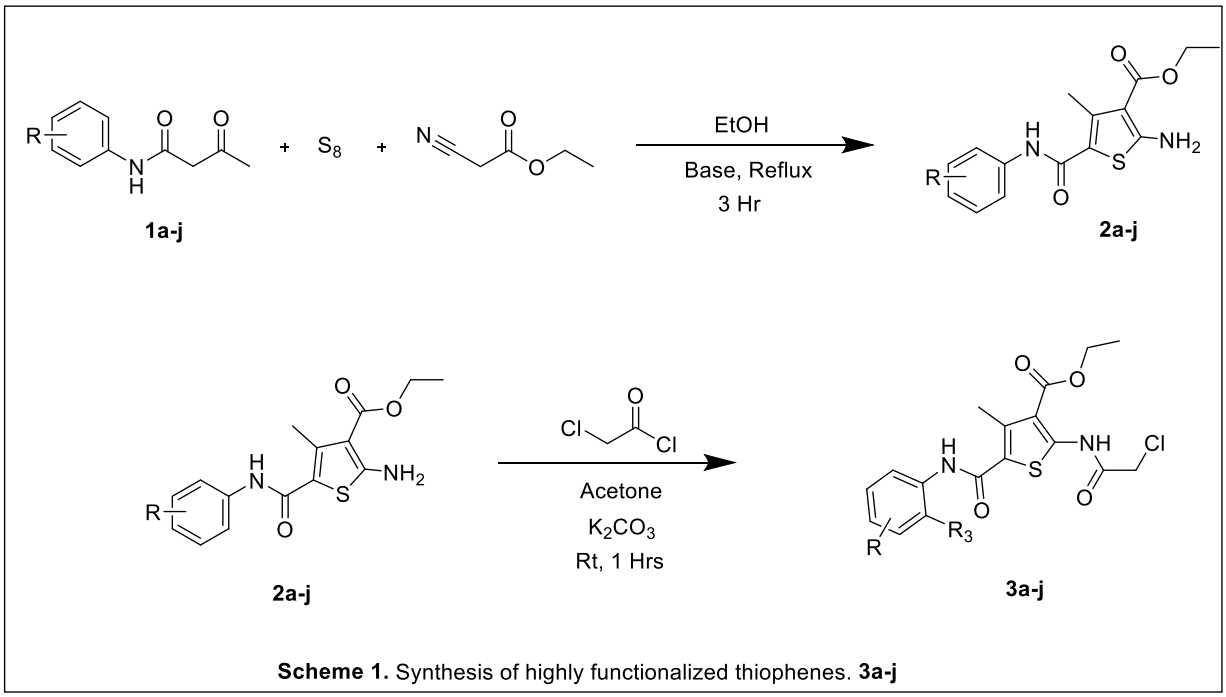
with UV light (254 and 365 nm) or with iodine vapor. IR spectra were recorded on a Shimadzu ATR FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE III (400 MHz) spectrometer in DMSO-d6. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were recorded using a direct inlet probe on Shimadzu GCMS QP2010 Ultra mass spectrometer. All reagents were purchased from Molychem, Loba, and CDH and used without further purification.

2.2. General synthesis of 3-oxo-*N*-arylbutanamide 1a-j

A mixture containing the primary amine (0.1 mol), ethyl acetoacetate (0.1 mol), and catalytic amount of sodium or potassium hydroxide lie (10 %) in toluene was refluxed at 110 °C for the approximately 12-15 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under vaccuo and the solid or oil was crystallized from methanol which afforded pure product **1a-j**. [21-25]

2.3. General synthesis of ethyl 2-amino-4-methyl-5- (arylcarbamoyl)thiophene-3-carboxylate 2a-j

Acetoacetanilide **1a-j** (0.01 mol), ethyl cyanoacetate (0.01 mol) and sulphur (0.01 mol) were refluxed in ethanol for 3 h using morpholine (0.01 mol) (Scheme 1). The hot solution was filtered and the solvent was evaporated under vacuuo and the resulting solid was crystallized from ethanol to obtain white crystals of the product **2a-j** (Scheme 1). [26– 27]



Scheme 1. Synthesis of highly functionalized thiophenes. **3a-j**

2.4. General synthesis of ethyl 2-(2-chloroacetamido)-4-methyl-5-(arylcarbamoyl)thiophene-3-carboxylate 3a-j

To a suspension of **2a-j** (0.01 mol) in dry Acetone (20 ml) containing anhydrous K_2CO_3 (0.01 mol), and chloroacetyl chloride (0.01 mol) was added. The reaction mixture was stirred at room temperature for 1 h, poured onto crushed ice, and then acidified with dilute hydrochloric acid. The obtained precipitate was filtered, washed with water, dried, and washed with n-hexane. Purification of all the compounds were done by repeated recrystallization in methanol to afford analytically pure products **3a-j** (Scheme 1)**.**

2.5. ethyl 2-(2-chloroacetamido)-5-((4 methoxyphenyl)carbamoyl)-4-methylthiophene-3-carboxylate 2a

White Crystals; mp 177-178 °C; MS (m/z): 410 (M+); FTIR (ATR, V_{max}, cm^{-1}): 3448, 3354 (2 NH), 1731 (C=O, ester), 1668, 1646 (2 C=O, amidic); ^{1}H NMR (400 MHz, DMSO) δ 11.80 (s, 1H), 10.04 (s, 1H), 7.58 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.1 Hz, 2H), 4.67 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 2.56 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

2.6. ethyl 2-(2-chloroacetamido)-5-((4-chlorophenyl)carbamoyl)-4-methylthiophene-3 carboxylate 2b

White Crystals; mp 170-171 °C; MS (m/z): 415 (M+); FTIR (ATR, V_{max}, cm^{-1}): 3455, 3361 (2 NH), 1735 (C=O, ester), 1670, 1650 (2 C=O, amidic); ^{1}H NMR (400 MHz, DMSO) δ 11.79 (s, 1H), 10.03 (s, 1H), 7.58 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.1 Hz, 2H), 4.66 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

2.7. ethyl 5-((4-bromophenyl)carbamoyl)-2-(2-chloroacetamido)-4-methylthiophene-3-carboxylate 2c

White Crystals; mp 185-186 °C; MS (m/z): 459 (M+); (ATR, V_{max}, cm^{-1}): 3439, 3355 (2 NH), 1739 (C=O, ester), 1665, 1653 (2 C=O, amidic); ^{1}H NMR (400 MHz, DMSO) δ 11.86 (s, 1H), 10.19 (s, 1H), 7.58 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 4.67 (s, 2H), 4.04 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

2.8. ethyl 2-(2-chloroacetamido)-5-((4-fluorophenyl)carbamoyl)-4-methylthiophene-3-carboxylate 2d

White Crystals; mp 162-163 °C; MS (m/z): 498 (M+); FTIR (ATR, V_{max}, cm^{-1}): 3443, 3359 (2 NH), 1738 (C=O, ester), 1662, 1658 (2 C=O, amidic); ^{1}H NMR (400 MHz, DMSO) δ 11.86 (s, 1H), 10.19 (s, 1H), 7.68 (dd, J = 9.1, 5.0 Hz, 2H), 7.17 (t, J = 8.9 Hz, 2H), 4.67 (s, 2H), 4.40 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

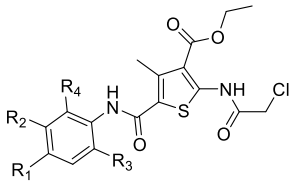
2.9. ethyl 2-(2-chloroacetamido)-5-((2,6-dimethylphenyl)carbamoyl)-4-methylthiophene-3-carboxylate 2e

White Crystals; mp 180-181 °C; MS (m/z): 408 (M+); FTIR (ATR, V_{max}, cm^{-1}): 3440, 3350 (2 NH), 1736 (C=O, ester), 1663, 1650 (2 C=O, amidic); ^{1}H NMR (400 MHz, DMSO) δ 11.79 (s, 1H), 10.03 (s, 1H), 7.18 (s, 3H), 4.66 (s, 2H), 4.41 (q, J = 7.1 Hz, 2H), 2.56 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H).

3. RESULT AND DISCUSSION

The synthetic strategies adopted for the preparation of the desired compounds are illustrated in **Schemes 1**. Various substituted 3-oxo-*N*-arylbutanamide **1a-j** were prepared by refluxing substituted amines and ethyl acetoacetate in toluene with a catalytic amount of NaOH or KOH (Scheme 1). The reaction mixtures were refluxed for 12-15 h. Ethyl 2-amino-4-methyl-5-(arylcarbamoyl)thiophene-3-carboxylate **2a-j** was easily accessible via the Gewald's reaction between acetoacetanilide **1a-j**, elemental sulfur, and ethyl cyanoacetate in the presence of base like morpholine or piperidine according to the method prescribed in literatures [18,19] **Scheme 1**. Next, 2 amino thiophenes **2a-j** reacted with chloroacetyl chloride in presence of potassium carbonate, in acetone at room temperature for 1 h to yield the target derivatives **3a-j** in high yields. [**Table 1**]

Table 1. Physicochemical characteristics of the novel thiophene derivatives 3a-j



Entry	R^1	R^2	R^3	R^4	Molecular weight	Molecular formula	Yield (%)	Melting point (°C)
1	OCH_3	H	H	H	410.87	$C_{18}H_{19}ClN_2O_5S$	83	177-178
2	Cl	H	H	H	415.29	$C_{17}H_{16}Cl2N_2O_4S$	91	170-171
3	Br	H	H	H	459.74	$C_{17}H_{16}BrClN_2O_4S$	72	185-186
4	F	H	H	H	398.83	$C_{17}H_{16}ClFN_2O_4S$	67	162-163
5	H	H	CH_3	CH_3	408.90	$C_{19}H_{21}ClN_2O_4S$	87	180-181
6	H	Cl	H	H	415.29	$C_{17}H_{16}Cl_2N_2O_4S$	89	171-172
7	H	F	H	H	398.83	$C_{17}H_{16}ClFN_2O_4S$	65	160-161
8	F	F	H	H	416.82	$C_{17}H_{15}ClF_2N_2O_4S$	60	155-156
9	OCH_3	OCH_3	H	H	440.90	$C_{19}H_{21}ClN_2O_6S$	86	188-189
10	H	H	H	OCH_3	410.87	$C_{18}H_{19}ClN_2O_5S$	90	176-177

3. CONCLUSION

In conclusion, the results of the present study indicate that the thiophene molecules are useful precursor, by virtue of its highly functionality, for the facile and convenient synthesis of different functionalized 2- chloro acetamido thiophenes. The compounds prepared are expected to be of pharmacological interest.

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