Research Article

Synthesis of Organic Ligands via Reactions of 4-Benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione with N-Nucleophiles

Hassan Kabirifard, Pardis Hafez Taghva, Hossein Teimouri, Niloofar Koosheshi, Parastoo Javadpour, Hanieh Bagherinejad, Soheila Seyfi, Maryam Hossein Roodbari, and Elaheh Golabian

Department of Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran

Correspondence should be addressed to Hassan Kabirifard; h_kabirifard@iau-tnb.ac.ir

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The reaction of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (1) with aminoheteroaryls, lamotrigine, 1,3-dia-minoheteroaryls, dapsone, NH2R (hydroxylamine, DL-1-phenylethylamine, and metformin), and 4,4′-bipyridine in THF/H2O (1:1) at room temperature led to 3-N-phenylthiocarbamoyl-2-butenamides 2–5, while that with naphthylamines and 1,3-phenylenediamine in ethanol at high temperature led to 5-phenylamino-2,5-dihydrothiophene-2-ones 6–8 as organic ligands in the medium to good yields. These showed the nucleophilic attacks of N-nucleophiles, except primary aromatic amines, on thioester carboxyl group of thiophene-2,3-dione ring I. However, the nucleophilic attacks of primary aromatic amines on the carbonyl group (C-3) of thiophene-2,3-dione 1 occurred in the form of substituted thiophenes.

1. Introduction

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is a member of the phenyltriazine drug category. This category has its main utility in the adjunctive treatment of partial seizures in epilepsy and generalized seizures of Lennox-Gastaut syndrome [1–4]. Maintenance treatment of bipolar I disorder and depression is an additional important use of the phenyltriazine category [5, 6]. Metformin (N,N-dimethylimidodicarbonimidic diamide) is a member of the biguanide class of compound. Currently, metformin is a US Food and Drug Administration approved drug for the first-line treatment of type 2 diabetes [7–9]. The United Kingdom Prospective Diabetic Study (UKPDS) has shown metformin to improve mortality rates in diabetes patients. Moreover, recent studies suggest metformin has additional utility. Positive effects have been noted in treating cancer, obesity, nonalcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), and metabolic syndrome [10]. Metformin has also been shown to alleviate weight gain associated with antipsychotic medication [11]. Dapsone (4,4′-diaminodiphenylsulfone) is structurally one of the simplest sulphones, yet, it is also recognized as an active therapeutic agent from this important family of compounds. As an antibiotic, dapsone is active against bacteria and protozoa by inhibiting dihydrofolic acid synthesis. This inhibition is mediated through dapsone competition with para-aminobenzoate for the active site of dihydropteroate synthase [12]. Furthermore, dapsone has been successfully used as an indispensable component for the treatment and prophylaxis of leprosy, actinomycetoma, Pneumocystis pneumonia, and malaria [13].

Recently, effective methods for the synthesis of 4-acetylated-5-substituted thiophene-2,3-diones through acylation of 3-oxo-N-phenyl-3-alkyl/aryl-propanethioamides [14] or methyl 3-oxo-3-arylpropanedithioates [15] by oxalyl chloride at the S atom and the active methylene group have been reported. However, we find the synthesis
of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (I) from the addition of ethyl benzoylpyruvate to phenyl isothiocyanate and KOH in DMF with stirring at room temperature [16]. In addition, 4-acylated-5-substituted thiophene-2,3-diones are feasible and beneficial intermediates for the synthesis of a vast variety of substituted heterocyclic compounds [17–19]. In addition, 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (I) has been recognized as a particularly significant starting material or intermediate for the synthesis of diverse sulfur- and nitrogen-containing heterocyclic compounds [16, 20–23]. In the previous study, we found that the reactions of 4-benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (I) with N-nucleophiles such as primary and secondary aliphatic amines and tertiary aromatic and aliphatic amines in THF/H2O (1:1) at room temperature gave amide derivatives that have N-phenylthio carbamoyl group [20] while those with primary aromatic amines in ethanol at high temperature provided substituted thiophenes [16] (Scheme 1). Regarding the significance and application of the corresponding amide and thioamide derivatives as an organic ligand [24–27], in the current study, we have achieved the reactions of 1 with aminoheteroaromatics, N-nucleophiles cum medicinal properties such as lamotrigine, dapsone, and metformin, and primary aromatic amines such as naphthyamines and 1,3-phenylenediamine for the first time (Scheme 2 and Scheme 3).

2. Materials and Methods

2.1. General Information. The reagents were purchased from Merck and used without further purification. Melting points were measured with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. These results agree favorably with the calculated values. Infrared spectra were measured from KBr disk using a Thermo Nicolet 8700 FT-IR spectrometer and frequencies were reported in cm−1. 1H NMR and 13C NMR spectra were recorded on a Bruker DRX-300 AVANCE instrument at 300 and 75 MHz, respectively, using TMS as internal standard and DMSO-d6 or CDCl3 as solvent. Chemical shifts and coupling constants were reported in ppm and Hz, respectively. Thin-layer chromatography was performed on “Silufol-UV 254” plates. Mass spectra were obtained by using an Agilent HP 5973 mass spectrometer operating at an ionization potential of 70 eV.

2.2. Materials. Ethyl benzoylpyruvate was prepared from diethyl oxalate (6.0 mmol) and aceto phenone (4.0 mmol) in the presence of sodium ethoxide (8.4 mmol) in absolute ethanol (30 mL) under N2 atmosphere [28]. 4-Benzoyl-5-phenylamino-2,3-dihydrothiophene-2,3-dione (I) was obtained by careful addition of phenyl isothiocyanate (10 mmol) to benzoylpyruvate (10 mmol) in KOH (10 mmol) and DMF (20 mL) with stirring for 24 h at room temperature [16].

2.3. Reactions of Compound I with Amines

2.3.1. General Procedure. To a stirred solution of I (0.309 g, 1.0 mmol) in THF/H2O (1:1, 10 mL) at room temperature or ethanol (10 mL) at 70°C was added either aminopyridines, lamotrigine, hydroxylamine, DL-1-phenylethylamine, metformin, and 1-phenylalanine (1.0 mmol), or 2,6-diaminopyridine, 2,4-diamino-6-phenyl-1,3,5-triazine, 2,4,6-triamino-1,3,5-triazine, 4,6-diamino-2-mercaptopyr-imidine, dapsone, 4,4′-bipyridine, 1,5-naphthalenediamine, and 1,3-phenylenediamine (0.5 mmol). The reaction mixture was then stirred for 6 h. The progress of the reaction was determined by TLC (eluent AcOEt/hexane 4:1). The solid in THF/H2O (1:1) was separated by filtration (or the ethanol was evaporated) and then was crystallized from a suitable solvent (ethanol, 2-propanol, H2O or EtOH/H2O (1:1)) or was washed with EtOH/H2O (1:1) to give 2–8, respectively.

2.4. Characterization Data of the Compounds 2–8

2.4.1. (2E)-N-2-Pyridyl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (2a). Brownish yellow powder (crystallized from ethanol); yield: 0.28 g (69%); mp 195°C–197°C; IR (KBr): ν 3436 (NH), 3050 (OH, enol), 1728 (C=O, amide), 1633 (C=O, ketone), 1619 (C=C), 1588 (NH), 1536, 1394, 1132 (C=N, NH, C=S, thioamide) cm−1; 1H NMR (DMSO-d6): δ 4.68 (1H, t, J = 6.7 Hz, CHmeta of C6H5N), 6.95 (1H, d, J = 8.8 Hz, CHmeta of C6H5N), 7.21 (2H, d, J = 7.5 Hz, 2CHortho of Ph-NH), 7.32–7.42 (6H, 2Ph, 2Py), 7.43 (1H, t, J = 7.4 Hz, CHpara of C6H5N), 7.62 (2H, d, J = 7.4 Hz, 2CHortho of Ph-CO), 7.89 (2H, br s, OH, NH), 7.91 (1H, d, J = 6.9 Hz, CHortho of C6H5N), 12.24 (1H, br s, NH); 13C NMR (DMSO-d6): δ 112.1 (Cδ), 113.1 (=C), 113.3 (Cδ), 127.3, 127.4, 128.0, 128.9, 129.4, 130.6 (10C, 2Ph), 134.9 (Cipso of Ph-CO), 136.2 (Cβ), 140.7 (Cipso of Ph-NH), 144.0 (Cα), 154.0 (Cγ), 163.2 (=C=O), 172.9 (C=O, amide), 189.1 (C=S), 197.1 (C=O, ketone) ppm; EI-MS: m/z (%): 403 (M+), 309 (M+), 305 (58), 280 (12), 252 (19), 220 (6), 162 (8), 105 (100), 77 (72), 51 (24). Anal. Calcld for C23H19N3O3S: C, 65.49%; H, 4.25%; N, 10.42%; found: C, 65.26%; H, 3.98%; N, 10.65%.

2.4.2. (2E)-N-4-Methyl-2-pyridyl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (2b). Orange powder (crystallized from ethanol); yield: 0.30 g (71%); mp 202°C (decomposition); IR (KBr):ν 3414, 3309 (NH), 3061 (OH, enol), 2920 (C=O, aliphatic), 1718 (C=O, amide), 1660 (C=O, ketone), 1626 (C=C), 1598 (NH), 1534, 1392, 1137 (C=N, NH, C=S, thioamide) cm−1; 1H NMR (CDCl3): δ 2.35 (3H, s, CH3), 6.55 (1H, d, J = 6.1 Hz, CHmeta of C6H5N), 6.86 (1H, s, CHmeta of C6H5N). 7.33 (2H, d, J = 7.3 Hz, 2CHortho of Ph-NH), 7.43–7.56 (6H and 1H, m, 2Ph and OH), 7.63 (2H, d, J = 7.4 Hz, 2CHortho of Ph-CO), 7.85 (1H, d, J = 6.1 Hz, CHortho of C6H5N), 7.86, 14.28 (2H, 2br s, 2NH); 13C NMR (CDCl3): δ 22.1 (CH3), 113.1 (=C), 114.5 (Cδ), 120.7 (Cγ), 128.0, 128.2, 128.6, 129.5, 129.8, 129.9 (10C, 2Ph), 134.1 (Cipso of Ph-CO), 139.2 (Cipso of Ph-NH), 154.4 (Cα), 156.4 (Cβ), 160.1 (Cγ), 163.8 (=C=O), 174.9 (C=O, amide), 189.2 (C=S), 200.0 (C=O, ketone) ppm; EI-MS: m/z (%) = 417.
2.4.3. 2,6-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)pyridine (3a). Yellowish orange powder (crystallized from ethanol); yield: 0.27 g (73%); mp 190°C–192°C; IR (KBr): v 3481, 3391 (NH), 3050 (OH, enol), 1727 (C=O, amide), 1634 (C=O, ketone), 1596 (C=C), 1577 (NH), 1518, 1381, 1139 (C=N, NH, C=S, thioamide) cm⁻¹; ¹H NMR (DMSO-d₆): δ 5.88 (2H, d, J = 8.2 Hz, 2CH-meta of C₆H₅N), 7.13 (2H, br s, 2OH, 2NH), 7.22 (2H, d, J = 7.6 Hz, 4CH-ortho of Ph-NH), 7.34–7.51 (2 (6H) and 1H, m, 4Ph and CH-meta of C₆H₅N), 6.73 (2H, d, J = 7.5 Hz, 4CH-ortho of Ph-CO), 12.06 (2H, br s, 2NH₃); ¹³C NMR (DMSO-d₆): δ 95.0 (C₆ and C₇), 113.1 (C=O), 127.3, 127.4, 128.1, 128.9, 129.4, 130.6 (2 (10C), 4Ph), 134.9 (2(C₆) of Ph-CO), 140.6 (2(C₆) of Ph-NH), 145.1 (C₆), 151.9 (C₁ and C₂), 163.3 (2(C=O), 172.8 (2(C=O), amide), 189.1 (2(C=S), 197.2 (2(C=O), ketone) ppm; EI-MS: m/z (%) = 309 (64), 280 (13), 252 (21), 221 (7), 162 (9), 105 (100), 77 (86), 51 (27). Anal. Calcd for C₂₃H₁₉N₅O₅S (432.47): C, 59.67%; H, 3.98%; N, 15.23%.

2.4.4. 2,6-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)pyridine (3b). Orange-yellow powder (crystallized from EtOH/H₂O (1:1)); yield: 0.31 g (76%); mp 243°C (decomposition); IR (KBr): v 3484, 3143 (NH), 1733, 1716 (C=O, amide), 1649 (C=O, ketone), 1529, 1380, 1137 (C=N, NH, C=S, thioamide) cm⁻¹; ¹H NMR (DMSO-d₆): δ 7.24 (2H, d, J = 7.3 Hz, 4CH-ortho of Ph-NH), 7.33–7.49 (2 (6H), m, 4Ph), 7.62 (2H, t, J = 7.5 Hz, 2CH-meta of Ph-6-triazine), 7.68 (2 (2H), d, J = 7.2 Hz, 4CH-ortho of Ph-CO), 7.72 (1H, t, J = 7.5 Hz, CH-meta of Ph-6-triazine), 8.09 (2H, d, J = 7.5 Hz, 2CH-ortho of Ph-6-triazine), 8.48 (2 (3H), br s, 2OH, 4NH); ¹³C NMR (DMSO-d₆): δ 113.5 (2(C)), 127.6, 127.7, 128.2, 128.3, 129.0, 129.1, 130.4, 130.6, 131.3 (2(C₅), 5Ph), 133.9 (C₃ of Ph-6-triazine), 134.5 (2(C₆) of Ph-CO), 139.7 (2(C₆) of Ph-NH), 160.6 (C₁ and C₂), 163.1 (C₆), 163.7 (2(C=O), 170.1 (2(C=O), amide), 189.0 (2(C=S), 197.6 (2(C=O), ketone) ppm; EI-MS: m/z (%) = 309 (39), 280 (9), 252 (16), 220 (5), 187 (50), 162 (64), 144 (10), 105 (100), 77 (95), 51 (27). Anal. Calcd for C₂₃H₁₉N₅O₅S₂ (805.88): C, 64.099%; H, 3.88%; N, 12.17%; found: C, 64.28%; H, 4.05%; N, 11.96%.

2.4.5. 2,4-(2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido-6-phenyl-1,3,5-triazine (3b). Orange powder (crystallized from ethanol); yield: 0.29 g (79%); mp 225°C–227°C; IR (KBr): v 3319, 3209 (NH), 1725, 1704 (C=O, amide), 1579, 1396, 1143 (C=N, NH, C=S, thioamide) cm⁻¹; ¹H NMR (DMSO-d₆): δ 7.22 (2H, d, J = 7.3 Hz, 4CH-ortho of Ph-NH), 7.31–7.47 (2 (6H), m, 4Ph), 7.64 (2H, f, J = 7.7 Hz, 4CH-ortho of Ph-CO), 7.67 (2 (3H) and 2H, br s, 2OH, 4NH, and NH₂); ¹³C NMR (DMSO-d₆): δ 113.2 (2(C)), 127.5, 127.5, 128.2, 129.0, 129.4, 130.9 (2 (10C), 4Ph), 134.8 (2(C₆) of Ph-CO), 140.4 (2(C₆) of Ph-NH), 159.4 (C₁ and C₂), 160.2 (C₆), 163.5 (2(C=O), 172.2 (2(C=O), amide), 189.2 (2(C=S), 197.4 (2(C=O), ketone) ppm; EI-MS: m/z (%) = 309 (11), 280 (3), 252 (6), 220 (3), 162 (4), 126 (25), 105 (96), 77 (100), 51 (31). Anal. Calcd for C₂₃H₁₉N₅O₅S₂ (744.80): C, 59.67%; H, 3.79%; N, 15.04%; found: C, 59.49%; H, 3.98%; N, 15.23%.

2.4.6. 2,4-Bis((2E)-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamido)-6-aminono-1,3,5-triazine (3e). Dark orange crystal (crystallized from EtOH/H₂O (1:1)); yield: 0.25 g (67%); mp 135°C–137°C; IR (KBr): v 3500, 3396, 3287 (NH), 1730 (C=O, amide), 1664 (C=O, ketone), 1579 (C=C), 1552, 1382, 1141 (C=N, NH, C=S, thioamide) cm⁻¹; ¹H NMR (DMSO-d₆): δ 5.59 (1H, s, CH of pyrimidine), 7.20 (2H, d, J = 7.6 Hz, 4CH-ortho of Ph-NH), 7.32–7.44 (2 (6H), 1H and 2 (1H), m, 4Ph, SH and 2OH), 7.62 (2 (2H), d, J = 7.5 Hz, 4CH-ortho of Ph-CO), 12.73 (2 (2H), br s, 4NH); ¹³C NMR (DMSO-d₆): δ 73.40 (C₁), 113.1 (C=O), 127.4, 127.4, 128.1, 129.0, 129.5, 130.7 (2 (10C), 4Ph), 134.9 (2(C₆) of Ph-CO), 140.6 (2(C₆) of Ph-NH), 155.2 (C₁ and C₂), 163.3 (2(C=O), 172.8 (C=O, amide), 189.2 (2(C=S), 197.2 (2(C=O), ketone) ppm; EI-MS: m/z (%) = 309 (29), 252 (7), 142 (5), 122 (39), 105 (23), 77 (100), 51 (36). Anal. Calcd for C₂₃H₁₉N₅O₅S₂ (760.86): C, 59.99%; H, 3.71%; N, 11.05%; found: C, 59.81%; H, 3.94%; N, 11.24%.
CO), 13.42 (2 (1H), br s, 2NH); 13C NMR (DMSO-d$_6$): δ 113.2 (2C), 125.5, 127.5, 127.7, 128.3, 128.6, 129.1, 129.4, 131.3 (2(14C), 4Ph), 134.7 (2C ipso of Ph-CO), 139.9 (2C ipso of Ph-SO$_2$), 141.1 (2C ipso of Ph-NHCS), 153.7 (2C ipso of Ph-NHCO), 163.5 (2C O-H), 170.4 (2C O, amide), 188.9 (2C S), 197.5 (2C O, ketone) ppm; EI-MS: m/z (%) 357 (1), 309 (9), 255 (20), 222 (15), 105 (100), 77 (81), 43 (69). Anal. Calcd for C$_{46}$H$_{34}$N$_4$O$_8$S$_3$ (866.98): C, 63.73; H, 3.95; N, 6.46. Found: C, 63.48; H, 4.21; N, 6.21.

2.4.9. (2E)-N-Hydroxy-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (4a). Brownish yellow powder (crystallized from 2-propanol); yield: 0.20 g (58%); mp 249°C (decomposition); IR (KBr): ν 3384 (NH), 3030 (OH, enol), 1761 (C=O, amide), 1712 (C=O, ketone), 1508 (C=C), 1583 (NH), 1541, 1534, 1133 (C=N, NH, C=S, thiocarbamoyl) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): δ 7.21 (2H, d, $J=7.8$ Hz, 2CH$_{ortho}$ of Ph-NH), 7.32–7.43 (6H and 1H, m, 2Ph and OH), 7.61 (2H, d, $J=7.6$ Hz, 2CH$_{ortho}$ of Ph-CO), OH and 2NH protons are missing in spectrum; $^{13}$C NMR (DMSO-d$_6$): δ 113.2 (=C), 127.4, 127.5, 128.1, 128.9, 129.4, 130.7 (10C, 2Ph), 134.9 (C$_{ipso}$ of Ph-CO), 140.4 (C$_{ipso}$ of Ph-NH), 163.3 (=C-OH), 172.4 (C=O, amide), 188.9 (C=S), 197.5 (C=O, ketone) ppm; EI-MS: m/z (%) = 342 (M+, 2), 309 (31), 280 (8), 252 (14), 220 (5), 187 (59), 162 (5), 144 (12), 105 (100), 77 (93), 51 (26). Anal. Calcd for C$_{17}$H$_{14}$N$_2$O$_4$S (342.37): C, 59.64%; H, 4.12%; N, 8.18%; found: C, 59.79%; H, 3.98%; N, 8.35%.

2.4.10. DL-(2E)-N-1-Phenylethyl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (4b). Orange crystal (crystallized from ethanol); yield: 0.33 g (76%); mp 186°C–188°C; IR (KBr): ν 3447 (NH), 3045 (OH, enol), 2940 (CH, aliphatic), 1733 (C=O, amide), 1648 (C=O, ketone), 1622 (C=C), 1596 (NH), 1537, 1380, 1141 (C=N, NH, C=S, thiocarbamide) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): δ 1.48 (3H, d, $J=6.8$ Hz, CH$_3$), 4.41 (1H, q, $J=6.8$ Hz, CH), 7.21 (2H, d, $J=7.7$ Hz, 2CH$_{ortho}$ of Ph-NH), 7.32–7.47 (11H, m, 3Ph), 7.62 (2H, d, $J=7.9$ Hz, 2CH$_{ortho}$ of Ph-CO), 8.19 (3H, br s, OH, 2NH); $^{13}$C NMR (DMSO-d$_6$): δ 20.6 (CH$_3$), 50.0 (CH), 113.1 (=C), 126.7, 127.3, 127.4, 128.1, 128.5, 128.7, 128.9, 129.4, 130.6 (15C, 2Ph), 131.0 (10C, 2Ph), 134.9 (C$_{ipso}$ of Ph-CO), 140.4 (C$_{ipso}$ of Ph-NH), 163.3 (=C-OH), 172.4 (C=O, amide), 189.1 (C=S), 197.2 (C=O, ketone) ppm; EI-MS: m/z (%) = 552 (M+, 2), 509 (31), 461 (14), 280 (8), 252 (14), 220 (5), 187 (59), 162 (5), 144 (12), 105 (100), 77 (93), 51 (26). Anal. Calcd for C$_{17}$H$_{14}$N$_2$O$_4$S (342.37): C, 59.64%; H, 4.12%; N, 8.18%; found: C, 59.79%; H, 3.98%; N, 8.35%.

Scheme 1: Earlier works of reactions of 1 with N-nucleophiles.
134.9 (C ipso of Ph-CO), 139.1 (C ipso of Ph-CH), 140.7 (C ipso of Ph-NH), 163.2 (C = O, amide), 172.9 (C = O, ketone) ppm; EI-MS: m/z (\%): 430 (M+, 2), 309 (60), 280 (11), 252 (19), 220 (6), 162 (7), 144 (5), 105 (100), 77 (79), 51 (27). Anal. Calcd for C25H22N2O3S (430.52): C, 69.75%; H, 5.15%; N, 6.51%; found: C, 69.89%; H, 5.41%; N, 6.39%.

2.4.11. (2E)-1,1-Dimethylbiguanido-5-yl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide (4c).

Orange powder (crystallized from 2-propanol); yield 0.31 g (71%); mp 98°C–100°C; IR (KBr): \(\nu\) 3397 (NH), 1700 (C = O, amide), 1638 (C = O, ketone), 1569 (C = C), 1579 (NH), 1542, 1387, 1138 (C-N, NH, C=S, thioamide) cm\(^{-1}\); \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 3.00 (6H, s, 2CH\(_3\)), 5.19 (3H, br s, 3NH), 7.25
(2H, d, 3J = 7.3 Hz, 2CH$_{ortho}$ of Ph-NH), 7.33–7.52 (6H, m, 2Ph), 7.68 (2H, d, 3J = 7.5 Hz, 2CH$_{ortho}$ of Ph-CO), 7.80, 8.37 (3H, 2br s, 2NH, OH); 13C NMR (DMSO-d$_6$): δ 39.50 (2CH$_3$), 113.3 (C), 126.9, 127.3, 128.5, 128.7, 129.4, 131.1 (10C, 2Ph), 134.7 (C$_{ipso}$ of Ph-CO), 140.1 (C$_{ipso}$ of Ph-NH), 154.7, 155.9 (2C=NH), 163.5 (=C-OH), 171.2 (C=O, amide), 189.1 (C=S), 197.5 (C=O, ketone) ppm; EI-MS: m/z (%) 309 (1), 282 (2), 149 (7), 113 (13), 85 (57), 57 (100), 41 (39). Anal. Calcd for C$_{21}$H$_{22}$N$_6$O$_3$S (438.50): C, 57.52; H, 5.06; N, 19.17. Found: C, 57.26; H, 5.29; N, 19.43.

2.4.12. 4,4′-Bipyridinium Bis((2E)-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamide-2-oxide) (5). Dark orange powder (crystallized from H$_2$O); yield: 0.24 g (63%); mp 153°C–155°C; IR (KBr): ν 3472 (NH), 3078 (OH, enol), 3057 (CH, aromatic), 1714 (C=O, amide), 1672 (C=O, ketone), 1627 (C=C), 1597 (NH), 1579, 1383, 1129 (C–N, NH, C=S, thioamide) cm$^{-1}$; $^1$H NMR (DMSO-d$_6$): δ 6.08 (2H, br s, 2NH), 7.26 (2H, d, J = 7.1 Hz, 4CH$_{ortho}$ of Ph-NH), 7.38–7.45 (2H, m, 4Ph), 7.71 (2H, d, J = 7.0 Hz, 4CH$_{ortho}$ of Ph-CO), 8.39 (2H, d, J = 5.1 Hz, 4CH$_{meta}$ of

Scheme 3: Reactions of 1 with naphthylamines and 1,3-phenylenediamine.

Figure 1: Overlapping between π-positive nitrogen orbital with π-negative oxygen orbital of 5.
Scheme 4: Formation of 3-(N-phenylthiocarbamoyl)-2-butenamide 2a and 5-phenylimino-2,5-dihydrothiophene-2-one 6.

C₄₃H₃₆N₄O₆S₂ (774.86): C, 68.20%; H, 3.90%; N, 7.23%; found: C, 68.35%; H, 3.78%; N, 7.42%.

2.4.13. 4-Benzoyl-3-(1-naphthylamino)-5-phenylimino-2,5-dihydrothiophene-2-one (6). Brownish yellow powder (crystallized from 2-propanol); yield: 0.29g (67%); mp 230°C–237°C; IR (KBr): 3446 (NH), 1754 (C=O, thioester), 1708 (C=O, amide), 1891 (2C=S), 1976 (2C=O, ketone) ppm; EI-MS: m/z (%): 740 (79), 522 (52), 450 (5), 408 (5), 227 (7), 165 (10), 123 (11), 105 (22), 91 (26), 77 (44), 57 (72), 43 (100). Anal. Calcd for C₄₄H₃₀N₄O₆S₂ (740.85): C, 71.33%; H, 3.81%; N, 7.56%; found: C, 71.58%; H, 4.08%; N, 7.74%.

2.4.14. 1,5-Bis(4-benzoyl-2-oxo-5-phenylimino-2,5-dihydrothiophene-3-ylamino)naphthalene (7). Green powder (crystallized from 2-propanol); yield: 0.26g (71%); mp 235°C–237°C; IR (KBr): ν 3497 (NH), 3059 (CH, aromatic), 1758 (C=O, thioester), 1698 (C=O, ketone), 1605 (C=N), 1584 (C=C), 1559 (NH) cm⁻¹; 1H NMR (CDCl₃): δ 6.99 (2H, d, J = 7.0 Hz, CH₂ of naphthylene), 7.16–7.56 (2 (10H) and 2H, m, 4Ph and, CH₃ and CH₂ of naphthylene), 8.02 (2H, d, J = 7.0 Hz, CH₄ and CH₂ of naphthylene), 14.23 (2 (1H), br s, 2NH); 13C NMR (DMSO-d₆): δ 105.6 (2-C), 122.2, 126.6, 127.4, 127.6, 128.0, 128.6, 128.7, 128.8, 130.0, 130.1 (2 (15C), 4Ph, naphthylene), 132.4 (2Cipso of naphthylene-NH), 133.3 (2Cipso of Ph-N=C), 159.8 (2-C=NH), 166.9 (2C=N), 175.7 (2C=O, thioester), 198.1 (2C=O, ketone) ppm; EI-MS: m/z (%): 740 (79), 522 (52), 450 (5), 408 (5), 227 (7), 165 (10), 123 (11), 105 (22), 91 (26), 77 (44), 57 (72), 43 (100). Anal. Calcd for C₄₄H₃₀N₄O₆S₂ (740.85): C, 71.33%; H, 3.81%; N, 7.56%; found: C, 71.58%; H, 4.08%; N, 7.74%.

3. Results and Discussion

Interaction of 1 with aminoheteroaromatics and lamotrigine in THF/H₂O (1:1) at room temperature provided the corresponding N₂-2-pyridyl and N-1,2,4-triazin-3-yl-2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butynamides 2a–c, while that with 1,3-diaminothiophene and dapson in a 1:0.5 ratio afforded bis(2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butynamido) pyridine 3a, 1,3,5-triazine 3b and 3c, pyrimidine 3d, and diphenyl sulfone 3e (Scheme 2). Treatment of 1 with NH₃R
(hydroxylamine, DL-1-phenethylamine, and metformin) in THF/H2O (1:1) at room temperature provided the corresponding 2-hydroxy-4-oxo-4-phenyl-3-(N-phenylthiocarbamoyl)-2-butenamides 4a–c (Scheme 2). Moreover, the reaction of 1 with 4,4’-bipyridine in THF/H2O (1:1) at room temperature in a 1:0.5 ratio led to stable 1,4-diionic nitrogen betaine 5 (Scheme 2). Reaction of 1 with α-naphthylamine in boiling ethanol yielded 4-benzoyl-3-(1-naphthylamino)-5-phenylimino-2,5-dihydrothiophene-2-one (6), while that with 1,5-naphthylenediamine and 1,3-phenylenediamine in a 1:0.5 ratio provided bis(4-benzoyl-2-oxo-5-phenylimino-2,5-dihydrothiophene-3-ylamino) naphthalene and benzene (7, 8) (Scheme 3). Similar to primary and secondary aliphatic amines and tertiary aromatic and aliphatic amines [20], it has been reported that primary heteroaromatic amines and dapsone reacted with compound 1 in THF/H2O (1:1) at room temperature to produce 3-N-phenylthiocarbamoyl-2-butenamides 2 and 3. The products of 2–8 were gained in moderate to good yields.

The structures of 2–8 were characterized by elemental analyses, IR, 1H, and 13C NMR spectroscopies and as well as mass spectrometry. The mass spectra of some products exhibited fairly weak molecular ion peaks. The structural analogy of 2–5 can easily be observed from their IR and 13C NMR spectra. Absorption bands of the enolic OH moiety (except 5), amide C=O, and thioamide C-N, NH, and C=S groups at 3078–3030, 1761–1700, 1579–1518, 1396–1314, and 1152–1129 cm−1, respectively, are structural characteristics. Their 13C NMR spectra also revealed signals at δ 163.20–163.75, 170.13–174.87, and 188.99–189.21 ppm due to the carbon atoms of the =C-OH (in Case 5, =C-O−), amide C=O, and thioamide C=S. In the 13C NMR spectra of compound 5, there was no decrease in the chemical shift of the =C and ketonic C=O groups denoting that the negative charge is not distributed on the central carbon atom and two oxygen atoms, and in this, the structure conjugation of negative oxygen with the benzoyl group due to overlapping between π-positive nitrogen orbital with π-negative oxygen orbital was absent (Figure 1) [20]. The 1H NMR spectra of 2–5 exhibited a broad singlet at δ 6.08–8.48 ppm for the NH and enolic OH protons. In the IR and 13C NMR spectra of products 6–8, the absorptions of the carbonyl group (C=O) were absent. IR and 13C NMR absorptions of the C=N group in 6–8 are found at 1617–1605 cm−1 and δ 164.62–167.52 ppm, respectively. Their 1H NMR spectra exhibited a broad singlet at δ 13.24–14.28 ppm for the enaminc NH proton and multiplet signals integrated for 16–26 protons of aromatic rings at δ 6.71–8.17 ppm.

These indicate the nucelophilic attacks of heteroaromatic amines, lamotrigine, dapsone, and metformin similar to primary and secondary aliphatic amines and tertiary aromatic and aliphatic amines [20] on thioester carboxyl group (C-2) of the thiophenedione ring I, because of the extremely high reactivity of the thioester carboxyl group in the polar aprotic solvent-water mixture (THF/H2O (1:1)) with high ionic strength. However, the nucelophilic attacks of primary aromatic amines insoluble in THF/H2O (1:1) such as naphthalenes and 1,3-phenylenediamine in polar protic solvent (ethanol) occur on the carbonyl group (C-3) [16] (Scheme 4). Therefore, nucelophile reaction pathways and selectivity of thiophene-2,3-dione 1 depend on the nucelophile and solvent.

4. Conclusion

The nucelophilic attacks of N-nucleophiles soluble in THF/H2O (1:1) such as aminoheteroaryl, lamotrigine, dapsone, and metformin occur on thioester carboxyl group (C-2) and N-nucleophiles insoluble in THF/H2O (1:1) likely primary aromatic amines on the carbonyl group (C-3) of thiophene-2,3-dione 1 for the synthesis of the corresponding amide and thiophene derivatives 2–8 as convenient organic ligands with medium to good yields.

Data Availability

The data used to support the findings of this study are included within the article and the supplementary information file(s).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Samples 2a–c, 3a–e, 4a–c, 5, 6, 7 and 8: IR, 1H NMR, 13C NMR and MS. (Supplementary Materials)

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