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Synthesis of new 1,2,4-oxadiazolidin-5-ylthiophenes and thienopyrimidine derivatives by aza-Wittig reaction using a thienyl carbodiimide

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Abstract

Azidation of aminothiophene derivative **1** afforded the corresponding azido derivative **2**. The latter reacted with triphenylphosphine to afford iminophosphorane derivatives **3**. Reacting **3** with phenylisocyanate gave the highly reactive carbodiimide intermediate **4**, which was reacted with different nitrones to afford new 1,2,4-oxadiazolidin-5-ylidene-aminothiophenes **5a–c**. Treatment of **4** with absolute EtOH at room temperature gave methyleneamino-5-(methylthio)thiophene **7**, (methylthio)-3-(3-phenylureidothiophene)-2-carboxylate **8** or thienopyrimidine **9** and **10** at refluxing temperature. Finally reaction of carbodiimide intermediate **4** with different secondary amines gave the new thienopyrimidines **11a–c**.

Keywords: Carbodiimide; Cycloaddition; 1,2,4-Oxadiazolidin-5-ylideneaminothiophene derivatives; Thienopyrimidine; Aza-Wittig reaction

Recently, the use of iminophosphoranes [1] has become a powerful tool in organic synthetic strategies directed towards the construction of nitrogen-containing heterocycles [2,3]. The aza-Wittig reaction of iminophosphoranes with isocyanates provides a valuable method for the synthesis of 5–7 membered nitrogen heterocycles such as oxazoles [4], pyridines [4,5], pyrimidine derivatives [6], and thienopyrimidine derivatives [7–9].

This work aims to develop new synthetic method of nitrogen heterocycles based on the 1,3-dipolar cycloaddition reaction of nitrones to thienyl carbodiimide intermediate. Consequently, we examined the dipolarophilic behavior of thienyl carbodiimide towards some *C*-aryl-*N*-phenyl nitrones. Moreover, the reactivity of thienyl carbodiimide towards alcohols and secondary amines was investigated.

Interestingly, and to the best of our knowledge, new 1,2,4-oxadiazolidin-5-ylthiophene derivatives have been synthesized for the first time by this route under the reaction conditions. Furthermore, new thienopyrimidine derivatives, which are an important class of heterocycles for their expected biological importance, were obtained [10].

We have been engaged in a program to investigate the reactivity of carbodiimide towards nitrones, alcohols and secondary amines with the aim of synthesizing new nitrogen heterocyclic compounds using aminothiophene ester **1**. The latter was prepared from ketene di(methylthio)acetal with ethyl thioglycolate [11]. Azidothiophene ester **2** was prepared by reacting aminothiophene **1** with sodium nitrite and sodium azide. Refluxing compound **2** with one

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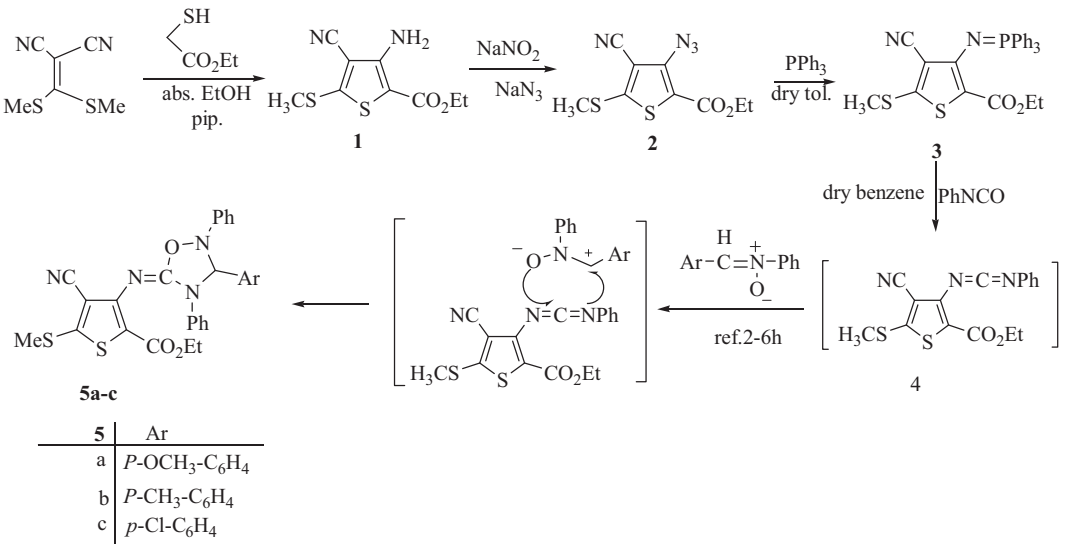


5	Ar
a	*P*-OCH_3-C_6H_4
b	*P*-CH_3-C_6H_4
c	*p*-Cl-C_6H_4

Scheme 1.

equivalent of triphenylphosphine in dry toluene for 30 min yields ethyl 4-cyano-5-(methylthio)-3-triphenylphosphinimino-thiophene-2-carboxylate (**3**) (Scheme 1).

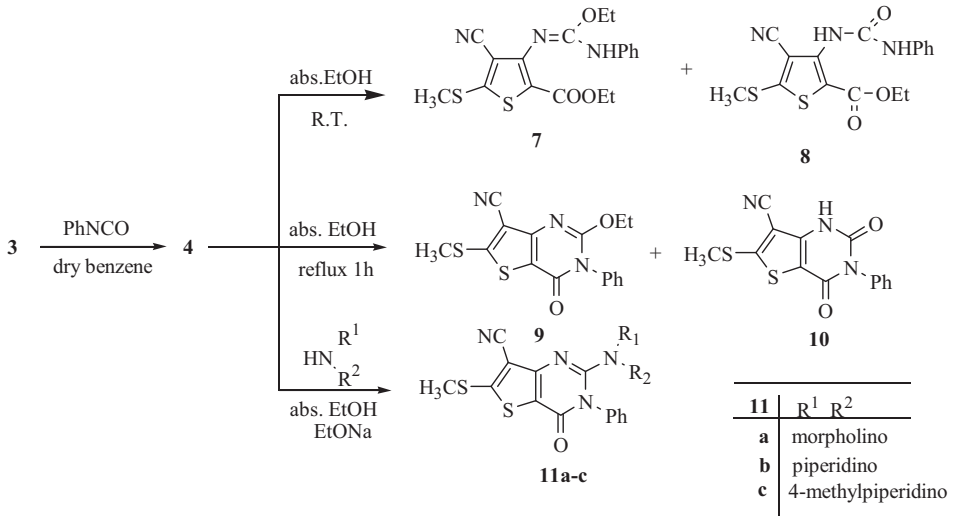
Iminophosphorane derivative **3** underwent aza-Wittig type reaction with phenyl isocyanate to give highly reactive carbodiimide intermediate **4**, which underwent 1,3-dipolar cycloaddition reaction with nitrones in dry benzene at refluxing temperature to afford new 1,2,4-oxadiazolidin-5-ylideneamino-5-(methylthio)thiophene derivatives **5a–c** in good yields (Scheme 1). The structures of **5a–c** were identified by mass spectroscopy fragmentation pattern, which showed a 1-(4-substituted phenyl)-*N*,*N*′-diphenylmethanediamine as the base peak. Elemental analysis and spectral data provide further confirmation for the structure of **5a–c**. The IR of the reaction products showed aromatic CH at ν 3072–3100 cm^{-1} and an ester CO group at ν 1702–1704 cm^{-1}. The ^1H NMR showed a singlet signal for the methine protons at δ 6.13–6.39 in addition to the aromatic protons. Furthermore, their structures were supported by ^{13}C NMR (see Section 1).

In order to extend the investigation of carbodiimide **4** reactivity, it was treated with ethyl alcohol, which afforded several products depending on the reaction conditions. (Methylthio)thiophene **7** and ureidothiophene **8** were isolated by treatment of **4** with absolute ethyl alcohol at room temperature. Reaction of **4** with absolute EtOH under refluxing conditions gave 4-oxothienopyrimidine **9** and 2,4-dioxothienopyimidine **10** *via* intramolecular heterocyclization of **7** and **8** (Scheme 2). Moreover, the reaction of carbodiimide **4** with secondary amines in sodium ethoxide afforded 2-aminothienopyrimdine derivatives **11a–c** *via* intramolecular heterocyclization reaction in good yields (Scheme 2).

In conclusion we have developed an efficient and simple route for the synthesis of new 1,2,4-oxadiazolidin-5-ylthiophene derivatives *via* a 1,3-dipolar cycloaddition reaction of nitrones with thienyl carbodiimide. To the best of our knowledge, this is the first reported synthesis of 1,2,4-oxadiazolidin-5-ylthiophene derivatives *via* cycloaddition reaction. Moreover, the reactivity of carbodiimide with alcohols and secondary amines interestingly afforded thienopyrimidine derivatives.

1. Experimental

*General procedure for the synthesis of compounds **5a–c***: To a solution of **3** (0.250 g, 0.50 mmol), in dry benzene, was added phenylisocyanate (0.600 g, 0.50 mmol). The reaction mixture was heated under reflux for 1 h. After cooling the reaction mixture, nitrones (0.50 mmol) were added. The reaction mixture was heated under reflux for 2–6 h. After concentration and cooling to room temperature, the resulting solid product was collected by filtration, washed well with petroleum ether, dried and recrystallized from ethanol to give **5a–c**. *Ethyl 4-cyano-3-(3-(4-methoxyphenyl)-2,4-diphenyl-1,2,4-oxadiazolidin-5-ylideneamino)-5(methylthio)thiophene-2-carboxylate* **(5a)**. Yellow crystals 0.255 g, 90% yield; mp 156–158 °C. IR (KBr): 3072 (arom. CH), 2976 (aliph. CH), 2224 (CN), 1702 (CO) cm^{-1}. ^1H NMR



Scheme 2.

(DMSO-d_6): δ 0.98 (t, 3H, J = 6.9 Hz, CH_3), 2.73 (s, 3H, SCH_3), 3.74 (s, 3H, OCH_3), 3.95 (q, 2H, J = 7.2 Hz, CH_2), 6.39 (s, 1H, CH), 6.92 (d, 2H, ArH, J = 8.4 Hz), 7.05 (d, 2H, ArH, J = 8.4 Hz), 7.13 (m, 2H, ArH), 7.33-7.43 (m, 6H, ArH), 7.64 (d, 2H, ArH, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6): δ 14.05 (CH_3), 16.75 (SCH_3), 54.77 (OCH_3), 60.29 (OCH_2), 100.25 (C-4), 101.38 (C-aryl) 105.43(C-2), 114.33 (CN), 120.63, 120.72, 122.04, 123.54, 124.44, 128.36, 128.92, 130.45, 138.04, 140.12, 143.51, 144.38 (Ar–C) 152.78 (C-3), 153.72 (C-5), 156.39(C=N), 159.86 (CO). MS (EI) m/z (%): 570 (M^+, 96), 540 (39), 524 (2), 462 (2), 403 (2), 358 (19), 344 (1), 330 (15), 314 (4), 302 (90), 301 (100), 274 (1), 267 (24), 239 (10), 209 (75), 195 (23), 167 (6), 107 (2), 100 (1), 77 (2), 73 (16). Elem. Anal. Calcd. for $C_{30}H_{26}N_4O_4S_2$ (570.68): C, 63.14; H, 4.59; N, 9.82; S, 11.24. Found: C, 63.35; H, 4.72; N, 9.96; S, 11.47.

*General procedure for the synthesis of compounds **7** and **8***: To a solution of iminophosphorane **3** (0.250 g, 0.50 mmol), in dry benzene, was added phenylisocyanate (0.060 g, 0.50 mmol). The reaction mixture was heated under reflux for 1 h. The solvent was removed under reduced pressure and absolute ethanol (10 mL) was added. The reaction mixture was stirred for 15 min at room temperature. After concentration, the reaction mixture was dissolved in acetone and then separated *via* preparative layer chromatography (PLC) using a suitable solvent mixture as eluent (toluene: ethyl acetate = 10:1) to afford **7** and **8**. *Ethyl 4-cyano-3-(ethoxy(phenylamino)-methyleneamino)-5-(methylthio)thiophene* **(7)**. Colourless crystals 0.105 g, 54% yield; mp 190–192 °C. IR (KBr): 3300 (NH), 3100 (arom. CH), 2990–2930 (aliph. CH), 2228 (CN), 1702 (CO), 1635 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.17 (t, 3H, J = 6.9 Hz, CH_3), 1.33 (t, 3H, J = 7.2 Hz, CH_3), 2.84 (s, 3H, SCH_3), 4.38 (q, 2H, J = 7.2 Hz, CH_2), 4.44 (q, 2H, J = 7.2 Hz, CH_2), 7.35–7.52 (m, 5H, ArH), 7.54 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 13.76 (CH_3), 14.05 (CH_3), 16.88 (SCH_3), 54.73 (CH_2), 60.28 (CH_2), 100.25 (C-2), 105.43 (C-4), 113.35 (CN), 120.22. 120.62. 122.04, 123.54, 128.36, 138.04 (Ar-C), 152.98 (C-3), 153.70 (C-5), 159.86 (CO). MS (EI): m/z (%): 389 (M^+, 8), 360 (30), 344 (2), 312 (3), 298 (15), 297 (5), 256 (12), 240 (9), 225 (16), 223 (61), 214 (5), 197 (12), 164 (5), 135 (25), 119 (97), 104 (11), 92 (28), 77 (100), 72 (8), 58 (18). Elem. Anal. Calcd. for $C_{18}H_{19}N_3O_3S_2$ (389.49): C, 55.51; H, 4.92; N, 10.79; S, 16.47. Found: C, 55.32; H, 5.12; N, 10.94; S, 16.21. *Ethyl 4-cyano-(methylthio)-3-(3-phenylureidothiophene)-2-carboxylate* **(8)**. Colourless crystals 0.050 g, 28% yield; mp 210–212 °C. IR (KBr): 3340 (NH), 3100 (arom. CH), 2990–2930 (aliph. CH), 2228 (CN), 1702 (CO), 1680 (CO) 1635 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.18 (t, 3H, J = 6.9 Hz, CH_3), 2.71 (s, 3H, SCH_3), 4.13 (q, 2H, J = 7.2 Hz, CH_2), 6.99–7.26 (m, 5H, ArH), 8.71 (s, 1H, NH), 10.70 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.08 (CH_3), 16.74 (SCH_3), 54.70 (OCH_2), 98.13 (C-4), 104.52 (C-2), 115.35 (CN), 120.22, 122.04, 123.54, 128.36, 138.04 (arom. C), 150.58 (C-3), 151.64 (C-5), 158.49 (CO), 160.89 (CO). MS (EI): m/z (%): 361 (M^+, 85), 316 (5), 288 (15), 269 (20), 225 (45), 209 (11), 164 (15), 135 (45), 119 (30), 104 (5), 92 (10), 77 (100), 72 (4). Elem. Anal. Calcd. for $C_{16}H_{15}N_3O_3S_2$ (361.44): C, 53.17; H, 4.18; N, 11.63; S, 17.74. Found: C, 53.29; H, 4.31; N, 11.43; S, 17.92.

*General procedure for the synthesis of compounds **9** and **10***: To a solution of iminophosphorane **3** (0.250 g, 0.50 mmol), in dry benzene, was added phenylisocyanate (0.060 g, 0.50 mmol). The reaction mixture was heated

under reflux for 1 h. The solvent was removed under reduced pressure and absolute ethanol (10 mL) was added. The reaction mixture was heated for 1 h. After cooling and concentration, the reaction mixture was dissolved in acetone and then separated *via* preparative layer chromatography (PLC) using a suitable solvent mixture as eluent (toluene:ethyl acetate = 10:2) to afford **9** and **10**. *2-Ethoxy-6-(methylthio)-4-oxo-3-phenyl-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile* **(9)**. Colourless crystals 0.094 g, 55% yield; mp 200–202 °C. IR (KBr): (arom. CH), 2990–2930 (aliph. CH), 2228 (CN), 1690 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.28 (t, 3H, J = 6.9 Hz, CH_3), 2.68 (s, 3H, SCH_3), 4.45 (q, 2H, J = 7.2 Hz, CH_2), 7.23–8.12 (m, 5H, ArH). ^{13}C NMR (DMSO-d_6): δ 13.66 (CH_3), 17.31 (SCH_3), 65.45 (CH_2), 101.83 (C-7), 112.18 (C4-a), 114.01 (CN), 128.22, 128.70, 128.91, 134.32 (arom. C), 154.98 (C-7a), 155.70 (C-2), 156.08 (C-6), 162.91 (CO). MS (EI): *m/z* (%): 343 (M^+, 66), 328 (4), 315 (45), 382 (4) 276 (11), 262 (14), 231 (12), 183 (100), 177 (71). Elem. Anal. Calcd. for $C_{16}H_{13}N_3O_2S_2$ (343.42): C, 55.96; H, 3.82; N. 12.24; S, 18.67. Found: C, 55.74; H, 3.69; N, 12.45; S, 18.87. *6-(Methylthio)-2,4-dioxo-3-phenyl-1,2,3,4-tetra-hydrothieno[3,2-d]pyrimidine-7-carbonitrile* **(10)**. Colourless crystals 0.055 g, 35% yield; mp 180–182 °C. IR (KBr): (arom. CH), 2990–2930 (aliph. CH), 2224 (CN), 1690 (CO), 1645 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.83 (s, 3H, SCH_3), 7.35–7.54 (m, 5H, ArH), 11.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 17.35 (SCH_3), 102.92 (C-7), 107.21 (C-4a), 116.01 (CN), 128.45. 128.56, 128.93, 138.05 (arom. C), 151.92 (C-7a), 156.39 (C-6), 159.75 (CO), 162.91 (CO). MS (EI): *m/z* (%): 315 (M^+, 78), 237 (15), 223 (20), 162 (78), 77 (15), 56 (100), 55 (78). Elem. Anal. Calcd. for $C_{14}H_9N_3O_2S_2$ (315.37): C, 53.32; H, 2.88; N, 13.32; S, 20.33. Found: C, 55.74; H, 3.01; N, 12.74; S, 20.59.

*General procedure for the synthesis of compounds **11a–c***: To a solution of **3** (0.250 g, 0.50 mmol), in dry benzene (10 mL), was added phenylisocyanate (60 mg, 0.50 mmol). The reaction mixture was heated under reflux for 1 h. After cooling the reaction mixture, secondary amines (0.50 mmol) were added. The reaction mixture was heated under reflux for 1 h. The solvent was removed under reduced pressure and sodium ethoxide (0.012 g, 0.50 mmol of Na in 10 mL abs. EtOH) was added. The reaction mixture was stirred for 5–10 min at room temperature. The resulting solid products was collected by filtration, washed from methanol, dried and recrystallized from ethanol to afford **11a–c**. *6-(Methylthio)-2-morpholino-4-oxo-3-phenyl-3,4-dihydrothieno[3,2-d]pyrimidine-7-carbonitrile* **(11a)**. Colourless crystals 0.165 g, 86% yield; mp 200–202 °C, IR (KBr): 2990, 2850 (aliph. CH), 2228 (CN), 1676 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.83 (s, 3H, SCH_3), 3.06-3.09 (m, 4H, NCH_2), 3.29–3.31 (m, 4H, OCH_2), 7.45–7.56 (m, 5H, arom. H). MS (EI) *m/z* (%): 383 $(M-H)^+$ (9), 384 (M^+, 17), 307 (18), 300 (14), 293 (18), 281 (2), 267 (14), 263 (10), 197 (68), 183 (3), 171 (8), 162 (12), 131 (6), 122 (2), 91 (21), 84 (7), 77 (100), 72 (3). Elem. Anal. Calcd. for $C_{18}H_{16}N_4O_2S_2$ (384.48): C, 56.23; H, 4.19; N, 14.57; S, 16.68. Found: C, 56.54; H, 4.43; N, 14.74; S, 16.82.

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