Synthesis of Novel *c*-Hetero-fused Thiophene Derivatives

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An efficient synthesis of novel 5-(4-nitrophenyl)-2-benzoxazol-2-yl-*c*-hetero-fused thiophenes was achieved by the condensation of 5-(4-nitrophenyl)-2-benzoxazol-2-yl-3,4-dichlorothiophene with ethylene glycol, ethylenediamine, substituted thioamides and 2-mercaptobenzimidazole using sodium carbonate in refluxing dimethyl formamide.

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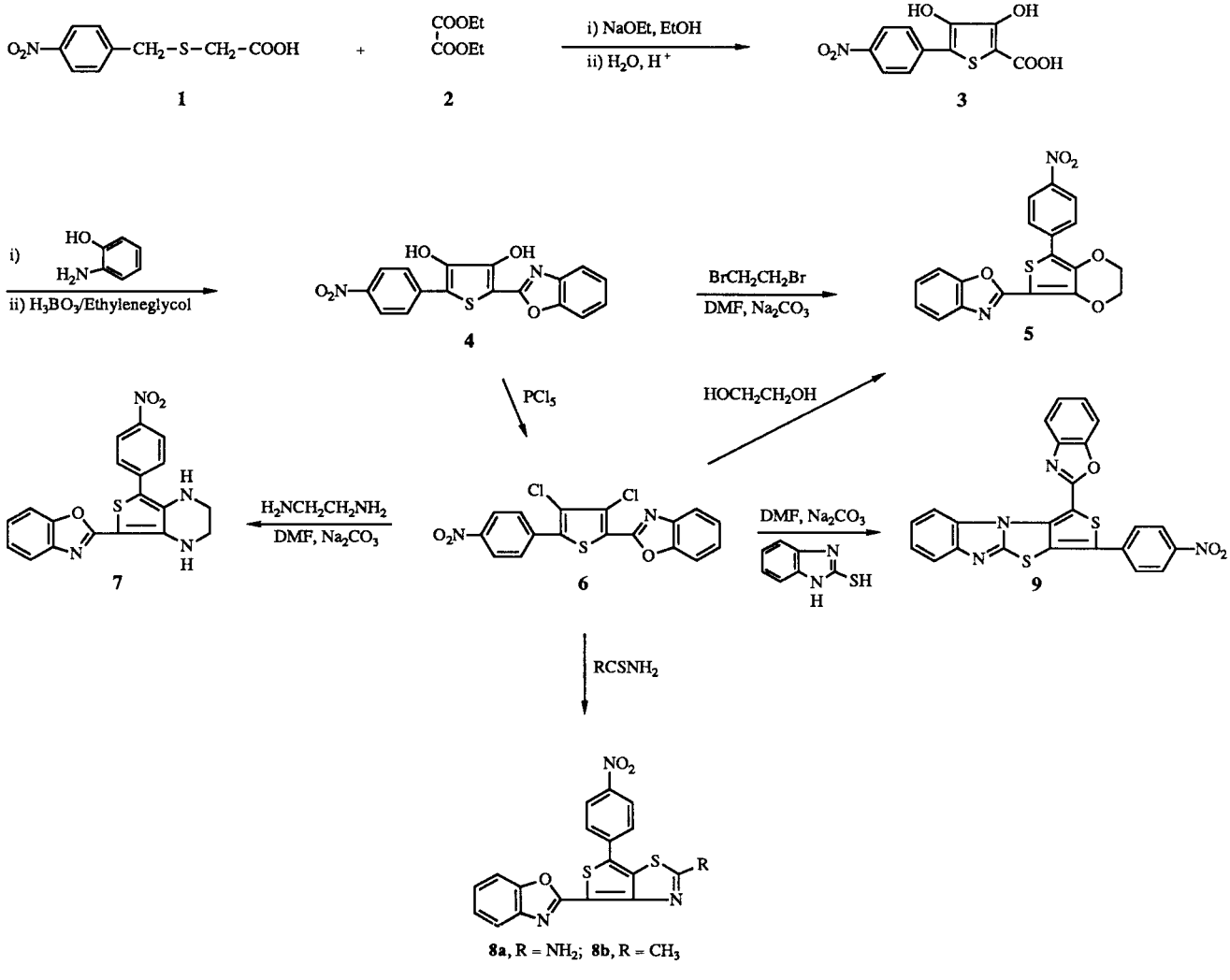
Compounds with fused heteroaryl thiophenes have been reported to be important for their biological activities [1-4]. Aryl and cycloalkyl fused thiophenes find interest in the field of dyestuff chemistry [5-7]. Although most of the fused heteroarylthiophenes described in the literature belong to *b*-heterofused thiophenes, there has been little exploitation of *c*-hetero-fused thiophenes [8-10].

In connection with our search for new structures of fluorophoric compounds and dyestuffs, we had earlier described the synthesis of pyrazolo[3,4-*d*]-1,2,3-triazoles [11] benzopyrano[3,4-*c*]pyridinones [12], 2-(1,2,3-triazol-2-yl)-benzo[*b*]thiophenes [13], indeno[2,1-*d*]thiazoles [14], [1,2,4]-triazolo[1,5-*a*]pyridines [15], pyrazolo[1,5-*a*]pyridines [16] and thiazolo[4,5-*b*]quinoxalines [17].

In the present note we wish to report the synthesis of *c*-hetero-fused thiophene derivatives.

The model *c*-hetero-fused thiophene compounds were synthesized by the condensation of 5-(4-nitrophenyl)-2-

Scheme 1



(benzooxazol-2-yl)-3,4-dichlorothiophene **6**, used as the key intermediate with a variety of compounds having dual nucleophilic groups, such as ethylene glycol, 1,2-ethylenediamine, substituted thioamides and benzimidazole-2-thiol.

The compound **6** was obtained by condensation of 4-nitrobenzylthioacetic acid **1** [18] with diethyl oxalate **2** using sodium ethoxide in refluxing ethanol following Hinsberg's synthesis [19]; reaction of the resulting 5-(4-nitrophenyl)-3,4-dihydroxythiophene-2-carboxylic acid **3** with 2-aminophenol and subsequent fusion of 5-(4-nitrophenyl)-2-(benzoxazol-2-yl)-3,4-dihydroxythiophene **4** with phosphorus pentachloride.

Compound **5** was synthesized by condensation of ethylene glycol with **6** and it was also obtained by the reaction of 1,2-dibromo ethane with **4**.

Compound **6** with ethylenediamine afforded 5-(benzoxazol-2-yl)-7-(4-nitrophenyl)-1,2,3,4-tetrahydrothieno[3,4-*b*]-pyrazine (**7**). Compound **6** also provided 2-amino-4-(benzoxazol-2-yl)-6-(4-nitrophenyl)thieno[3,4-*d*]thiazole (**8a**) when allowed to react with thiourea. Likewise **6** when allowed to react with thioacetamide afforded 4-(benzoxazol-2-yl)-2-methyl-6-(4-nitrophenyl)thieno[3,4-*d*]thiazole (**8b**). Furthermore the reaction of **6** with benzimidazole-2-thiol gave 1-(benzoxazol-2-yl)-3-(4-nitrophenyl)thieno[3',-4':4,5]thiazole[3,2-*a*]benzimidazole (**9**), a novel heterocyclic ring system.

EXPERIMENTAL

All melting points uncorrected and are in °C. The infrared spectra were recorded on Perkin-Elmer Model 397 spectrophotometer in Nujol mull. The ^{1}H nmr spectra were recorded on Varian-60 MHz instrument EM-360-L using TMS as internal standard and the chemical shifts are given in δ (ppm). Mass spectra were recorded on Varian Mat-311 instrument (70 eV).

5-(4-Nitrophenyl)-3,4-dihydroxythiophene-2-carboxylic Acid (**3**).

To a solution prepared by addition of sodium 0.46 g (0.02 g-atom) in 200 ml of absolute ethanol was dissolved 4.54 g (0.02 mole) of 4-nitrobenzylthioacetic acid (**1**) with constant stirring for 0.5 hours at 0-5°. To the reaction mixture 2.92 ml (0.02 mole) of diethyl oxalate **2** was added and the resultant mixture was heated to reflux and the reflux was maintained for about 5 hours. The solution was cooled to room temperature and neutralised with dilute hydrochloric acid (10%). The dark red-brown solid which separated was filtered, washed with water and dried. Recrystallisation from dimethylformamide ethanol (1:1) yielded 2.50 g (89%) of **3** as red-brown crystals, mp >360°; ir (nujol): 3280-3400, 1710 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 7.6-7.75 (m, 2H, aromatics H-2', H-6'), 7.9-8.15 (m, 2H, aromatics, H-3',H-5'), 11.3 (b, 2H, deuterium oxide exchangeable -OH), 12.8 (b, 1H, deuterium oxide exchangeable -COOH); ms: m/z 281 (M$^+$).

Anal. Calcd. for $C_{11}H_7NO_6S$: C, 46.97; H, 2.49; N, 4.98; S, 11.38. Found: C, 46.90; H, 2.53; N, 4.90; S, 11.32.

5-(4-Nitrophenyl)-2-(benzoxazol-2-yl)-3,4-dihydroxythiophene (**4**).

To a mixture of 2.81 g (0.01 mole) of **3** and 1.09 g (0.01 mole) of 2-aminophenol and a catalytic amount (0.5 g) of boric acid was added and the reaction mixture was refluxed in 15 ml ethylene glycol for 5 hours. The resultant mixture was cooled to room temperature and then slowly added to 100 ml of cold water with vigorous stirring. The dark brown solid which separated was filtered, washed with water and dried. It was recrystallised from dimethylformamide-ethanol (1:1) to yield 2.90 g (82%) of **4** as a brown crystalline solid, mp >360°; ir (nujol): 3260-3410 cm^{-1}; ms: m/z 354 (M$^+$).

Anal. Calcd. for $C_{17}H_{10}N_2O_5S$: C, 57.62; H, 2.82; N, 7.90; S, 9.03. Found: C, 57.64; H, 2.81; N, 7.83; S, 9.00.

5-(Benzooxazol-2-yl)-7-(4-nitrophenyl)thieno[3,4-*b*]-1,4-dioxin (**5**).

To a solution of 3.54 g (0.01 mole) of **4** in 20 ml of *N*,*N*-dimethylformamide was added an excess of (about 10 ml) 1,2-dibromoethane and sodium carbonate (0.5 g). The reaction mixture was slowly heated in an oil bath so that it refluxed. The temperature was maintained at gentle reflux for 6 hours. The reaction mixture was then cooled and added to 100 ml of cold water with vigorous stirring. The dirty brown solid which separated was filtered, washed with water and dried. Recrystallised from dimethylformamide yielded 2.75 g (73%) of **5** as a light brown crystalline solid, mp 312°; ^{1}H nmr (trifluoroacetic acid): δ 2.8 (t, 4H, 2H-11', 2H-12' OCH_2), 7.26-8.0 (m, 6H, aromatics H-2', H-6', H-7', H-8', H-9', H-10') 8.2-8.35 (d, 2H, aromatics H-3', H-5'); ms: m/z 380 (M$^+$).

Anal. Calcd. for $C_{19}H_{12}N_2O_5S$: C, 60.00; H, 3.15; N, 7.36; S, 8.42. Found: C, 60.06; H, 3.19; N, 7.29; S, 8.36.

5-(4-Nitrophenyl)-2-(benzoxazol-2-yl)-3,4-dichlorothiophene (**6**).

A mixture of 35.4 g (0.1 mole) of **4** and an excess of 207.5 g (1 mole) of phosphorus pentachloride was slowly heated in an oil bath so that it refluxed gently at 180°. The refluxed temperature was maintained at 180° for a period of 8 hours. The mixture was then cooled and slowly added to ice-water with constant stirring. The light yellowish-brown solid separated was filtered and recrystallised from dimethyl formamide-ethanol mixture (1:1) to yield 24.63 g (63%) of **6** as a light creamy solid, mp >360°; ms: m/z 391 (M$^+$) and 393 (M+2$^+$).

Anal. Calcd. for $C_{17}H_8Cl_2N_2O_3S$: C, 52.17; H, 2.04; Cl, 18.15; N, 7.16; S, 8.18. Found: C, 52.22; H, 1.98; Cl, 18.13; N, 7.09; S, 8.14.

The same procedure as described for **5** was used except that **6** and 1,2-ethandiol were used for condensation in place of **4** and 1,2-dibromoethane. Compound **5** thus obtained in 2.66 g (70%) yield, was identical in all respects with compound **5** as described previously.

5-(Benzoxazol-2-yl)-7-(4-nitrophenyl)-1,2,3,4-tetrahydrothieno[3,4-*b*]pyriazine (**7**).

To a solution of 3.91 g (0.01 mole) of **6** in 20 ml of *N*,*N*-dimethylformamide was added an excess (10 ml) of 1,2-ethylenediamine and a catalytic amount (0.5 g) of sodium carbonate. The reaction mixture was brought to reflux temperature and was maintained at reflux for the next 5 hours. The mixture was cooled and added to ice-water with constant stirring. The precipitated solid was filtered, washed with water and dried. It was recrystallised from DMF to yield 2.19 g (58%) of **7** as a crystalline brownish red solid, mp 263°; ms: m/z 378 (M$^+$).

Anal. Calcd. for $C_{19}H_{14}N_4O_3S$: C, 60.31; H, 3.70; N, 14.81; S,

8.46. Found: C, 60.25; H. 3.63; N, 14.75; S, 8.39.

2-Amino-4-(benzoxazol-2-yl)-6-(4-nitrophenyl)thieno[3,4-*d*]thiazole (**8a**).

The same procedure as described for **7** was used except that 0.76 g (0.01 mole) of thiourea was used in place of 1,2-ethylenediamine to yield crude **8a**. Recrystallisation from DMF-ethanol (1:1) yielded 2.99 g (76%) of **8a**, mp 323°; ir (nujol): 3210, 3360-3420 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 7.3-8.0 (m, 6H, aromatics, H-2', H-6', H-7', H-8', H-9', H-10'), 8.25 (d, 2H, aromatics, H-3', H-5'), 9.25 (b, 2H, deuterium oxide exchangeable NH_2); ms: m/z 394 (M^+).

Anal. Calcd. for $C_{18}H_{10}N_4O_3S_2$: C, 54.82; H, 2.53; N, 14.21; S, 16.24. Found: C, 54.79; H, 2.50; N, 14.17; S, 16.28.

4-(Benzoxazol-2-yl)-2-methyl-6-(4-nitrophenyl)-thieno[3,4-*d*]thiazole (**8b**).

The same procedure as described for **7** was used except 0.75 g (0.01 mole) of thioacetamide was used in place of 1,2-ethylenediamine to give crude **8b**. Recrystallisation from DMF yielded 2.79 g (71%) of **8b**, mp >360°; ^1H nmr (deuteriochloroform-trifluoroacetic acid): δ 2.8 (S, 3H, CH_3), 7.0-7.75 (m, 6H aromatics, H-2', H-6', H-7', H-8', H-9', H-10'), 8.25 (d, 2H, aromatics, H-3', H-5'); ms: m/z 393 (M^+).

Anal. Calcd. for $C_{19}H_{11}N_3O_3S_2$: C, 58.01; H, 2.79; N, 10.68; S, 16.28. Found: C, 58.09; H, 2.71; N, 10.60; S, 16.30.

1-(Benzoxazol-2-yl)-3-(4-nitrophenyl)thieno[3',4':4,5]thiazolo[3,2-*a*]benzimidazole (**9**).

The same procedure as described for **7** was used except that 1.50 g (0.01 mole) of benzimidazole-2-thiol was used in place of 1,2-ethylenediamine. Recrystallisation from DMF-ethanol mixture (1:1) yielded 2.48 g (53%) of **9**, mp >360°; ^1H nmr (trifluoroacetic acid): δ 7.0-8.15 (m, 10H, aromatics, H-2', H-6', H-7', H-8', H-9', H-10', H-13', H-14', H-15', H-16'), 8.35 (d, 2H, aromatics, H-3', H-5').

Anal. Calcd. for $C_{24}H_{12}N_4O_3S_2$: C, 61.53; H, 2.56; N, 11.96; S, 13.67. Found: C, 61.40; H, 2.50; N, 11.88; S, 13.60.

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