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Synthesis Of N-Substituted Thienopyrroles And Thienoisoindoles From Vicinal Thiophene And Benzothiophene Dicarbaldehydes

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ABSTRACT

The reaction of 2,3-thiophene and 5,6- benzo[b]thiophene dicarbaldehydes in the presence of 1,2-ethanedithiol with 5-amino-1-aryl-3-pyridyl pyrazoles in alcoholic medium gave the mono and dicondensated products of N-substituted thienopyrroles and thienoisoindoles. By carrying out the reaction in absence of thiol in dry ether and DMF or xylene medium gave the thienopyrrol-6-one and thienoisoindol-7-one derivatives, while the reaction with excess amino compounds lead to the formation of mono and dicondensation products.

KEYWORDS

2,3-Thiophene dicarbaldehyde;
Benzo[b]thiophene dicarbaldehyde;
1,2-Ethanedithiol;
5-Amino pyrazole;
Thienopyrroles and thienoisoindoles.

INTRODUCTION

In the view of the potential activity of isoindoline moiety as antianalgestic and anti-inflammatory agents[1- 4]. Pyrazoles derivatives are used as anti-inflammatory[5], antibacterial[6,7] and fungicidal agents[8]. We report a study of the synthesis of thiophene[9] and benzo[b]thiophene[10] fused with the isoindoline moiety.

It is well known that the reaction of o-phthaldehyde in the presence of reducing agent as 2-mercaptoethanol or 1,2-ethanedithiol in ethanol with amino compounds gave a highly fluorescent products which allowed to detect picomole quantities of amino acids, peptides and proteins[11,12]. This fact was the driving motive to apply this idea with several o-heterocyclic dialdehydes **(1)** and **(2)**.

EXPERIMENTAL

All melting points were measured in open capillary tubes and were uncorrected. The IR spectra were

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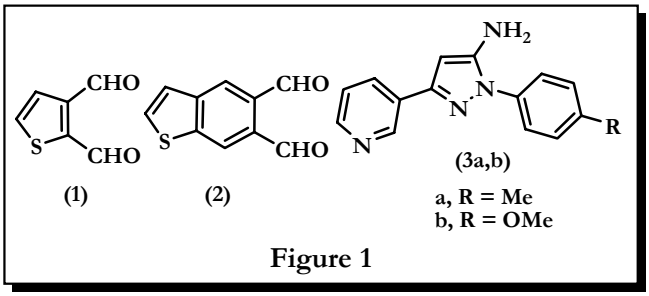

Figure 1

recorded on a Perkin-Elmer 1430 spectrometer using KBr disk technique. The NMR spectra were recorded on a Bruker 250FT spectrometer with tetramethylsilane as internal standard. The mass spectra were recorded using electron ionization(EI) on a Finnigan MAT 8222 spectrometer. The microanalyses were measured at the microanalysis unit, faculty of science, Tanta University. The experimental results are reported in TABLE 1, and the spectral data are reported in TABLE 2.

Synthesis of compounds (4-7)

Method A

A solution of 1,2-ethandithiol(0.92mL, 0.011 mol) in absolute ethanol(20mL) was added dropwise to a well stirred solution of compound **(1)** and/or **(2)** in absolute ethanol(30mL). The reaction mixture was stirred at RT for 30min., then a solution of compound **(3a,b)** (0.011mol) in absolute ethanol (70mL) was added dropwise to the reaction mixture and stirred at RT overnight.

The solvent was evaporated under reduced pressure and the residual material was crystallized by EtOH/EtOAc(1:1, v/v) to afford compounds **(4a,b)** and/or **(5a,b)**, respectively.

Method B

By carrying out method A but with using 4 eq. of 1,2-ethandithiol relative to compound **(1)**.

The residual material from evaporating the solvent of the reaction mixture was dissolved in ether(10mL) and chromatographed on a column of silica gel using benzene/acetone(3:1, v/v) to separate compounds **(4a,b)** and **(5a,b)**, from **(6a,b)** and **(7a,b)**.

2-({5-[1-(4-methylphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]-5H-thieno[2,3-c]pyrrol-4-yl}thio)ethanethiol (4a)

Pale yellow solid; yield 60%; mp 222-224°C (from ether/EtOAc); IR(KBr) ν cm^{-1}: 2588(SH); ^{1}HNMR(DMSO-d_6) δ ppm: 2.31(s, 3H, CH_3), 2.86(q, 2H, CH_2-SH), 3.13(t, 2H, S-CH_2), 6.50(s, 1H, δ-pyrazolyl), 6.96(d, 1H, β-thienyl), 7.12(d, 1H, α-thienyl), 7.22-8.80(m, 8H, H_{arom}); EI MS m/z:449 [$(M+1)^+$, 14%], 250(100%).

Anal.calcd. for $C_{23}H_{20}N_4S_3$ (448.63): C, 61.58; H, 4.49; N, 12.49; S, 21.40. Found:C, 62.06; H, 4.28; N, 12.30; S, 21.17.

2-({5-[1-(4-Methoxyphenyl)-3-pyridin-3-yl-1H-pyrazol-5-yl]-5H-thieno[2,3-c]pyrrol-4-yl}thio)ethanethiol (4b)

Pale yellow solid; yield 62%; mp 250-252°C (from ether/EtOAc); IR (KBr)ν cm^{-1}: 2528 (SH)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:2.80(q, 2H, CH_2-SH), 3,17 (t, 2H, SCH_2), 3,70(s, 3H, CH_3), 6.31(s, 1H, δ-pyrazolyl), 6.92(d, 1H, β-thienyl), 7.00(s, 1H, α-pyrrolyl), 7.05(d, 1H, α-thienyl), 7.09-8.71(m, 8H, H_{arom}); EI MS m/z: 464(M^+, 15%), 51(100%).

Anal.calcd. for $C_{23}H_{20}N_4OS_3$ (464.63): C, 59.46; H, 4.34; N, 12.06; S, 20.70. Found:C, 59.74; H, 4.51; N, 12.32; S, 20.29.

2-({4-[(2-Mercaptoethyl)thio]-5-[1-(4-methylphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]-5H-thieno[2,3-c]pyrrol-6-yl}thio)ethanethiol (6a)

Yellow solid, yield 15%; mp 213-215°C(from ether); IR(KBr) ν cm^{-1}: 2584(SH) cm^{-1}; ^{1}HNMR (DMSO-d_6) δ ppm: 2.35(s, 3H, CH_3), 2.91(m, 4H, 2 CH_2-SH), 3.21(m, 4H, 2 S-CH_2), 6.42(s, 1H, δ-pyrazolyl), 6.95-8.78(m, 10H, H_{arom}); EI MS m/z:540 (M^+, 14%), 59(100%).

Anal.calcd. for $C_{25}H_{24}N_4S_5$ (540.82): C, 55.52; H, 4.47; N, 10.36; S, 29.65. Found: C, 55.75; H, 4.61; N, 10.18; S, 29.73.

2-({4-[(2-Mercaptoethyl)thio]-5-[1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]-5H-thieno[2,3-c]pyrrol-6-yl}thio)ethanethiol (6b)

Yellow solid; yield 10%; mp 235-237°C(from ether); IR(KBr) ν cm^{-1}: 2586(SH) cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:2.92(m, 4H, 2 CH_2-SH), 3.23(m, 4H, 2 S-CH_2), 3.73(s, 3H, O-CH_3), 6.40(s, 1H, δ-pyrazolyl), 6.97-8.76(m, 10H, H_{arom}); EI MS m/z:556(M^+, 18%), 51(100%).

Anal.calcd. for $C_{25}H_{24}N_4OS_5$ (556.81): C, 53.93; H, 4.34; N, 10.06; S, 28.79. Found: C, 54.14; H, 4.53;

N, 9.85; S, 29.01.

2-({6-[1-(4-Methylphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]-6H-thieno[2,3-f]isoindol-5-yl}thio)ethanethiol (5a)

Pale yellow solid; yield 65%; mp 230-232°C (from ether/EtOAc); IR(KBr) ν cm^{-1}: 2585(SH) cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm: 2.35(s, 3H, CH_3), 2.90 (q, 2H, CH_2-SH), 3.20(t, 2H, S-CH_2), 6.40(s, 1H, δ-pyrazolyl), 7.21-8.79(m, 13H, H_{arom}); EI MS m/z:498 (M^+, 20%), 103(100%).

Anal.calcd. for $C_{27}H_{22}N_4S_3$ (498.69):C, 65.03; H, 4.45; N, 11.23; S, 19.29. Found:C, 64.77; H, 4.24; N, 11.56; S, 19.01.

2-({6-[1-(4-Methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]-6H-thieno[2,3-f]isoindol-5-yl}thio)ethanethiol (5b)

Pale yellow solid, yield 64%; mp 263-265°C (from ether/EtOAc); IR(KBr) ν cm^{-1}:2581(SH)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:2.88(q, 2H, CH_2-SH), 3.18(t, 2H, S-CH_2), 3.70(s, 3H, CH_3), 6.35(s, 1H, δ-pyrazolyl), 7.05-8.75(m, 13H, H_{arom}); EI MS m/z:514 (M^+, 14%), 144(100%).

Anal.calcd. for $C_{27}H_{22}N_4OS_3$ (514.69):C, 63.01; H, 4.31; N, 10.89; S, 18.69. Found:C, 62.82; H, 4.52; N, 11.04; S, 18.80.

2-{[5-[(2-mercaptoethyl)thio]-6-[1-(4-methylphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-6H-thieno[2,3-f]isoindol-7-yl]thio}ethanethiol (7a)

Yellow solid; yield 12%; mp 202-204°C(from ether); IR(KBr) ν cm^{-1}:2589 (SH) cm^{-1}; ^{1}HNMR (DMSO-d_6) δ ppm:2.33(s, 3H, CH_3), 2.88(m, 4H, 2 CH_2-SH), 3.20(m, 4H, 2 S-CH_2), 6.42(s, 1H, δ-pyrazolyl), 7.11-8.80(m, 12H, H_{arom}); EI MS m/z: 590(M^+, 15%), 103(100%).

Anal.calcd. for $C_{29}H_{26}N_4S_5$ (590.87):C, 58.95; H, 4.44; N, 9.48; S, 27.13. Found:C, 58.88; H, 4.61; N, 9.29; S, 27.46.

2-{[5-[(2-Mercaptoethyl)thio]-6-[1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-6H-thieno[2,3-f]isoindol-7-yl]thio}ethanethiol (7b)

Yellow solid; yield 14%; mp 217-219°C(from ether); IR(KBr) ν cm^{-1}:2580(SH) cm^{-1}; ^{1}HNMR (DMSO-d_6) δ ppm:2.86(m, 4H, 2 CH_2-SH), 3.20(m, 4H, 2 S-CH_2), 3.72(s, 3H, CH_3), 6.38(s, 1H, δ-pyrazolyl), 6.96-8.76(m, 10H, H_{arom}); EI MS m/z: 605[(M-1)$^+$, 17%], 83(100%).

Anal.calcd. for $C_{29}H_{26}N_4OS_5$ (606.87): C, 57.39; H, 4.32; N, 9.23; S, 26.42. Found:C, 57.61; H, 4.48; N, 9.15; S, 26.71.

Synthesis of compounds (8a,b) and (9a,b)

Compound **(1)** and/or **(2)** (0.01mol) and 5-amino pyrazole derivative **(3a,b)** (0.03mol) were dissolved in dry ether(50mL) and DMF(1mL), the solution was stirred at room temperature for 18 hours. The solid product formed was filtered off, washed with cold ether to give pure compounds **(8a,b)** and/or **(9a,b)**, respectively.

(E)-N-{4,5-Dihydro-5-[3-(pyridin-3-yl)-1-p-tolyl-1H-pyrazol-5-yl]thieno[2,3-c]pyrrol-6-ylidene}-3-(pyridin-3-yl)-1-p-tolyl-1H-pyrazol-5-amine (8a)

Yellowish green solid; yield 55%; mp 210-212°C (from ether); IR(KBr) ν cm^{-1}:1634(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:2.31(s, 6H, 2 CH_3), 3.89 (s, 2H, α-pyrrolyl), 6.40(s, 2H, 2 d-pyrazolyl), 6.68 (d, 1H, β-thienyl), 6.90(d, 1H, α-thienyl), 7.10-8.77 (m, 16H, H_{arom}); EI MS m/z:604(M^+, 76%), 91(100%).

Anal.calcd. for $C_{36}H_{28}N_8S$(604.22): C, 71.50; H, 4.67; N, 18.53; S, 5.30. Found:C, 71.59; H, 4.83; N, 18.11; S, 5.04.

(E)-N-{4,5-dihydro-5-[1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]thieno[2,3-c]pyrrol-6-ylidene}-1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-amine (8b)

Yellowish green solid; yield 58%; mp 179-180°C (from ether); IR(KBr) ν cm^{-1}: 1638(C=N)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:3.72(s, 6H, 2 O-CH_3), 3.90(s, 2H, α-pyrrolyl), 6.41(s, 2H, 2 δ-pyrazolyl), 6.70(d, 1H, β-thienyl), 6.88(d, 1H, α-thienyl), 6.96-8.779(m, 16H, H_{arom}); EI MS m/z:637(M^+, 30%), 249(100%).

Anal.calcd. for $C_{36}H_{28}N_8O_2S$ (636.73): C, 67.91; H, 4.43; N, 17.60; S, 5.04. Found:C, 68.04; H, 4.48; N, 17.39; S, 4,81.

(E)-N-{5,6-Dihydro-6-[3-(pyridin-3-yl)-1-p-tolyl-1H-pyrazol-5-yl]thieno[3,2-f]isoindol-7-ylidene}-3-(pyridin-3-yl)-1-p-tolyl-1H-pyrazol-5-amine (9a)

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Yellowish green solid; yield 60%; mp 259-261°C (from ether); IR(KBr) ν cm^{-1}:1630(C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ ppm:2.35(s, 6H, 2 CH_3), 3.85 (s, 2H, α-pyrrolyl), 6.42(s, 2H, 2 δ-pyrazolyl), 7.10-8.80(m, 20H, H_{arom}); EI MS m/z: 654[$(M-1)^+$, 18%], 105(100%).

Anal.calcd. for $C_{40}H_{30}N_8S$(654.23):C, 73.37; H, 4.62; N, 17.11; S, 4.90. Found:C, 73.61; H, 4.37; N, 16.92; S, 4.66.

(E)-N-{5,6-Dihydro-6-[1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]thieno[3,2-f]isoindol-7-ylidene}-1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-amine (9b)

Yellowish green solid; yield 56%; mp 240-241°C (from ether); IR(KBr) ν cm^{-1}: 1642(C=N) cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:3.73(s, 6H, 2 O-CH_3), 3.90(s, 2H, α-pyrrolyl), 6.46(s, 2H, 2 δ-pyrazolyl), 6.88-8.79(m, 20H, H_{arom}); EI MS m/z:687(M^+, 14%), 93(100%).

Anal.calcd. for $C_{40}H_{30}N_8O_2S$(686.78): C, 69.95; H, 4.40; N, 16.32; S, 4.67. Found:C, 70.21; H, 4.15; N, 15.87; S, 4.34.

Synthesis of compounds (10a,b) and (11a,b)

Method A

A solution of compound **(1)** and/or **(2)** (0.01mol) and 5-amino pyrazple derivative **(3a,b)** (0.01mol) in dry ether(50mL) and DMF(1mL) was stirred at room temperature for 18 hours. The solid product formed was filtered off, washed with cold ether to give pure compounds **(10a,b)** and/or **(11a,b)**, respectively.

Method B

A stirred solution of compound **(1)** and/or **(2)** (0.01mol) and 5-amino pyrazole derivative **(3a,b)** (0.01mol) in dry xylene was refluxed for 6h. The reaction mixture was cooled to RT and the solvent was concentrated under reduced pressure to 10mL, ether(50mL) was added with shaking. The solid product formed was filtered off, washed with cold ether to give pure compounds **(10a,b)** and/or **(11a,b)**, respectively.

Note: Ether and DMF were replaced by dry xylene (50 mL) and the reaction mixture was refluxed for 6 hours to give the same yields of the products.

4,5-Dihydro-5-[3-(pyridin-3-yl)-1-p-tolyl-1H-pyrazol-5-yl]thieno[2,3-c]pyrrol-6-one (10a)

Oranges solid; yield 72%; mp 220-221°C (from ether/EtOAc); IR(KBr)ν cm^{-1}: 1734(C=O)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:2.34(s,3H,CH_3), 4.20(s, 2H, α-pyrrolyl), 6.38(s, 1H, δ-pyrazolyl), 6.74(d, 1H, β-thienyl), 7.10-8.77(m, 9H, α-thienyl and H_{arom}); EI MS m/z:372(M^+, 14%), 55(100%).

Anal.calcd. for $C_{21}H_{16}N_4OS$ (372.44):C, 67.72; H, 4.33; N, 15.04; S, 8.61. Found:C, 67.50; H, 4.13; N, 14.81; S, 8.44.

4,5-Dihydro-5-[1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]thieno[2,3-c]pyrrol-6-one (10b)

Orange solid; yield 68%; mp 208-210°C(from ether/EtOAc); IR(KBr) ν cm^{-1}:1730(C=O)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:3.70(s, 3H, O-CH_3), 4.22 (s, 2H, α-pyrrolyl), 6.44(s, 1H, δ-pyrazolyl), 6.78(d, 1H, β-thienyl), 7.20-8.78(m, 9H, α-thienyl and H_{arom}); EI MS m/z: 388(M^+, 22%), 254(100%).

Anal.calcd. for $C_{21}H_{16}N_4O_2S$ (388.44): C, 64.93; H, 4.15; N, 14.42; S, 8.25. Found:C, 65.16; H, 3.78; N, 14.22; S, 8.46.

5,6-Dihydro-6-[3-(pyridin-3-yl)-1-p-tolyl-1H-pyrazol-5-yl]thieno[3,2-f]isoindol-7-one (11a)

Orange solid; yield 70%; mp 198-200°C(from ether/EtOAc); IR(KBr) ν cm^{-1}:1738 (C=O)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:2.31(s, 3H, CH_3), 4.05 (s, 2H, α-pyrrolyl), 6.38(s, 1H, δ-pyrazolyl), 7.10-8.80 (m, 12H, H_{arom}); EI MS m/z:423 [$(M+1)^+$, 82%], 57(100%).

Anal.calcd. for $C_{25}H_{18}N_4OS$ (422.50):C, 71.07; H, 4.29; N, 13.26; S, 7.59. Found:C, 70.83; H, 4.51; N, 13.04; S, 7.89.

5,6-Dihydro-6-[1-(4-methoxyphenyl)-3-(pyridin-3-yl)-1H-pyrazol-5-yl]thieno[3,2-f]isoindol-7-one (11b)

Orange solid; yield 74%; mp 216-218°C(from ether/EtOAc); IR(KBr) ν cm^{-1}: 1735(C=O) cm^{-1}; ^{1}HNMR(DMSO-d_6) δ ppm:3.71(s, 3H, O-CH_3), 4.00 (s, 2H, α-pyrrolyl), 6.42(s, 1H, δ-pyrazolyl), 6.80-8.76(m, 12H, H_{arom}); EI MS m/z:438(M^+, 100%).

Anal.calcd. for $C_{25}H_{18}N_4O_2S$(438.50):C, 68.48; H, 4.14; N, 12.78; S, 7.59. Found:C, 70.83; H, 4.51; N, 12.44; S, 6.98.

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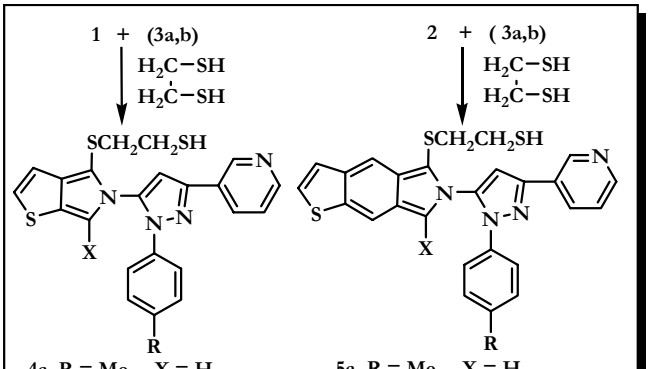
RESULTS AND DISCUSSION

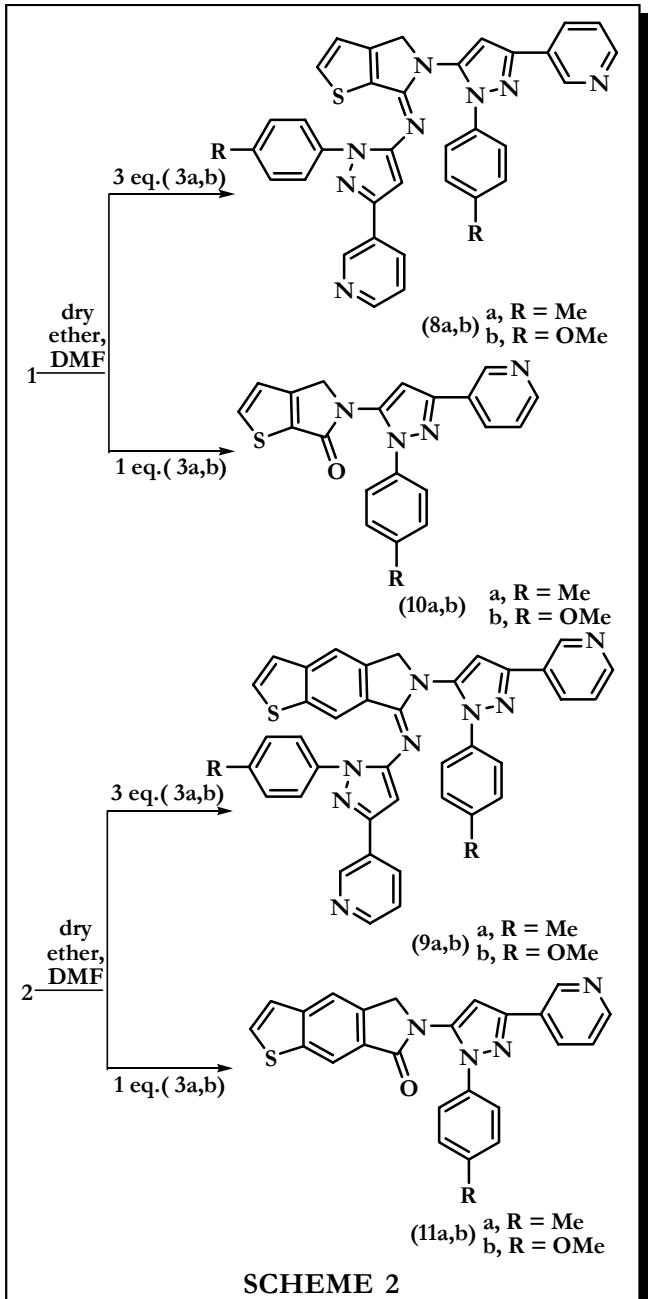
Using equimolar reaction of 2,3-thiophene dicarbaldehyde and/or benzo[b]thiophene dicarbaldehyde and 1,2-ethanedithiol with 5-amino pyrazole derivatives[13] **(3a,b)** gave the substituted products **(4a,b)** and/or **(5a,b)** in good yields, respectively (SCHEME 1).

Aiming to obtain the disubstituted products **(6a,b)** and/or **(7a,b)**, the molar ration of 1,2-ethanditiol relative to the dicarbaldehyde was increased by dropwise addition to the reaction mixture. The maximum intensity of the disubstituted spots (TLC) was reached with 4 eq. of 1,2-ethanedi thiol but as minor product beside the major products **(4a,b)** and/or **(5a,b)**.

It is worthily to mention that the above reaction in the presence of excess amino compound(1:4) gave the mono and dicondensated products **(4-7)**. The monocondensation products were the major in about 60-65% yield and the dicondensation products were the minor products in about 10-15% yield which could be separated easily by silica gel column chromatography using benzene/acetone as an eluent(3:1, v/v), while it gave the monocondensated products by using equimolecular ratio of the o-dicarbaldehyde and the amino compounds **(3a,b)**.



SCHEME 1



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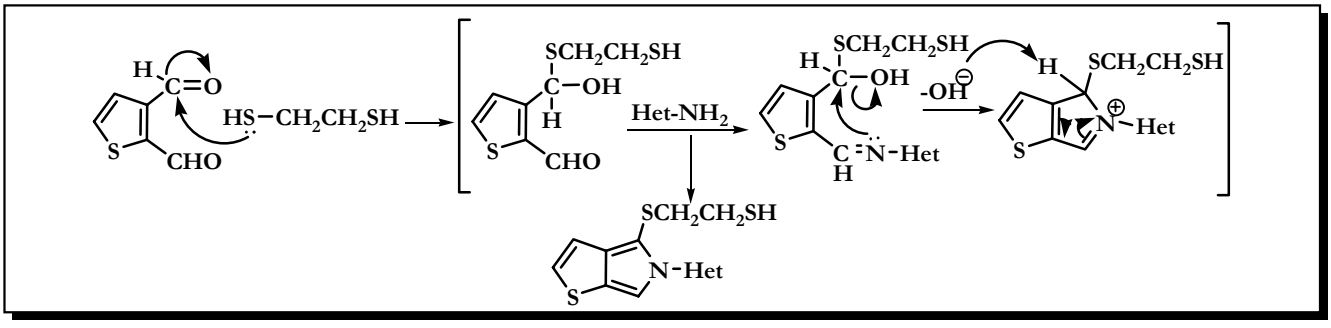

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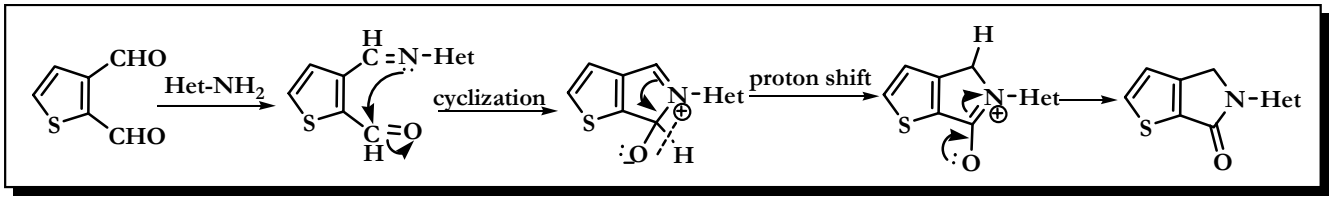

The following mechanism was proposed for the formation of monocondensed products **(4)** and **(5)**. Previously kametani and co-workers[14] mentioned that the condensation of o-phthaldehyde with p-aminoacetophenone gave the diimine intermediate which could be cyclized by acetic acid followed by several steps to get the(± indoprofen). Recently takahashi and co-workers[15] reported that the condensation of o-phthaldehyde with aromatic amines in dry diethyl ether and small quantity of DMF, gave the double Mannish condensated products based on X-ray analysis. Takahashi's results[15] are in harmony with the previously published work in 1988[16].

By carrying out the condensation between 2,3-thiophenedicarbaldehyde(and/or 5,6-benzo[b] thiophenedicarbaldehyde) and amino compounds **(3a,b)** in excess(1-3), under Takahashi experimental conditions, the dicondensated products **(8)** and **(9)** in moderate yields were obtained (SCHEME 2). These results were in accordance with Takahashi results[15].

Moreover, by carrying out the above reaction using equimolecular ratio(1:1) between o-dicarbaldehyes **(1)** and **(2)** with the amino compounds **(3a,b)** in dry ether and DMF at room temperature for 18 hours, gave the monocondensated products **(10)** and **(11)** in good yield . This reaction could also be carried out in dry xylene[17] for 6 hours, to give the same products (SCHEME 2).

A possible reaction mechanism starts with the condensation of the amine compound with the formyl group in position 3 of the compound **(1)** or **(2)** followed by cyclization via a 1,3-hydride shift to give compounds **(10)** and **(11)**.

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