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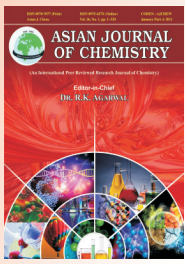

Synthesis of Some Novel Pyrazolopyridooxazine, Pyrazoloquinolizines, Pyrazoloindolizine and Pyrazolopyranopyrimidinone Derivatives

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Different pyrazolone derivatives were prepared as starting materials for the synthesis of pyrazolopyridooxazine, pyrazoloquinolizines, pyrazoloindolizine, 1,4-oxazinopyrazolines and pyrazolopyranopyrimidinone derivatives *via* reactions with different reagents applying the one pot multicomponent reaction using microwave and ultrasound irradiation in some cases.

Keywords: Chloropyrazolecarbaldehyde, Pyrazolopyridooxazine, Pyrazoloquinolizines, Pyrazoloindolizine, Pyrazolopyranopyrimidinone.

INTRODUCTION

Several heterocyclic compounds containing pyrazole ring are very useful as intermediates for pharmaceuticals[1-4] and have shown several biological activities such as antiinflammatory agents[5-7], antibacterial[8-12], antifungal[9], antiviral[13,14], antitumor[15-19] and insecticidal[20,21]. Numerous pyrazole derivatives are also used in dye industry[22]. In our continued interest in the development of highly expedient methods for the synthesis of diverse heterocyclic compounds of biological significance, we report herein the synthesis of some novel pyrazole derivatives which are pyrazolinoquinolizines, 1,4-oxazinopyrazolines, 6-amino-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile and 4,6-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin-5(1*H*)-one. Moreover, in some cases we used a one pot multicomponents reaction using microwave and ultrasound irradiation.

EXPERIMENTAL

Melting points were determined using an Electrothermal IA9000 series digital capillary melting point apparatus and are uncorrected. IR spectra were obtained as KBr discs on a 1000-Perkin Elmer FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECP-300 NMR in $CDCl_3$ (or DMSO-d_6) using TMS as an internal standard. Chemical shifts are given in ppm on the δ scale and coupling constants (*J*) are given in Hz. Electron impact (EI) MS spectra were acquired with the aid of a Shimadzu GCMSQP5050A spectrometer, equipped with a 30 m × 0.25 mm DB-1 glass column, operating with an ionization energy of 70 eV, at the Chemistry Department, College of Science, King Saud University. Electrospray ionization (ESI) MS spectra were acquired with LC-MSMS Acquity UPLC/Qutlro Premier Xe at research center King Faisal Specialist Hospital. Ultrasonication was performed in a J.P. Selecta ultrasound cleaner with a frequency of 60 Hz and an output power of, 770 W. Microwave irradiated reactions were carried out on a Galanz microwave oven, operating at 1000 W, generating 60 Hz frequency.

Synthesis of 1,3-disubstituted 1*H*-pyrazol-5(4*H*)-one (2a-f): They were synthesized by reaction of β-ketoester with appropriate hydrazines according to the literature procedures[23].

Synthesis of 5-chloro-3-substituted 1-phenyl-1*H*-pyrazole-4-carbaldehyde (3a-d): They were synthesized from the 5-pyrazolones employing Vilsmeier-Haack chloroformylation[24].

Synthesis of 3,5-disubstituted-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4a-e): A mixture of **3a-d** (10 mmol) and cyclic *sec*-amines (*viz.*, morpholine, piperidine and pyrrolidine) (5 mmol) in dry ethanol (20 mL) containing dry triethylamine (1 mL) was heated under reflux for 17-22 h (monitored by TLC). After completion, ethanol was removed in a rotavapor, the residue was treated with water and was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate overnight and concentrated *in vacuo*. The product was then subjected to column chromatography to afford pure **4a-e** [25].

3-Methyl-5-morpholin-4-yl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4a): Fine pale yellow cubes, m.p. 109-111 °C; Yield 13 %; IR (KBr, ν_{max}, cm^{-1}): 2851 (CHO), 1656 (C=O);

^{1}H NMR ($CDCl_3$): 2.45 (3H, s, CH_3), 3.13 (4H, t, J = 4.6, CH_2-N-CH_2), 3.67 (4H, t, J = 4.6, CH_2-O-CH_2), 7.38-7.50 (5H, m, Ar-H), 9.95 (1H,s, CHO); ^{13}C NMR: 12.9 (CH_3), 50.1, 66.0 (morpholinyl group carbons), 111.3, 124.2, 127.7, 128.5, 138.3,151.0, 151.5 (sp^2 carbons), 182.5 (C=O); MS: *m/z* (%) 271 [M^+] (18) ($C_{15}H_{17}N_3O_2$), 226 [M-CH_3-CHO-H] (7), 211 [M-C_3H_6O-2H] (28), 143 [M-C_2H_3N-HCN] (36), 91 [$C_6H_5N^+$] (36), 77 [$C_6H_5^+$] (82), 51 [77-C_2H_2] (100).

5-Morpholin-4-yl-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (4b): Fine orange cubes, m.p. 147-149 °C; Yield 31 %; IR (KBr, ν_{max}, cm^{-1}): 2738-2858 (CHO), 1657 (C=O); ^{1}H NMR ($CDCl_3$): 3.19 (4H, t, J = 4.6, CH_2-N-CH_2), 3.73 (4H, t, J = 4.6, CH_2-O-CH_2), 7.42-7.56 (6H, m,, H-3',3",4',4",5',5"), 7.66 (4H, dd, ^3J = 7.5, ^4J = 2.9, H-2',2",6',6"), 9.82 (1H,s, CHO); ^{13}C NMR: 50.0, 66.3 (morpholinyl group carbons), 110.3, 124.8, 128.0, 128.5, 128.7, 131.1, 138.6, 150.5, 155.5 (sp^2 carbons), 183.8 (C=O); MS: *m/z* (%) 333 [M^+] (18) ($C_{20}H_{19}N_3O_2$), 332 [M-H] (11), 302 [M-CHO-2H] (24), 274 [M-C_3H_6O-H] (21), 171 [274-C_7H_5N] (15), 144 [171-HCN] (20), 104 [M-$C_{13}H_{14}N_2O_2$+H] (42), 91 [$C_6H_5N^+$] (30), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (49).

1,3-Diphenyl-5-piperidino-1*H*-pyrazole-4-carbaldehyde (4c): Fine pale beige cubes, m.p. 115-116°C; Yield 28 %; IR (KBr, ν_{max}, cm^{-1}): 2752-2852 (CHO), 1669 (C=O); ^{1}H NMR ($CDCl_3$): 1.56 (6H, br. peak, 3CH_2 of the piperidino group), 3.14 (4H, br. peak, CH_2-N-CH_2),7.38-7.58 (6H, m, H-3',3",4',4",5',5"), 7.68 (4H, dd, ^3J = 7.5, ^4J = 2.9, H-2',2",6',6"), 9.83 (1H, s, CHO); ^{13}C NMR: 23.2, 25.3, 51.4 (piperidino group carbons), 110.4, 124.7, 127.7, 128.0, 128.3, 128.6, 131.6, 139.1, 152.4, 155.2 (sp^2 carbons), 183.8 (C=O); MS: *m/z* (%) 331 [M^+] (82) ($C_{21}H_{21}N_3O$), 330 [M-H] (29), 302 [M-CHO] (13), 262 [M-C_5H_{10}+H] (23), 144 [M-C_5H_{10}N-C_7H_5N] (36), 91 [$C_6H_5N^+$] (23), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (64).

3-Ethyl-1-phenyl-5-pyrrolidino-1*H*-pyrazole-4-carbaldehyde (4d): Fine pale beige cubes, m.p. 82-83 °C; Yield 45 %; IR (KBr, ν_{max}, cm^{-1}): 2878 (CHO), 1628 (C=O); ^{1}H NMR ($CDCl_3$): 1.22 (3H, t, J = 7.3, CH_3), 2.81 (2H, quint, J = 7.3, CH_2), 1.78-1.83 (4H, m, 2CH_2 of the pyrrolidino group), 3.19-3.23 (4H, m, CH_2-N-CH_2), 7.29-7.39 (5H, m, Ar-H), 9.92 (1H, s, CHO); ^{13}C NMR: 12.5 (CH_3), 21.3 (CH_2), 25.1, 51.6 (pyrrolidino group carbons), 108.1, 125.4, 127.4, 128.3, 139.5, 150.8, 156.6 (sp^2 carbons), 182.0 (C=O); MS: *m/z* (%) 269 [M^+] (35) ($C_{16}H_{19}N_3O$),268 [M-H] (14), 239 [M-CHO-H] (26), 213 [M-2C_2H_4] (13), 143 [M-C_4H_8N-C_3H_5N-H] (19), 91 [$C_6H_5N^+$] (13), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (58).

1-Phenyl-3-propyl-5-pyrrolidino-1*H*-pyrazole-4-carbaldehyde (4e): Fine pale orange cubes, m.p. 94-95 °C; Yield 51 %; IR (KBr, ν_{max}, cm^{-1}): 2863 (CHO), 1634 (C=O); ^{1}H NMR ($CDCl_3$): 0.97 (3H, t, J = 7.3, CH_3), 1.69 (2H, sext, J = 7.3, CH_2), 2.77 (2H, t, J = 7.3, CH_2), 1.80-1.85 (4H, m, 2CH_2 of the pyrrolidino group), 3.21-3.26 (4H, m, CH_2-N-CH_2), 7.31-7.40 (5H, m, Ar-H), 9.92 (1H, s, CHO); ^{13}C NMR: 13.6 (CH_3), 21.7 (CH_2), 30.0 (CH_2), 25.1, 51.7 (pyrrolidino group. carbons), 108.4, 125.6, 127.6, 128.5, 139.7, 150.8, 155.6 (sp^2 carbons), 182.0 (C=O); MS: *m/z* (%) 283 [M^+] (41) ($C_{17}H_{21}N_3O$), 282 [M-H] (30),254 [M-CHO] (27), 240 [M-C_3H_7] (36), 227 [M-2C_2H_4] (39),144 [M-C_4H_8N-C_4H_7N](27), 91 [$C_6H_5N^+$] (21), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (45).

Synthesis of 2-[(3,5-disubstituted 1-phenyl-1*H*-pyrazol-4-yl)methylene]malononitrile (5a-c); 2-cyano-3-(3-ethyl-1-phenyl-5-pyrrolidino-1*H*-pyrazol-4-yl)acrylamide (5d) and 2-cyano-3-(1-phenyl-3-propyl-5-pyrrolidino-1*H*-pyrazol-4-yl)prop-2-enethioamide (5e): A mixture of **4a-e** (2.5 mmol) in dry ethanol (15 mL) was added the active methylene compounds (*viz.* malonodinitrile, cyanoacetamide and cyanothioacetamide) (2.5 mmol) and allowed to reflux for 5-8 h. The progress of the reaction was monitored by TLC. After completion and usual work-up followed by column chromatography gave pure **5a,b,d,e**. Compound **5c** was recrystallized from petroleum ether 60-80 °C[25].

2-(3-Methyl-5-morpholino-1-phenyl-1*H*-pyrazol-4-ylmethylene)malononitrile (5a): Fine yellow cubes, m.p. 133-144 °C; Yield 71 %; IR (KBr, ν_{max}, cm^{-1}): 2225 (CN), 1583 (C=C); ^{1}H NMR ($CDCl_3$): 2.42 (3H, s,CH_3), 2.99 (4H, t, J = 4.2, CH_2-N-CH_2), 3.67 (4H, t, J = 4.2, CH_2-O-CH_2), 7.45-7.52 (5H, m, Ar-H),7.66 (1H,s, H-C=C); ^{13}C NMR: 15.1 (CH_3), 50.2, 65.9 (morpholino group carbons), 78.2, 106.1, 124.5, 128.5, 128.7, 137.8, 148.6, 150.4, 151.4 (sp^2 carbons), 113.0, 114.0 (CN); MS: *m/z* (%) 319 [M^+] (44) ($C_{18}H_{17}N_5O$), 303 [M-CH_3-H] (13), 290 [M-HCN-2H] (16), 260 [M-C_3H_6O-H] (29), 207 [260-HCN-CN] (11), 91 [$C_6H_5N^+$] (28), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (79).

2-(5-Morpholino-1,3-diphenyl-1*H*-pyrazol-4-ylmethylene)malononitrile (5b): Fine yellow needles, m.p. 177-178 °C; Yield 59 %; IR (KBr, ν_{max}, cm^{-1}): 2222 (CN), 1582 (C=C); ^{1}H NMR ($CDCl_3$): 3.06 (4H, t, J = 4.6, CH_2-N-CH_2), 3.71 (4H, t, J = 4.6, CH_2-O-CH_2), 7.45-7.56 (10H, m, Ar-H), 7.83 (1H,s, H-C=C); ^{13}C NMR: 49.5, 66.1 (morpholino group carbons), 82.1, 104.4, 125.2, 127.6, 128.8, 129.0, 131.4, 138.5, 150.4, 151.1, 151.7 (sp^2 carbons), 112.1, 114.0 (CN); MS: *m/z* (%) 381 [M^+] (38) ($C_{23}H_{19}N_5O$), 352 [M-HCN-2H] (7), 324 [352-HCN-H] (9), 322 [M-C_3H_6O-H] (14), 91 [$C_6H_5N^+$] (16), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (49).

2-(1,3-Diphenyl-5-piperidin-1-yl-1*H*-pyrazol-4-ylmethylene)malononitrile (5c): Yellow needles, m.p. 138-139°C; Yield 99 %; IR (KBr, ν_{max}, cm^{-1}): 2224 (CN), 1578 (C=C); ^{1}H NMR ($CDCl_3$): 1.56 (6H, br. peak, 3CH_2 of the piperidino group), 3.05 (4H, br. peak, CH_2-N-CH_2), 7.42-7.56 (10H, m, Ar-H), 7.84 (1H,s, H-C=C); ^{13}C NMR: 23.1, 25.3, 51.0 (piperidino group carbons), 77.1, 104.0, 124.9, 127.6, 128.5, 128.8, 129.0, 131.9, 138.8, 151.3, 151.8, 152.3 (sp^2 carbons), 112.3, 114.6 (CN); MS: *m/z* (%) 379 [M^+] (52) ($C_{24}H_{21}N_5$), 324 [M-2HCN-H] (16), 323 [M-2C_2H_4] (8), 246 [M-2C_2H_4-C_6H_5] (8),115 [M-C_4HN_2-C_5H_{10}N-C_7H_5N](6),91 [$C_6H_5N^+$] (17), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (41).

2-Cyano-3-(3-ethyl-1-phenyl-5-pyrrolidino-1*H*-pyrazol-4-yl)acrylamide (5d): Fine dark yellow cubes, m.p. 183-184°C; Yield 13 %; IR (KBr, ν_{max}, cm^{-1}): 2209 (CN), 1588 (C=C), 1674 (C=O), 3318, 3370 (NH_2); ^{1}H NMR ($CDCl_3$): 1.25 (3H, t, J = 7.5, CH_3), 2.76 (2H, quint, J = 7.5, CH_2), 1.83-1.87 (4H, m, 2CH_2 of the pyrrolidino group), 3.10-3.14 (4H, m, CH_2-N-CH_2), 5.93 and 6.25 (1H, br. s and 1H, br. s, NH_2),7.33-7.43 (5H, m, Ar-H), 8.38(1H,s, H-C=C); ^{13}C NMR: 12.2 (CH_3), 21.0 (CH_2), 25.1, 50.0 (pyrrolidino group carbons), 97.3, 103.0, 125.0, 127.5, 128.5, 139.3, 146.1, 148.9, 154.3 (sp^2 carbons), 117.3 (CN), 163.1 (C=O); MS: *m/z* (%) 335

[M^+] (62) ($C_{19}H_{21}N_5O$), 291 [M-$CONH_2$] (80),252 [M-$2C_2H_4$-HCN] (43), 222 [252-C_2H_4-2H] (26), 91 [$C_6H_5N^+$] (38), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (64).

2-Cyano-3-(1-phenyl-3-propyl-5-pyrrolidino-1*H*-pyrazol-4-yl)prop-2-enethioamide (5e): Fine orange cubes, m.p. 176-177°C; Yield 76%; IR (KBr, ν_{max}, cm^{-1}): 2204 (CN), 1645 (C=C), 1509 (C=S), 3289, 3334 (NH_2);^{1}H NMR ($CDCl_3$): 0.96 (3H, t, J = 7.3, CH_3), 1.69 (2H, sext, J = 7.3, CH_2), 2.75 (2H, t, J = 7.3, CH_2), 1.80-1.85 (4H, m, $2CH_2$ of the pyrrolidino group), 3.21-3.26 (4H, m, CH_2-N-CH_2), 7.58 (2H, br. s, NH_2),7.38-7.48 (5H, m, Ar-H), 8.95 (1H,s, H-C=C); ^{13}C NMR: 13.7 (CH_3), 21.5 (CH_2), 30.5 (CH_2), 25.4, 51.1 (pyrrolidinogroup carbons),101.2, 104.5, 125.5, 128.0, 128.8, 139.6, 150.2, 151.8, 153.6 (sp^2 carbons), 116.8 (CN), 193.0 (C=S); MS: *m/z* (%) 365 [M^+] (25) ($C_{20}H_{23}N_5S$), 332 [M-NH_2-CH_3-2H] (37), 303 [M-$CSNH_2$-2H] (78), 266 [M-$2C_2H_4$-C_3H_7] (23), 91 [$C_6H_5N^+$] (21), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (48).

Synthesis of 3-substituted 1-phenyl-1,4,5a,6,8,9-hexahydro-5*H*-pyrazolo[4',3':5,6]pyrido[2,1-c][1,4]-oxazine-5,5-dicarbonitrile (6a,b); 1,3-diphenyl-1,4,6,7,8,9-hexahydropyrazolo[4,3-c]quinolizine-5,5(5a*H*)-dicarbonitrile (6c); 5-cyano-3-ethyl-1-phenyl-4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-e]indolizine-5-carboxamide (6d) and 5-cyano-1-phenyl-3-propyl-4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-e]indolizine-5-carbothioamide (6e): A mixture of **5a-e** (2.5 mmol) in dry toluene (15 mL) was added anhydrous zinc chloride (2.5 mmol) and the resulted mixture was refluxed for 7-17 h under anhydrous conditions. After completion, (monitored by TLC) the reaction mixture was cooled, water was added and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate overnight and concentrated *in vacuo*. Evaporation of the solvent followed by column chromatography gave pure **6a-e**. The compound **6c** was recrystallized from benzene/petroleum ether 60-80°C[25].

3-Methyl-1-phenyl-1,4,5a,6,8,9-hexahydro-5*H*-pyrazolo[4',3':5,6]pyrido[2,1-c][1,4]oxazine-5,5-dicarbonitrile (6a): Pale beige cubes, m.p. 151-152°C; Yield 36 %; IR (KBr, ν_{max}, cm^{-1}): 2243 (CN);^{1}H NMR ($CDCl_3$): 2.21 (3H, s,CH_3), 2.73 (1H, ddd,$^2J_{9ax\text{-}9eq}$ = 12.1,$^3J_{9ax\text{-}8ax}$ = 6.8,$^3J_{9ax\text{-}8eq}$ = 3.4, H_{ax}-9), 3.31-3.37[2H, m, H-5a, (X part of ABX system) and H_{eq}-9], 3.26[1H, d, $^2J_{4ax\text{-}4eq}$ = 15.4, H_{ax}-4, (A part of AB system)], 3.46 [1H, d, $^2J_{4ax\text{-}4eq}$ = 15.4, H_{eq}-4, (B part of AB system)], 3.62-3.76 (2H, m, H_2-8), 4.17 [1H, dd,$^2J_{6ax\text{-}6eq}$ = 13.5,$^3J_{5aax\text{-}6ax}$ = 5.9,H_{ax}-6, (A part of ABX system)], 4.24 [1H, dd,$^2J_{6ax\text{-}6eq}$ = 13.5,$^3J_{5aax\text{-}6eq}$ = 3.3,H_{eq}-6, (B part of ABX system)], 7.32 (1H, t, J = 7.3, H-4'), 7.43 (2H, t, J = 7.3, H-3',5'),7.55 (2H, d, J = 7.3, H-2',6'); ^{13}C NMR: 11.1 (CH_3), 31.2 (C-4), 59.0 (C-5a), 66.2 (C-6), 65.0 (C-8), 46.3 (C-9), 112.4, 113.2 (CN), 30.3, 95.1, 143.3, 145.7 (C-5,3a,10a,3),122.5, 126.8, 128.5, 138.6 (phenyl carbons); MS: *m/z* (%) 319 [M^+] (100) ($C_{18}H_{17}N_5O$), 290 [M-HCN-2H] (16), 262 [290-HCN-H] (29), 254 [M-C_3N_2-H] (26), 198 [M-C_2H_4O-C_6H_5] (31), 91 [$C_6H_5N^+$] (26), 77 [$C_6H_5^+$] (87), 51 [77-C_2H_2] (62).

1,3-Diphenyl-1,4,5a,6,8,9-hexahydro-5*H*-pyrazolo-[4',3':5,6]pyrido[2,1-c][1,4]oxazine-5,5-dicarbonitrile (6b): Pale yellow cubes, m.p. 266-267°C; Yield 39 %; IR (KBr, ν_{max}, cm^{-1}): 2248 (CN); ^{1}H NMR ($CDCl_3$): 2.79 (1H, ddd, $^2J_{9ax\text{-}9eq}$ = 12.0,$^3J_{9ax\text{-}8ax}$ = 6.0,$^3J_{9ax\text{-}8eq}$ = 3.3,H_{ax}-9), 3.40 (1H, ddd, $^2J_{9ax\text{-}9eq}$ = 12.0,$^3J_{9ax\text{-}8ax}$ = 6.0,$^3J_{9ax\text{-}8eq}$ = 3.7,H_{eq}-9), 3.45 (1H, t, J = 5.8, H-5a), 3.57 [1H, d, $^2J_{4ax\text{-}4eq}$ = 15.4, H_{ax}-4, (A part of AB system)], 3.72 [1H, d, $^2J_{4ax\text{-}4eq}$ = 15.4, H_{eq}-4, (B part of AB system)], 3.67-3.77 (2H, m, H_2-8), 4.26 (2H, d, J = 5.1, H_2-6), 7.35-7.51 (6H, m, H-3',3'',4',4'',5'.5''), 7.65 (4H, d, J = 7.0, H-2',2'',6',6''); ^{13}C NMR: 32.8 (C-4), 59.0 (C-5a), 66.4 (C-6), 65.1 (C-8), 46.4 (C-9), 112.9, 113.4 (CN), 30.5, 94.5, 144.1, 148.3 (C-5,3a,10a,3),122.9, 126.1, 127.2, 127.7, 128.1, 128.8, 131.4, 138.8 (phenyl group carbons); MS: *m/z* (%) 381 [M^+] (60) ($C_{23}H_{19}N_5O$), 352 [M-HCN-2H] (11), 324 [352-HCN-H] (4), 316 [M-C_3N_2-H] (6), 260 [M-C_2H_4O-C_6H_5] (5), 91 [$C_6H_5N^+$] (10), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (46).

1,3-Diphenyl-1,4,6,7,8,9-hexahydropyrazolo[4,3-c]quinolizine-5,5(5a*H*)-dicarbonitrile (6c): White powder, m.p. 209-210°C; Yield 21 %; IR (KBr, ν_{max}, cm^{-1}): 2253 (CN); ^{1}H NMR ($CDCl_3$): 1.54 (3H, br. peak, H_2-7,H_{ax}-8),1.86-2.05 [2H, m, H_{ax}-6, (A part of ABX system) and H_{eq}-8], 2.33 [1H, d, $^2J_{6ax\text{-}6eq}$ = 12.4, H_{eq}-6, (B part of ABX system)], 2.47-2.55 (1H, m, H_{ax}-9), 3.28 [1H, dd, $^3J_{5aax\text{-}6ax}$ = 9.0, $^3J_{5aax\text{-}6eq}$ = 2.5, H-5a, (X part of ABX system)], 3.43 (1H, d, $^2J_{9ax\text{-}9eq}$ = 11.5, H_{eq}-9), 3.53 [1H, d, $^2J_{4ax\text{-}4eq}$ = 15.1, H_{ax}-4, (A part of AB system)], 3.61 [1H, d, $^2J_{4ax\text{-}4eq}$ = 15.1, H_{eq}-4, (B part of AB system)], 7.33-7.50 (6H, m, H-3',3'',4',4'',5'.5''), 7.62 (4H, d, J = 7.0, H-2',2'',6',6''); ^{13}C NMR: 32.2 (C-4), 62.6 (C-5a), 23.3 (C-6), 22.3 (C-7), 27.5 (C-8), 49.7 (C-9), 112.7, 113.9 (CN), 36.6, 93.9, 145.0, 148.6 (C-5,3a,10a,3),123.1, 126.4, 127.2, 127.7, 128.1, 128.7, 131.6, 139.6 (phenyl group carbons); MS: *m/z* (%) 379 [M^+] (100) ($C_{24}H_{21}N_5$), 351 [M-HCN-H] (10), 325 [M-2HCN] (5), 314 [M-C_3N_2-H] (37), 246 [M-$2C_2H_4$-C_6H_5] (16),115 [M-C_7H_5N-$C_9H_{11}N_3$] (23), 91 [$C_6H_5N^+$] (12), 77 [$C_6H_5^+$] (92), 51 [77-C_2H_2] (52).

5-Cyano-3-ethyl-1-phenyl-4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-e]indolizine-5-carboxamide (6d): Yellow scales, m.p. 204-206 °C; Yield 31 %; IR (KBr, ν_{max}, cm^{-1}): 2229 (CN), 1692 (C=O), 3305, 3386 (NH_2); ^{1}H NMR ($CDCl_3$): 0.83 (3H, t, J = 8.1, CH_3), 2.61 (2H, quint, J = 8.1, CH_2), 1.86-2.11 (3H, m, H_{ax}-6, H_2-7), 2.32-2.37 (1H, m, H_{eq}-6), 2.91-3.00 (1H, m, H_{ax}-8), 3.07-3.20 (3H, m, H_2-4, H_{eq}-8), 3.97 (1H, dd, $^3J_{5aax\text{-}6ax}$ = 7.7, $^3J_{5aax\text{-}6eq}$ = 4.4, H-5a), 5.80 and 6.53 (1H, br. s and1H, br. s, D_2O exchangeable, NH_2), 7.29 (1H, t, J = 7.9, H-4'), 7.41 (2H, t, J = 7.9, H-3',5'),7.53 (2H, d, J = 7.9, H-2',6'); ^{13}C NMR: 12.3 (CH_3), 21.7 (CH_2),36.1 (C-4), 63.4 (C-5a), 22.9 (C-6), 27.0 (C-7), 43.3 (C-8), 48.9, 93.8, 143.0, 150.9 (C-5,3a,9a,3),123.3, 126.0, 128.0,138.8 (phenyl group carbons), 119.2 (CN),168.1 (C=O); MS: *m/z* (%) 335 [M^+] (62) ($C_{19}H_{21}N_5O$), 291 [M-$CONH_2$] (96), 252 [M-$2C_2H_4$-HCN] (12), 248 [291-C_2H_4-CH_3] (13),91 [$C_6H_5N^+$] (17), 77 [$C_6H_5^+$] (100), 51 [77-C_2H_2] (47).

5-Cyano-1-phenyl-3-propyl-4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-e]indolizine-5-carbothioamide (6e): Orange cubes, m.p. 186 °C; Yield 46%; IR (KBr, ν_{max}, cm^{-1}): 2234 (CN), 1526 (C=S), 3358, 3423 (NH_2); ^{1}H NMR ($CDCl_3$): 0.97 (3H, t, J = 7.3, CH_3), 1.67 (2H, sext, J = 7.3, CH_2), 2.55 (2H, t, J = 7.3, CH_2), 1.81-1.94 (2H, m, H_{ax}-6, H_{ax}-7), 2.01-2.06 (1H, m, H_{eq}-7), 2.27-2.38 (1H, m, H_{eq}-6), 2.93-3.02 (1H, m, H_{ax}-8), 3.05 [1H, d, $^2J_{4ax\text{-}4eq}$ = 15.4, H_{ax}-4, (A part of AB system)], 3.17-3.23 (1H, m, H_{eq}-8), 3.49[1H, d, $^2J_{4ax\text{-}4eq}$ = 15.4, H_{eq}-4, (B part of AB system)], 4.22 (1H, dd, $^3J_{5aax\text{-}6ax}$ = 6.0, $^3J_{5aax\text{-}6eq}$ = 4.8, H-5a), 7.28 (1H, t, J = 7.6, H-4'), 7.41 (2H, t,

J = 7.6, H-3',5'),7.52 (2H, d, *J* = 7.6, H-2',6'), 7.81 and8.81 (1H, br. s and 1H, br. s D_2O exchangeable, NH_2); ^{13}C NMR: 13.4 (CH_3), 21.8 (CH_2), 28.8 (CH_2), 33.5 (C-4), 67.2 (C-5a), 23.1 (C-6), 27.0 (C-7), 49.4 (C-8), 50.2, 95.4, 143.1, 150.0 (C-5,3a,9a,3),123.7, 126.4, 128.3,139.1 (phenyl group carbons), 119.0 (CN),201.3 (C=S); MS: *m/z* (%) 365 [M^+] (70) ($C_{20}H_{23}N_5S$), 332 [M-NH_2-CH_3-2H] (67), 303 [M-$CSNH_2$-2H] (100), 267 [M-$C_3H_2N_2S$] (11), 91 [$C_6H_5N^+$] (36), 77 [$C_6H_5^+$] (94), 51 [77-C_2H_2] (42).

Synthesis of 2-arylidenemalononitriles (8): They were synthesized by reaction of aromatic aldehyde with malononitrile according to the literature procedures [26].

Synthesis of 6-amino-1,4-disubstituted 3-propyl-1,4-dihydro-pyrano[2,3-c]pyrazole-5-carbonitrile (9a-c): They were synthesized by following different methods.

Method A: They were synthesized using the reported method[27].

Method B: A mixture of **2e,f** (1.25 mmol), aromatic aldehyde **7a-c** (1.25 mmol), malononitrile (1.25 mmol) and piperidine (few drops) was placed in a 100 mL beaker covered with a watch glass and was then irradiated with microwave (for 5 min at 300 W for **9b** and 15 min at 300 W then 15 min at 400 W for **9a,c**), (monitored by TLC) the solid product obtained after cooling was collected by filtration, washed with ethanol to give pure **9a**. The cold reaction mixture was treated with ethyl acetate or ether, the solid product was filtered and recrystallized from water/ethanol to give **9b,** the solid product was then subjected to column chromatography to give pure **9c**.

Method C: A mixture of **2e,f** (1.25 mmol), **7a-c**(1.25 mmol), malononitrile (1.25 mmol) and cetyltrimethylammonium chloride (CTACl) in water (10 mL) was placed in a 25 mL conical flask and was then irradiated in water bath of an ultrasonic cleaner for 1.5 h, the solid product was filtered, washed with water to give pure **9a**. The reaction mixture was extracted with dichloromethane (3 × 20 mL). The combined organic phases were concentrated *in vacuo* and treated with ethyl acetate then with ether, the solid product was filtered and recrystallized from water/ethanol to give **9b and** thesolid product was subjected to column chromatography to give pure **9c**.

6-Amino-3-propyl-1-(2-pyridinyl)-4-(3',4',5'-trimethoxy-phenyl)-1,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile (9a): White fine needles, m.p. 162-163°C; Yield 79[A], 88[B], 51[C]%; IR (KBr, ν_{max}, cm^{-1}): 2198 (CN), 3323, 3466 (NH_2); ^1H NMR (DMSO-d_6): 0.72 (3H, t, *J* = 7.3, CH_3CH_2), 1.10-1.24 (1H, m), 1.27-1.44 (1H, m), (CH_2 of the propyl group near the chiral carbon C-4), 2.08-2.23 (2H, m, $CH_3CH_2CH_2$),3.64 (3H, s, OCH_3), 3.72 (6H, s, $2OCH_3$), 4.66 (1H, s, H-4), 6.55 (2H, s, H-2'',6''), 7.08 (2H, br.s, NH_2) (D_2O exchangeable), 7.36 (1H, dd, $^3J_{4,5}$ = 7.7, $^3J_{5,6}$ = 5.1, H-5'), 7.71 (1H, d, $^3J_{3,4}$ = 7.7, H-3'),7.96 (1H, td, ^3J = 7.7, $^4J_{4,6}$ = 1.8, H-4'), 8.49 (1H, d, $^3J_{5,6}$ = 5.1, H-6'); ^{13}C NMR: 13.6 (CH_3), 20.6 (CH_3CH_2), 28.8 (CH_2CH_2), 36.9 (C-4),55.8 ($2OCH_3$), 59.9 (OCH_3),119.8 (CN),115.1 (C-3'), 121.9 (C-5'), 138.9 (C-4'), 148.1 (C-6'), 57.9, 98.6, 104.9, 136.3, 139.4, 144.2, 149.9, 150.3, 152.7, 159.4 (sp^2 carbons); MS (ESI): *m/z* (%) 448 [M+H]$^+$ (100) ($C_{24}H_{25}N_5O_4$+H), 430 [M+H-NH_3-H] (5), 382 [M+H-$C_3H_2N_2$] (60), 280 [M+H-$C_9H_{11}O_3$-H] (55), 251 [280-C_2H_5] (12).

6-Amino-1-methyl-3-propyl-4-(2-thienyl)-1,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile (9b): Pale green cubes, m.p. 166-168°C; Yield 25[A], 26[B], 8[C]%; IR (KBr, ν_{max}, cm^{-1}): 2189 (CN), 3314, 3380 (NH_2); ^1H NMR (DMSO-d_6): 0.91 (3H, t, *J* = 7.3, CH_3), 1.54 (2H, sext, *J* = 7.3, CH_2), 2.45-2.50 (2H, m, CH_2 within H_2O in DMSO, (2.52, 2H, t, *J* = 7.3 in $CDCl_3$)), 3.36 (3H, br s, N-CH_3 with DMSO, (3.45, 3H, s, in $CDCl_3$)), 4.88 (1H, s, H-4), 6.54 (2H, d, $^3J_{3,4}$ = 3.5, H-3'), 6.82 (1H, dd, $^3J_{4,5}$ = 5.0, $^3J_{3,4}$ = 3.5, H-4'), 7.20 (1H, d, $^3J_{4,5}$ = 5.0, H-5'), 14.0(2H, br.s, NH_2) (D_2O exchangeable); MS (ESI): *m/z* (%) 301[M+H]$^+$ (not observed) ($C_{15}H_{16}N_4OS$+H), 235 [M+H-$C_3H_2N_2$] (90), 141 [M+H-$C_8H_6N_2S$+2H] (100).

6-Amino-4-(2-furyl)-1-methyl-3-propyl-1,4-dihydro-pyrano[2,3-*c*]pyrazole-5-carbonitrile (9c): Pale green cubes, m.p. 166-168°C; Yield 25[A], 26[B], 8[C]%; IR (KBr, ν_{max}, cm^{-1}): 2209 (CN), 3355, 3414 (NH_2); MS (ESI): *m/z* (%) 285 [M+H]$^+$ (30) ($C_{15}H_{16}N_4O_2$+H), 268 [M+H-NH_3] (100),240 [M+H-HCN-H] (20), 151 [M+H-$C_3H_2N_2$-C_4H_3O-H] (5), 99 [M+H-$C_{10}H_6N_2O_2$] (4).

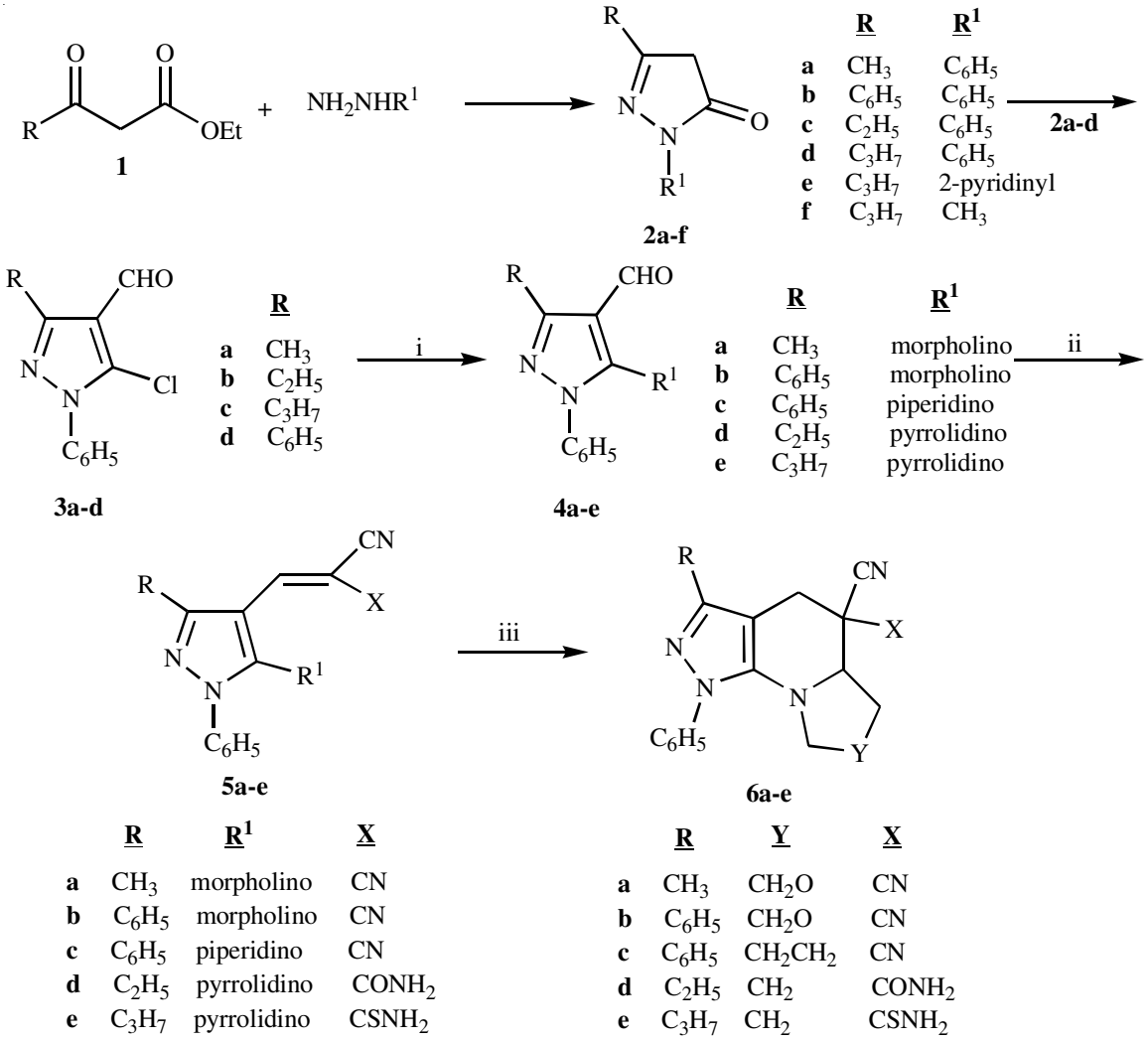
Synthesis of 1,4-disubstituted-7-Methyl-3-propyl-4,6-dihydropyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one (11a,b): They were synthesized using the reported method[26].

7-Methyl-3-propyl-1-(2-pyridinyl)-4-(3,4,5-tri-methoxyphenyl)-4,6-dihydropyrazolo[4',3':5,6]pyrano-[2,3-*d*]pyrimidin-5(1*H*)-one (11a): Pale yellow powder, m.p. >300 °C (from ethanol); Yield 57%; IR (KBr, ν_{max}, cm^{-1}): 3449 (NH), 1655 (C=O); ^1H NMR (DMSO-d_6): 0.78 (3H, t, *J* = 7.3, CH_3), 1.17-1.29 (1H, m), 1.35-1.46 (1H, m) (CH_2 of the propyl group near the chiral carbon C-4),, 2.29-2.34 (5H, m, CH_2, CH_3 at C-7), 3.60 (3H, s, OCH_3), 3.69 (6H, s, $2OCH_3$), 5.01 (1H, s, H-4), 6.56 (2H, s, H-2'',6''), 7.36 (1H, ddd, $^3J_{4,5}$ = 7.9, $^3J_{5,6}$ = 4.9, $^4J_{3,5}$ = 1.1, H-5'), 7.72 (1H, d, $^3J_{3,4}$ = 7.9, H-3'), 7.97 (1H, td, ^3J = 7.9, $^4J_{4,6}$ = 1.8, H-4'), 8.52 (1H, dd, $^3J_{5,6}$ = 4.9,$^4J_{4,6}$ = 1.8, H-6'); ^{13}C NMR: 13.6, 20.7, 20.8, 28.9, 34.8 (Pr carbons, CH_3 at C-7, C-4), 55.7 ($2OCH_3$), 59.8 (OCH_3), 100.3, 100.4, 105.4, 114.7, 121.7, 136.0, 138.9, 139.9, 145.1, 148.1, 150.3, 150.6, 152.4, 158.5, 160.7 (sp^2 carbons), 162.6 (C=O); MS (ESI): *m/z* (%) 490[M+H]$^+$ (25) ($C_{26}H_{27}N_5O_5$+H), 460 [M+H-C_2H_5-H] (5), 382 [M+H-$C_5H_4N_2O$] (5), 322 [M+H-$C_9H_{11}O_3$-H] (100), 281 [280-CH_3-HCN-H] (75).

1,7-Dimethyl-3-propyl-4-(2-thienyl)-4,6-dihydro-pyrazolo[4',3':5,6]pyrano[2,3-*d*]pyrimidin-5(1*H*)-one (11b): Pale green powder, m.p. >3 00 °C; Yield 38%; IR (KBr, ν_{max}, cm^{-1}): 3484 (NH), 1625 (C=O); ^1H NMR (DMSO-d_6): 0.93 (3H, t, *J* = 7.1, CH_3), 1.61-1.54 (2H, m, CH_2), 2.73-2.66 (2H, m, CH_2), 2.50 (3H, s, CH_3 at C-7), 3.52 (3H, s, N-CH_3), 5.15 (1H, s, H-4), 6.39 (1H, d, $^3J_{3,4}$ = 3.4, H-3'), 6.87-6.85 (2H, m, H-4',5'); ^{13}C NMR: 12.8, 21.4, 25.1, 27.7, 30.6, 33.0 (Pr carbons, CH_3 at C-7,N-CH_3, C-4), 103.4, 122.4, 124.3, 127.0, 128.9, 144.9, 145.7, 149.2, 152.0, 157.4 (sp^2 carbons), 159.5 (C=O); MS(ESI): *m/z* (%) 343 [M+H]$^+$ (not observed) ($C_{17}H_{18}N_4O_2S$+H), 315 [M+H-C_2H_4] (75), 233 [M+H-$C_5H_4N_2O$-2H] (2), 141 [M+H-$C_{10}H_8N_2OS$+2H] (100).

RESULTS AND DISCUSSION

The starting materials, namely pyrazolones **2a-f** were synthesized by the reactions of the appropriate hydrazine with β-ketoesters using microwave and ultrasound irradiation according to literature procedure [23] (**Scheme-I**). 5-Chloro-3-substituted 1-phenyl-1*H*-pyrazole-4-carbaldehyde **3a-d** were



	R	R^1
a	CH_3	C_6H_5
b	C_6H_5	C_6H_5
c	C_2H_5	C_6H_5
d	C_3H_7	C_6H_5
e	C_3H_7	2-pyridinyl
f	C_3H_7	CH_3

	R
a	CH_3
b	C_2H_5
c	C_3H_7
d	C_6H_5

	R	R^1
a	CH_3	morpholino
b	C_6H_5	morpholino
c	C_6H_5	piperidino
d	C_2H_5	pyrrolidino
e	C_3H_7	pyrrolidino

	R	R^1	X
a	CH_3	morpholino	CN
b	C_6H_5	morpholino	CN
c	C_6H_5	piperidino	CN
d	C_2H_5	pyrrolidino	$CONH_2$
e	C_3H_7	pyrrolidino	$CSNH_2$

	R	Y	X
a	CH_3	CH_2O	CN
b	C_6H_5	CH_2O	CN
c	C_6H_5	CH_2CH_2	CN
d	C_2H_5	CH_2	$CONH_2$
e	C_3H_7	CH_2	$CSNH_2$

Scheme-I: (i) cyclic *sec*-amine, dry EtOH, dry Et_3N, reflux, 17-22 h; (ii) $CNCH_2X$, dry EtOH, reflux, 5-8 h; (iii) $ZnCl_2$, dry toluene, 7-17 h

prepared from the pyrazolones employing Vilsmeier-Haack chloroformylation[24] by heating pyrazolones with an excess phosphorus oxychloride in DMF. The structures of compounds **3a-d** were confirmed from their IR, ^{1}H NMR, ^{13}C NMR and MS spectra data. Compounds **3a-d** were subjected to aromatic nucleophilic substitution with several cyclic *sec*-amines (*viz.* pyrrolidine, piperidine and morpholine) resulted in smooth conversion to the 3,5-disubstituted 1-phenyl-1*H*-pyrazole-4-carbaldehyde **4a-e**[25]. The structures of **4a-e** were assigned on the basis of spectroscopic analyses. Thus, IR spectrum showed band at 1669-1628 cm^{-1} for C=O stretching, in addition to bands in the range 2878-2738 cm^{-1} which are characteristic to C-H stretching of aldehyde group. Mass spectral data have been found to be in conformity with the assigned structure. The ^{1}H NMR spectrum of **4a** showed two triplets (J = 4.7), each integrated for 4 protons at δ 3.13 ppm (CH_2-N-CH_2) and 3.67 ppm (CH_2-O-CH_2) beside the one proton singlet at δ 9.95 ppm for the CHO. The chemical shifts of other proton absorptions in the latter spectrum of **4a** as well as the whole carbon signals in the ^{13}C NMR spectrum were in complete consistent with its structure.

Compounds **4a-e** were then used in the Knoevenagel condensation reactions with compounds containing active methylene group, namely, malononitrile, cyanoacetamide and cyanothioacetamide to give the corresponding olefinic products **5a-e**, where intramolecular cyclization occurs between the β-carbon of a vinylic group possessing electron withdrawing substituents at the β-position and α-carbon of an *tert*-amino group in the presence of anhydrous zinc chloride to get the corresponding pyrazolopyridooxazine, pyrazoloquinolizines and pyrazoloindolizine derivatives **6a-e**[25]. The structures of **5a-e** were confirmed by the analysis of its various spectroscopic data. Its IR spectrum showed an band at 2225-2204 cm^{-1} attributed for CN stretching and band at 1645-1578 cm^{-1} due to C=C stretching. Mass spectral data have been found to be in conformity with the assigned structure. The ^{1}H NMR spectra of **5a-e** revealed singlet at range δ 7.66-8.95 ppm for the olefinic proton. The spectrum of **5d** also showed two broad singlet at δ 5.93 and 6.25 ppm for the NH_2, because the two protons are in magnetically different environments and have slightly different chemical shifts[28]. All other proton signals in the latter compounds were in consistence with their structures (Experimental Section). The ^{13}C NMR spectra of these compounds displayed signals for all carbons atoms in the molecule. The spectra showed two signals at δ 77.1-101.2 ppm and δ 146.1-151.8 ppm assigned to two carbons at positions 2 and 3, respectively, while CN appeared in the range δ 112.1-117.3 ppm.

The structures of **6a-e** were characterized by high resolution spectral analysis of DEPT, ^{1}H-^{1}H Cosy and ^{1}H -^{13}C Cosy techniques. Their IR spectra showed bands at 2229-2253 cm^{-1} attributed for CN stretching. The ^{1}H NMR spectra of **6a-e** showed the absence of the olefinic protons. The IR, ^{1}H NMR, ^{13}C NMR and MS spectral data of **6a-e** were in complete agreement with their structures.

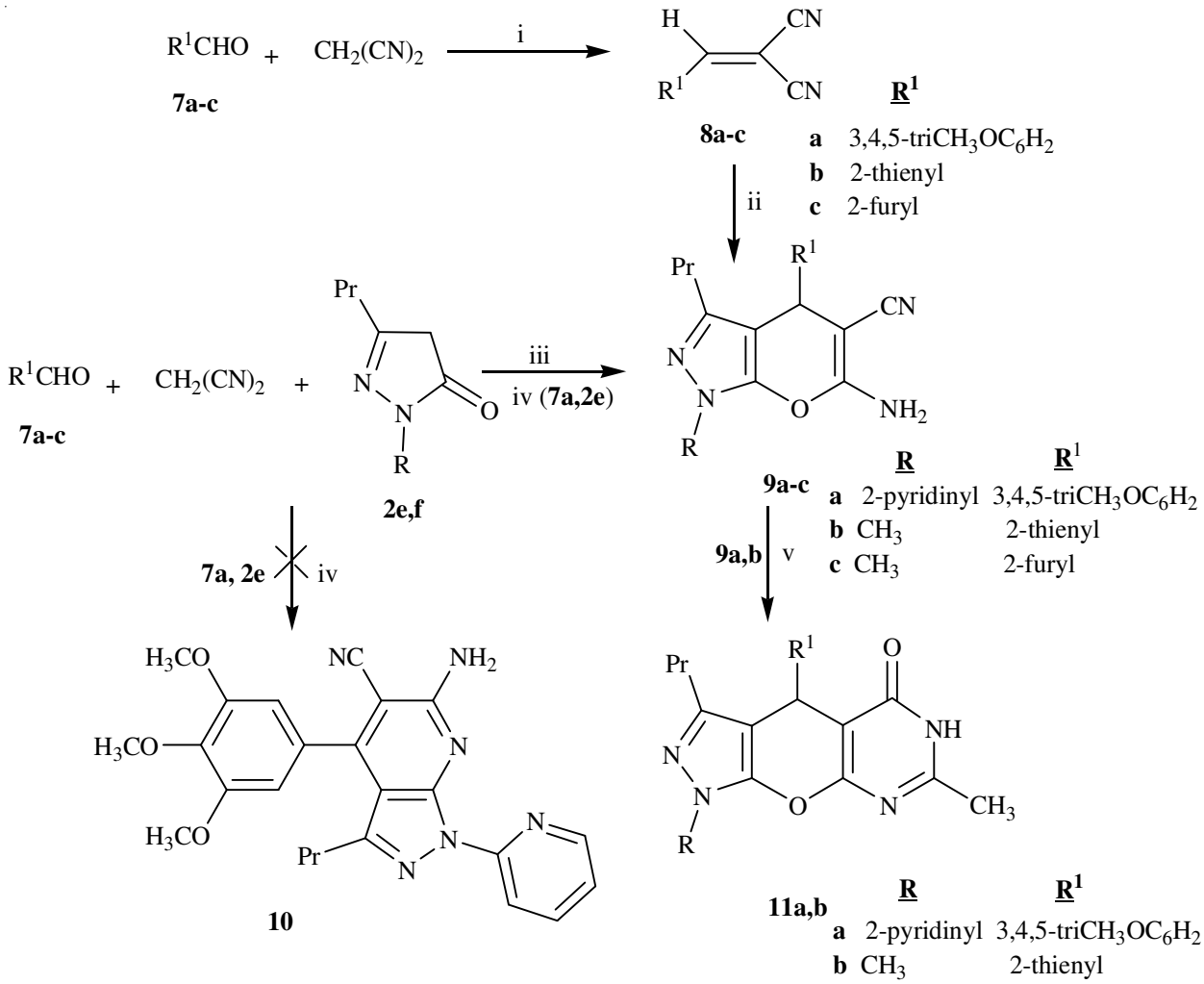
Treatment of **2e-f** with 2-arylidenemalononitriles **8a-c** (**Scheme-II**), either by stirring overnight [27] or one pot four components synthesis using ultrasound irradiation in aqueous medium in the presence of catalyst and using microwave irradiation yielded the same product **9a-c** (IR, TLC, m.p. and mixed m.p.). IR spectra of **9a-c** displayed characteristic bands at 2189-2209, 3314-3355 and 3380-3466 cm^{-1}, due to absorption of CN and NH_2 groups, respectively. The mass spectra of these compounds were in accordance with the assigned structures. The ^{1}H NMR spectrum of **9a** showed a singlet at δ 4.66 for H-4, broad singlet at δ 7.08 ppm (D_2O exchangeable) for NH_2 besides the other proton signals in the latter compounds which were in consistence with its structure (experimental section). The assignment of all protons and carbons in **9a** were verified by the aid of the analysis of DEPT, ^{1}H-^{1}H Cosy and ^{1}H-^{13}C Cosy techniques.

Attempts were made to prepare 6-amino-3-propyl-1-(2-pyridinyl)-4-(3',4',5'-trimethoxy-phenyl)-1*H*-pyrazolo[3,4-b]pyridine-5-carbonitrile (**10**) by one pot four component reaction using traditional reflux method, microwave and ultrasound irradiation of mixture aldehyde **7a**, pyrazolone **2e** and malononitrile in the presence of ammonium acetate were not successful[26]. Instead we obtained the same product **9a** as indicated by the ^{1}H NMR data of the reaction product (**Scheme-II**).

Cyclization of **9a,b** with acetic anhydride in the presence of conc. H_2SO_4 afforded pyrano[2,3-d]pyrimidin-5-one derivatives **11a,b**[26] (**Scheme-II**). IR spectrum of these compounds exhibited the absence of stretching band of cyano group and a broad absorption bands of the NH/OH stretching in the region of 3484-3449 cm^{-1} beside bands at the range of 1625-1655 cm^{-1} due to C=O stretching. All other spectral analysis match the structures of the prepared **11a,b**.

Conclusion

We have synthesized a series of novel pyrazolopyridooxazine, pyrazoloquinolizines and pyrazoloindolizine derivatives from the intermolecular α-cyclization of *tertiary* amines in good yields. We have also demonstrated the use one pot four compo-



Scheme-II: (i) **1** drop piperidine, EtOH, reflux, 15 min; (ii) **2e,f**, MeOH, morpholine, overnight; (iii) **a**: piperidine, MW, 5-30 min; **b**: CTACl, H_2O, US, 1.5 h; (iv) NH_4OAc, **a**: EtOH, reflux 5 h; **b**: MW, 3 min; **c**: EtOH, US, 1 h; (v) Ac_2O, heat, H_2SO_4, room temperature, 24 h

nents reaction using traditional reflux, microwave and ultrasound irradiation methods for the synthesis the pyrano[2,3-*c*]pyrazole derivatives. Cyclization of the later derivatives afforded pyrazolopyranopyrimidinone derivatives.

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