

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 pharmaceuticals¹⁻⁴ and have shown several biological activities such as antiinflammatory agents⁵⁻⁷, antibacterial⁸⁻¹², antifungal⁹, antiviral^{13,14}, antitumor¹⁵⁻¹⁹ and insecticidal^{20,21}. Numerous pyrazole derivatives are also used in dye industry²². 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. ¹H NMR and ¹³C NMR spectra were recorded on a JEOL ECP-300 NMR in CDCl₃ (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 $\times$ 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/Quattro 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 procedures²³.

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 chloroformylation²⁴.

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 $\times$ 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-e²⁵.

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

¹H NMR (CDCl₃): 2.45 (3H, s, CH₃), 3.13 (4H, t, *J* = 4.6, CH₂-N-CH₂), 3.67 (4H, t, *J* = 4.6, CH₂-O-CH₂), 7.38-7.50 (5H, m, Ar-H), 9.95 (1H, s, CHO); ¹³C NMR: 12.9 (CH₃), 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) (C₁₅H₁₇N₃O₂), 226 [M-CH₃-CHO-H] (7), 211 [M-C₃H₆O-2H] (28), 143 [M-C₂H₃N-HCN] (36), 91 [C₆H₅N⁺] (36), 77 [C₆H₅⁺] (82), 51 [77-C₂H₂] (100).

5-Morpholin-4-yl-1,3-diphenyl-1H-pyrazole-4-carbaldehyde (4b): Fine orange cubes, m.p. 147-149 °C; Yield 31 %; IR (KBr, *v*_{max}, cm⁻¹): 2738-2858 (CHO), 1657 (C=O); ¹H NMR (CDCl₃): 3.19 (4H, t, *J* = 4.6, CH₂-N-CH₂), 3.73 (4H, t, *J* = 4.6, CH₂-O-CH₂), 7.42-7.56 (6H, m, H-3',3'',4',4'',5',5''), 7.66 (4H, dd, ³*J* = 7.5, ⁴*J* = 2.9, H-2',2'',6',6''), 9.82 (1H, s, CHO); ¹³C 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) (C₂₀H₁₉N₃O₂), 332 [M-H] (11), 302 [M-CHO-2H] (24), 274 [M-C₃H₆O-H] (21), 171 [274-C₇H₅N] (15), 144 [171-HCN] (20), 104 [M-C₁₃H₁₄N₂O₂+H] (42), 91 [C₆H₅N⁺] (30), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (49).

1,3-Diphenyl-5-piperidino-1H-pyrazole-4-carbaldehyde (4c): Fine pale beige cubes, m.p. 115-116 °C; Yield 28 %; IR (KBr, *v*_{max}, cm⁻¹): 2752-2852 (CHO), 1669 (C=O); ¹H NMR (CDCl₃): 1.56 (6H, br. peak, 3CH₂ of the piperidino group), 3.14 (4H, br. peak, CH₂-N-CH₂), 7.38-7.58 (6H, m, H-3',3'',4',4'',5',5''), 7.68 (4H, dd, ³*J* = 7.5, ⁴*J* = 2.9, H-2',2'',6',6''), 9.83 (1H, s, CHO); ¹³C 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) (C₂₁H₂₁N₃O), 330 [M-H] (29), 302 [M-CHO] (13), 262 [M-C₅H₁₀+H] (23), 144 [M-C₅H₁₀N-C₇H₅N] (36), 91 [C₆H₅N⁺] (23), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (64).

3-Ethyl-1-phenyl-5-pyrrolidino-1H-pyrazole-4-carbaldehyde (4d): Fine pale beige cubes, m.p. 82-83 °C; Yield 45 %; IR (KBr, *v*_{max}, cm⁻¹): 2878 (CHO), 1628 (C=O); ¹H NMR (CDCl₃): 1.22 (3H, t, *J* = 7.3, CH₃), 2.81 (2H, quint, *J* = 7.3, CH₂), 1.78-1.83 (4H, m, 2CH₂ of the pyrrolidino group), 3.19-3.23 (4H, m, CH₂-N-CH₂), 7.29-7.39 (5H, m, Ar-H), 9.92 (1H, s, CHO); ¹³C NMR: 12.5 (CH₃), 21.3 (CH₂), 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) (C₁₆H₁₉N₃O), 268 [M-H] (14), 239 [M-CHO-H] (26), 213 [M-2C₂H₄] (13), 143 [M-C₄H₈N-C₃H₅N-H] (19), 91 [C₆H₅N⁺] (13), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (58).

1-Phenyl-3-propyl-5-pyrrolidino-1H-pyrazole-4-carbaldehyde (4e): Fine pale orange cubes, m.p. 94-95 °C; Yield 51 %; IR (KBr, *v*_{max}, cm⁻¹): 2863 (CHO), 1634 (C=O); ¹H NMR (CDCl₃): 0.97 (3H, t, *J* = 7.3, CH₃), 1.69 (2H, sext, *J* = 7.3, CH₂), 2.77 (2H, t, *J* = 7.3, CH₂), 1.80-1.85 (4H, m, 2CH₂ of the pyrrolidino group), 3.21-3.26 (4H, m, CH₂-N-CH₂), 7.31-7.40 (5H, m, Ar-H), 9.92 (1H, s, CHO); ¹³C NMR: 13.6 (CH₃), 21.7 (CH₂), 30.0 (CH₂), 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) (C₁₇H₂₁N₃O), 282 [M-H] (30), 254 [M-CHO] (27), 240 [M-C₃H₇] (36), 227 [M-2C₂H₄] (39), 144 [M-C₄H₈N-C₄H₇N] (27), 91 [C₆H₅N⁺] (21), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (45).

Synthesis of 2-[(3,5-disubstituted 1-phenyl-1H-pyrazol-4-yl)methylene]malononitrile (5a-c); 2-cyano-3-(3-ethyl-1-phenyl-5-pyrrolidino-1H-pyrazol-4-yl)acrylamide (5d) and 2-cyano-3-(1-phenyl-3-propyl-5-pyrrolidino-1H-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.* malononitrile, 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 °C²⁵.

2-(3-Methyl-5-morpholino-1-phenyl-1H-pyrazol-4-yl)methylene)malononitrile (5a): Fine yellow cubes, m.p. 133-144 °C; Yield 71 %; IR (KBr, *v*_{max}, cm⁻¹): 2225 (CN), 1583 (C=C); ¹H NMR (CDCl₃): 2.42 (3H, s, CH₃), 2.99 (4H, t, *J* = 4.2, CH₂-N-CH₂), 3.67 (4H, t, *J* = 4.2, CH₂-O-CH₂), 7.45-7.52 (5H, m, Ar-H), 7.66 (1H, s, H-C=C); ¹³C NMR: 15.1 (CH₃), 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) (C₁₈H₁₇N₅O), 303 [M-CH₃-H] (13), 290 [M-HCN-2H] (16), 260 [M-C₃H₆O-H] (29), 207 [260-HCN-CN] (11), 91 [C₆H₅N⁺] (28), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (79).

2-(5-Morpholino-1,3-diphenyl-1H-pyrazol-4-yl)methylene)malononitrile (5b): Fine yellow needles, m.p. 177-178 °C; Yield 59 %; IR (KBr, *v*_{max}, cm⁻¹): 2222 (CN), 1582 (C=C); ¹H NMR (CDCl₃): 3.06 (4H, t, *J* = 4.6, CH₂-N-CH₂), 3.71 (4H, t, *J* = 4.6, CH₂-O-CH₂), 7.45-7.56 (10H, m, Ar-H), 7.83 (1H, s, H-C=C); ¹³C 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) (C₂₃H₁₉N₅O), 352 [M-HCN-2H] (7), 324 [352-HCN-H] (9), 322 [M-C₃H₆O-H] (14), 91 [C₆H₅N⁺] (16), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (49).

2-(1,3-Diphenyl-5-piperidin-1-yl-1H-pyrazol-4-yl)methylene)malononitrile (5c): Yellow needles, m.p. 138-139 °C; Yield 99 %; IR (KBr, *v*_{max}, cm⁻¹): 2224 (CN), 1578 (C=C); ¹H NMR (CDCl₃): 1.56 (6H, br. peak, 3CH₂ of the piperidino group), 3.05 (4H, br. peak, CH₂-N-CH₂), 7.42-7.56 (10H, m, Ar-H), 7.84 (1H, s, H-C=C); ¹³C 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) (C₂₄H₂₁N₅), 324 [M-2HCN-H] (16), 323 [M-2C₂H₄] (8), 246 [M-2C₂H₄-C₆H₅] (8), 115 [M-C₄HN₂-C₅H₁₀N-C₇H₅N] (6), 91 [C₆H₅N⁺] (17), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (41).

2-Cyano-3-(3-ethyl-1-phenyl-5-pyrrolidino-1H-pyrazol-4-yl)acrylamide (5d): Fine dark yellow cubes, m.p. 183-184 °C; Yield 13 %; IR (KBr, *v*_{max}, cm⁻¹): 2209 (CN), 1588 (C=C), 1674 (C=O), 3318, 3370 (NH₂); ¹H NMR (CDCl₃): 1.25 (3H, t, *J* = 7.5, CH₃), 2.76 (2H, quint, *J* = 7.5, CH₂), 1.83-1.87 (4H, m, 2CH₂ of the pyrrolidino group), 3.10-3.14 (4H, m, CH₂-N-CH₂), 5.93 and 6.25 (1H, br. s and 1H, br. s, NH₂), 7.33-7.43 (5H, m, Ar-H), 8.38 (1H, s, H-C=C); ¹³C NMR: 12.2 (CH₃), 21.0 (CH₂), 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) (C₁₉H₂₁N₅O), 291 [M-CONH₂] (80), 252 [M-2C₂H₄-HCN] (43), 222 [252-C₂H₄-2H] (26), 91 [C₆H₅N⁺] (38), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (64).

2-Cyano-3-(1-phenyl-3-propyl-5-pyrrolidino-1H-pyrazol-4-yl)prop-2-enethioamide (5e): Fine orange cubes, m.p. 176-177°C; Yield 76%; IR (KBr, $\nu_{\max}$, cm⁻¹): 2204 (CN), 1645 (C=C), 1509 (C=S), 3289, 3334 (NH₂); ¹H NMR (CDCl₃): 0.96 (3H, t, $J = 7.3$, CH₃), 1.69 (2H, sext, $J = 7.3$, CH₂), 2.75 (2H, t, $J = 7.3$, CH₂), 1.80-1.85 (4H, m, 2CH₂ of the pyrrolidino group), 3.21-3.26 (4H, m, CH₂-N-CH₂), 7.58 (2H, br. s, NH₂), 7.38-7.48 (5H, m, Ar-H), 8.95 (1H, s, H-C=C); ¹³C NMR: 13.7 (CH₃), 21.5 (CH₂), 30.5 (CH₂), 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) (C₂₀H₂₃N₅S), 332 [M-NH₂-CH₃-2H] (37), 303 [M-CSNH₂-2H] (78), 266 [M-2C₂H₄-C₃H₇] (23), 91 [C₆H₅N⁺] (21), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (48).

Synthesis of 3-substituted 1-phenyl-1,4,5a,6,8,9-hexahydro-5H-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(5aH)-dicarbonitrile (6c); 5-cyano-3-ethyl-1-phenyl-4,5,5a,6,7,8-hexahydro-1H-pyrazolo[3,4-e]indolizine-5-carboxamide (6d) and 5-cyano-1-phenyl-3-propyl-4,5,5a,6,7,8-hexahydro-1H-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°C²⁵.

3-Methyl-1-phenyl-1,4,5a,6,8,9-hexahydro-5H-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, $\nu_{\max}$, cm⁻¹): 2243 (CN); ¹H NMR (CDCl₃): 2.21 (3H, s, CH₃), 2.73 (1H, ddd, ³ $J_{9ax-9eq} = 12.1$, ³ $J_{9ax-8ax} = 6.8$, ³ $J_{9ax-8eq} = 3.4$, H_{ax}-9), 3.31-3.37 (2H, m, H-5a, (X part of ABX system) and H_{eq}-9), 3.26 [1H, d, ² $J_{4ax-4eq} = 15.4$, H_{ax}-4, (A part of AB system)], 3.46 [1H, d, ² $J_{4ax-4eq} = 15.4$, H_{eq}-4, (B part of AB system)], 3.62-3.76 (2H, m, H₂-8), 4.17 [1H, dd, ² $J_{6ax-6eq} = 13.5$, ³ $J_{5aax-6ax} = 5.9$, H_{ax}-6, (A part of ABX system)], 4.24 [1H, dd, ² $J_{6ax-6eq} = 13.5$, ³ $J_{5aax-6eq} = 3.3$, 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'); ¹³C NMR: 11.1 (CH₃), 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) (C₁₈H₁₇N₅O), 290 [M-HCN-2H] (16), 262 [290-HCN-H] (29), 254 [M-C₃N₂-H] (26), 198 [M-C₂H₄O-C₆H₅] (31), 91 [C₆H₅N⁺] (26), 77 [C₆H₅⁺] (87), 51 [77-C₂H₂] (62).

1,3-Diphenyl-1,4,5a,6,8,9-hexahydro-5H-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, $\nu_{\max}$, cm⁻¹): 2248 (CN); ¹H NMR (CDCl₃): 2.79 (1H, ddd, ² $J_{9ax-9eq} = 12.0$, ³ $J_{9ax-8ax} = 6.0$, ³ $J_{9ax-8eq} = 3.3$, H_{ax}-9), 3.40 (1H, ddd, ² $J_{9ax-9eq} =$

12.0, ³ $J_{9ax-8ax} = 6.0$, ³ $J_{9ax-8eq} = 3.7$, H_{eq}-9), 3.45 (1H, t, $J = 5.8$, H-5a), 3.57 [1H, d, ² $J_{4ax-4eq} = 15.4$, H_{ax}-4, (A part of AB system)], 3.72 [1H, d, ² $J_{4ax-4eq} = 15.4$, H_{eq}-4, (B part of AB system)], 3.67-3.77 (2H, m, H₂-8), 4.26 (2H, d, $J = 5.1$, H₂-6), 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''); ¹³C 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) (C₂₃H₁₉N₅O), 352 [M-HCN-2H] (11), 324 [352-HCN-H] (4), 316 [M-C₃N₂-H] (6), 260 [M-C₂H₄O-C₆H₅] (5), 91 [C₆H₅N⁺] (10), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (46).

1,3-Diphenyl-1,4,6,7,8,9-hexahydropyrazolo[4,3-c]quinolizine-5,5(5aH)-dicarbonitrile (6c): White powder, m.p. 209-210°C; Yield 21 %; IR (KBr, $\nu_{\max}$, cm⁻¹): 2253 (CN); ¹H NMR (CDCl₃): 1.54 (3H, br. peak, H₂-7, 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, ² $J_{6ax-6eq} = 12.4$, H_{eq}-6, (B part of ABX system)], 2.47-2.55 (1H, m, H_{ax}-9), 3.28 [1H, dd, ³ $J_{5aax-6ax} = 9.0$, ³ $J_{5aax-6eq} = 2.5$, H-5a, (X part of ABX system)], 3.43 (1H, d, ² $J_{9ax-9eq} = 11.5$, H_{eq}-9), 3.53 [1H, d, ² $J_{4ax-4eq} = 15.1$, H_{ax}-4, (A part of AB system)], 3.61 [1H, d, ² $J_{4ax-4eq} = 15.1$, 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''); ¹³C 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) (C₂₄H₂₁N₅), 351 [M-HCN-H] (10), 325 [M-2HCN] (5), 314 [M-C₃N₂-H] (37), 246 [M-2C₂H₄-C₆H₅] (16), 115 [M-C₇H₅N-C₉H₁₁N₃] (23), 91 [C₆H₅N⁺] (12), 77 [C₆H₅⁺] (92), 51 [77-C₂H₂] (52).

5-Cyano-3-ethyl-1-phenyl-4,5,5a,6,7,8-hexahydro-1H-pyrazolo[3,4-e]indolizine-5-carboxamide (6d): Yellow scales, m.p. 204-206 °C; Yield 31 %; IR (KBr, $\nu_{\max}$, cm⁻¹): 2229 (CN), 1692 (C=O), 3305, 3386 (NH₂); ¹H NMR (CDCl₃): 0.83 (3H, t, $J = 8.1$, CH₃), 2.61 (2H, quint, $J = 8.1$, CH₂), 1.86-2.11 (3H, m, H_{ax}-6, H₂-7), 2.32-2.37 (1H, m, H_{eq}-6), 2.91-3.00 (1H, m, H_{ax}-8), 3.07-3.20 (3H, m, H₂-4, H_{eq}-8), 3.97 (1H, dd, ³ $J_{5aax-6ax} = 7.7$, ³ $J_{5aax-6eq} = 4.4$, H-5a), 5.80 and 6.53 (1H, br. s and 1H, br. s, D₂O exchangeable, NH₂), 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'); ¹³C NMR: 12.3 (CH₃), 21.7 (CH₂), 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) (C₁₉H₂₁N₅O), 291 [M-CONH₂] (96), 252 [M-2C₂H₄-HCN] (12), 248 [291-C₂H₄-CH₃] (13), 91 [C₆H₅N⁺] (17), 77 [C₆H₅⁺] (100), 51 [77-C₂H₂] (47).

5-Cyano-1-phenyl-3-propyl-4,5,5a,6,7,8-hexahydro-1H-pyrazolo[3,4-e]indolizine-5-carbothioamide (6e): Orange cubes, m.p. 186 °C; Yield 46%; IR (KBr, $\nu_{\max}$, cm⁻¹): 2234 (CN), 1526 (C=S), 3358, 3423 (NH₂); ¹H NMR (CDCl₃): 0.97 (3H, t, $J = 7.3$, CH₃), 1.67 (2H, sext, $J = 7.3$, CH₂), 2.55 (2H, t, $J = 7.3$, CH₂), 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, ² $J_{4ax-4eq} = 15.4$, H_{ax}-4, (A part of AB system)], 3.17-3.23 (1H, m, H_{eq}-8), 3.49 [1H, d, ² $J_{4ax-4eq} = 15.4$, H_{eq}-4, (B part of AB system)], 4.22 (1H, dd, ³ $J_{5aax-6ax} = 6.0$, ³ $J_{5aax-6eq} = 4.8$, 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 and 8.81 (1H, br. s and 1H, br. s D₂O exchangeable, NH₂); ¹³C NMR: 13.4 (CH₃), 21.8 (CH₂), 28.8 (CH₂), 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) (C₂₀H₂₃N₅S), 332 [M-NH₂-CH₃-2H] (67), 303 [M-CSNH₂-2H] (100), 267 [M-C₃H₂N₂S] (11), 91 [C₆H₅N⁺] (36), 77 [C₆H₅⁺] (94), 51 [77-C₂H₂] (42).

Synthesis of 2-arylidene malononitriles (8): They were synthesized by reaction of aromatic aldehyde with malononitrile according to the literature procedures²⁶.

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 method²⁷.

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 the solid product was subjected to column chromatography to give pure **9c**.

6-Amino-3-propyl-1-(2-pyridinyl)-4-(3',4',5'-trimethoxyphenyl)-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, $\nu_{\max}$, cm⁻¹): 2198 (CN), 3323, 3466 (NH₂); ¹H NMR (DMSO-*d*₆): 0.72 (3H, t, $J = 7.3$, CH₃CH₂), 1.10-1.24 (1H, m), 1.27-1.44 (1H, m), (CH₂ of the propyl group near the chiral carbon C-4), 2.08-2.23 (2H, m, CH₃CH₂CH₂), 3.64 (3H, s, OCH₃), 3.72 (6H, s, 2OCH₃), 4.66 (1H, s, H-4), 6.55 (2H, s, H-2'',6''), 7.08 (2H, br.s, NH₂) (D₂O exchangeable), 7.36 (1H, dd, ³ $J_{4,5} = 7.7$, ³ $J_{5,6} = 5.1$, H-5'), 7.71 (1H, d, ³ $J_{3,4} = 7.7$, H-3'), 7.96 (1H, td, ³ $J = 7.7$, ⁴ $J_{4,6} = 1.8$, H-4'), 8.49 (1H, d, ³ $J_{5,6} = 5.1$, H-6''); ¹³C NMR: 13.6 (CH₃), 20.6 (CH₃CH₂), 28.8 (CH₂CH₂), 36.9 (C-4), 55.8 (2OCH₃), 59.9 (OCH₃), 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) (C₂₄H₂₅N₅O₄+H), 430 [M+H-NH₃-H] (5), 382 [M+H-C₃H₂N₂] (60), 280 [M+H-C₉H₁₁O₃-H] (55), 251 [280-C₂H₅] (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, $\nu_{\max}$, cm⁻¹): 2189 (CN), 3314, 3380 (NH₂); ¹H NMR (DMSO-*d*₆): 0.91 (3H, t, $J = 7.3$, CH₃), 1.54 (2H, sext, $J = 7.3$, CH₂), 2.45-2.50 (2H, m, CH₂ within H₂O in DMSO, (2.52, 2H, t, $J = 7.3$ in CDCl₃)), 3.36 (3H, br s, N-CH₃ with DMSO, (3.45, 3H, s, in CDCl₃)), 4.88 (1H, s, H-4), 6.54 (2H, d, ³ $J_{3,4} = 3.5$, H-3'), 6.82 (1H, dd, ³ $J_{4,5} = 5.0$, ³ $J_{3,4} = 3.5$, H-4'), 7.20 (1H, d, ³ $J_{4,5} = 5.0$, H-5'), 14.0 (2H, br.s, NH₂) (D₂O exchangeable); MS (ESI): m/z (%) 301 [M+H]⁺ (not observed) (C₁₅H₁₆N₄OS+H), 235 [M+H-C₃H₂N₂] (90), 141 [M+H-C₈H₆N₂S+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, $\nu_{\max}$, cm⁻¹): 2209 (CN), 3355, 3414 (NH₂); MS (ESI): m/z (%) 285 [M+H]⁺ (30) (C₁₅H₁₆N₄O₂+H), 268 [M+H-NH₃] (100), 240 [M+H-HCN-H] (20), 151 [M+H-C₃H₂N₂-C₄H₃O-H] (5), 99 [M+H-C₁₀H₆N₂O₂] (4).

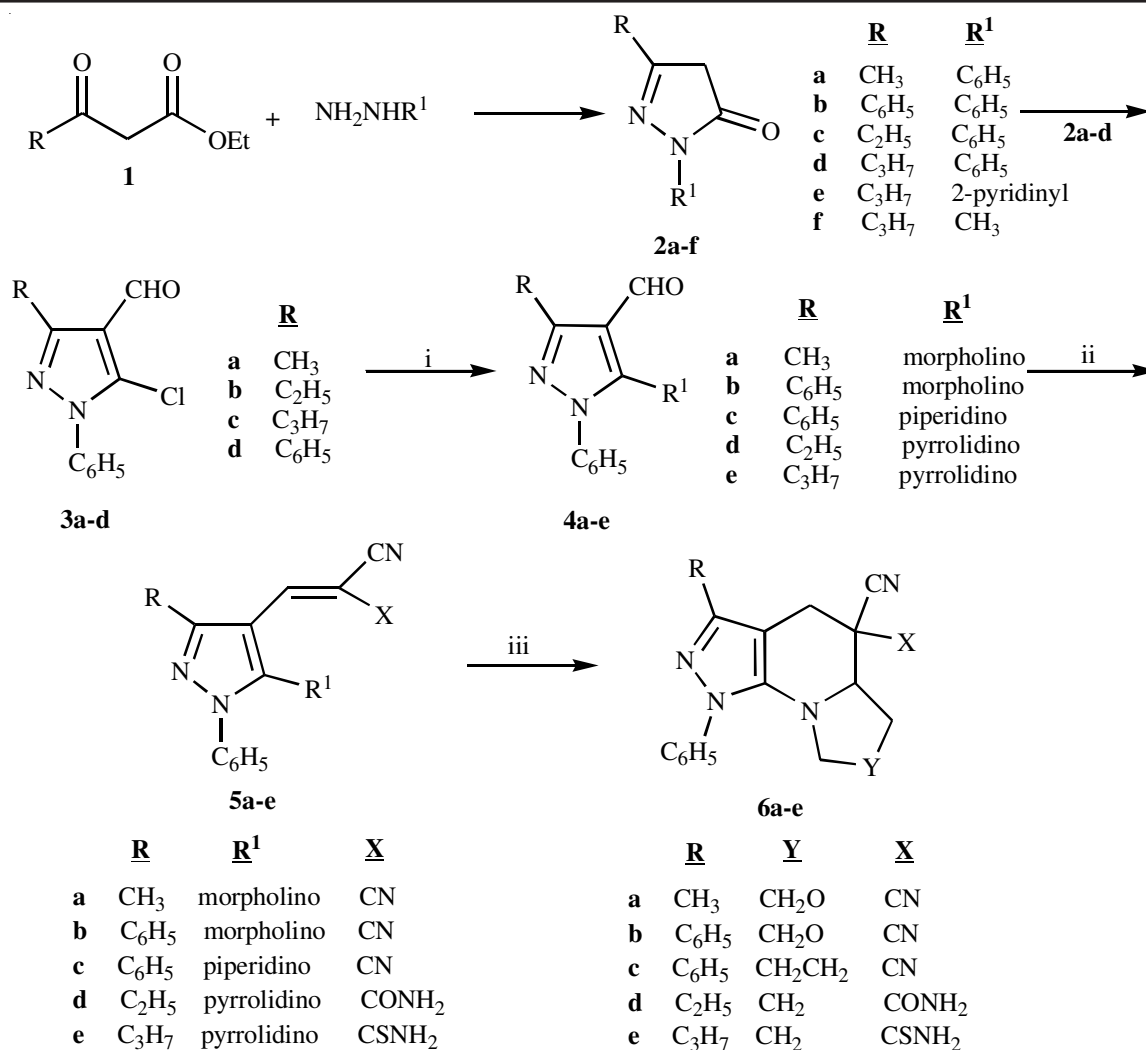
Synthesis of 1,4-disubstituted-7-Methyl-3-propyl-4,6-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin-5(1H)-one (11a,b): They were synthesized using the reported method²⁶.

7-Methyl-3-propyl-1-(2-pyridinyl)-4-(3,4,5-trimethoxyphenyl)-4,6-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin-5(1H)-one (11a): Pale yellow powder, m.p. >300 °C (from ethanol); Yield 57%; IR (KBr, $\nu_{\max}$, cm⁻¹): 3449 (NH), 1655 (C=O); ¹H NMR (DMSO-*d*₆): 0.78 (3H, t, $J = 7.3$, CH₃), 1.17-1.29 (1H, m), 1.35-1.46 (1H, m) (CH₂ of the propyl group near the chiral carbon C-4), 2.29-2.34 (5H, m, CH₂, CH₃ at C-7), 3.60 (3H, s, OCH₃), 3.69 (6H, s, 2OCH₃), 5.01 (1H, s, H-4), 6.56 (2H, s, H-2'',6''), 7.36 (1H, ddd, ³ $J_{4,5} = 7.9$, ³ $J_{5,6} = 4.9$, ⁴ $J_{3,5} = 1.1$, H-5'), 7.72 (1H, d, ³ $J_{3,4} = 7.9$, H-3'), 7.97 (1H, td, ³ $J = 7.9$, ⁴ $J_{4,6} = 1.8$, H-4'), 8.52 (1H, dd, ³ $J_{5,6} = 4.9$, ⁴ $J_{4,6} = 1.8$, H-6''); ¹³C NMR: 13.6, 20.7, 20.8, 28.9, 34.8 (Pr carbons, CH₃ at C-7, C-4), 55.7 (2OCH₃), 59.8 (OCH₃), 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) (C₂₆H₂₇N₅O₅+H), 460 [M+H-C₂H₅-H] (5), 382 [M+H-C₅H₄N₂O] (5), 322 [M+H-C₉H₁₁O₃-H] (100), 281 [280-CH₃-HCN-H] (75).

1,7-Dimethyl-3-propyl-4-(2-thienyl)-4,6-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidin-5(1H)-one (11b): Pale green powder, m.p. >300 °C; Yield 38%; IR (KBr, $\nu_{\max}$, cm⁻¹): 3484 (NH), 1625 (C=O); ¹H NMR (DMSO-*d*₆): 0.93 (3H, t, $J = 7.1$, CH₃), 1.61-1.54 (2H, m, CH₂), 2.73-2.66 (2H, m, CH₂), 2.50 (3H, s, CH₃ at C-7), 3.52 (3H, s, N-CH₃), 5.15 (1H, s, H-4), 6.39 (1H, d, ³ $J_{3,4} = 3.4$, H-3'), 6.87-6.85 (2H, m, H-4',5'); ¹³C NMR: 12.8, 21.4, 25.1, 27.7, 30.6, 33.0 (Pr carbons, CH₃ at C-7, N-CH₃, 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) (C₁₇H₁₈N₄O₂S+H), 315 [M+H-C₂H₄] (75), 233 [M+H-C₅H₄N₂O-2H] (2), 141 [M+H-C₁₀H₈N₂OS+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 procedure²³ (**Scheme-I**). 5-Chloro-3-substituted 1-phenyl-1H-pyrazole-4-carbaldehyde **3a-d** were



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 chloroformylation²⁴ by heating pyrazolones with an excess phosphorus oxychloride in DMF. The structures of compounds **3a-d** were confirmed from their IR, ^1H 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 $1669\text{--}1628\text{ cm}^{-1}$ for $\text{C}=\text{O}$ stretching, in addition to bands in the range $2878\text{--}2738\text{ cm}^{-1}$ 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 ^1H NMR spectrum of **4a** showed two triplets ($J = 4.7$), each integrated for 4 protons at δ 3.13 ppm ($\text{CH}_2\text{--N--CH}_2$) and 3.67 ppm ($\text{CH}_2\text{--O--CH}_2$) 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 $2225\text{--}2204\text{ cm}^{-1}$ attributed for CN stretching and band at $1645\text{--}1578\text{ cm}^{-1}$ due to $\text{C}=\text{C}$ stretching. Mass spectral data have been found to be in conformity with the assigned structure. The ^1H 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 shifts²⁸. 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, ^1H - ^1H Cosy and ^1H - ^{13}C Cosy techniques. Their IR spectra showed bands at 2229-2253 cm^{-1} attributed for CN stretching. The ^1H NMR spectra of **6a-e** showed the absence of the olefinic protons. The IR, ^1H NMR, ^{13}C NMR and MS spectral data of **6a-e** were in complete agreement with their structures.

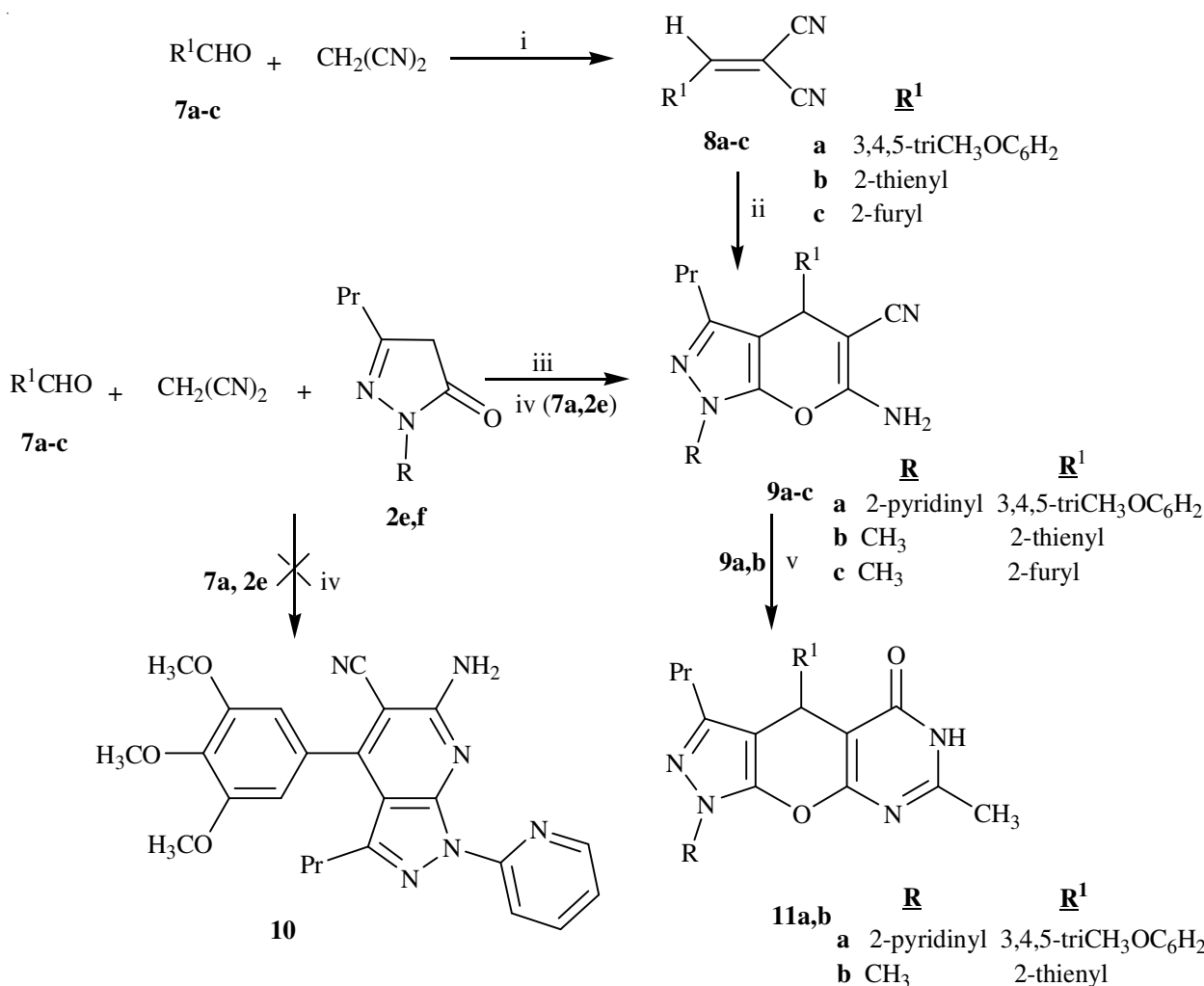
Treatment of **2e-f** with 2-arylidene malononitriles **8a-c** (Scheme-II), either by stirring overnight²⁷ or one pot four components synthesis using ultrasound irradiation in aqueous medium in the presence of catalyst and using microwave irradiation yielded the same product **9a-c** (IR, TLC, m.p. and 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 ^1H 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 consistency with its structure (experimental section). The assignment of all protons and carbons in **9a** were verified by the aid of the analysis of DEPT, ^1H - ^1H Cosy and ^1H - ^{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 successful²⁶. Instead we obtained the same product **9a** as indicated by the ^1H 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.

ACKNOWLEDGEMENTS

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REFERENCES

1. I. Çelik, N. KanIskan and S. Kökten, *Tetrahedron*, **65**, 328 (2009).
2. T.D. Penning, J.J. Talley, S.R. Bertenshaw, J.S. Carter, P.W. Collins, S. Docter, M.J. Graneto, L.F. Lee, J.W. Malecha, J.M. Miyashiro, R.S. Rogers, D.J. Rogier, S.S. Yu, G.D. Anderson, E.G. Burton, J.N. Cogburn, S.A. Gregory, C.M. Koboldt, W.E. Perkins, K. Seibert, A.W. Veenhuizen, Y.Y. Zhang and P.C. Isakson, *J. Med. Chem.*, **40**, 1347 (1997).
3. M. Rinaldi-Carmona, F. Barth, M. Héaulme, D. Shire, B. Calandra, C. Congy, S. Martinez, J. Maruani, G. Néliat, D. Caput, P. Ferrara, P. Soubrié, J.C. Brelière and G. Le Fur, *FEBS Lett.*, **350**, 240 (1994).
4. H.A. DeWald, S. Lobbstaël and B.P.H. Poschel, *J. Med. Chem.*, **24**, 982 (1981).
5. K.S. Girisha, B. Kalluraya and V. Narayana, *Eur. J. Med. Chem.*, **45**, 4640 (2010).
6. A.M. Isloor, B. Kalluraya and K. Sridhar Pai, *Eur. J. Med. Chem.*, **45**, 825 (2010).
7. A.M. Youssef, M. Sydney White, E.B. Villanueva, I.M. El-Ashmawy and A. Klegeris, *Bioorg. Med. Chem.*, **18**, 2019 (2010).
8. P.-C. Lv, J. Sun, Y. Luo, Y. Yang and H.-L. Zhu, *Bioorg. Med. Chem. Lett.*, **20**, 4657 (2010).
9. S. Bondock, R. Rabie, H.A. Etman and A.A. Fadda, *Eur. J. Med. Chem.*, **43**, 2122 (2008).
10. X.-H. Liu, J. Zhu, A. Zhou, B.-A. Song, H.-L. Zhu, L.-S. Bai, P.S. Bhadury and C.-X. Pan, *Bioorg. Med. Chem.*, **17**, 1207 (2009).
11. N.P. Rai, V.K. Narayanaswamy, S. Shashikanth and P.N. Arunachalam, *Eur. J. Med. Chem.*, **44**, 4522 (2009).
12. H.A. Abdel-Aziz, A.A.I. Mekawey and K.M. Dawood, *Eur. J. Med. Chem.*, **44**, 3637 (2009).
13. A.E. Rashad, M.I. Hegab, R.E. Abdel-Megeid, N. Fathalla and F.M.E. Abdel-Megeid, *Eur. J. Med. Chem.*, **44**, 3285 (2009).
14. A.E. Rashad, M.I. Hegab, R.E. Abdel-Megeid, J.A. Micky and F.M.E. Abdel-Megeid, *Bioorg. Med. Chem.*, **16**, 7102 (2008).
15. M.M. Ghorab, F.A. Ragab, S.I. Alqasoumi, A.M. Alafeefy and S.A. Aboulmagd, *Eur. J. Med. Chem.*, **45**, 171 (2010).
16. H.A. Abdel-Aziz, H.S.A. El-Zahabi and K.M. Dawood, *Eur. J. Med. Chem.*, **45**, 2427 (2010).
17. B.P. Bandgar, J.V. Totre, S.S. Gawande, C.N. Khobragade, S.C. Warangkar and P.D. Kadam, *Bioorg. Med. Chem.*, **18**, 6149 (2010).
18. F. El-Baih and H.M. Al-Hazimi, *Asian J. Chem.*, **23**, 1309 (2011).
19. A.M. Farag, K.A.K. Ali, T.M.A. El-Debss, A.S. Mayhoub, A.-G.E. Amr, N.A. Abdel-Hafez and M.M. Abdulla, *Eur. J. Med. Chem.*, **45**, 5887 (2010).
20. S.K. Meegalla, D. Doller, G.M. Silver, N. Wisniewski, R.M. Soll and D. Dhanoa, *Bioorg. Med. Chem. Lett.*, **13**, 4035 (2003).
21. G.P. Lahm, T.M. Stevenson, T.P. Selby, J.H. Freudenberger, D. Cordova, L. Flexner, C.A. Bellin, C.M. Dubas, B.K. Smith, K.A. Hughes, J.G. Hollingshaus, C.E. Clark and E.A. Benner, *Bioorg. Med. Chem. Lett.*, **17**, 6274 (2007).
22. S. Gupta, A. Sivasubramanian, L.M. Rodrigues, A.P. Esteves, R. Hrdina and A.M.F. Oliveira-Campos, *Dyes Pigments*, **75**, 82 (2007).
23. A.A. Al-Mutairi, F.E.M. El-Baih and H.M. Al-Hazimi, *J. Saudi Chem. Soc.*, **14**, 287 (2010).
24. J. Becher, P.L. Joergensen, K. Pluta, N.J. Krake and B. Falt-Hansen, *J. Org. Chem.*, **57**, 2127 (1992).
25. D. Prajapati and K.J. Borah, *Beilstein J. Org. Chem.*, **3**, 43 (2007).
26. T.M. Al-Mutairi, H.M. Al-Hazimi and F.E.M. El-Baih, *J. Saudi Chem. Soc.*, **13**, 199 (2009).
27. Y.A. Sharanin, V.K. Promonenkov and L.G. Sharanina, *J. Org. Chem. (USSR)*, **18**, 544 (1982).
28. D.L. Pavia, G.M. Lampman, G.S. Kriz and J.R. Vyvyan, *Introduction to Spectroscopy*, Thomson Learning, edn. 4 (2009).