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New and Facile Synthesis of Substituted Pyrrole, Pyridine, Pyrazolo[4,3-*b*] Pyridine, Pyrano[3,2-*c*] Quinoline, Napthopyran, Naphthodipyran and Coumarin Derivatives

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ABSTRACT

Several new pyrazolo[4,3-*b*] pyridines **7a**, **b** were prepared by reacting arylidenemalononitriles **1a**, **c** or **1i**, **j** with 4-nitrosoantipyrine **4**. Reacting **1a**, **b**, **d** with 4-azidomethylcarbonylantipyrine **8** give 2-aminopyrrole **14**. Pyrano[3,2-*c*] quinolines **20a**, **b** and **23** were obtained by reacting 4-hydroxyquinoline **15** with **1g**, **h**, **2b** respectively. Reaction of **1** with naphthalenediols **24**, **27** and **29** yield naphthodipyrans **26a**, **b**, **28a**, **b** and **30a**, **b** respectively. Spironaphthodipyrans **32**, **33** and spironaphthopyrans **36**, **37** were prepared through reaction of **2a** with naphthalenediols **24**, **27**, **34** and **35** respectively. Condensation of thioxothiazole **38** with 3,5-dibromo-2-hydroxybenzaldehyde give 2H-chromene-3-carboxamide **42**. **38** also reacted with **1c** and **2a** to give 3,5-dicyanopyridines **45** and **47** respectively. Reaction of 2-cyano-*N*'-(1-thiophen-2-yl)ethylidene) acetohydrazide **49** with **1a**, **b** afforded 3,5-dicyanopyridines **53**.

Keywords: Pyrrole; Pyridine; Pyrazolo[4,3-*b*] Pyridine; Pyrano[3,2-*c*] Quinoline; Naphthopyran; Naphthodipyrans and Coumarin

1. Introduction

Polyfunctionally substituted aromatic and heteroaromatic derivatives are important class of compounds. Amomg these derivatives are biologically interesting antimicrobials [1,2], antimalarials [3], as pharmaceuticals [4], antitumor activity [5], as nonpeptide human deficiency virus (HIV) protease inhibitors [6] and antischistosomal agents [7]. Some years ago, our main interest was focused on a program aimed at developing of new synthetic approaches to Polyfunctionally substituted heterocycles [8,9] utilizing simple, inexpensive and readily available starting materials. The present work has resulted in the formation of pyrrole, pyridine, pyrazolopyridine, pyranoquinoline, naphthodipyran and coumarin derivatives.

2. Experimental

All melting points are uncorrected and measured on Griffin & George MBF010T (London) apparatus. Recorded yields correspond to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer SP-880 spectrophotometer and 1H-NMR spectra were measured on a Varian 500 MHz at Minnesota (USA) University spectrometer in DMSO-d6 as solvent and TMS as an internal standard (Chemical shifts are reported in δ units ppm). Microanalysis were performed on LECOCHN-932 and carried out in the Microanalytical Data Units at Cairo and Damietta Universities.

Synthesis of 6-aryl-1-methyl-3-oxo-1,2,3-trihydro-2-phenyl-pyrazolo[4,3-*b*]pyridine-5-carbonitriles (7a,b)

A solution of 1,2-dihydro-2,3-dimethyl-4-nitroso-1-phenyl-5-oxopyrazole **(4)** (0.01 mol) and the arylidenes **1a**, **c** or **1i**, **j** (0.01 mol) in ethanol (50 ml) containing a catalytic amount of piperidine (0.1 ml) was heated under reflux for one hour, then left to cool. The solid products so formed were collected by filtration, recrystallized from the suitable solvents and then identified as **7a**, **b**.

6-(5-Bromothiophen-2-yl)-2,3-dihydro-1-methyl-3-oxo-1,2,3-trihydro-2-phenyl-1H-pyrazolo[4,3-*b*] pyridine-5-carbonitrile (7a)

Yellow crystals from ethanol/dimethylformamide, m.p. 240˚C - 242˚C, yield 85%.-IR (υ_{max}/cm^{-1}): 2225 (conjugated CN), 1691 (CO).-^{1}H-NMR (DMSO-d$_6$) (δ, ppm): 3.35 (s, 3H, N-CH$_3$), 6.97 - 7.59 (m, 7H, aromatic protons), 8.37 (s, 1H, pyridine H-4).-$C_{18}H_{11}BrN_4SO$ (411.28) Calcd. C 52.57 H 2.70 N 13.62; Found C 52.36 H 3.04 N

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13.50.

6-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydro-1-methyl-3-oxo-1,2,3-trihydro-2-phenyl-1H-pyrazolo [4,3-*b*] pyridin-5-carbonitrile (7b)

Red crystals from ethanol, m.p. 260˚C - 262˚C, yield 83%.-IR (υ_{max}/cm^{-1}): 3065 (br, OH), 2224 (conjugated CN), 1661 (CO).-^{1}H-NMR (DMSO-d$_6$) (δ, ppm): 3.4 (s, 3H, N-CH$_3$), 3.87 (s, 3H, OCH$_3$), 6.97 - 7.59 (m, 8H, aromatic protons), 8.37 (s, 1H, pyridine H-4), 9.64 (s, 1H, OH). $C_{21}H_{16}N_4O_3$ (372.38).-Calcd. C 67.73 H 4.33 N 15.05; Found C 67.64 H 4.4 N 15.13.

2-Amino-4-(aryl)-5-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)pyrrol-3-carbonitriles (14a-c)

A solution of 4-azidmethylcarbonyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one **(8)** (0.01 mol) and the appropriate amounts of **1a**, **b**, **d** (0.01 mol) in ethanol (50 ml) was heated with piperidine (0.1 ml) under reflux for one hour then left to cool at room temperature. The solid products, so formed, were collected by filtration, recrystallized and identified as **14a-c**.

2-Amino-4-(5'-bromo-2'-thienyl)-5-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)pyrrol-3-carbonitrile (14a)

Yellow crystals from ethanol/1,4-dioxane, m.p. 286˚C - 288˚C, yield 65%-IR (υ_{max}/cm^{-1}): 3470, 3360 (NH$_2$, NH), 2203 (conjugated CN), 1685 (CO), 1650 (CO).-^{1}H-NMR (DMSO-d$_6$) (δ, ppm): 2.40 (s, 3H, CH$_3$), 3.33 (s, 3H, N-CH$_3$), 7.45 - 7.63 (m, 9H, 7H, aromatic protons and 2H, NH$_2$), 8.5 (s, 1H, NH).- $C_{21}H_{16}BrN_5SO_2$ (482.37) Calcd. C 52.29 H 3.34 N 14.52; Found C 52. 12 H 3.51 N 14.63.

2-Amino-4-(4'-nitro-2'-pyrryl)-5-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)pyrrol-3-carbonitrile (14b)

Brown crystals from DMF, m.p. 263˚C - 265˚C, yield 63%.-IR (υ_{max}/cm^{-1}): 3452, 3358, 3137 (NH$_2$, NH), 2191 (conjugated CN), 1680 (CO), 1660(CO).-$C_{24}H_{21}N_5O_4$ (443.45) Calcd. C 65.00 H 4.77 N 15.79; Found C 65.12 H 5.00 N 15.68.

2-Amino-4-(3-chlorophenyl)-5-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)pyrrol-3-carbonitrile (14c)

Yellow crystals from ethanol, 1,4-dioxane, m.p. 284˚C - 286˚C, yield 65%.-IR(υ_{max}/cm^{-1}): 3441, 3341 (NH$_2$, NH), 2203 (conjugated CN), 1685 (CO), 1620 (CO).-$C_{23}H_{18}ClN_5O_2$ (431.87) Calcd. C 63.96 H 4.20 N 16.22; Found C 63.89 H 4.31 N16.14.

Synthesis of 4*H*-pyrano[3,2-*c*]quinolin-3-carbonitriles (20a,b) and spiro-4*H*-pyrano[3,2-*c*] quinolin-3-carboxylate (23*)*

A solution of 3-acetyl-4-hydroxy-1-methyl-2-oxo-1H-quinoline **(15)** (0.01 mole) and (0.01 mol) of either **1g**, **h** or ethyl 2-(2-oxoindolin-3-ylidene) cyanoacetate **(2b)** in ethanol/pyridine (1:1) (60 ml), were refluxed for six hours. The solvent was then evaporated in vacuo and the precipitates formed were collected by filtration recrystallized and identified as **20a**, **b** and **23** respectively.

4-(4-Methoxyphenyl)-5,6-dihydro-2-hydroxy-6-methyl-5-oxo-4H-pyrano [3,2-*c*]quinolin-3-carbonitrile (20a)

Colorless crystals from ethanol, m.p. 190˚C - 192˚C, yield 75%.-IR (υ_{max}/cm^{-1}): 3447, 3366, 3304 (OH), 2206 (conjugated CN), 1699 (CO).-^{1}HNMR: (DMSO-d$_6$) (δ, ppm): 3.10 (s, 3H, CH$_3$), 3.83 (s, 3H, CH$_3$), 4.43 (s, 1H, pyran H-4), 6.90 - 8.16 (m, 8H, aromatic protons).-$C_{21}H_{16}N_2O_4$ (360.36) Calcd. C 69.99 H, 4.48 N 7.77; Found C 70.02 H 4.73 N 7.68.

4-(4-Bromophenyl)-5,6-dihydro-2-hydroxy-6-methyl-5-oxo-4H-pyrano[3,2-*c*]quinolin-3-carbonitrile (20b)

Faint yellow crystals from ethanol/dimethylformamide, m.p. 220˚C - 222˚C, yield 80 %.-IR (υ_{max}/cm^{-1}): 3451, 3409, 3325 (OH), 2200 (conjugated CN), 1682 (CO).-^{1}HNMR : (DMSO-d$_6$) (δ, ppm): 3.0 (s, 3H, CH$_3$), 4.50 (s, 1H, pyran H-4), 7.35 - 8.16 (m, 8H, aromatic protons).-$C_{20}H_{13}BrN_2O_3$ (409.23) Calcd. C 58.70 H 3.20 N 6.85; Found C 58.65 H 3.34 N 6.80.

Ethyl 2-amino-5,6-dihydro-5-oxo-6-methyl-4-(1',3'-dihydro-2'H-indole-2-on)spiro-4H-pyrano[3,2-*c*]quinolin-3-carboxylate (23)

Yellow crystals from ethanol/DMF, m.p. 270˚C - 272˚C, yield 76%.-IR (υ_{max}/cm^{-1}): 3395, 3284, 3196 (NH$_2$, NH), 1688 (CO), 1659 (CO), 1631 (CO). -^{1}HNMR: (DMSO-d$_6$) (δ, ppm): 0.82 - 0.85 (t, J = 7.5 Hz, 3H, CH$_3$), 2.87 (s, 3H, CH$_3$), 3.73 - 3.76 (q, J = 7.5 Hz, 2H, CH$_2$), 6.69 - 8.14 (m, 10H, 8H, aromatic protons and 2H, NH$_2$), 10.28 (s, 1H, NH).-$C_{23}H_{19}N_3O_5$ (417.41) Calcd. C 66.18 H 4.59 N 10.07; Found C 66.22 H 4.33 N 10.13.

General procedure for preparation of (26a,b), (28a,b) and (31a,b)

A mixture of (0.01 mol) of each 1,5-naphthalenediol **(24)**, 2,6-naphthalenediol **(27)** or 2,7-naphthalenediol **(31)** and (0.02 mol) of the arylidenemalononitriles **1** in ethanol (50 ml) was refluxed for thirty minutes in the presence of piperidine (0.1 ml). The obtained solid products were collected by filtration and recrystallized from the proper solvents yielding corresponds compounds **26**, **28** and **31** respectively.

2,8-Diamino-4,10-di(4-hydroxyphenyl)-4,10-dihydronaphtho[1,2-*b*:5,6-*b*']dipyran-3,10-dicarbonitrile (26a)

Yellow crystals from ethanol/DMF, m.p., >300˚C, yield 60%.-IR (υ_{max}/cm^{-1}): 3421, 3321 (NH$_2$, OH), 2187 (conjugated CN), 1653 (δNH$_2$).-^{1}H-NMR (DMSO-d$_6$) (δ, ppm): 4.77 (s, two equivalent pyran 4-H), 6.69 - 7.88 (m, 16H, 12H, aromatic protons and 4H, 2NH$_2$), 9.32 (s, 2H,

2OH).-$C_{30}H_{20}N_4O_4$ (500.50) Calcd. C 71.99 H 4.03 N 11.19; Found C 71.03 H 4.34 N 11.22.

2,8-Diamino-4,10-di(3-chlorophenyl)-4,10-dihydron aphtho[1,2-*b*:5,6-*b*'] dipyran-3,10-dicarbonitrile (26b)

Yellow crystals from DMF, m.p., > 300˚C, yield 63%.-IR (υ_{max}/cm^{-1}): 3499, 3325, 3197 (NH_2), 2196 (conjugated CN), 1665 (δ NH_2).-$C_{30}H_{18}Cl_2N_4O_2$ (537.39) Calcd. C 67.05 H 3.38 N 10.43; Found C 67.23 H 3.42 N 10.33.

3,9-Diamino-1,7-di(3-chlorophenyl)-1,7dihydronaphtho[2,1-*b*:6,5-*b*'] dipyran-3,9-dicarbonitrile (28a)

Yellow crystals from DMF m.p. > 300˚C, yield 64%.-IR: (υ_{max}/cm^{-1}): 3458, 3326, 3199 (NH_2), 2193 (conjugated CN), 1657 (δ NH_2).-$C_{30}H_{18}Cl_2N_4O_2$ (537.39) Calcd. C 67.05 H 3.38 N 10.43; Found C 67.00 H 3.27 N 10.51.

3,9-Diamino-1,7-di(4-bromophenyl)-1,7dihydronaphtho[2,1-*b*:6,5-*b*'] dipyran-3,9-dicarbonitrile (28b)

Faint yellow from ethanol/DMF m.p. > 300˚C, yield 65%.-IR (υ_{max}/cm^{-1}): 3457, 33327, 3197 (NH_2), 2191 (conjugated CN).-^{1}H-NMR (DMSO-d_6) (δ, ppm): 5.34 (s, two equivalent pyran 4-H), 6.99 - 7.89 (m, 16H, 12H, aromatic protons and 4H, $2NH_2$). $C_{30}H_{18}Br_2N_4O_2$ (626.29) Calcd. C 57.53 H 2.90 N 8.95; Found C 57.64 H 3.02 N 8.83.

3-Amino-9-hydroxy-1-(4-hydroxyphenyl)-1*H*-benzo[*f*]chromen-2-carbonitrile (31a)

Yellow crystals from ethanol/dimethylformamide, m.p. 260˚C - 262˚C, yield 75%.-IR (υ_{max}/cm^{-1}): 3482, 3377, 3162 (NH_2, OH), 2183 (conjugated CN), 1651 (δ, NH_2).-^{1}H-NMR (DMSO-d_6) (δ, ppm): 4.89 (s, 1H, pyran 4-H), 6.65 - 7.77 (m, 11H, 9H aromatic protons and 2H, NH_2), 9.26, 9.8 (2s, 2H, 2OH).-$C_{20}H_{14}N_2O_3$ (330.33) Calcd. C 72.72 H 4.27 N8.48; Found C 72.82 H 4.15 N 8.51.

3-Amino-9-hydroxy-1-(4-bromophenyl)-1*H*-benzo [*f*]chromen-2-carbonitrile (31b)

Yellow crystals from DMF, m.p. 268˚C - 270˚C, yield 70%. IR (υ_{max}/cm^{-1}): 3480 - 3338 (NH_2, OH), 2189 (conjugated CN), 1648 (δ NH2).-$C_{20}H_{13}BrN_2O_2$ (393.23) Calcd. C 61.09 H 3.33 N 7.12; Found C 61.32 H 3.51 N 7.30.

Synthesis of 2,8-Diamino-4,10-di[1',3'-dihydro-2'*H*-indol-2-on)spiro] naphtho [1,2-*b*:5,6-*b*']dipyran-3,9-dicarbonitrile (32) and 3,9-Diamino-1,7-di[1',3'-dihydro-2'*H*-indol-2-on) spiro]naphtho [2,1-*b*:6,5-*b*'] dipyran-2,8-dicabonitrile (33): Genaral procedure:

A suspension of (0.01 mol) of each of 1,5-naphthalenediol **(24)** or 2,6-naphthalenediol **(27)** and 2-(2-oxoindolin-3-ylidene) malononitrile **(2a)** (0.02 mol) in ethanol (50 ml) containing few drops of piperidine was refluxed for one hour. The solids deposited were collected by filtration, recrystallized and identified as **32** and **33** respectively.

2,8-Diamino-4,10-di[1',3'-dihydro-2'*H*-indol-2-on) spiro]naphtho [1,2-*b*:5,6-*b*']dipyran-3,9-dicarbonitrile (32)

Yellow crystals from DMF, m.p. > 300˚C, yield 80%.-IR (υ_{max}/cm^{-1}): 3448, 3368, 3313 (NH_2, NH), 2195 (conjugated CN), 1713 (CO), 1655 (δ NH_2).-^{1}H-NMR (DMSO-d_6) (δ, ppm): 6.73 - 7.94 (m, 16H, 12H, aromatic protons and 4H, $2NH_2$), 10.71 (s, 2H, 2NH). $C_{32}H_{18}N_6O_4$ (550.52) Calcd. C 69.81 H 3.30 N 15.27; Found C 69.76 H 3.41 N 15.30.

3,9-Diamino-1,7-di[1',3'-dihydro-2'*H*-indol-2-on) spiro]naphtho [2, 1-*b*:6,5-*b*']dipyran-2,8-dicabonitrile (33)

Red crystals from ethanol/1,4-dioxane, m.p. 230˚C - 232˚C, yield 85%.-IR (υ_{max}/cm^{-1}): 3405, 3259 (NH_2, NH), 2231 (conjugated CN), 1718 (CO), 1620 (δ NH_2).-$C_{33}H_{20}N_6O_4$ (564.54) Calcd. C 70.21 H 3.57 N 14.89; Found C 70.10 H 3.44 N 14.78.

General method for preparation of 2-amino-4-hydroxy-4-(1',3'-dihydro-2'*H*-indol-2-oxo) spironaptho [1,2-*b*]pyran-3-carbonitrile (36) and 2-amino-6-hdroxy-4-(1',3'-dihydro-2'*H*-indol-2-oxo) spironaphtho [1,2-*b*]pyran-3-carbonitrile (37):

A mixture of each of 1,4-naphthalenediol **(34)** or 1,6-naphthalenediol **(35)** (0.01 mol) in ethanol (50 ml) containing piperidine (0.1 ml) was treated with (0.01 mol) of **2a**. The reaction mixture was refluxed for six hours and then left to cool to room temperature. The precipitates formed were collected by filtration, recrystallized and identified as naphthopyrans **36** and **37** respectively.

2-Amino-4-hydroxy-4-(1',3'-dihydro-2'*H*-indol-2-oxo) spiro naptho[1,2-*b*]pyran-3-carbonitrile (36)

Brown crystals from ethanol/DMF, m.p. > 300˚C, yield 75%.-IR (υ_{max}/cm^{-1}): 3423, 3301, 3200 (NH_2, NH, OH), 2219 (conjugated CN), 1721 (CO), 1646 (δ NH_2).-$C_{21}H_{13}N_3O_3$ (355.34). Calcd. C 70.98 H 3.69 N 11.83; Found C 70.62 H 3.53 N 11.69.

2-Amino-6-hdroxy-4-(1',3'-dihydro-2'*H*-indol-2-oxo) spiro naphtho[1,2-*b*] pyran-3-carbonitrile (37)

Colorless crystals from ethanol/1,4-dioxan, m.p. > 300˚C, yield 65%.-IR (υ_{max}/cm^{-1}): 3482, 3328, 3171 (NH_2, NH, OH), 2199 (Conjugated CN), 1699 (CO), 1653 (δ NH_2).-^{1}H-NMR (DMSO-d_6) (δ, ppm): 6.43 - 6.45 (d, J = 9 Hz, 1H, aromatic proton), 6.96 - 7.28 (m, 7H, aromatic protons), 7.41 (s, 2H, NH_2), 8.13 - 8.14 (d, J = 9 Hz, 1H, aromatic proton), 10.05 (s, 1H, OH), 10.65 (s, 1H, NH). $C_{21}H_{13}N_3O_3$ (355.34) Calcd. C 70.98 H 3.69 N 11.83; Found C 70.88 H 3.76 N 11.75.

6,8-Dibromo-*N*-[4-(2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)-2-thioxothiazol-3-yl]coumarin-3-carboxamide (42)

A solution of (0.01 mol) of thiazole derivative **39** and (0.01 mol) of 3,5-dibromo-2-hydroxybenzaldehde **(40)** in ethanol (50 ml) containing acetic acid (1 ml) was refluxed for one hour, then left to cool. The formed precipitate was collected by filtration, recrystallized from

ethanol to give **42** as colorless crystals, m.p. 194˚C - 196˚C, yield 85%.-IR (υ_{max}/cm^{-1}): 3400, 3061 (NH), 1729 (CO coumarinyl), 1660 (CO antipyrinyl).-$C_{24}H_{16}Br_2N_4S_2O_4$ (648.34) Calcd. C 44.46 H 2.49 N 8.64; Found C 44.69 H 2.53 N 8.55.

2-Cyano-2-(4'-hydroxy-3-methoxybenzylidene)-*N*-[4-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl)-2-thioxothiazol-3-yl] acetamide (43)

A solution of thiazole derivative **39** (0.01 mol) and the appropriate amount of aromatic aldehyde (0.01 mol) in ethanol (50 ml) containing (0.1 ml) of piperidine was refluxed for three hours, then left to cool. The resulting solid obtained on standing was collected by filtration and recrystallized from ethanol to give **43** as colorless crystals, m.p. 258˚C - 260˚C, yield 60%.-IR (υ_{max}/cm^{-1}): 3250 (NH, 2214 conjugated CN), 1634 (CO antipyrinyl).-$C_{25}H_{21}N_5S_2O_4$ (519.59) Calcd. C 57.79 H 4.07 N 13.48; Found C 57.82 H 4.34 N 13.54.

6-Amino-1-[4'-(2,3-dimethyl-1-phenyl-3-prazolin-5-oxo-4-yl)-2'-thioxothiazol-3'-yl]-4-aryl-3,5-dicyano-2-oxo-1*H*-pyridine (45)

Method A:

A solution of thiazole derivative **(39)** (0.01 mol) in ethanol (50 ml) containing (0.1 ml) of triethylamine, was treated with (0.01 mol) of cinnamonitrile **1c**. The reaction mixture was refluxed for three hours, then left to cool. The solid product formed was collected by filtration and recrystalized from ethanol to give colorless crystals of **45** m.p., 290˚C - 292˚C, yield 65%.

Method B:

A suspension of the arylidene derivative **43** (0.01 mol) in ethanol (50 ml) was treated with malononitrile (0.01 mol) and dry pyridine (20 ml). The reaction mixture was refluxed for five hours and the solvent was concentrated in vacuo and the solid formed was recrystallized and identified (m.p. and mixed m.p. as **45**).-IR (υ_{max}/cm^{-1}): 3323, 3198 (NH_2, NH), 2215 (conjugated CN), 1636 (CO antipyrinyl).).-$C_{29}H_{23}N_7S_2O_4$ (597.66) Calcd. C 58.28 H 3.88 N 16.40; Found C 58.11 H 4.00 N 16.32.

Formation of 2-amino-1-[4'-(2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)2'-thioxothiazol-3'-yl]-4 (1',3'-dihydro-2'*H*-indol-2-on) spiro-6-hydroxy-3,5-dicyanopyridine (47)

To a mixture of thiazole derivative **39** (0.01 mol) and 2-(2-oxoindolin-3-ylidene)malononitrile **(2a)** (0.01 mol) in ethanol (50 ml), few drops of piperidine was added. The reaction mixture was refluxed four hours, then cooled and the formed precipitate was collected by filtration and recrystallized from ethanol/DMF to give red crystals of **47**, m.p. 192˚C - 194˚C, yield 70%.-IR (υ_{max}/cm^{-1}): 3250, 3063 (NH), 1723 (CO), 1641 (CO antipyrinyl).-$C_{28}H_{20}N_8S_2O_3$ (580.64) Calcd. C 57.92 H 3.47 N 19.30; Found C 57.81 H 3.55 N 19.11.

Preparation of 6-amino-4-aryl-3,5-dicyano-1-[1'-(2''-thienyl)ethylid-enemino] pyridine-2-(1*H*)-ones (53a,b)

A solution of the hydrazone derivative **49** (0.01 mol) and (0.01 mol) of arylidenemalononitriles **1a**, **b** in ethanol (50 ml) was heated at reflux temperature for half hour. The resulting solids were collected by filtration and recrystallized from suitable solvents to yield compounds **53a**, **b**.

6-Amino-4-(5'-bromo-2'-thienyl)-3,5-dicyano-1-[1'-(2''-thienyl) ethylidenemino] pyridine-2-(1*H*)-one (53a)

Yellow crystals from ethanol/1,4-dioxan, m.p. 216˚C - 218˚C, yield 80%.-IR (υ_{max}/cm^{-1}): 3451. 3362 (NH_2, NH), 2214 (conjugated CN), 1655 (CO), 1619 (δ NH_2).-$C_{17}H_{10}N_7SO_3$ (444.33) Calcd. C 45.95 H 2.27 N 15.76; Found C 45.85 H 2.36 N 15.82.

6-Amino-4-(4'-nitro-2'-pyrryl)-3,5-dicyano-1-[1'-(2''-thienyl) ethylidenemino] pyridine-2-(1*H*)-one (53b)

Colorless crystals from ethanol/DMF, m.p. 248˚C - 250˚C, yield 75%.-IR (υ_{max}/cm^{-1}): 3447, 3320, 3150 (NH_2, NH), 2211 (conjugated CN), 1658 (CO).-^{1}H-NMR (DMSO-d_6) (δ, ppm): 2.43 (s, 3H, CH_3), 7.09 - 8.08 (m, 5H, 3H, aromatic protons and 2H, NH_2), 8.13 (s, 1H, aromatic proton), 8.35 (s, 1H, aromatic proton), 12.92 (s, 1H, NH).-$C_{17}H_{11}N_7SO_3$ (393.38) Calcd. C 51.90 H 2.82 N 24.92; Found C 51.82 H 2.57 N 24.86.

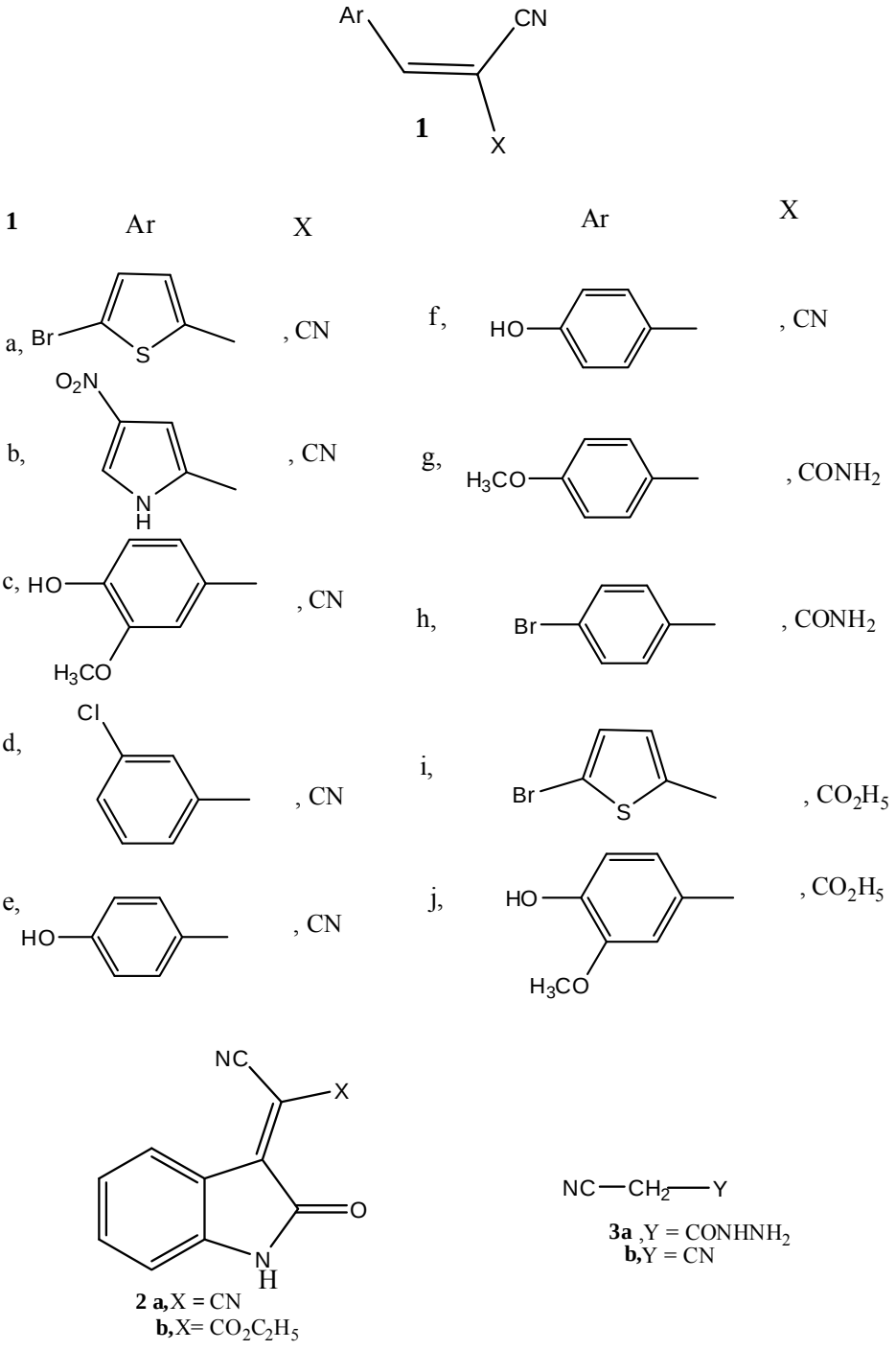
3. Results and Discussion

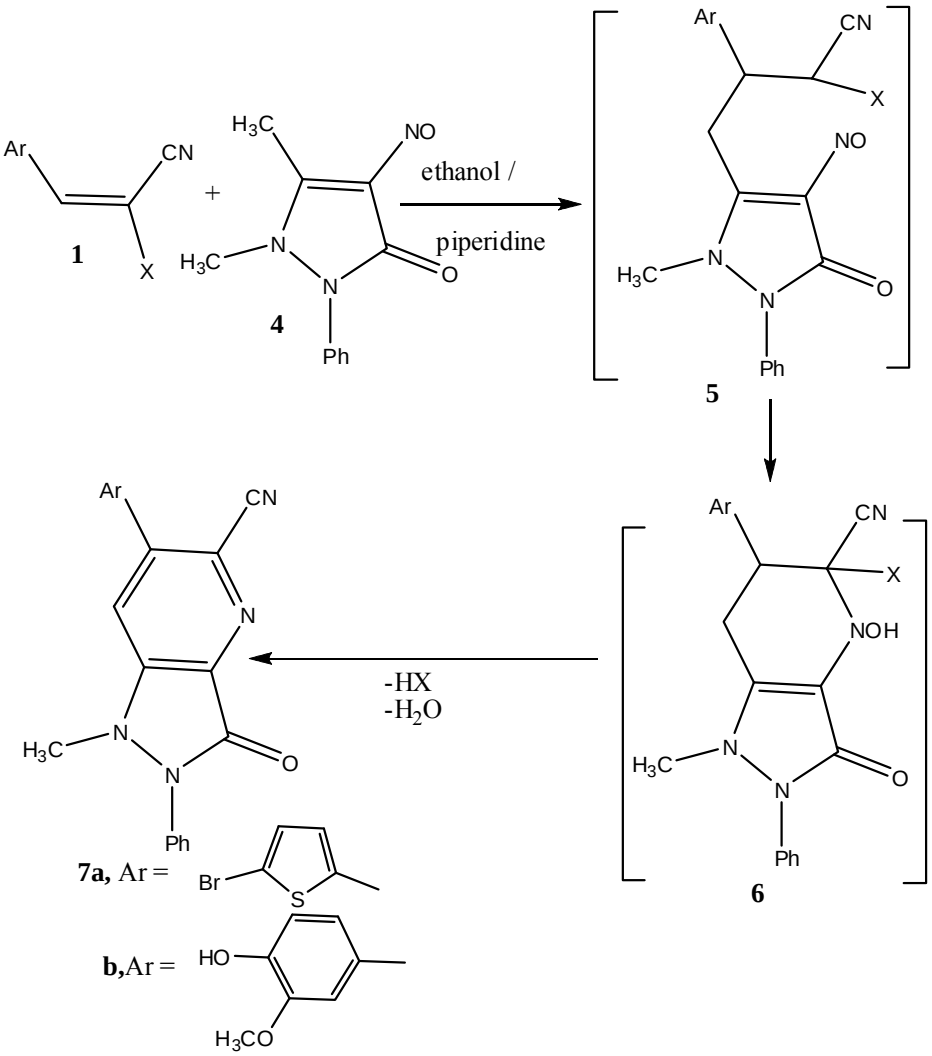
It has been found that, arylidenemalononitriles **1a**, **c** reacted readily with 1,2-dihydro-2,3-dimethyl-4-nitroso-1-phenyl-5-oxopyrazole**(4)**to give 6-aryl-1-methyl-3-oxo-1,2,3-trihydro-2-phenylpyrazolo[4,3-*b*] pyridine-5-carbonitriles (**7a**, **b)** *via* hydrogen cyanide and water elimination. Structures **7a**, **b** were assigned as reaction products based on their elemental and spectral data (*cf*. experimental). The same products were obtained by reacting ethyl arylidenecyanoacetates **1i**, **j** with **4** *via* elimination of one mole of carbon monoxide, ethanol and water. Compounds **7** were assumed to be formed *via* addition of the active methyl group in **4** to the activated double bond in **1** to give the adducts **5** which cyclized to give the intermediates **6**. The later aromatized through elimination of hydrogen cyanide or ethyl formate and water. Similar sequence for the formation of similar systems has been reported before [3,7] (*cf*. **Scheme 1**).

When equimolecular amounts of arylidenemalononitriles **1a**, **b**, **d** and 4-azidomethylcarbonyl-1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one **(8)** reacted in ethanolic/piperidine, products resulting *via* elimination of nitrogen from phenylpyrazol-5-oxo-4-yl)-3-aryl-aziridine-2,2-dicarbonitriles **(10)**, 3-amino-4-(aryl)-6-(2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl)-2-oxo-2H-

pyran-3-carbonitrile **(13)** and 2-amino-4-(aryl)-5-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl) pyrrol-3-carbonitriles **(14)** were thus considered. The aziridine structures **(10)** were ruled out by ^{1}H-NMR spectra of the reaction products which clearly indicates the absence of methylene groups signals at $\delta \approx 4.0$ ppm. The α-pyrone structures **13** were excluded by IR spectra which clearly indicate the absence of $\upsilon \approx 1700$ cm^{-1} α-pyrone carbonyl function. Thus, the pyrrole structures **(14a**, **b)** were given for the reaction products. Compounds **14** were formed via stepwise mechanism demonstrated in **Scheme 2**.

Also, 3-acetyl-4-hydroxy-1-methyl-2-oxo1H-quinoline **(15)** reacted with arylidenes **1g**, **h** in ethanol/pyridine (1:1) to yield 1:1adducts for which two structures 2-amino-4-(aryl)-5,6-dihydro-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*] quinoline-3-carboxamide (**19)** and 4-(aryl)-5,6-dihydro-2-hydroxy-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*]quinolin-3-



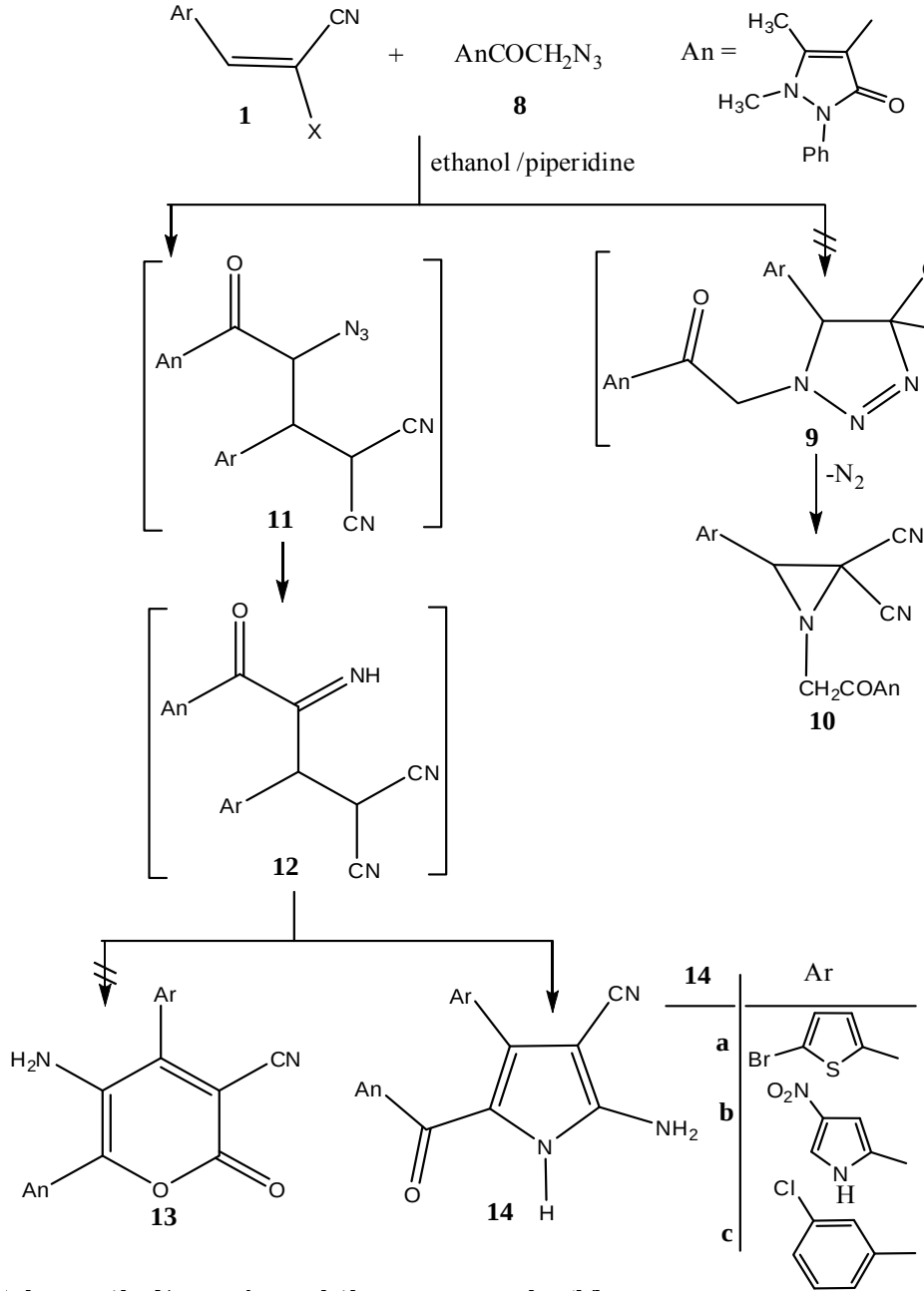


Scheme 1. Formation of pyrazolo[4,3*b*]pyridines 7a, b.

carbonitriles **(20a**, **b)** seemed possible. 4-(Aryl)-5,6-dihydro-2-hydroxy-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*]quinolin-3-carbonitriles **(20a**, **b)** were established for the reaction products based on the elemental analysis and IR spectral data which showed signals at ($\upsilon_{CN} \approx 2200$ - 2206 cm^{-1}). Structure **20** was also supported through the formation from reaction of 4-hydroxy-1-methylquinolin-2(1*H*)one **(18)** with arylidenes **1g**, **h** utilizing the same reaction conditions. 4-(Aryl)-5,6-dihydro-2-hydroxy-6-methyl-5-oxo-4*H*-pyrano[3,2-*c*] quinolin-3-carbonitriles (**20a**, **b)** were proposed to be formed *via* the stepwise mechanism (*cf*. **Scheme 3**).

Similarly, compound **15** reacted with ethyl 2-(2-oxoindolin-3-ylidene)cyanoacetate **(2b)** to yield ethyl 2-amino-5,6-dihydro-5-oxo-6-methyl-4-(1',3'-dihydro-2'*H*-indole-2-on)spiro-4*H*-pyrano[3,2-*c*] quinolin-3-carboxylate (**23)**.Compound **23** was authentically prepared *via* reaction of **2b** with 4-hydroxy-1-methylquinolin-2(1*H*)-one (**18)** using the same reaction conditions (*cf.* **Scheme 3**).

The behavior of several napthalenediols towards arylidenemalononitrles **1** was investigated. Thus, it has been found that, arylidenemalononitriles **1** reacted readily with 1,5-naphthalenediol **(24)** in a molar ratio (2:1) in refluxing ethanol containing piperidine as catalyst to afford 2:1 diadducts. Two possible isomeric structures 4-amino-1,5-diaryl-2,5-dihydro-8-hydroxynaphtho[1,2-*b*] pyrano[2',3'-*b*'] pyridine-3,3-dicarbonitriles **(25)** and 2,8-diamino-4,10-di(4-hydroxyphenyl)-4,10-dihydronaphtho [1,2-*b*:5,6-*b*']dipyran-3,10-dicarbonitriles (**26)**. 2,8-Diamino-4,10-diaryl-4,10-dihydronaphtho[1,2-*b*:5,6-*b*'] dipyran-3,10-dicarbonitriles **(26a**, **b)**. Structures **26a**, **b** were established for the products based on ^{1}H-NMR spectra which revealed the presence of two magnetically equivalent 4H-pyran protons at $\delta \approx 5.0$ ppm. The reaction products **25**, were excluded due to two magnetically non-equivalent protons for 4H-pyran and pyridine H-2. Similarly, arylidenemalononitriles **1** reacted with 2,6-

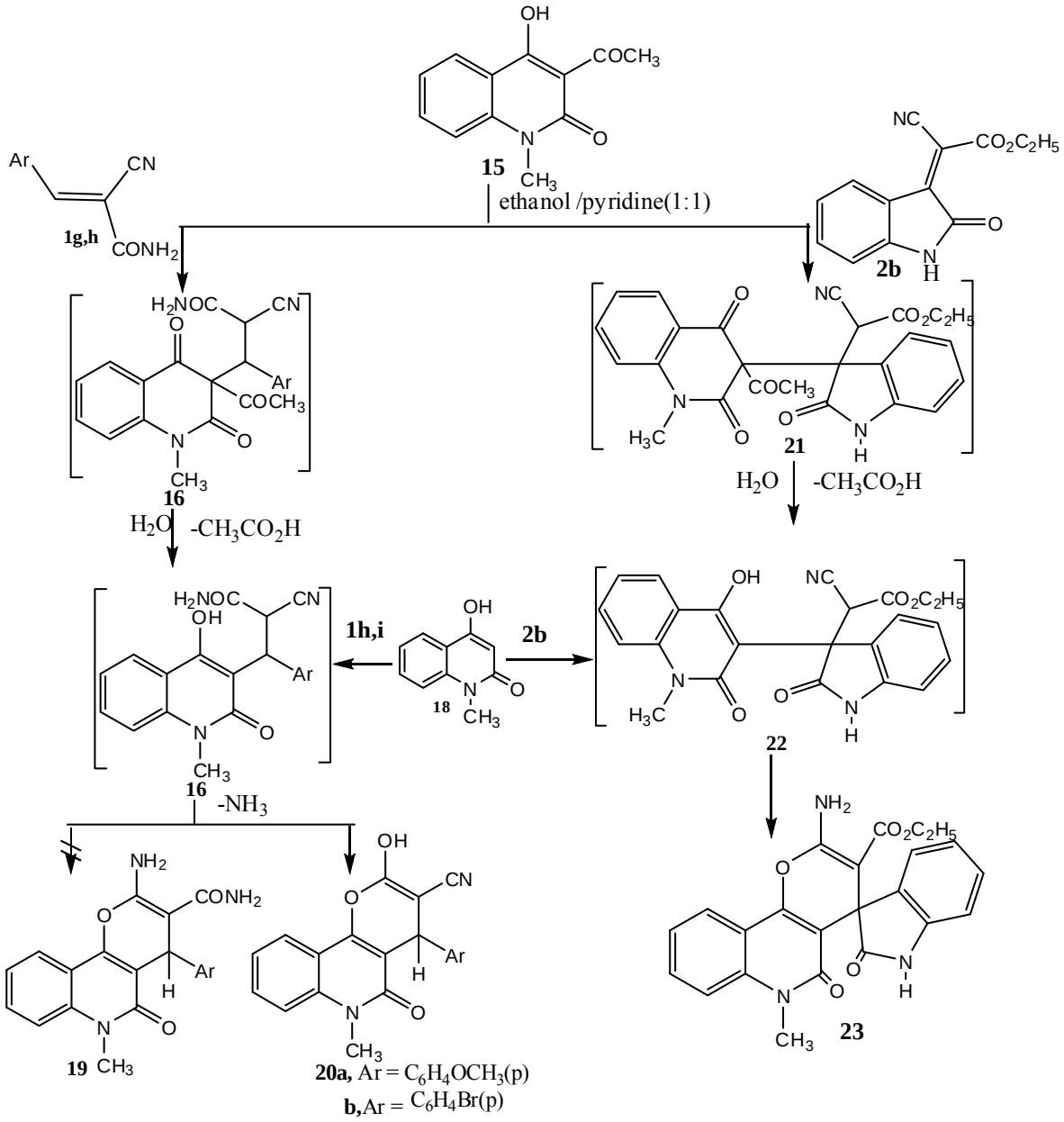


Scheme 2. Formation of 2-aminopyrroles 14a-c.

naphthalenediol **(27)** in ethanol catalyzed with piperidine to afford 2:1diadducts which corresponds to 3,9-diamino-1,7-diaryl-1,7-dihydronaphtho[2,1-*b*:6,5-*b*'] dipyran-3,9-dicarbonitriles **(28)**. Trials to isolate a 1:1 adduct were failed. ^{1}H-NMR spectra of **28** revealed the presence of two magnetically equivalent 4H-pyran protons as one signal at $\delta \approx 5.34$ ppm. It is of value to note that the pyran H-4 in **28** is deshielded by 0.34 ppm in comparison with **26** as a result of van der Waal's effect of the adjacent aromatic protons (*cf*. experimental).

Also, compound **1** reacted with 2,7-naphthalenediol **(29)** in ethanol and in the presence of piperidine as catalyst to afford the adducts corresponds to 3-amino-9-hydroxy-1-(aryl)-1H-benzo[*f*]chromen2-carbonitriles **(31a**, **b)**. Structures **31a**, **b** were preferred over possible naphthodipyrans **(30)** on the basis of elemental and spectral analysis. Also, structure **31** were found to be highly sterically hindered by the two aryl groups at C-1 and C-12. Trials to isolate a 2:1 diadducts 30 were found unsuccessful (*cf*. **Scheme 4**).

Reaction of 2-(2-oxoindolin-3-ylidene)malononitrile **(2a)** with 1,5-naphthalenediol **(24)** and 2,6-naphtha-



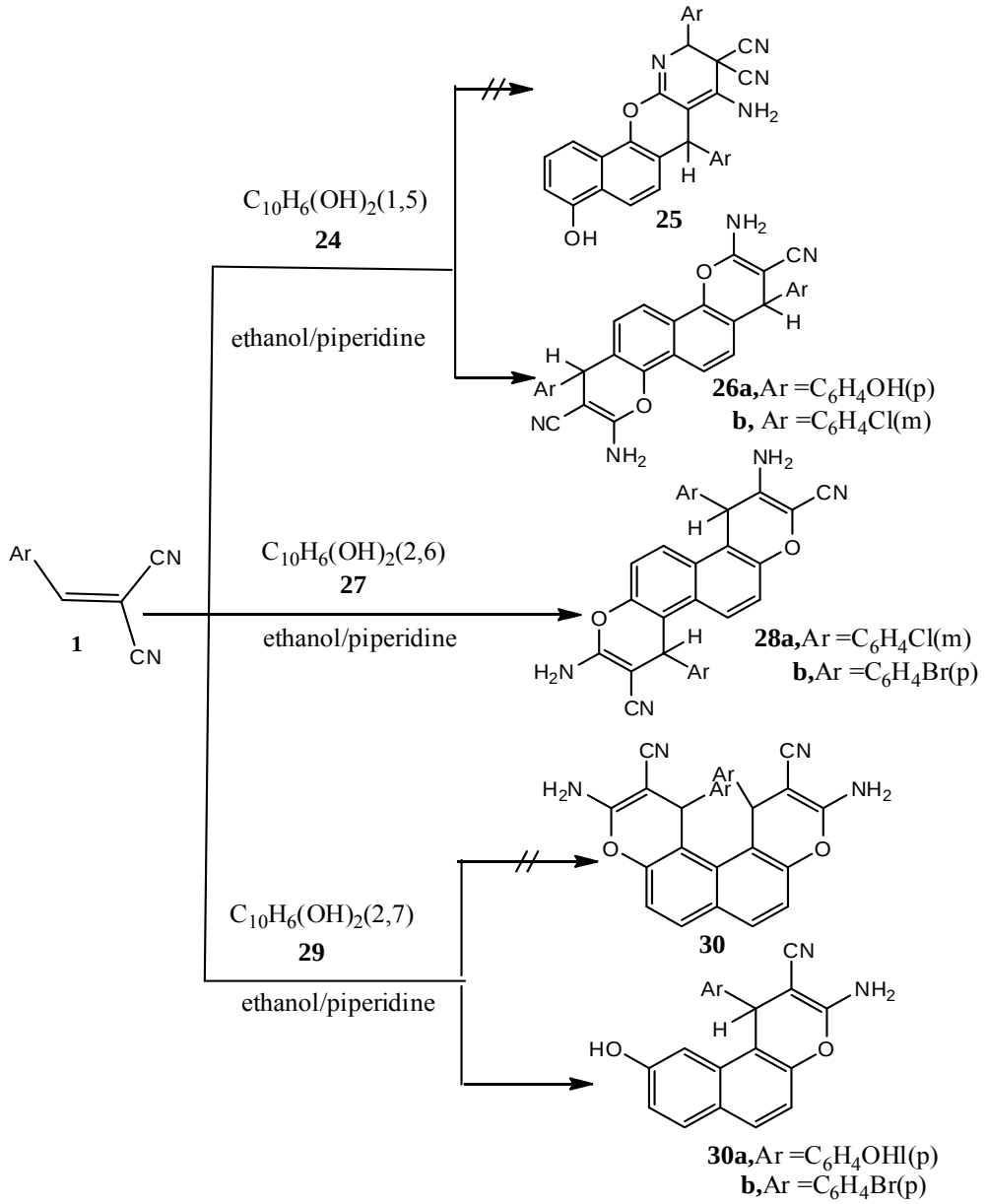
Scheme 3. Formation of pyrano[3,2-c] quinolines 20 and 23.

lenediol **(27)** in ethanol containing few drops of piperidine afforded a 2:1 diadducts. Structures 2,8-diamino-4,10-di[1',3'-dihydro-2'*H*-indol-2-on)spiro]naphtho[1,2-*b*:5,6-*b*']dipyran-3,9-dicarbonitrile **(32)** and 3,9-dia-mino-1,7-di[1',3'-dihydro-2'*H*-indol-2-on)spiro]naphtha [2,1-*b*:6,5-*b*']dipyran-2,8-dicabonitrile **(33)** (*cf*. **Scheme 5**) were assigned for the reaction products based on their elemental and spectral analysis (*cf*. experimental).

On the other hand, reaction of both of 1,4-naphthalenediol **(34)** and 1,6-naphthalenediol **(35)** with 2-(2-oxoindolin-3-ylidene)malononitrile **(2a)** in a molar ratio (1:1) or (1:2) in ethanolic-piperidine, resulted in the formation of naphthopyans 2-amino-4-hydroxy-4-(1',3'-dihydro-2'*H*-indol-2-oxo)spiro naphtho[1,2-*b*]pyran-3-carbonitrile **(36)** and 2-amino-6-hdroxy-4-(1',3'-dihydro-2'*H*-indol-2-oxo)spironaphtho[1,2-*b*]pyran-3-carbonitrile **(37)** respectively (*cf*. **Scheme 5**). Elemental and spectral data are compatible with naphthopyran structures **36 - 38** (*cf*. experimental).

Trials to prepare naphthodipyans *via* reacting **2a** with 1,4-naphthalenediol **(34)** and 1,6-naphthalenediol **(35)** were found failure. This many be attributed to the molecular overcrowding arising from the difficult formation of two pyran moities located at 3,4-,5,6 and 9, 10-in positions the naphthalene ring (*cf*. **Scheme 5**).

The utility of 2-cyanoethanoic acid hydrazide **(3a)** as

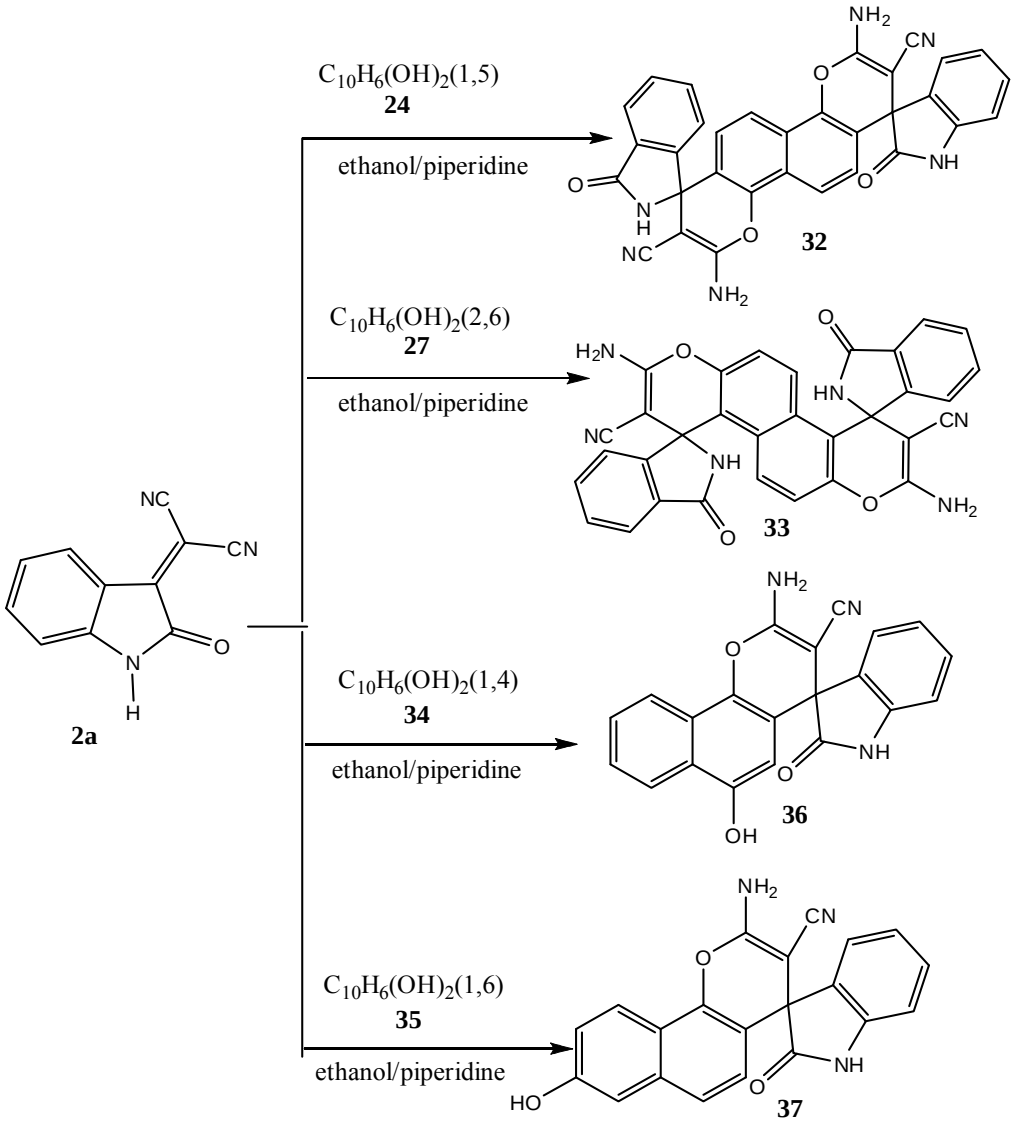


Scheme 4. Reaction of arylidenes 1 with dihydroxynaphthalenes.

starting material for synthesis of heterocyclic compounds was investigated. Thus, 2-ethanoic acid hydrazide **(3a)** when treated with carbon disulphide in dimethylformamide under basic conditions in potassium hydroxide/ dimethylformamide, followed by reaction with 4-chloroacetyl-1-phenyl-2,3-dimethyl-3-pyrazolin-5-one **(38)** afforded 2-cyano-*N*-4-(2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl)-2-thioxothiazol-3-yl)]acetamide **(39)** [9].

We have studied the chemical reactivity of **39** towards different reagents. For example, compound **39** condensed with 3,5-dibromo-2-hydroxybenzaldehyde **(40)** in ethanol containing catalytic amount of acetic acid to afford 6,8-dibromo-*N*-4-[(2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)-2-thioxothiazol-3-yl]coumarin-3-carboxamide **(42)**. Formation of **42** was assumed to proceed *via* the formation of the intermediate arylidene derivative **41**, followed cyclization *via* addition of the hydroxyl group to the cyano group and ammonia elimination.

Refluxing 2-cyano-*N*-4-(2,3-dimethyl-1-phenyl-3-pyrazolin-5-on-4-yl)-2-thioxothiazol-3-yl)]acetamide **(39)** with the arylidenemalononitriles **1** in ethanol containing catalytic amount of triethylamine resulted in the formation of 6-amino-1-[4'-(2,3-dimethyl-1-phenyl-3-prazolin-5-oxo-4-yl)-2'-thioxo-thiazol-3'-yl]-4-aryl-3,5-dicyano-2-oxopyridines **(44)** or the 4H-pyrans **45**. Struc-

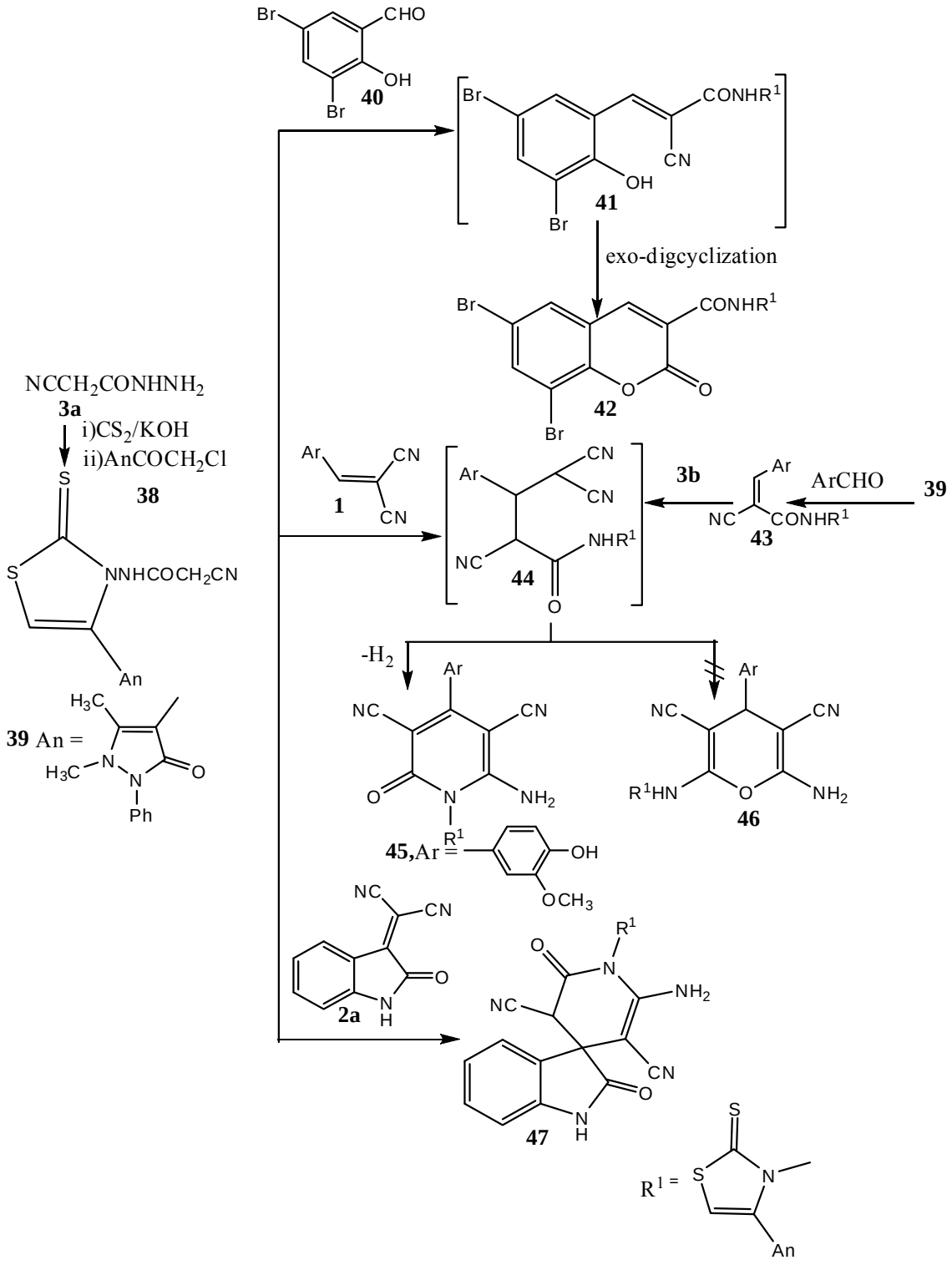


Scheme 5. Reaction of arylidenes 2a with dihydroxynaphthalenes.

tures **44** were proposed as reaction products based on their elemental and spectral analysis. If the reaction products are **45**, ^{1}H-NMR spectra would show signal at ≈ 4.5 - 5.00 ppm for pyran H-4. Moreover, compounds **44** were also prepared *via* the reaction of the 2-cyano-2-(4'-hydroxy-3-methoxybenzlidene)-*N*-[4-(1,2-dihydro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)-2-thioxothiazol-3-yl]acetoamide (**46)** with malononitrile **3b** in ethanolic-pyridine. Formation of **44** were suggested to take place *via* Michael type addition of the active methylene group in **39** to the π-deficient centre in **1** to give Michael adduct intermediate **43**, which cyclized and readily eliminate of one molecule of hydrogen to yield 6-amino-1-[4'-(2,3-dimethyl-1-phenyl-3-prazolin-5-oxo-4-yl)-2'-thioxothiazol-3'-yl]-4-aryl-3,5-dicyano-2-pyridone.

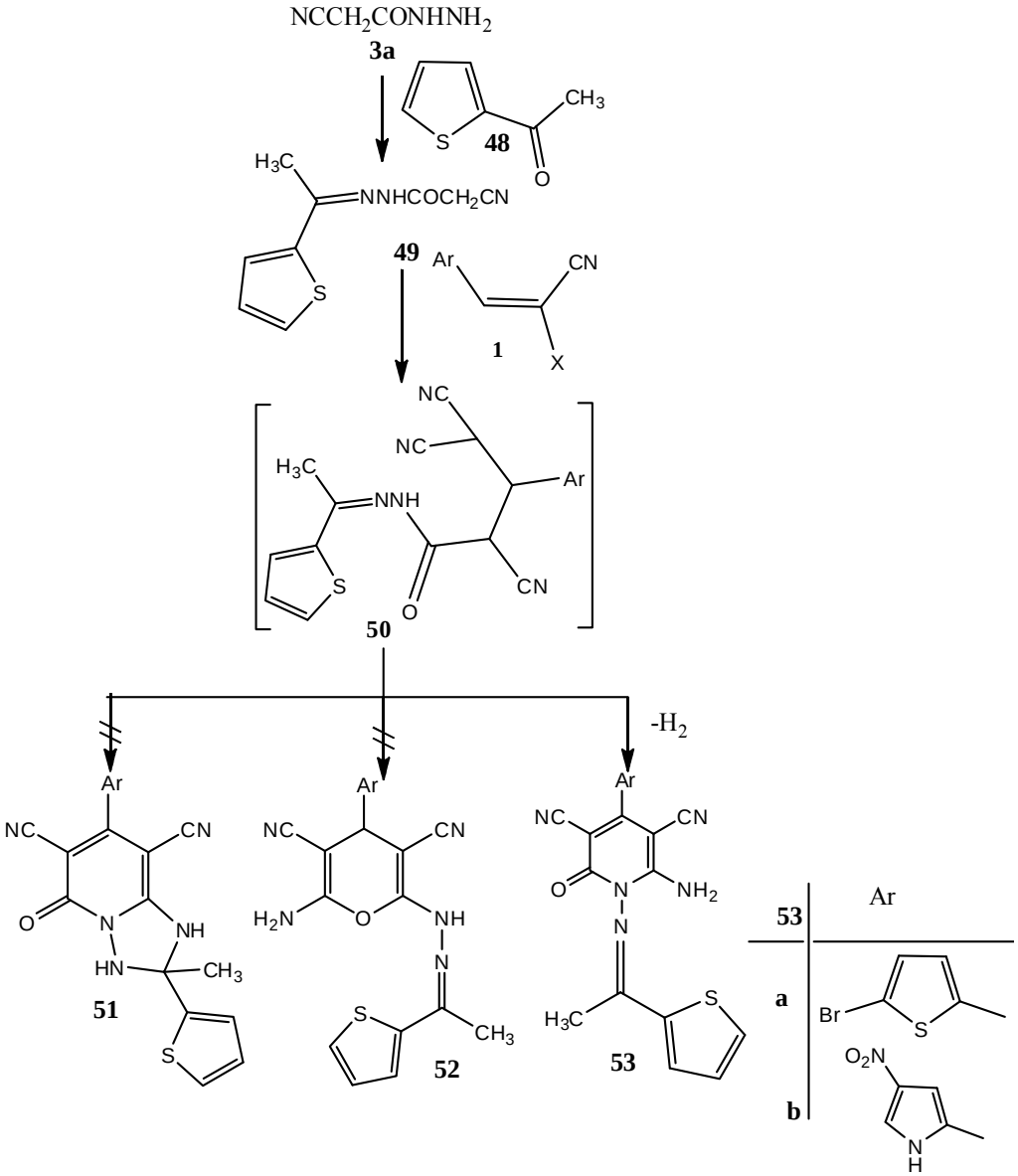
Similarly, compound **39** reacted with **2a** to yield 2-amino-1-[(4'-(2,3-dimethyl-1-phenyl-3-pyrazolin-5-oxo-4-yl)-2'-thioxothiazo-l,3'-yl]-4-(1',3'-dihydro-2'-*H*-indol-2-on)spiro-6-hydroxy-3,5-dicyanopyridine **(47)** (*cf.* **Scheme 6**).

Finally, 2-cyano-*N*'-(1-thiophen-2-yl)ethylidene)acetohydrazide **(49)** [10] prepared by condensing 2-cyanoethanoic acid hydrazide **(3a)** with 2-acetylthiophene **(48)**, reacted with the arylidenemalonnitriles **1** in ethanol catalyzed by piperidine to give 7-(aryl)-1,2,3,5-tetrahydro-2-methyl-5-oxo-2-(thiophen-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitriles **(51)**, 2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)-6-amino-4-(aryl)-4*H*-pyran-3,5-dicarbonitrile **(52)** or 6-amino-4-aryl-3,5-dicyano-1-[1'-(2''-thienyl)ethylid-enemino]pyridine-2-(1*H*)-ones **(53)**. Structures **51** excluded by ^{1}H-NMR spectrum which clearly indicate the absence of two singlets due to two



Scheme 6. Formation of coumarin 42 and pyridines 45, 47.

NH groups. Also, ^{1}H-NMR spectrum of the products clearly showed the absence of 4H-pyran proton at $\delta \approx 4.5$ - 5.0 ppm for structure **52**. Consequently, the pyridine structures **53** were elucidated as reaction products. Compounds **53** were suggested to be obtained *via* the addition of the active methylene group in **49** to the π-deficient carbon in **1** to give the adducts **50** which cyclized and dehydrogenated to give 6-amino-4-aryl-3,5-



Scheme 7. Formation of pyridines 53.

dicyano-1-[1'-(2"-thienyl) ethylidenemino]-2-oxo-1H-pyridines **(53)** (*cf.* **Scheme 7**).

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