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RESEARCH ARTICLE

SYNTHESIS AND REACTIONS OF SOME 4H-PYRANS USING NEW NATURAL CATALYST

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ABSTRACT

In ethanolic medium and in the presence of the basalt and gabbro as new naturally reusable heterogeneous catalysts, an easy and efficient one-pot multicomponent protocol, 6-amino-5-cyano-4*H*-pyrans 1 were synthesized. Also, we report here that compounds 1 are useful and easily available as starting materials for the preparation of functionalized azines in a series of ring transformation in which the amino group furnishes the required nitrogen rings. Structures of the all isolated products 1 - 22 were established based on their elemental and spectroscopic analysis.

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INTRODUCTION

Polyfunctionalized 4*H*-pyran, a major constituent of many natural products (Hatakeyama *et al*., 1988; Singh *et al*., 1996 and Martin *et al*., 1993), is known for its wide array of biological activities such as antitumor, antibacterial, antiviral, spasmolytic, and antianaphylactic (Kumar *et al*., 2009; Martinez-Grau and Marco, 1997; Wang *et al*., 2000 and Bonsignore *et al*., 1993). Recent findings have suggested that the compounds having 4*H*-pyran are useful for the treatment of Alzheimer, Schizophrenia, and Myoclonus diseases (Konkoy *et al*., 1993). Development of efficient and practical catalyst for organic transformation to synthesize valuable target compounds is one of the most important research areas in academia and industry (Cornils *et al*., 2007 and Sheldon *et al*., 2007). Heterogeneous catalysts are getting increasing importance in organic syntheses due to their easy removal from reactions. Of late, the emergence of combinatorial synthesis in recent years, primarily synthesis by multicomponent reaction has brought about a paradigm shift in synthetic reaction designs which are made to address the issues of atom economy, economy of steps, and environmental safety. Therefore, the discovery of new naturally heterogeneous catalysts and novel synthetic methodologies to facilitate the preparation of compound libraries using multicomponent reactions is the focal point in industry and academia (Thompson, 2000 and Nefzi *et al*., 1997).

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Zhang *et al.* (2012) have reported a novel $MgO–SnO_2$ solid superbase as a high efficiency catalyst for one-pot solvent-free synthesis of polyfunctionalized 4*H*-pyran derivatives, but application of this system is limited by the requirement of catalyst synthesis before use. Recently various catalysts such as reusable silica nanoparticles (Banerjee, 2011), pot.phthalimide (Kiyani, 2014), alum (Mohammadi, 2013), amm.acetate (Moshtaghi Zonouz *et al*., 2012), ammonia (Moshtaghi *et al*., 2014 and Nazeruddin *et al*., 2014) baker yeast (Pratap *et al*., 2011) and Sod. Pot. Tartarate (El-Maghraby, 2014) have been used for synthesis of 4H-pyran derivatives. Also, M. Bihani *et al.* (2013) reported that, one-pot three-component coupling of aldehyde and malononitrile with active methylene compounds such as acetylacetone and ethyl acetoacetate for the synthesis of polyfunctionalized 4*H*-pyrans has been catalyzed by using of Amberlyst A21. As it was found that the composition of Basalt and Gabbro have a high content of basic oxides such as magnesium oxide, zinc oxide and calcium oxide (Le Bas *et al*., 1986; Bloomer *et al*., 1991; Coogan *et al*., 2001 and Hébert *et al*., 1991). So we have used them as new naturally heterogeneous basic catalysts in one-pot multicomponent protocol for the synthesis of some polyfunctionalized 4*H*- pyrans.

MATERIAL AND METHOD

All melting points are uncorrected and measured with a Gallenkamp apparatus. The IR spectra were recorded of samples in KBr on a Shimadzu FT-IR 8101 PC infrared spectrophotometer. ^{1}H NMR spectra were run at 300 MHz and

recorded in $CDCl_3$/[D6]DMSO using TMS as the internal standard. Chemical shifts were related to that of the solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. TLC was conducted on 0.25- mm pre-coated silica gel plates (60F-254). Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. EDXRF analyses were carried out at the Central Laboratory of South Valley University, Qena, Egypt on a JEOL JSX 3222 element analyzer with energy dispersive X-ray flourescens system (Jeol, Japan). The catalyst was ground until it became fine powder.

General procedure for the synthesis of Ethyl 6-amino-5-cyano-4H-pyran-3-carboxylate derivatives (1a-p)

A mixture of aldehyde (1 mmol), 1, 3-dicarbonyl compound (1 mmol), malononitrile (1 mmol) and basalt or gabbro as base catalyst (1 gram) in ethanol (15 mL) heated under reflux for required time. After completion of the reaction as monitored by T.L.C. the reaction mixture was filtered to separate the catalyst. Solid product precipitated on cooling. The solid product was filtered under suction, then recrystallized from ethanol to afford pure product.

Ethyl 6-Amino-4-(3-benzyloxy-phenyl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1a)

m.p. = 118-120°C. I.R. (KBr): ν̃= 3400, 3250 (NH_2), 3000(C-H aliphatic), 2200(CN), 1700(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 1.11 (t, 3H, -O-CH_2-CH_3), 2.36 (s, 3H, -CH_3), 4.03 (q, 2H, -O-CH_2-CH_3), 4.42 (s, 1H, 4-CH-), 4.50 (s, 2H, -NH_2), 5.04 (s, 2H, -O-CH_2-Ph), 6.82-6.85 (m, 3H, aromatic protons), 7.19-7.46 (m, 6H, aromatic protons) ppm. Mass: m/z (%): 390 [M^+, 10.30]; 299 [15.20]; 207 [21.38]; 91 [100.0]; 65[8.43]. $C_{23}H_{22}N_2O_4$ (390): Calculated, %: C 70.75, H 5.68, N 7.17; Found, %: C 71.08 , H 5.23 , N 7.82.

Ethyl 6-Amino-4-(3-benzyloxy-phenyl)-5-cyano-2-phenyl-4*H*-pyran-3-carboxylate (1b)

m.p. = 146-148°C. I.R. (KBr): ν̃= 3400, 3250 (NH_2), 2920(CH-aliphatic), 2200(CN), 1700(C=O) cm^{-1}. ^1H NMR (DMSO): δ= 0.72 (t, 3H, -O-CH_2-CH_3), 2.49 (s, 2H, -NH_2), 3.35 (s, 1H, 4-CH-), 3.75 (q, 2H, -O-CH_2-CH_3), 5.06 (s, 2H, -OCH_2-Ph), 6.83-7.47 (m, 14H, aromatic protons) ppm. Mass: m/z (%): 452.5 [M^+, 0.50]; 275 [22.72]; 361.30 [1.76]; 269.20 [2.48]; 241.15 [1.10]; 91.10 [100.0]. $C_{28}H_{24}N_2O_4$ (452.5): Calculated, %: C 74.32, H 5.35, N 6.19; Found, %: C 74.77 , H 6.03 , N 5.96.

Ethyl 6-Amino-4-(2, 5-dimethoxybenzene)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1c)

m.p. = 140-142°C. I.R. (KBr): ν̃= 3450, 3350(NH_2), 2950(C-H aliphatic), 2200(CN), 1680(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 1.07 (t,3H, -O-CH_2-CH_3), 2.36 (s, 3H, -CH_3), 3.73 (s, 3H, -OCH_3), 3.79 (s, 3H, -OCH_3), 4.00 (q, 2H, -O-CH_2-CH_3), 4.45 (s, 2H, -NH_2), 4.84 (s, 1H, 4-CH-), 6.62-6.81 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 344 [M^+, 93.58]; 313 [75.68]; 267 [100.0]; 77[71.52]; 67[74.95]. $C_{18}H_{20}N_2O_5$ (344): Calculated, %: C 62.78, H 5.85, N 8.13; Found, %: C 62.49 , H 5.99 , N 7.82.

Ethyl 6-Amino-4-(3-dimethoxybenzene)-5-cyano-2-phenylyl-4*H*-pyran-3-carboxylate (1d)

m.p. = 154-156°C. I.R. (KBr): ν̃= 3423, 3330(NH_2), 2986(CH-aliphatic), 2189(CN), 1707(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 0.82 (t, 3H, -O-CH_2-CH_3), 3.75 (s, 3H, -OCH_3), 3.78 (s, 3H, -OCH_3), 3.84 (q, 2H, -O-CH_2-CH_3), 4.50 (s,2H, -NH_2), 4.95 (s, 1H, 4-CH-), 6.73-6.84 (m, 3H, aromatic protons), 7.26-7.44 (m, 5H, aromatic protons) ppm. Mass: m/z (%): 406.40[M^+, 19.21]; 329 [53.34]; 105.15 [100.0]; 77.10 [69.34]. $C_{23}H_{22}N_2O_5$ (406.43): Calculated, %: C 67.97, H 5.46, N 6.89; Found, %: C 66.54 , H 5.82 , N 7.03.

Ethyl 6-Amino-4-(2, 3-dimethoxybenzene)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1e)

m.p. = 146-150°C. I.R. (KBr): ν̃= 3350, 3200(NH_2), 2920(C-H aliphatic), 2200(CN), 1710(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 1.08 (t, 3H, -O-CH_2-CH_3), 2.35 (s, 3H, -CH_3), 3.84 (s, 3H, -OCH_3), 3.88 (s, 3H, -OCH_3), 4.01 (q, 2H, -O-CH_2-CH_3), 4.51 (s, 2H, -NH_2), 4.76 (s, 1H, 4-CH-), 6.69-6.99 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 344 [M^+, 36.82]; 313 [78.14]; 298 [28.54]; 267 [100.0]; 255 [63.52]; 225 [52.59]. $C_{18}H_{20}N_2O_5$ (344): Calculated, %: C 62.78, H 5.85, N 8.13; Found, %: C 62.89 , H 6.14 , N 7.88.

Ethyl 6-Amino-4-(2, 3-dimethoxybenzene)-5-cyano-2-phenyl-4H-pyran-3-carboxylate (1f)

m.p. = 148-150°C. I.R. (KBr): ν̃= 3448, 3349(NH_2), 2938(CH-aliphatic), 2196(CN), 1712(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 0.80 (t, 3H, -O-CH_2-CH_3), 3.82 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3), 3.85 (q, 2H, -O-CH_2-CH_3), 4.52 (s, 2H, -NH_2), 4.93 (s, 1H, 4-CH-), 6.81-7.44 (m, 8H, aromatic protons) ppm. Mass: m/z (%): 406.40 [M^+, 29.11]; 375.35 [61.45]; 329 [100.0]; 105 [96.99]. $C_{23}H_{22}N_2O_5$ (406.43): Calculated, %: C 67.97, H 5.46, N 6.89, O 19.68; Found, %: C 67.53 , H 5.92 , N 6.22 , O 20.33.

Ethyl 6-Amino-4-(3, 4, 5-trimethoxybenzene)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1g)

m.p. = 170-172°C. I.R. (KBr): ν̃= 3500, 3370(NH_2), 2950(C-H aliphatic), 2220(CN), 1705(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 1.13 (t, 3H, -O-CH_2-CH_3), 2.37 (s, 3H, -CH_3), 3.81 (s, 3H, -OCH_3), 3.84 (s, 6H, 2(-OCH_3)), 4.08 (q, 2H, -O-CH_2-CH_3), 4.41 (s, 1H, 4-CH-), 4.51 (s, 2H, -NH_2), 6.40 (s, 2H, aromatic protons) ppm. Mass: m/z (%): 374.20 [M^+, 93.95]; 285 [28.95]; 244 [19.99]; 207 [100.0]; 179 [31.12]. $C_{19}H_{22}N_2O_6$ (374): Calculated, %: C 60.95, H 5.92, N 7.48; Found, %: C 61.05 , H 5.63 , N 7.28.

Ethyl 6-Amino-4-(3, 4, 5-trimethoxybenzene)-5-cyano-2-phenyl-4*H*-pyran-3-carboxylate (1h)

m.p. = 186-187°C. I.R. (KBr): ν̃= 3418, 3329(NH_2), 2936(CH-aliphatic), 2195(CN), 1709(C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 0.83 (t, 3H, -O-CH_2-CH_3), 3.82 (s, 3H, -OCH_3), 3.83 (s, 6H, 2(-OCH_3)), 3.87 (q, 2H, -O-CH_2-CH_3), 4.56 (s, 1H, 4-CH-), 4.66 (s, 2H, -NH_2), 7.27-7.45 (m, 7H, aromatic protons) ppm. Mass:

m/z (%): 436.40 [M^+, 58.61]; 346.30 [70.90]; 105.10 [100.0]; 77.10 [51.82]. $C_{24}H_{24}N_2O_6$ (436.46): Calculated, %: C 66.04, H 5.54, N 6.42; Found, %: C 66.75 , H 5.39 , N 20.5

Ethyl 6-Amino-4-(2, 6-dichlorobenzene)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1i)

m.p. = 188-190^{o}C. I.R. (KBr): ν̃= 3500, 3300(NH_2), 3000(C-H aliphatic), 2220(CN), 1720(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 1.05 (t, 3H, -O-CH_2-CH_3), 2.34 (s, 3H, -CH_3), 4.02 (q, 2H, -O-CH_2-CH_3), 4.56 (s, 2H, -NH_2), 5.54 (s, 1H, 4-CH-), 7.16-7.27 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 353 [M^+, 7.48]; 352 [32.75], 323 [48.00]; 207 [100.0]; 179 [30.01]. $C_{16}H_{14}Cl_2N_2O_3$ (353): Calculated, %: C 54.41, H 4.00, Cl 20.08, N 7.93; Found, %: C 55.02 , H 3.74 , Cl 19.96 , N 7.63.

Ethyl 6-Amino-4-(2, 6-dichlorobenzene)-5-cyano-2-phenyl-4*H*-pyran-3-carboxylate (1j)

m.p.= 181-183^{o}C. I.R. (KBr): ν̃= 3458, 3287(NH_2), 2972(CH-aliphatic), 2195(CN), 1711(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 0.81 (t, 3H, -O-CH_2-CH_3), 3.83 (q, 2H, -O-CH_2-CH_3), 4.63 (s, 2H, -NH_2), 5.71 (s, 1H, 4-CH-), 7.71-7.46 (m, 8H, aromatic protons) ppm. Mass: m/z (%): 415.30 [M^+, 8.57]; 385.25 [41.23]; 269.20 [83.66]; 105.10 [100.0]. $C_{21}H_{16}Cl_2N_2O_3$ (415): Calculated, %: C 60.74, H 3.88, Cl 17.07, N 6.75; Found%: C 61.01 , H 3.39 , Cl 16.91, N 6.84.

Ethyl 6-Amino-4-(morpholine)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1k)

m.p.= 158-160^{o}C. I.R. (KBr): ν̃= 3350, 3250(NH_2), 3000(C-H aliphatic), 2250(CN), 1725(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 1.29 (t, 8H, -CH_2-), 1.57 (t, 3H, -O-CH_2-CH_3), 2.62 (s, 3H, -CH_3), 4.19 (q, 2H, -O-CH_2-CH_3), 5.78 (s, 2H, -NH_2), 6.06 (s, 1H, 4-CH-) ppm. Mass: m/z (%): 293 [M^+, 2.79]; 269 [90.91]; 236 [88.68]; 209 [100.0]; 195[99.45]. $C_{14}H_{19}N_3O_4$ (293): Calculated, %: C 57.33, H 6.53, N 14.33; Found, %: C 57.94 , H 7.03 , N 14.25.

Ethyl 6-Amino-5-cyano-2, 4-dimethyl-4*H*-pyran-3-carboxylate (1l)

m.p. = 170-172^{o}C. I.R. (KBr): ν̃= 3450, 3350(NH_2), 2970(C-H aliphatic), 2200(CN), 1680(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 1.21 (d, 3H, 4-CH_3), 1.30 (t, 3H, -O-CH_2-CH_3), 2.25 (s, 3H, 6-CH_3), 3.38 (q, 1H, 4-CH-), 4.25 (q, 2H, -O-CH_2-CH_3), 4.48 (s, 2H, -NH_2) ppm. Mass: m/z (%): 222 [M^+, 22.11]; 207 [100.0]; 179 [67.97]; 161 [40.15]. $C_{11}H_{14}N_2O_3$ (222): Calculated, %: C 59.45, H 6.35, N 12.60; Found, %: C 59.95 , H 5.87 , N 12.74.

Ethyl 6-Amino-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1m)

m.p.= 156-158^{o}C. I.R. (KBr): ν̃= 3350, 3250(NH_2), 3000(C-H aliphatic), 2230(CN), 1725(C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 1.32 (t, 3H, -O-CH_2-CH_3), 2.25 (s, 3H, -CH_3), 3.41 (s, 2H, 4-CH_2-), 4.24 (q, 2H, -O-CH_2-CH_3), 4.48 (s, 2H, -NH_2) ppm. Mass: m/z (%): 208 [M^+, 44.99]; 195 [75.39]; 170 [73.58]; 149 [100.0]; 88 [35.52]. $C_{10}H_{12}N_2O_3$ (208): Calculated %: C 57.68, H 5.81, N 13.45; Found, %: C 58.04 , H 5.33 , N 14.07.

Ethyl 6-Amino-4-(4-chlorobenzene)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1n)

m.p. (Found) = 169- 171 ^{o}C; m.p. (Reported) = 171-172 ^{o}C (Nazeruddin *et al*., 2014).

Ethyl 6-Amino-4-(4-methoxybenzene)-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1o)

m.p. (Found) = 140-142 ^{o}C; m.p. (Reported) = 142-144 ^{o}C (Nazeruddin *et al*., 2014).

Ethyl 6-Amino-4-phenyl-5-cyano-2-methyl-4*H*-pyran-3-carboxylate (1p)

m.p. (Found) = 182-184 ^{o}C; m.p. (Reported) = 178-179 ^{o}C (Nazeruddin *et al*., 2014)

General procedure for synthesis of Ethyl-7-amino-4-aryl-8-cyano-5, 6-dihydro-2-methyl-5-oxo-[1, 6] naphthyridine-3-carboxylate derivatives (5a, b):

Method (A)

Equimolar amounts of pyran 1 and malononitrile (1 mmol) in ethanol (10 mL) were treated with two drops of piperidine. The reaction mixture was refluxed for 3h. The solid product, formed after cooling, then was collected by filtration and recrystallized from ethanol to afford 5.

Method (B)

Mixture of malononitrile (2mmol), ethylacetoacetate (1 mmol), aldehydes(1mmol) and basalt or gabbro as base catalyst (1 gram) in ethanol (15 mL) heated under reflux for required time. After completion of the reaction as monitored by T.L.C. the reaction mixture was filtered to separate the catalyst. Solid product precipitated on cooling. The solid product was filtered under suction, then recrystallized from ethanol to afford pure product **5**.

Ethyl 7-amino-4-(3-(benzyloxy) phenyl-8-cyano-5,6-dihydro-2-methyl-5-oxo-[1,6]naphthyridine-3-carboxylate (5a)

Yield (88%). m.p. = 163-165°C. I.R. (KBr): ν̃= 3392, 3317 (NH_2), 3159 (NH), 2853(C-H aliphatic), 2191(CN), 1695(ester CO), 1649 (ring CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 1.16 (t, 3H, -O-CH_2-CH_3), 2.33 (s, 3H, -CH_3), 4.08 (q, 2H, -O-CH_2-CH_3), 5.03 (s, 2H, -O-CH_2-Ph), 5.92 (s, 2H, -NH_2), 6.85-6.94 (m, 4H, aromatic protons), 7.19-7.44 (m, 5H, aromatic protons), 8.31 (s, 1H, -NH-) ppm. Mass: m/z (%): 454.30 [M^+, 33.55]; 431.30 [35.14]; 299.20 [56.55]; 64.05 [100.0]; 50.05[1.60]. $C_{26}H_{22}N_4O_4$ (454.5): Calculated, %: C 68.71, H 4.88, N 12.33; Found, %: C 67.85 , H 5.06 , N 12.81.

Ethyl 7-amino-8-cyano-5, 6-dihydro-4-(2,3-dimethoxyphenyl)-2-methyl-5-oxo-[1, 6]naphthyridine-3-carboxylate (5b)

Yield (63%). m.p. = 212-214°C. I.R. (KBr): ν̃= 3390, 3326 (NH_2), 3195 (NH), 2948 (C-H aliphatic), 2229(CN), 1708(ester CO), 1656 (ring CO) cm^{-1}. ^{1}H NMR (DMSO): δ= 1.11 (t, 3H, -

O-CH_2-CH_3), 2.41 (s, 3H, -CH_3), 3.87 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 4.04 (q, 2H, -O-CH_2-CH_3), 5.72 (s, 2H, -NH_2), 6.73 (d, 1H, aromatic proton), 6.87 (d, 1H, aromatic proton), 6.98 (t, 1H, aromatic proton), 8.15 (s, 1H, -NH-) ppm. Mass: m/z (%): 410.40 [M^+, 71.95]; 358.30 [73.78]; 336.30 [100.0]; 284.30 [77.44]; 225.20[87.20]. $C_{21}H_{20}N_4O_5$ (408): Calculated, %: C 61.76 , H 4.94 , N 13.72; Found, %: C 61.87 , H 5.06 , N 14.17.

General procedure for the synthesis of 6-amino-4-aryl-1, 4-dihydro-3-methylpyrano [2, 3-c] pyrazole-5-carbonitrile derivatives (8a,d)

A mixture of pyran 1 (1 mmol), hydrazine hydrate (1 mmol) and piperidine as a base catalyst (two drops) in ethanol (15 mL) heated under reflux on water bath for required time until completion of reaction. The solid product was filtered under suction, then recrystallized to afford pure product.

6-Amino-4-(3-benzyloxy) phenyl)-1, 4-dihydro-3-methylpyrano [2, 3-*c*] pyrazole-5-carbonitrile (8a)

The solid product precipitated on hot and recrystallized from ethanol/glacial acetic acid (2:1). m.p. = 236-238°C. I.R. (KBr): ν̃= 3420, 3380 (NH_2), 3200 (NH), 2995 (C-H aliphatic), 2195(CN) cm^{-1}. ^{1}H NMR (DMSO): δ= 1.77 (s, 3H, -CH_3), 2.49 (s, 2H, -OCH_2-Ph), 4.55 (s, 1H, 4-CH-), 5.06 (s, 2H, -NH_2), 6.74-7.43 (m, 9H, aromatic protons), 12.01 (s, 1H, -NH-) ppm. Mass: m/z (%): 358.20 [M^+, 25.52]; 292.15 [6.85]; 91.05 [100.0]; 65[10.83]. $C_{21}H_{18}N_4O_2$ (358.39): Calculated, %: C 70.38, H 5.06, N 15.63; Found, %: C 70.97 , H 5.18 , N 15.76.

6-Amino-4- (2, 3-dimethoxy) phenyl) -1, 4-dihydro-3-methylpyrano [2, 3-*c*] pyrazole-5-carbonitrile (8b)

The solid product precipitated after cooling and recrystallized from ethanol. m.p. = 238-240°C. I.R. (KBr): ν̃= 3413, 3328 (NH_2), 3159 (NH), 2967(C-H aliphatic), 2203(CN) cm^{-1}. ^{1}H NMR (DMSO): δ= 2.05 (s, 3H, -CH_3), 3.35 (s, 3H, -OCH_3), 3.70 (s, 3H, -OCH_3), 5.30 (s, 1H, 4-CH-), 5.54 (s, 2H, -NH_2), 6.82-7.15 (d, d, 3H, aromatic protons), 9.57 (s, 1H, -NH-) ppm. Mass: m/z (%): 312.10 [M^+, 22.07]; 284.10 [31.01]; 167.05 [50.89]; 123.30 [68.59]; 71.10 [100.0]; 66.05 [72.17]. $C_{16}H_{16}N_4O_3$ (312.32): Calculated, %: C 61.53 , H 5.16 , N 17.94; Found, %: C 61.94 , H 5.79 , N 17.06.

6-Amino-4- (2,5-dimethoxy) phenyl) -1, 4-dihydro-3-methylpyrano 2, -*c*] pyrazole-5-carbonitrile (8c)

The solid product precipitated on hot and recrystallized from methanol with drops of glacial acetic acid. m.p. = 230-232°C. I.R. (KBr): ν̃= 3500, 3350 (NH_2), 3200 (NH), 3000(C-H aliphatic), 2220(CN) cm^{-1}. ^{1}H NMR (DMSO): δ= 0.87 (t, 3H, -CH_3), 2.33 (s, 3H, -OCH_3), 2.93 (s, 3H, -OCH_3), 4.49 (s, 1H, 4-CH-), 5.74 (s, 2H, -NH_2), 7.27-7.48 (m, 3H, aromatic protons), 10.92 (s, 1H, -NH-) ppm. Mass: m/z (%): 312.20 [M^+, 84.41]; 297.20 [55.36]; 281.20 [86.04]; 175.15[92.24]; 77.25 [100.0]; 65.10[11.55]. $C_{16}H_{16}N_4O_3$ (312.32): Calculated, %: C 61.53 , H 5.16 , N 17.94; Found, %: C 61.83 , H 5.03 , N 18.12.

6-Amino-4- (2, 6-dichloro) phenyl) -1,4-dihydro-3-methylpyrano [2,3-*c*] pyrazole-5-carbonitrile (8d)

The solid product precipitated on hot and recrystallized from methanol. m.p. = 276-278°C. I.R. (KBr): ν̃= 3450, 3350 (NH_2), 3250 (NH), 2950(C-H aliphatic), 2200(CN) cm^{-1}. ^{1}H NMR (DMSO): δ= 1.70 (t, 3H, -CH_3), 4.15 (s, 1H, 4-CH-), 5.98 (s, 2H, -NH_2), 6.86-7.21 (m, 3H, aromatic protons), 11.16 (s, 1H, -NH-) ppm. Mass: m/z (%): 321.10 [M^+, 25.08]; 305.10 [38.07]; 163.15 [50.10]; 143.20 [62.02]; 81.15[100.0]; 59.05[10.45]. $C_{14}H_{10}Cl_2N_4O$ (321.16): Calculated, %: C 52.36 , H 3.14 , Cl 22.08 , N 17.45; Found, %: C 53.04 , H 2.97 , Cl 21.76 , N 17,35.

General procedure for synthesis of Ethyl 6-amino-4-aryl-5-cyano-2-methylnicotinate derivatives (9a,b)

To a solution of pyran 1 (1 mmol) in 20 mL glacial acetic acid was added 1 gm of ammonium acetate and the mixture was refluxed for the required time, then left to cool and some of solvent evapourate. The precipitated solid was filtered off, washed with ethanol and recrystallized to afford 9.

Ethyl 6-Amino-5-cyano-4- (3-benzyloxy) phenyl) -2-methylnicotinate (9a)

Time of reaction: 11h.; Yield (71%). The precipitated product was recrystallized from ethanol. m.p. = 179-182°C. I.R. (KBr): ν̃= 3350, 3250 (NH_2), 3000(C-H aliphatic), 2200(CN), 1690(CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ= 0.87 (t, 3H, -O-CH_2-CH_3), 1.70 (s, 2H, -OCH_2-Ph), 2.51 (s, 3H, -CH_3), 3.93 (q, 2H, -O-CH_2-CH_3), 5.48 (s, 2H.-NH_2), 6.92-7.45 (m, 9H, aromatic protons) ppm. Mass: m/z (%): 387.30 [M^+, 2.59]; 358.25 [1.37]; 223.10 [1.69]; 91.10 [100.0]; 65.05[10.58]. $C_{23}H_{21}N_3O_3$ (387.43): Calculated, %: C 71.30 , H 5.46 , N 10.85; Found, %: C 71.44 , H 5.59 , N 10.27.

Ethyl 6- Amino- 5-cyano-4- (2,3-dimethoxy) phenyl)-2-methylnicotinate (9b)

Time of reaction: 15h; Yield (83%). The precipitated product was crystallized from methanol. m.p. = 194-195°C. I.R. (KBr): ν̃= 3385, 3326 (NH_2), 2935(C-H aliphatic), 2222(CN), 1705(CO) cm^{-1}. ^{1}H NMR (DMSO): δ= 0.77 (t, 3H, -O-CH_2-CH_3), 2.39 (s, 3H, -CH_3),2.48 (s, 6H, 2(-OCH_3)), 3.41 (q, 2H, -O-CH_2-CH_3), 5.59 (s, 2H, -NH_2), 6.60-7.29 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 341.30 [M^+, 85.36]; 310.25 [64.83]; 296.20 [29.21]; 282.20 [100.0]; 238.15[25.97]. $C_{18}H_{19}N_3O_4$ (341.36): Calculated, %: C 63.33 , H 5.61 , N 12.31; Found, %: C 64.01 , H 5.72 , N 12.49.

General procedure for synthesis of Ethyl 2-methyl-4-oxo-3,5-dihydro-4H-pyrano [2,3-d] pyrimidine-6-carboxylate derivatives (12a,b)

A solution of pyran 1 (1 gm) in acetic anhydride (10 mL) was refluxed for required time. The solid product was collected by filtration, and then recrystallized from ethanol.

Ethyl 4, 5-dihydro-2, 5,7-Trimethyl-4-oxo-3*H*-pyrano[2,3-*d*]pyrimidine-6-carboxylate (12a)

The solid product formed after cooling, then was collected by filtration and recrystallized from ethanol. Time of reaction: 4h; Yield (92.5%). m.p. = 249-250°C. I.R. (KBr): ν̃= 3100 (NH), 2940 (C-H aliphatic), 1713(ester CO), 1670 (ring CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.15 (t, 3H, -O-CH_2-CH_3), 2.27 (d, 3H, 5-CH_3), 2.49 (s, 3H, -CH_3), 2.60 (s, 3H, -CH_3), 4.06 (q, 2H, -O-CH_2-CH_3), 4.89 (q, 1H, 5-CH-), 11.64 (s, 1H, -NH-) ppm. Mass: m/z (%): 264.20 [M^+, 1.84]; 249.25 [100.0]; 235.15 [2.89]; 211.15 [38.32]. $C_{13}H_{16}N_2O_4$ (264.28): Calculated, %: C 59.08 , H 6.10 , N 10.60; Found, %: C 59.27 , H 6.83 , N 9.73.

Ethyl 4, 5-dihydro-5- (3,4,5-Trimethoyphenyl) -2-methyl-4-oxo-7-phenyl-3*H*-pyrano [2,3-*d*] pyrimidine-6-carboxylate (12b)

The reaction mixture was allowed to cool at room temperature, then was treated with about 100mL cold water. The solid product so formed was collected by filtration and recrystallized from ethanol. Time of reaction: 15h; Yield (73.6%). m.p. = 218-220°C. I.R. (KBr): ν̃= 3260 (NH), 2980 (C-H aliphatic), 1719(ester CO), 1667 (ring CO) cm^{-1}. ^1H NMR (DMSO): δ= 0.83 (t, 3H, -O-CH_2-CH_3), 2.26 (s, 3H, -CH_3), 3.72 (s, 9H, 3(-OCH_3)), 3.84 (q, 2H, -O-CH_2-CH_3), 4.87 (s, 1H, 5-CH-), 6.60 (s, 2H, aromatic protons), 7.47 (s, 5H, aromatic protons), 12.54 (s, 1H, -NH-) ppm. Mass: m/z (%): 478.15 [M^+, 92.03]; 447.15 [26.14]; 401.10 [72.57]; 105.05 [100.0]; 77.05[26.23]. $C_{26}H_{26}N_2O_7$ (478.49): Calculated, %: C 65.26 , H 5.48 , N 5.85; Found, %: C 65.72 , H 5.53 , N 6.02.

General procedure for synthesis of Ethyl 3-amino-6-methyl-isoxazolo [3,4-b]pyridine-5-carboxylate derivatives (15a-e)

A suspention of pyran 1 (1 mmol) in pyridine (10 mL) was treated with hydroxylamine hydrochloride (1mmol). The reaction mixture was heated for 3 h. The remaining product was triturated with water and the resulting solid product was collected by filtration and recrystallized to afford 15.

Ethyl 3-Amino-4-(3-benzyloxy) phenyl)-6-methyl-isoxazolo [3, 4-*b*] pyridine-5-carboxylate (15a)

The precipitated solid was recrystallized from ethanol. Yield (61.4%). m.p. = 256-258°C. I.R. (KBr): ν̃= 3386, 3315 (NH_2), 2940(C-H aliphatic), 1705(CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.10 (t, 3H, -O-CH_2-CH_3), 2.27 (s, 3H, -CH_3), 4.01 (q, 2H, -O-CH_2-CH_3), 5.05 (s, 2H, -O-CH_2-Ph), 5.15 (s, 2H, -NH_2), 6.79-6.94 (m, 4H, aromatc protons), 7.23-7.45 (m, 5H, aromatic protons) ppm. Mass: m/z (%): 404 [M^+, 61.41]; 377 [17.03]; 80 [100.0]; 64 [83.59]; 52[58.82]. $C_{23}H_{21}N_3O_4$ (403.43): Calculated, %: C 68.47, H 5.25, N 10.42; Found, %: C 68.13, H 5.74, N 10.38.

Ethyl 3-Amino-4-(2,3-dimethoxy)phenyl)-6-methyl-isoxazolo [3,4-*b*] pyridine-5-carboxylate (15b)

The precipitated solid was recrystallized from ethanol. Yield (82.7%). m.p. = 248-250°C. I.R. (KBr): ν̃= 3448, 3317 (NH_2), 2982(C-H aliphatic), 1707(CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.10 (t, 3H, -O-CH_2-CH_3), 2.42 (s, 3H, -CH_3), 3.86 (s,3H, -OCH_3), 3.93 (s,3H, -OCH_3), 4.05 (q, 2H, -O-CH_2-CH_3), 5.72 (s, 2H, -NH_2), 6.70 (d, 1H, aromatic proton), 6.88 (d, 1H, aromatic proton), 6.99 (t, 1H, aromatic proton) ppm. Mass: m/z (%): 357 [M^+, 26.61]; 149 [34.11]; 113 [28.42]; 80 [100.0]; 64 [54.78]; 51 [5.43]. $C_{18}H_{19}N_3O_5$ (357.36): Calculated, %: C 60.50 , H 5.36 , N 11.76; Found, %: C 60.22 , H 5.39 , N 11.48.

Ethyl 3-Amino-4-(2,6-dichloro)phenyl)-6-methyl-isoxazolo[3,4-*b*]pyridine-5-carboxylate (15c)

The precipitated solid was recrystallized from ethanol. Yield (54.9%). m.p. = 229-231°C. I.R. (KBr): ν̃= 3267, 3208 (NH_2), 2978(C-H aliphatic), 1701(CO) cm^{-1}. ^1H NMR (DMSO): δ= 0.37 (t, 3H, -O-CH_2-CH_3), 1.12 (s, 3H, -CH_3), 3.48 (q, 2H, -O-CH_2-CH_3), 4.49 (s, 2H, -NH_2), 7.28-7.91 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 366.20 [M^+, 77.78]; 325.20 [25.93]; 279.20 [35.56]; 245.20 [84.44]; 149.10[82.22]; 134.10[100.0]; 113.10[81.48]. $C_{16}H_{13}Cl_2N_3O_3$ (366.20): Calculated, %: C 52.48 , H 3.58 , Cl 19.36 , N 11.47; Found, %: C 52.99 , H 3.61 , Cl 19.52 , N 11.38.

Ethyl 3-Amino-4, 6-methyl-isoxazolo [3,4-*b*]pyridine-5-carboxylate (15d)

The precipitated solid was recrystallized from ethanol. Yield (66.2%). m.p. = 250-252°C. I.R. (KBr): ν̃= 3331, 3276 (NH_2), 2952(C-H aliphatic), 1679(CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.14 (t, 3H, -O-CH_2-CH_3), 2.33 (s, 3H, -CH_3), 2.93 (s, 3H, -CH_3), 4.06 (q, 2H, -O-CH_2-CH_3), 5.92 (s, 2H, -NH_2) ppm. Mass: m/z (%): 235.20 [M^+, 4.35]; 113.20 [4.48]; 94.20 [5.70]; 79.10 [100.0]; 52.10[95.57]. $C_{11}H_{13}N_3O_3$ (235.24): Calculated, %: C 56.16 , H 5.57 , N 17.86; Found, %: C 56.84 , H 5.22 , N 17.58.

Ethyl 3-Amino-6-methyl-isoxazolo [3,4-*b*]pyridine-5-carboxylate (15e)

The precipitated solid was recrystallized from methanol. Yield (41.8%). m.p. = 150-152°C. I.R. (KBr): ν̃= 3440, 3345 (NH_2), 2936(C-H aliphatic), 1713(CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.08(t, 3H, -O-CH_2-CH_3), 2.41 (s, 3H, -CH_3) 4.06 (q, 2H, -O-CH_2-CH_3), 4.48 (s, 1H, -CH=), 5.72 (s, 2H, -NH_2) ppm. Mass: m/z (%): 221.20 [M^+, 92.33]; 183.20 [67.43]; 158.20 [42.23]; 73.20 [100.0]; 57.15[12.57]. $C_{10}H_{11}N_3O_3$ (221.21): Calculated, %: C 54.29 , H 5.01 , N 19.00; Found, %: C 53.77 , H 5.68 , N 18.50.

General procedure for synthesis of Ethyl 5-cyano-2-methyl-6-semicarbazidopyridine -3-carboxylate derivatives (16a-c)

Equimolar amounts of pyran 1 and semicarbazide hydrochloride (1 mmol) in ethanol (20 mL) were treated with three drops of piperidine. The reaction mixture was refluxed for 5h. The solid product formed was collected by filtration and recrystallized to afford 16.

Ethyl 4- (3-benzyloxy) phenyl) -5-cyano-2-methyl-6-semicarbazidopyridine-3-carboxylate (16a)

The solid product formed after cooling, then was collected by filtration and recrystallized from ethanol. Yield (69%). m.p. = 224-226°C. I.R. (KBr): ν̃= 3469, 3397 (NH_2), 3235 (NH), 2917(C-H aliphatic), 2234(CN), 1741(ester CO), 1666 (amidic CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 0.84 (t, 3H, -O-CH_2-CH_3), 2.60 (s, 3H, -CH_3), 3.35 (s, 2H, -OCH_2-Ph), 4.01 (q, 2H, -O-CH_2-CH_3), 5.74 (s, 2H, -NH_2), 7.49-7.64 (m, 9H, aromatic protons), 9.87 (s, 1H, -NH-), 10.52 (s, 1H, -NH-) ppm. Mass: m/z (%): 444.20 [M^+, 69.28]; 339.20 [75.82]; 319.20 [87.58]; 113.20 [100.0]; 102.20[75.82]. $C_{24}H_{23}N_5O_4$ (445.47): Calculated, %: C 64.71 , H 5.20 , N 15.72; Found, %: C 64.41 , H 5.92 , N 16.05.

Ethyl 4-(2, 3-dimethoxy) phenyl)-5-cyano-2-methyl-6-semicarbazidopyridine-3-carboxylate (16b)

The solid product formed after cooling, then was collected by filtration and recrystallized from ethanol. Yield (77.4%). m.p. = 166-168°C. I.R. (KBr): ν̃= 3438, 3382 (NH_2), 3241 (NH), 3139 (NH), 2979 (C-H aliphatic), 2252 (CN), 1704 (ester CO), 1638 (amidic CO) cm^{-1}. Mass: m/z (%): 400.30 [M^+, 23.80]; 299.25 [40.92]; 223.25 [53.03]; 163.20 [100.0]; 134.20[51.98]. $C_{19}H_{21}N_5O_5$ (399.40): Calculated, %: C 57.14 , H 5.30 , N 17.53; Found, %: C 57.86 , H 5.58 , N 17.09.

Ethyl 5-cyano-2, 4-dimethyl-6-semicarbazidopyridine-3-carboxylate (16c)

The solid product formed on hot, then was collected by filtration and recrystallized from ethanol/DMF (1:1). Yield (81.1%). m.p. = 244-246°C. I.R. (KBr): ν̃= 3383, 3324 (NH_2), 3284 (NH), 2943(C-H aliphatic), 2222(CN), 1703 (ester CO), 1642 (amidic CO) cm^{-1}. ^1H NMR (DMSO): δ= 0.84 (t, 3H, -O-CH_2-CH_3), 2.40 (s, 3H, -CH_3), 3.17 (s, 3H, -CH_3), 3.87 (q, 2H, -O-CH_2-CH_3), 6.34 (s, 2H, -NH_2), 10.05 (s, 1H, -NH-), 10.82 (s, 1H, -NH-) ppm. Mass: m/z (%): 277.20 [M^+, 73.43]; 192.20 [76.92]; 173.20 [74.13]; 167.20 [88.11]; 127..20[100.0]; 121.20[77.62]; 69.05[43.36]. $C_{12}H_{15}N_5O_3$ (277.28): Calculated, %: C 51.98 , H 5.45 , N 25.26; Found, %: C 51.26 , H 4.93 , N 25.74.

General procedure for synthesis of Ethyl 4-(aryl)-5-cyano-2-methyl-6-thiosemicarbazidopyridine-3-carboxylate derivatives (17a,b)

Equimolar amounts of pyran 1 and thiosemicarbazide (1 mmol) in ethanol (20 mL) were treated with three drops of piperidine. The reaction mixture was refluxed for 5h. The solid product formed after cooling, then was collected by filtration and recrystallized from ethanol to afford 17.

Ethyl 4-(3-benzyloxy) phenyl) -5-cyano-2-methyl-6-thiosemicarbazidopyridine-3-carboxylate (17a)

Yield (58.2%). m.p.= 194-196°C. I.R. (KBr): ν̃= 3268, 3210 (NH_2), 3094 (NH), 2983(C-H aliphatic), 2206(CN), 1704(CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 0.71 (t, 3H, -O-CH_2-CH_3), 2.49 (s, 3H, -CH_3), 3.34 (s, 2H, -O-CH_2-Ph), 3.74 (q, 2H, -O-CH_2-CH_3), 4.50 (s, 2H, -NH_2), 7.19-7.58 (m, 9H, aromatic protons), 9.78 (s, 1H, -NH-), 10.51 (s, 1H, -NH-) ppm. Mass: m/z (%): 463.20 [M^+, 9.43]; 354.20 [9.41]; 328.20 [9.34]; 164 [100.0]; 155[30.13]; 150[11.81]. $C_{24}H_{23}N_5O_3S$ (461.54): Calculated, %: C 62.46 , H 5.02 , N 15.17 , O 10.40 , S 6.95 ; Found, %: C 62.91 , H 5.49 , N 15.03 , O 9.96 , S 6.61.

Ethyl 4-(2, 3-dimethoxy) phenyl)) -5-cyano-2-methyl-6-thiosemicarbazidopyridine-3-carboxylate (17b)

Yield (47.5%). m.p.= 234-236°C. I.R. (KBr): ν̃= 3441, 33369 (NH_2), 3254 (NH), 3154 (NH), 2992(C-H aliphatic), 2200(CN), 1717(ester CO) cm^{-1}. Mass: m/z (%): 415.20 [M^+, 0.05]; 354.20 [0.06]; 239.25 [50.76]; 163.20 [100.0]; 149.20[65.24]. $C_{19}H_{21}N_5O_4S$ (415.47): Calculated, %: C 54.93 , H 5.09 , N 16.86, S 7.72 ; Found, %: C 54.33 , H 4.85 , N 16.72, S 8.89.

Ethyl 5-amino-7-(4-chlorophenyl)-6-cyano-4-(2,3-dimethoxy)phenyl)-2-methyl-4H-pyrano[2,3-b]pyridine-3-carboxylate (18)

A mixture of pyran 1 (1 mmol) and 2-(4-chloro-benzylidene)-malononitrile (1 mmol) in ethanol (10 mL) was treated with 3 drops of piperidine and was refluxed for 4h. The reaction mixture was then allowed to cool at room temperature, then was treated with about 10mL diluted hydrochloric acid solution. The solid product so formed was collected by filtration and recrystallized from benzene with drops of toluene to afford 18. Yield (49.7%). m.p. = 166-168°C. I.R. (KBr): ν̃= 3415, 3326 (NH_2), 2941(C-H aliphatic), 2207(CN), 1714(CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ= 0.97 (t, 3H, -O-CH_2-CH_3), 2.49 (s, 3H, -CH_3), 3.14 (s, 6H, 2(–OCH_3), 4.02 (q, 2H, -O-CH_2-CH_3), 4.64 (s, 1H, 4-CH-), 5.06 (s, 1H, 7-CH-), 6.66 (s, 2H, -NH_2), 7.27-7.41 (m, 4H, aromatic protons), 7.57-7.68 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 533.35 [M^+, 37.76]; 432.25 [42.28]; 202 [9.77]; 91.10 [100.0]; 77.05[49.58]. $C_{28}H_{25}ClN_4O_5$ (532.97): Calculated, %: C 63.10 , H 4.73 , Cl 6.65 , N 10.51; Found, %: C 62.73 , H 4.96 ,Cl 6.42, N 11.03.

General procedure for synthesis of Ethyl 5, 8-diamino-6-cyano-2-methyl-7-oxo-7, 8-dihydro-1, 8-naphthyridine-3-carboxylate (19a, b)

Equimolar amounts of pyran 1 and cyano-acetic acid hydrazide (1 mmol) in ethanol (10 mL) were treated with three drops of piperidine. The reaction mixture was refluxed for required time. The solid product was collected by filtration and recrystallized to afford 19.

Ethyl 5, 8-diamino-6-Cyano-4-(2, 3-dimethoxy)phenyl)-2-methyl-7-oxo-7, 8-dihydro-1, 8-naphthyridine-3-carboxylate (19a)

The solid product formed after cooling and recrystallized from ethanol. Time of reaction: 30 min.; Yield (61.6%). m.p. = 206-208°C. I.R. (KBr): ν̃= 3329-3196 (NH_2), 2950 (C-H aliphatic), 2210 (CN), 1677(ester CO), 1625 (ring CO) cm^{-1}. ^1H NMR (DMSO): δ= 0.84 (t, 3H, -O-CH_2-CH_3), 2.60 (s, 6H, 2(-OCH_3)), 3.35 (s, 3H, -CH_3), 4.03 (q, 2H, -O-CH_2-CH_3), 5.74 (s, 2H, -NH_2), 6.53 (s, 2H, -NH_2), 7.49-7.64 (m, 3H, aromatic protons) ppm. Mass: m/z (%): 425.40 [M^+, 1.06]; 311.30

[100.0]; 295.25 [39.47]; 228.20 [14.87]. $C_{21}H_{23}N_5O_5$ (423.44): Calculated, %: C 59.29 , H 5.45 , N 16.46; Found, %: C 59.55 , H 5.28 , N 16.76.

Ethyl 5,8-diamino-6-Cyano-2,4-dimethyl-7-oxo-7,8-dihydro-1,8-naphthyridine-3-carboxylate (19b)

The solid product formed on hot and recrystallized from methanol. Time of reaction: 5 min.; Yield (73%). m.p. = 304-306°C. I.R. (KBr): ν̃= 3421- 3212 (NH_2), 2979(C-H aliphatiic), 2209(CN), 1705(ester CO), 1685 (ring CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.13 (t, 3H, -O-CH_2-CH_3), 2.42 (s, 3H, -CH_3), 3.05 (s, 3H, -CH_3), 4.05 (q, 2H, -O-CH_2-CH_3), 5.72 (s, 2H, -NH_2), 6.67 (s, 2H, -NH_2) ppm. Mass: m/z (%): 303.20 [M^+, 3.23]; 295.25 [26.45]; 251.20 [70.97]; 176.15 [98.71]; 108.15[100.0]; 66.05[87.74]. $C_{14}H_{17}N_5O_3$ (303.32): Calculated, %: C 55.44 , H 5.65 , N 23.09; Found, %: C 55.71, H 5.37, N 22.69.

General procedure for the synthesis of Ethyl 5-amino-6, 7, 8, 9-tetrahydro-4-aryl-2-phenyl-4H-pyrano [2, 3-b] quinoline-3-carboxylate derivatives (20a, b)

A mixture of cyclohexanone (1 mmol) with pyran 1 (1 mmol) in 15 mL ethanol in the presence of piperidine was refluxed for required time. The solid product, so formed, was filtered off and recrystallized to give 20.

Ethyl 5-amino-6, 7, 8, 9-tetrahydro-4-(3, 4, 5-trimethoxy) phenyl)-2-phenyl-4*H*-pyrano [2, 3-b] quinoline-3-carboxylate (20a)

The solid product formed on hot and recrystallized from methanol. Time of reaction: 5h.; Yield (39.5%). m.p. = 252-254°C. I.R. (KBr): ν̃= 3280, 3235 (NH_2), 2936(C-H aliphatic), 1670(CO) cm^{-1}. ^1H NMR (DMSO): δ= 0.89 (t, 3H, -O-CH_2-CH_3), 1.94 (s, 6H, 2(-OCH_3)), 2.18 (s, 3H, -OCH_3), 2.77-2.91 (m, 8H, 4(-CH_2-), 3.89 (q, 2H, -O-CH_2-CH_3),4.66 (s, 1H, 4-CH-), 6.38 (s, 2H, -NH_2), 7.35-7.54 (m, 5H, aromatic protons), 7.74 (s, 2H, aromatic protons) ppm. Mass: m/z (%): 515.40 [M^+, 6.44]; 510.40 [70.63]; 484.40 [34.90]; 292.75 [100.0]; 256.60[10.56]. $C_{30}H_{32}N_2O_6$ (516.58): Calculated, %: C 69.75 , H 6.24 , N 5.42; Found, %: C 69.18 , H 6.75 , N 5.34.

Ethyl 5-amino-6,7,8,9-tetrahydro-4-(2,3-dimethoxy)phenyl) -2-phenyl-4*H*-pyrano[2,3-b]quinoline-3-carboxylate (20b)

The solid product formed after cooling and recrystallized from ethanol. Time of reaction: 6h.; Yield (61.3%). m.p.= 206-208°C. I.R. (KBr): ν̃= 3442, 3347 (NH_2), 2935, 2910 (C-H aliphatic), 1713(CO) cm^{-1}. Mass: m/z (%): 486 [M^+, 45.5]; 333 [100.0]; 145 [54.5]; 60 [100.0]. $C_{29}H_{30}N_2O_5$ (486.56): Calculated, %: C 71.59 , H 6.21 , N 5.76; Found, %: C 72.01 , H 6.83 , N 5.35.

Ethyl 5-amino-4-(2, 3-dimethoxy)phenyl)-2-phenyl-4,6,7,8-tetrahydropyrano[3,2-e]pyridine-3-carboxylate *(21)*

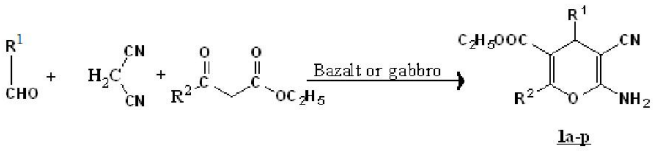
A mixture of cyclopentanone (1 mmol) with pyran 1 (1 mmol) in 15 mL ethanol in the presence of piperidine was refluxed for 6 h. The solid product, so formed after cooling, was filtered off and recrystallized from ethanol to give 21. Yield (85.7%). m.p. = 208-210°C. I.R. (KBr): ν̃= 3421, 3328 (NH_2), 2984(C-H aliphatic), 1705(CO) cm^{-1}. ^1H NMR (DMSO): δ= 0.94 (t, 3H, -O-CH_2-CH_3), 2.23 (s, 6H, 2(-OCH_3)), 3.42 (s, 2H, -CH_2-), 3.53 (s, 4H, 2(-CH_2-)), 3.90 (q, 2H, -O-CH_2-CH_3), 4.96 (s, 1H, 8-CH-), 6.28 (s, 2H, -NH_2), 7.05-7.36 (m, 8H, aromatic protons) ppm. Mass: m/z (%): 472 [M^+, 45.1]; 218 [12.4]; 151 [100.0]; 91 [21.8]. $C_{28}H_{28}N_2O_5$ (472.53): Calculated, %: C 71.17 , H 5.97 , N 5.93; Found, %: C 71.66 , H 5.31 , N 5.82.

Ethyl 6- (4-chlorobenzylideneamino)-5-cyano-4-(3, 4, 5-trimethoxy) phenyl) -2-phenyl -4*H*-pyran-3-carboxylate (22)

A mixture of 4-chlorobenzaldehyde (1 mmol) with pyran 1 (1 mmol) in 15 mL ethanol in the presence of piperidine was refluxed for 6 h. The solid product, so formed after cooling, was filtered off and recrystallized from ethanol to give 22. Yield (92.4%). m.p.= 223-224°C. I.R. (KBr): ν̃= 2930(C-H aliphatic), 2240(CN),1750(CO) cm^{-1}. ^1H NMR (DMSO): δ= 1.13 (t, 3H, -O-CH_2-CH_3), 2.39 (s, 6H, 2(-OCH_3), 2.45 (s, 3H, -OCH_3), 3.05 (s, 1H, -N=CH-), 4.06 (q, 2H, -O-CH_2-CH_3), 4.85 (s, 1H, 4-CH-), 7.04-7.36 (m, 11H, aromatic protons) ppm. Mass: m/z (%): 562.3 [M^+, 35.7]; 95 [35.7]; 55.2 [100.0]; 53.2[57.1]. $C_{31}H_{27}ClN_2O_6$ (559.01): Calculated, %: C 66.61, H 4.87, Cl 6.34, N 5.01; Found, %: C 66.94 , H 4.03 ,Cl 5.99 , N 5.61.

RESULTS AND DISCUSSION

Herein, we report an efficient one-pot multicomponent protocol for the synthesis of polyfunctionalized 4*H*-pyrans in refluxing ethanol in the safe and cheap Basalt and Gabbro as new naturally reusable heterogeneous basic catalysts (Scheme 1).



1a-p

Scheme 1

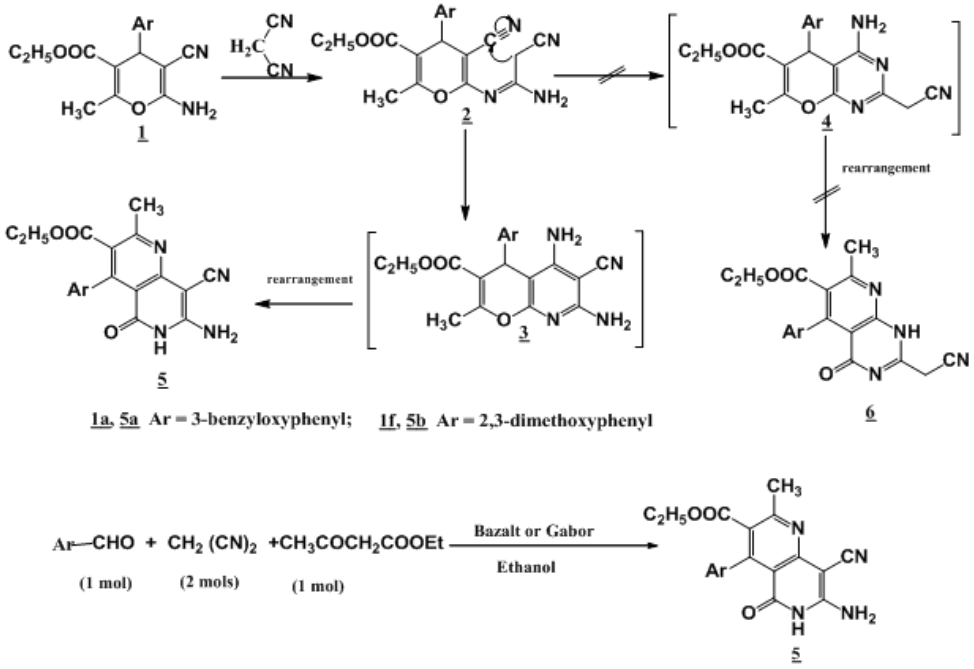
Thus, heating of a mixture of 3-benzyloxybenzaldehyde, malononitrile and ethylacetoacetate in ethanol and in the presence of catalytic amount of grinded basalt or gabbro to give a product with molecular formula ($C_{23}H_{22}N_2O_4$) *m/z* =390. It seems logical to assume the ethyl 6-amino-5-cyano-4-(3-benzyloxy-phenyl)-2-methyl-4*H*-pyran-3-carboxylate 1a for the isolated product on the basis of its elemental and spectral analysis. To popularize the idea of using basalt and gabbro as catalysts in the syntheses of 4*H*-pyrans, we heated mixtures from variety of aromatic and heterocyclic aldehydes with malononitrile and ethylacetoacetate or ethylbenzoylacetate in refluxing ethanol and in the presence of catalytic amounts of grinded basalt or grinded gabbro to give the corresponding 2-amino-4*H*-pyran derivatives 1b-k (Scheme 1). In the main time, mixtures of aliphatic aldehydes such as acetaldehyde and formaldehyde, malononitrile and ethylacetoacetate were heated under the same previous experimental techniques, the corresponding 6-amino-5-cyno-4*H*-pyrans 1l and 1m were isolated. Structures of the isolated products were established on the basis of their elemental and spectral data. (Table 1)

Table 1. Synthesis of Ethyl-2-amino-3-cyano-4H-pyran-5-carboxylate derivatives 1 using Basalt and Gabbro

Entry	R_1	R_2	Basalt (Yield%)	Gabbro (Yield%)
1_a	3-benzoyloxyphenyl	methyl	40	58.46
1_b	3-benzoyloxyphenyl	phenyl	40	64.69
1_c	2,5-dimethoxyphenyl	methyl	70.69	77.01
1_d	2,5-dimethoxyphenyl	phenyl	79.51	71.22
1_e	2,3-dimethoxyphenyl	methyl	70.12	72.99
1_f	2,3-dimethoxyphenyl	phenyl	77.56	79.02
1_g	3,4,5-trimethoxyphenyl	methyl	67.20	70.37
1_h	3,4,5-trimethoxyphenyl	phenyl	93.18	89.09
1_i	2,6-dichlorophenyl	methyl	69.66	66.29
1_j	2,6-dichlorophenyl	Phenyl	75.71	79.52
1_k	morpholine	methyl	38.51	34.46
1_l	methyl	methyl	52.68	56.25
1_m	H	methyl	34.30	30.97
1_n	4-chlorophenyl	methyl	78.09	78.68 (Nazeruddin *et al*., 2014)
1_o	4-methoxyphenyl	methyl	66.43	69.81(Nazeruddin *et al*., 2014)
1_p	Phenyl	methyl	82.39	85.42 (Nazeruddin *et al*., 2014)

On the other hand, we report that the 6-amino-5-cyno-4*H*-pyrans 1 are useful and easily available as starting materials for the preparation of functionalized azines in a series of ring transformation in which the amino group furnishes the required nitrogen ring. Thus, compounds 1a and 1e were reacted with malononitrile in refluxing ethanolic piperidine solution to yield 1:1 adducts.

absence of a pyran H-4 signal. Thus, we expected that the formed condensed pyran derivative undergo further rearrangement yielding either the 5,6-dihydro-1,6-naphthyridine 5 or 1,4-dihydropyrido[2,3-d]pyrimidine 6 (Scheme 2). Structure 6 can be readily eliminated based on ^{1}H-NMR which revealed the presence of a signal at 5.037 ppm due to benzyloxy CH_2 only for the 5a. Thus, the 5,6-dihydro-1,6-naphthyridine structure 5a can be suggested for the reaction product. By the same way 5,6-dihydro-1,6-naphthyridine 5b was formed *via* reaction of the 2-amino-4*H*-pyran 1f with malononitrile. On the other hand, 5, 6-dihydro-1,6-naphthyridines 5 were obtained *via* treatment of two moles of malononitrile with one mole the corresponding aldehydes and one mole of ethylacetoacetate in ethanol and in the presence of basalt and gabbro as catalysts. (Scheme 2). Pyrazoles are representive class of heterocyclic compounds having many derivatives with a wide range of interesting properties. Thus, 4*H*-pyrans 1a, 1c, 1e and 1i Scheme 3 were treated with hydrazine hydrate in refluxing ethanolic piperidine to afford the corresponding pyrano[2,3-*c*]pyrazoles 8a-d in good yields. The formation of pyranopyrazole 8 can be rationalized by assuming that pyrans 1 is in equilibrium with a chain tautomer which is in equilibrium with ethylacetoacetate and the corresponding cinnamonitriles (which formed *in situ*), then hydrazine reacted with the ethylacetoacetate to form 3-methyl-2-pyrazolin-5-one 7 which then reacts with corresponding cinnamonitriles to give the corresponding pyrano [2,3-*c*]pyrazoles 8 Also pyranopyrazoles 8 were synthesized *via*

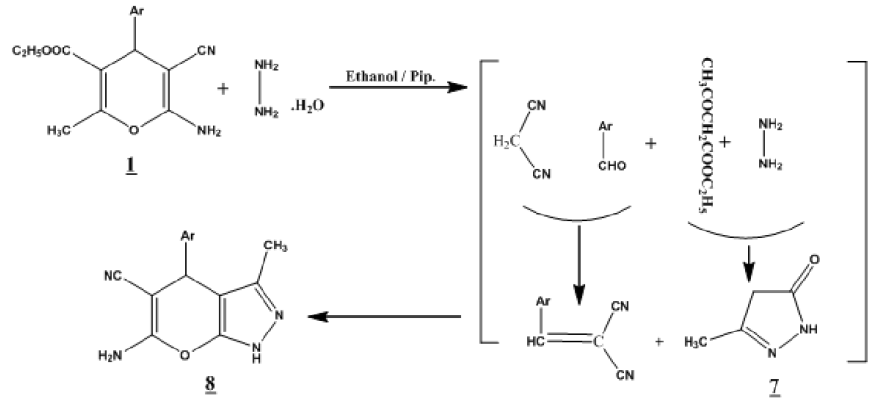


Scheme 2

We can assume that the addition of the amino function in 1 to the cyano function in malononitrile to afford amidines 2 which may then transformed to the corresponding pyrano[2,3-*b*]pyridine 3 *via* addition of the side chain methylene to the cyano function at C-5. Alternatively, pyrano[2,3-*d*]pyrimidine 4 may be formed by addition of the amidine amino function to the cyano function at C-5. However, ^{1}H-NMR revealed the four reactants in one-pot multicomponent reaction using hydrazine hydrate, ethylacetoacetate, malononitrile and the corresponding aldehyde. On the other hand, pyrans 1a and 1e rearranged on treatment with refluxing acetic acid in the presence of ammonium acetate to give the corresponding ethyl 6-amino-5-cyano-2-methylnicotinate 9a,b (Scheme 4) based on the microanalytical, and spectral data of the isolated products

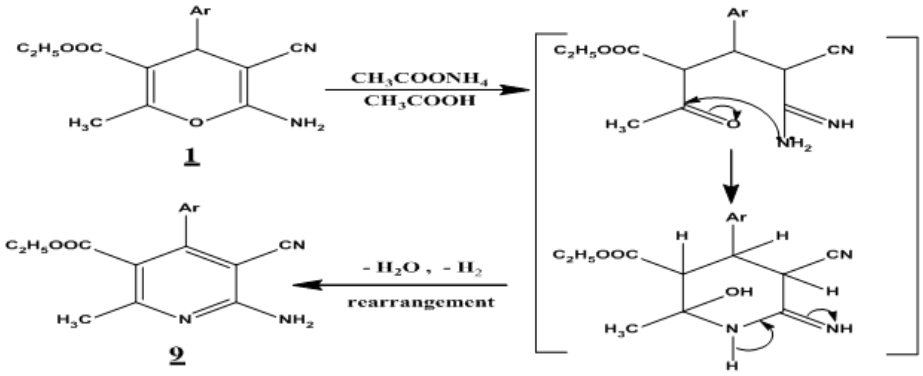
which revealed the absence of the characteristic signal due to the H-4 pyran at 4.42 ppm. Compounds 9 are assumed to be formed *via* addition of the NH_3 (launched from ammonium acetate by heating) to the double bond at C-6 in pyran ring. This is followed by ring opening and recyclization to give nicotinate 9.

At the same time, pyrans 1l and 1h were refluxed with acetic anhydride to give products which can be formulated as ethyl 2-amino-2,5,7-trimethyl-4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*] pyrimidine-6-carboxylate derivatives 12a,b (Scheme 5) based on its ^{1}H-NMR spectrum which revealed the presence of signal at 4.89 ppm due to the H-3 of 3*H*-pyrano[2,3-*d*]pyrimidine derivative 12a and signal at 4.87 ppm due to the H-3 of 3*H*-pyrano[2,3-*d*]pyrimidine derivative 12b.



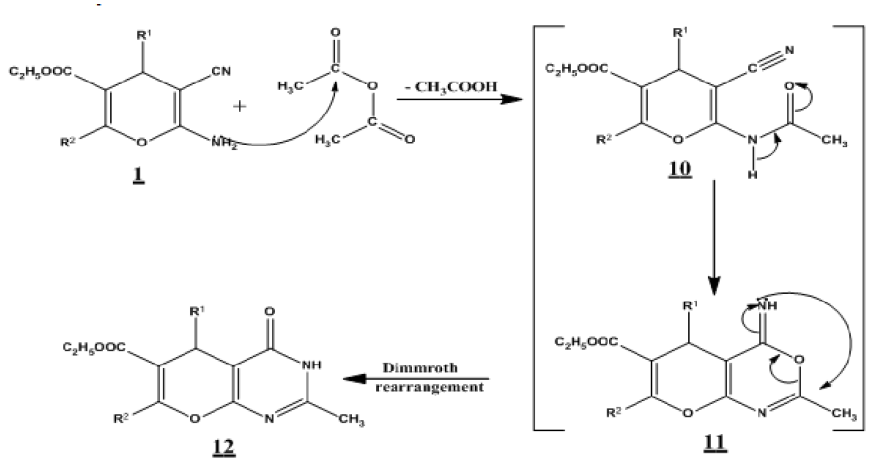
1a, 8a Ar = 3-benzyloxyphenyl; 1e, 8b Ar = 2,3-dimethoxyphenyl;
1c, 8c Ar = 2,5-dimethoxyphenyl; 1i, 8d Ar = 2,6-dichlorophenyl

Scheme 3



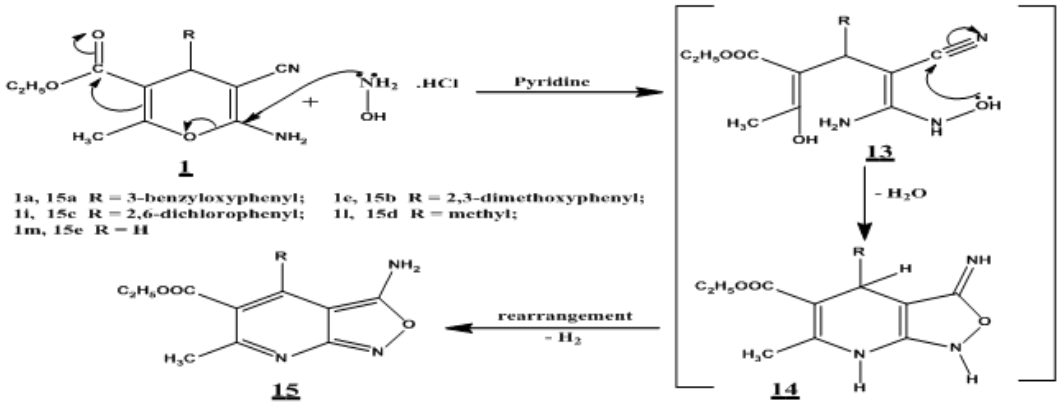
1a, 9a Ar = 3-benzyloxyphenyl; 1e, 9b Ar = 2,3-dimethoxyphenyl

Scheme 4



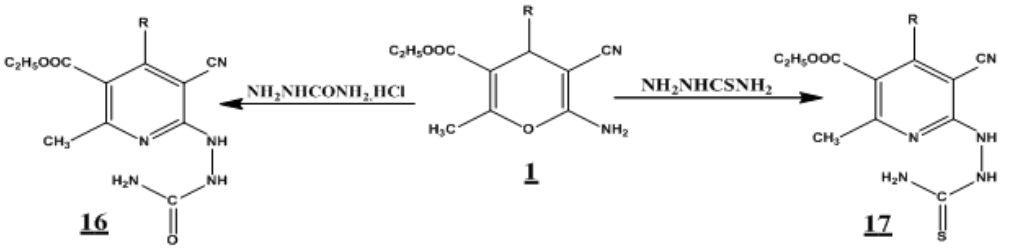
1l, 12a R^1 = methyl, R^2 = methyl; 1h, 12b R^2 = phenyl, R^1 = 3,4,5-trimethoxyphenyl

Scheme 5



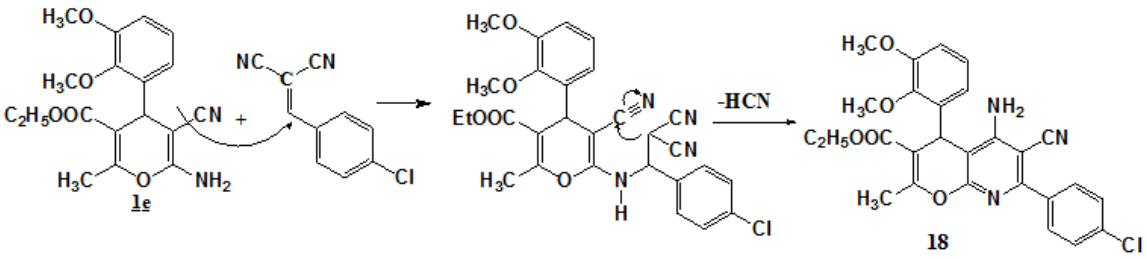
1a, 15a R = 3-benzyloxyphenyl; 1e, 15b R = 2,3-dimethoxyphenyl;
1i, 15c R = 2,6-dichlorophenyl; 1l, 15d R = methyl;
1m, 15e R = H

Scheme 6

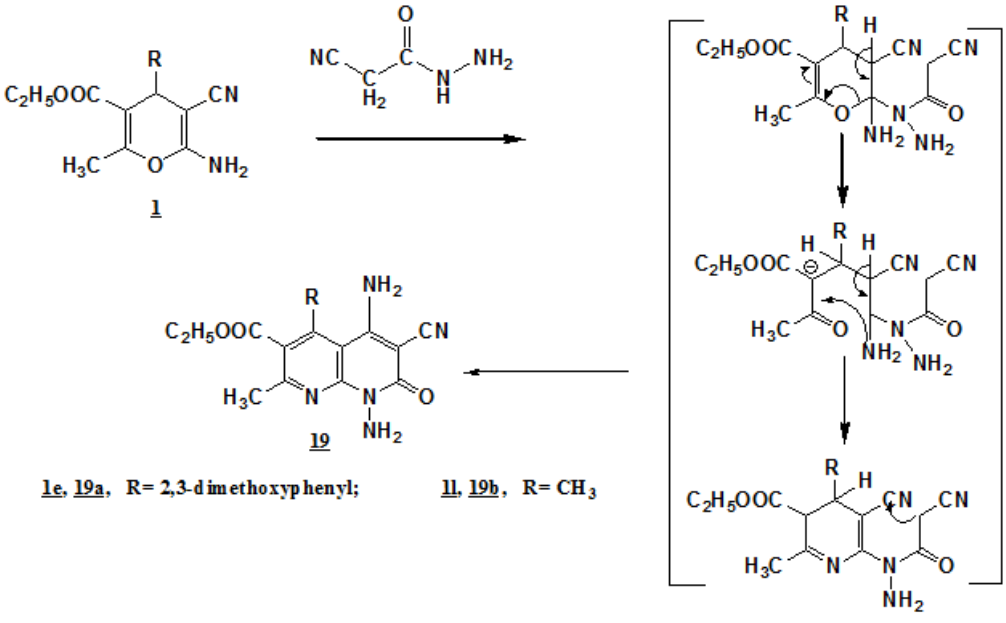


1a, 16a, 17a R= 3-benzyloxyphenyl
1e, 16b, 17b R = 2,3-dimethoxyphenyl
1l, 16c R= methyl

Scheme 7



Scheme 8



1e, 19a, R= 2,3-dimethoxyphenyl; 1l, 19b, R= CH_3

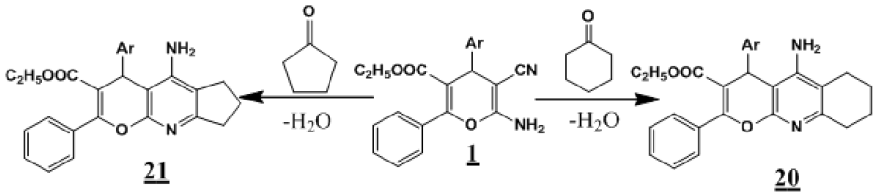
Scheme 9

The IR spectrum revealed also, the absence of nitrile function absorption at 2200 cm^{-1} as was expected for an acetyl amino derivative of the 4*H*-pyran 10. Also, the IR spectrum did not

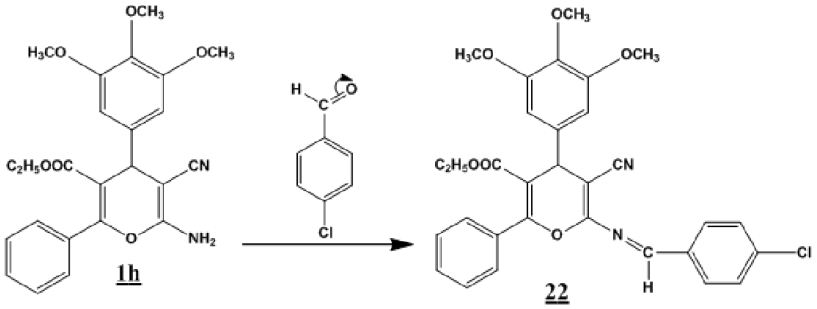
reveal a signal for an exocyclic C=NH as would be expected for the corresponding pyrano[2,3-*d*]oxazine 11. Thus, the pyrano [2,3-*d*] pyrimidine derivative can be formed *via* acetylation of the 2-amino function in pyran 1 to give the acetyl amino derivative 10 which then cyclized to the corresponding pyrano [2,3-*d*] oxazine derivative 11 which rearranged to the isolated pyrano [2,3-*d*] pyrimidine 12. In contrast to the behaviour of hydrazine hydrate, toward 2-amino-4*H*-pyran 1, pyrans 1a, 1e, 1i, 1l and 1m were reacted with hydroxylamine hydrochloride to afford the corresponding isoxazolo[3,4-*b*] pyridinederivatives 15a-e. Compounds 15 are assumed to be formed by addition of hydroxylamine to the double bond at C-6 in pyran 1 giving the corresponding non isolated intermediates 13 and 14 by ring opening and recyclization which affords the isolable product 15 (Scheme 6).

On the other hand, pyran 1e underwent nucleophilic addition with 2-(4-chloro-benzylidene) malononitrile in refluxing ethanolic piperidine solution to afford 5-amino -4*H*-pyrano [2, 3-*b*] pyridine derivative 18 based on the microanalytical and spectral data of the isolated products which revealed the presence of absorption bands at 3415 and 3326 cm^{-1} (NH_2) and at 2207 cm^{-1} (CN) in IR spectrum. Formation of 18 is assumed to occur *via* initial formation of the Michael addition of the amino group in compound 1 to the activate double bond in 2-(4-chloro-benzylidene) malononitrile followed by intramolecular cyclization and HCN elimination to afford 18. (Scheme 8)

Pyrans 1e, 1l were reacted with cyanoacetic acid hydrazide in ethanolic piperidine solution to give the corresponding naphthyridine derivatives 19a,b respectively. Formation of 19 from pyrans 1 is assumed to proceed *via* sequence shown in equations (Scheme 9). Structures of 19 were established based on their microanalytical and spectral data.



Scheme 10



Scheme 11

Structures of the isoxazopyridines 15 were established based on microanalytical and spectral data. Thus, IR spectra of the isolated products revealed the absence of CN absorption at 2220 cm^{-1}. Also, the pyran H-4 signal at 4.42 ppm was absent in the ^{1}H-NMR of the isolated products. Pyrans 1a, 1e, and 1l were reacted with semicarbazide hydrochloride and thiosemicarbazide in ethanolic piperidine solution to give 1:1 adducts *via* H_2O elimination which were formulated as the corresponding ethyl-3-cyano-6-methyl-2-(1-semicarbazido-5-pyridine carboxylate derivatives 16a-c and the corresponding ethyl-3-cyano-6-methyl-2-(1-thiosemicarbazido)-5-pyridine carboxylate derivatives 17a,b respectively based on their microanalytical and spectral data. Thus, the IR spectra revealed the presence of CN group at 2220-2260 cm^{-1} function absorption as was expected for cyanopyridine derivatives. Also, the ^{1}H-NMR spectra revealed the absence of the pyran H-4 signal; and the presence of triplet, quartet centered at 0.84 and 4.01 ppm due to the ester ethyl function in all cases. (Scheme**7**).

Also, it has been found that pyrans 1 react with cyclohexanone and cyclopentanone in ethanolic piperidine solution to give the corresponding ethyl 5-amino-4-aryl-2-phenyl-5,6,7,8-tetrahydro-4*H*-pyrano[2,3-b]quinoline-3-carboxylates 20a,b and ethyl 5-amino-4-(2,3-dimethoxyphenyl)-2-phenyl-4,6,7,8-tetrahydropyrano[3,2-e]pyridine-3-carboxylate 21 respectively (Scheme 10). Structures of compounds 20 and 21 were confirmed based on their microanalytical and spectral data.

Also, pyran 1h was condensed with aromatic aldehyde such as p-chlorobenzaldehyde in ethanolic piperidine solution to give the corresponding ethyl 6- (4-chlorobenzylideneamino)-5-cyano-2-phenyl-4-(3,4,5-trimethoxyphenyl)-4*H*-pyran-3-carboxylate 22 (Scheme 11). Structure of compound 22 was assumed for the reaction product based on its microanalytical and spectral data. The IR spectrum revealed the absence of signals at 3418, 3329 cm^{-1} for NH_2 functional group and ^{1}H-NMR spectrum revealed the disappearance of singlet signal at 4.66 for NH_2 group protons.

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