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Note

Synthesis of some novel ethyl 5-methyl-6-cyano-7-substituted-2-oxo-2*H*-pyrano [2, 3-*b*] pyridine-3-carboxylate derivatives

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Ethyl 5-methyl-6-cyano-7-substituted-2-oxo-2*H*-pyrano[2, 3-*b*]pyridine-3-carboxylates **4a-j** have been prepared starting from 2, 6-dihyroxy-3-cyano-4-methyl pyridine **1**. The compound **1** reacts with *N*,*N*-dimethylaminoethylenemalonate in acetic acid under reflux conditions to give 5-methyl-6-cyano-7-hydroxy -2*H*-pyrano[2,3-*b*]pyridine-2-one **2**, which is further treated with phosphorous oxychloride to obtain ethyl 5-methyl-6-cyano-7-chloro-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-carboxylate **3**. This chloride derivative **3** is finally converted to various amino derivatives **4a-j** by condensation with corresponding amines. These compounds are expected to have antihypertensive activity.

Keywords: Pyridine, pyridine-3-carboxylates, antihypertensive activity

IPC: Int.Cl.^{8} C07D

Pyranopyridines have been found to have blood pressure lowering activity, useful in the treatment of hypertension[1,2] and also K^+ channel activators[3] which indicates that they are of potential use in the treatment of disorders associated with smooth muscle contraction of the gastro-intestinal tract, respiratory system, uterus or urinary tract[4] such disorders include peptic ulcers, irritable bowel syndrome and diverticular disease, reversible airways obstruction and asthma.

This note reports studies on synthesis of the 2*H*-pyrano [2, 3-*b*] pyridine starting from 2, 6-dihydroxy-3-cyano-4-methyl pyridine by reacting ethyl *N*,*N*-dimethylaminomethylenemalanoate using the procedure developed by Stanovnik[5] *et al*., and followed by the synthesis of some novel 7-substituted-pyranopyridines.

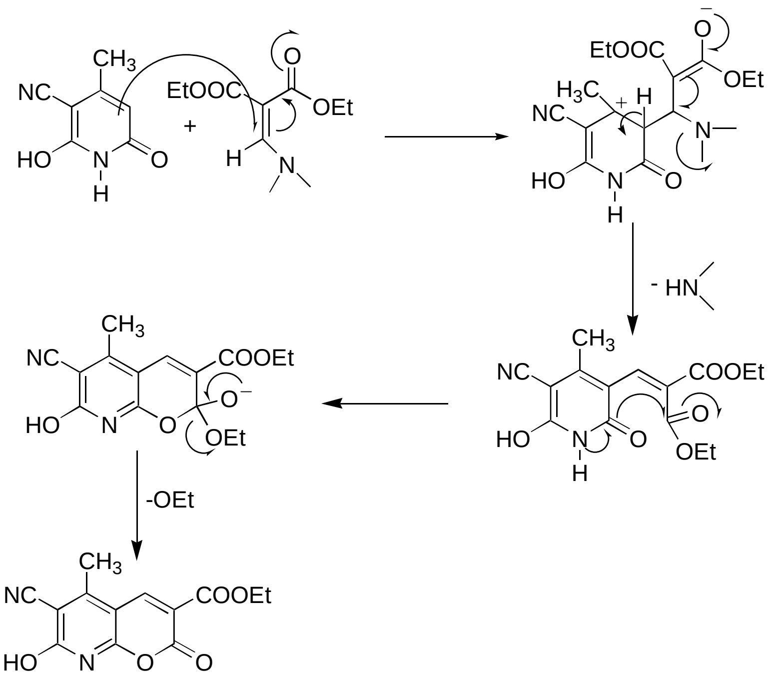
Results and Discussion

Ethyl 5-methyl-6-cyano-7-hydroxy-2-oxo-2*H*-pyrano [2, 3-*b*] pyridine-3-carboxylate **2** has been prepared from 2, 6-dihydroxy-3-cyano-4-methyl pyridine[6] **1** by reacting it with *N*,*N*-dimethylaminoethylenemalonate in acetic acid at reflux temperature in good yield. Diethyl *N*,*N*-dimethylaminomethylenemalanoate was selected and prepared from diethyl malonate and *N*,*N*-dimethylformamide dimethyl acetal as described previously[7]; it reacts with C-nucleophiles to give substituted 2-pyranones. Diethyl *N*,*N*-dimethylaminomethylenemalonate reacts with substituted pyridine nucleophiles in refluxing acetic acid followed by cyclisation without the isolation of the intermediate (**Scheme I**). Structure of the compound **2** was established by its IR and ^{1}H NMR spectra. The IR spectrum of **2** exhibited absorptions at 3431 cm^{-1} indicating the presence of hydroxyl group, absorption at 2215 cm^{-1} indicating the presence of cyano group, sharp absorption bands at 1738 cm^{-1} and 1697 cm^{-1} indicating the presence of ester carbonyl and coumarinyl carbonyl, respectively. The ^{1}H NMR spectrum of **2** showed a triplet at δ 1.20-1.27 (*J* =7.07 Hz) for $-CH_2CH_3$, a singlet for $-CH_3$ at δ 2.43, a broad singlet at δ 3.37 (D_2O exchangeable), quatrate at δ 4.12– 4.23 (*J* = 7.07 Hz) for $-CH_2CH_3$ and a singlet at δ 8.37 C_4-H for coumarinyl ring respectively. The mass spectrum of compound **2** showed M^{+1} as its molecular ion peak, further supporting its structure.

The compound **2** was treated with phosphorous oxychloride at room temperature to get ethyl 5-methyl-6-cyano-7-chloro-2-oxo-2*H*-pyrano[2,3-*b*] pyridine-3-carboxylate **3**. The IR spectrum of **3** in KBr showed peaks at 2235 cm^{-1} indicating the presence of cyano group, 1793 cm^{-1} for ester carbonyl and 1680 cm^{-1} for the presence of coumarinyl carbonyl. The ^{1}H NMR of **3** in DMSO-d_6 showed a triplet at δ 1.25-1.32 (*J* = 7.06 Hz) for $-CH_2CH_3$, a singlet for CH_3 (C_5) at δ 2.63, a quatrate between δ 4.22-4.25 (*J* = 7.06 Hz) due to $-CH_2CH_3$, a singlet at δ 8.59 corresponds to (C_4)-H. The mass spectrum of compound **3** showed (m/z 292) as M^+. The compound **3** was further condensing with deferent amines yielded the title compounds ethyl 5-methyl-6-cyano-7-substituted-2-oxo-2*H*-pyrano [2, 3-*b*] pyridine-3-carboxylate. (**4a-j**, **Table I**, **Scheme II**)

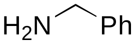
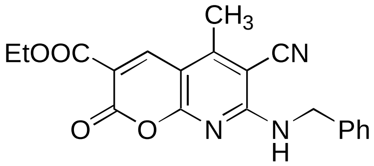
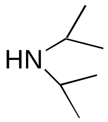
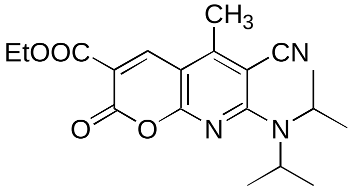
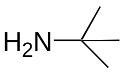
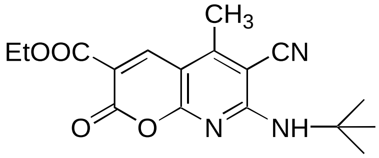
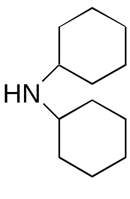
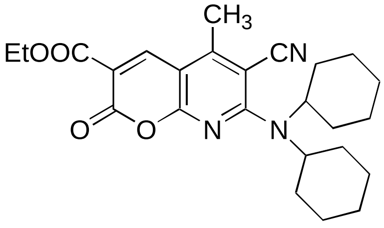
Experimental Section

Melting points were determined on Buchi 545 melting point apparatus and are uncorrected. IR



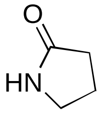
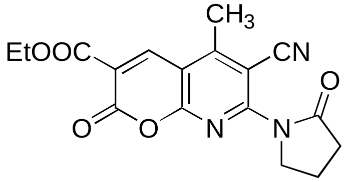
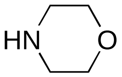
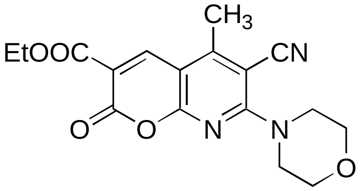
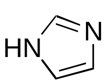
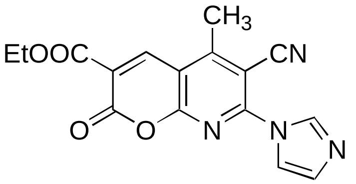
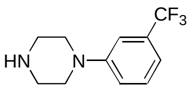
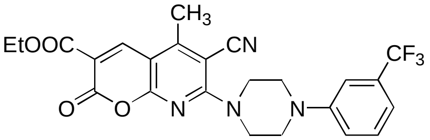
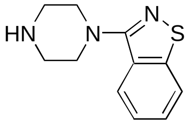
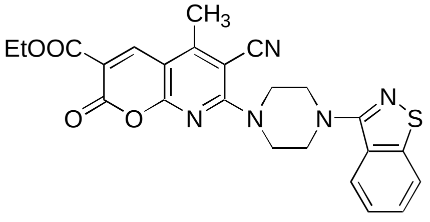
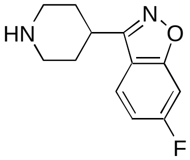
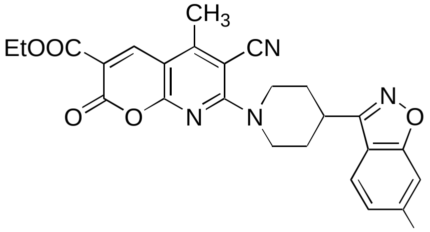
Scheme I

Table I — Reaction of ethyl 5-methyl -7-chloro-6-cyano -2-oxo-2*H*-pyrano [2,3-*b*] pyridine-3-carboxylate with appropriate amines and their spectral data

Entry	Amine	Product	Spectral data	mp °C	Yield (%)
4a			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (t, 3H, $-CH_2-C\mathit{H}_3$), 2.4 (s, 3H $-CH_3$), 4.2-4.3 (q, 2H, $-C\mathit{H}_2-CH_3$), 4.7 (s, 2H, $-C\mathit{H}_2$-Ph), 7.2-7.3 (m, 5H -Ar.), 8.4 (s, 1H, C_4-H); Mass (m/z): 335 corresponding to $C_{18}H_{13}N_3O_4$	244	85
4b			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.1-1.2 (m, 15H, 4 $-C\mathit{H}_3$ & $-CH_2-C\mathit{H}_3$), 2.4 (s, -CH_3), 3.2-3.3 (q, 2H $-C\mathit{H}$ $(CH_3)_2$, 4.1-4.2 (q, 2H, $-C\mathit{H}_2-CH_3$), 8.39 (s, 1H, C_4-H); Mass (m/z): 357 corresponding to $C_{19}H_{23}N_3O_4$	221-22	52
4c			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (s, 9H, $-C\ (C\mathit{H}_3)_3$), 1.3 (t, 3H, $-CH_2-C\mathit{H}_3$), 2.1 (s, 3H, $-C\mathit{H}_3$), 4.0 (q, 2H, $-C\mathit{H}_2-CH_3$), 7.39 (s, 1H, C_4H); Mass (m/z): 329 corresponding to $C_{17}H_{19}N_3O_4$	172	70
4d			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.05-1.9 (m, 23H), 2.4 (s, $-C\mathit{H}_3$), 3.09 (m, 2H), 4.1-4.2 (q, 2H, $-C\mathit{H}_2-CH_3$), 8.3 (s, 1H, C_4-H); Mass (m/z): 437 corresponding to $C_{25}H_{31}N_3O_4$	238	45

—*Contd*

Table I — Reaction of ethyl 5-methyl -7-chloro-6-cyano -2-oxo-2*H*-pyrano [2,3-*b*] pyridine-3-carboxylate with appropriate amines and their spectral data—*Contd*

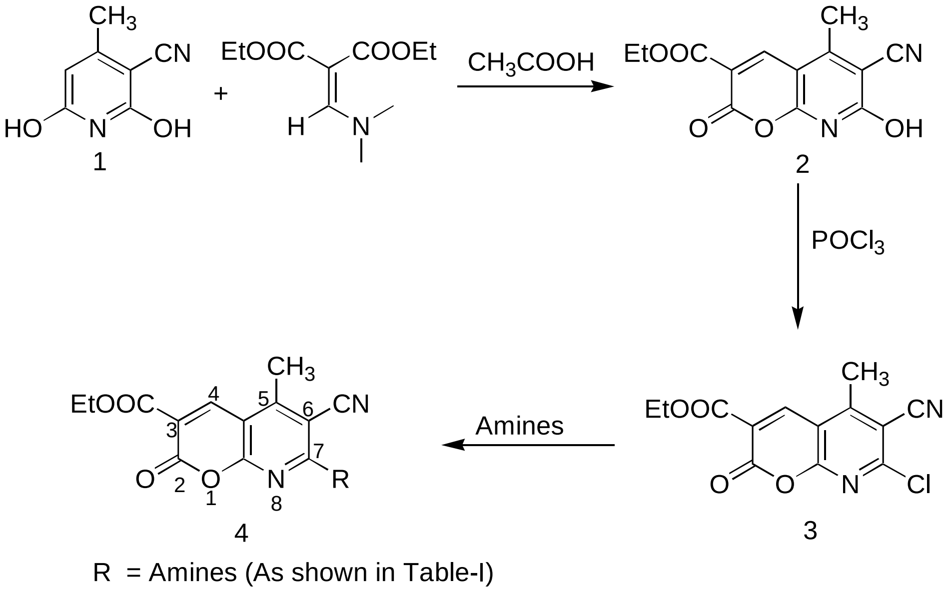
Entry	Amine	Product	Spectral data	mp °C	Yield (%)
4e			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2-1.3 (t, 3H, -CH$_2$-CH_3), 1.9-2.09 (m, 4H), 2.6 (s, 3H, -CH_3), 3.1-3.2 (t, 2H), 4.2-4.3 (q, 2H, -CH_2-CH$_3$), 7.3 (s, 1H, C$_4$H); Mass (m/z): 341 corresponding to $C_{17}H_{15}N_3O_5$	160	68
4f			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (t, 3H, -CH$_2$-CH_3), 2.4 (s, 3H, -CH_3), 3.0-3.1 (t, 4H), 3.7 (t, 4H), 4.1-4.2 (q, 2H, -CH_2-CH$_3$), 8.3 (s, 1H, C$_4$-H); Mass (m/z): 343 corresponding to $C_{17}H_{17}N_3O_5$	188	74
4g			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (t, 3H, -CH$_2$-CH_3), 2.4 (s, 3H, -CH_3), 4.1-4.2 (q, 2H, -CH_2-CH$_3$), 7.3 (s, 3H) 8.3 (s, 1H, C$_4$-H), Mass (m/z): 324 corresponding to $C_{16}H_{12}N_4O_4$	400	86
4h			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2-1.3 (t, 3H, -CH$_2$-CH_3), 2.6 (s, 3H, -CH$_3$), 3.2 (m, 4H), 3.4 (m, 4H), 4.2-4.3 (q, 2H, -CH_2-CH$_3$) 7.1 (d, 1H), 7.2 (d, 2H), 7.4 (t, 1H), 8.5 (s, 1H, C$_4$-H); Mass (m/z): 486 corresponding to $C_{24}H_{21}F_3N_4O_4$	207	89
4i			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.1-1.2 (t, 3H, -CH$_2$-CH_3), 2.4 (s, 3H, -CH$_3$), 3.31-3.39 (m, 4H), 3.6 (m, 4H), 4.1-4.2 (q, 2H, -CH_2-CH$_3$), 7.4-7.6 (m, 2H), 8.0-8.1 (d, 2H), 8.3 (s, 1H, C4-H); Mass (m/z): 475 corresponding to $C_{24}H_{21}N_5O_4S$	222	80
4j			^{1}H NMR (200 MHz, DMSO-d_6): δ 1.2 (t, 3H, -CH$_2$-CH_3), 2.0-2.18(m, 4H), 2.4 (s, 3H, -CH$_3$), 3.1-3.4 (m, 4H), 4.1-4.2 (q, 2H, -CH_2-CH$_3$), 7.3 (m, 1H), 7.7 (d, 1H), 8.0 (d, 1H), 8.3 (s, 1H, C$_4$-H); Mass (m/z): 476 corresponding to $C_{25}H_{21}FN_4O_5$	241	82

spectrum was recorded in KBr on a Perkin-Elmer 1650 spectrometer, ^{1}H NMR was recorded in DMSO-d_6 using 200 MHz Bruker spectrometer (chemical shifts in δ ppm) with TMS as internal standard and mass spectra on a HP-5989A spectrometer. The Analytical Research Department of Lupin Limited (Lupin Research Park) carried out all analytical work. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel sheets obtained from Merck & Co, Germany, which were visualized using UV light.

Preparation of 2

A mixture of **1** (5.0 g, 0.033 mole), diethyl *N*,*N*-dimethylaminoethylenemalonate (14.19 g, 0.066 mole)



Scheme II

and acetic acid was heated under reflux for 4 hr. The acetic acid was evaporated under vacuum. The reaction mass was cooled, acetone was added and the mass was stirred to precipitate out the solid. The solid obtained was filtered and washed with acetone to give **2**, which was crystallized from ethanol. Yield 94%. m.p.; 176-78°C.

Preparation of 3

A solution of **2** (5 g, 0.018 mole) in $POCl_3$ (50 mL) was stirred at room temperature for 12 hr. The reaction mixture was poured gradually into crushed ice, and was extracted with ethyl acetate (3×50 mL). The combined extract was washed with water (2×50 mL), the extract was dried over Na_2SO_4, upon evaporation of the solvent, and the obtained crude product was stirred in cyclohexane. The free flowing solid obtained was filtered to get **3**, which was crystallized from ethanol. Yield: 85 %; m.p.; 166-168°C;

Preparation of compounds 4a-j

A mixture of compound **3** (1.0 g, 0.0038 mole) and alkyl amine (5 mL) was refluxed in ethanol (10 mL) for 6-12 hr. The precipitated solid was filtered which was crystallized from ethanol (**Table I**).

Acknowledgement

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