SYNTHESIS OF 2-AMINO-4*H*-PYRAN-3-CARBONITRILES: ITS REACTION TO CHLOROACETYL CHLORIDE

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Abstracts. Some 2-amino-4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyrans were synthesized by reaction of by using three-component reaction included ethyl acetoacetate, malononitrile and appropriate substituted benzaldehydes. The role of different catalysts was examined, including organic and inorganic substances and ionic liquids. Some 2-amino-4*H*-pyran-3-carbonitriles were converted by reacting to chloroacetyl chloride. The structures of the obtained compounds were confirmed by the modern spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR).

Keywords: Catalysis, chloroacetyl chloride, ionic liquid, 4*H*-pyran.

1. Introduction

Six-membered heterocyclic compounds containing oxygen such as 4*H*-pyrans constitute an important class of biologically active natural and synthetic products, playing a fundamental role in bioorganic chemistry and continue to attract interest. Among nitrogen and oxygen containing heterocyclic compounds, pyranopyrimidine and isoxazole pharmacophores are widely used in medicinal chemistry [1,2]. Polyfunctionalized 4*H*-pyran derivative exhibits antibacterial and anti-cancer activity, is an inhibitor of EAAT1 [3] and their fused derivatives, pyranopyrimidines, are important synthetic bioactive compounds. In the recent years the synthesis of pyranopyrimidine derivatives gained renewed interest in the field of medicinal chemistry for their wide range of biological activity including antiplatelet [4], antiviral [5], antimicrobial [6,7], antimalarial [8], antigenic [9], antitumor [10], anti-inflammatory [11], antihistamine [12], ect. properties. We reprted herein the synthesis of 2-amino-4*H*-pyran-3-carbonitriles and its reaction with chloroacetyl chloride.

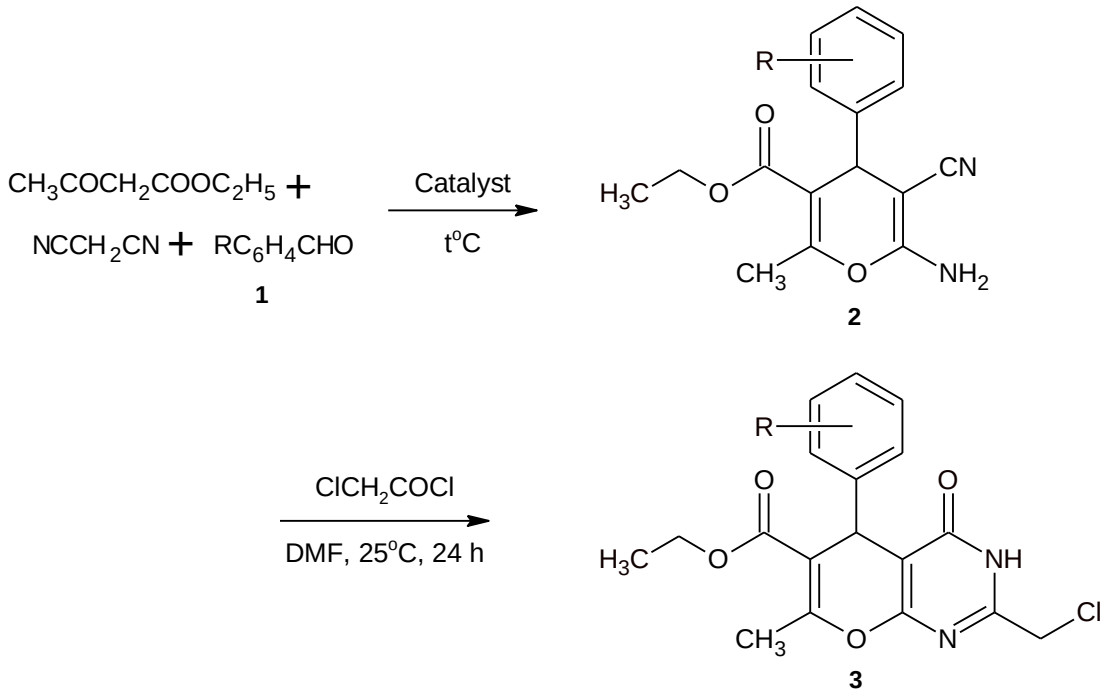
2. Results and discussion

2-Amino-4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyrans (**2a-e**) have been synthesized by reaction of ethyl acetoacetate, malononitrile and corresponding substituted benzaldehyde in 96% ethanol in the present of the catalyst. Some different catalysts for synthesis of compounds **2a-e** have been investigated initially. Substances were used as catalyst, such as 25-28% ammonium hydroxide, some ionic liquids such as [Bmim]Br, [Bmim]OH, [Et_3N]OAc and [Et_3N]For [13,14]. Results were shown in Table 1.

Table 1. Reaction conditions optimisation for the synthesis of 5a

Entry	Solvent	Temperature/°C	Time/h	Yield (%)
NH_4OH solution (25−28%)	96%-Ethanol	25	3	63
$[Et_3N]OAc$	96%-Ethanol:water (1:1)	Refluxing	2	No
$[Et_3N]For$	96%-Ethanol:water (1:1)	Refluxing	2	No
[Bmim]Br	96%-Ethanol:water (1:1)	Refluxing	2	No
[Bmim]OH	96%-Ethanol:water (1:1)	Refluxing	2	80

Note: Ac=acetyl, For=formyl, Bmim=*N*-butylimidazole.



Scheme 1. Route to 4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidines, where **1**,**2**,**3:** R=H (**a**), 3-NO_2 (**b**), 4-Cl (**c**), 2-Cl (**d**), 2-NO_2 (**e**).

Obtained ethyl esters of were in white or pale yellow crystalline forms, soluble easily in organic solvents (ethanol, methanol, DMF, DMSO, acetone, toluene…), insoluble in water, having high melting points. The IR spectra of these esters of acid 6-amino-5-cyano-2-methyl-4-aryl-4*H*-pyran-3-carboxylic had three absorption bands in region of 3429-3393, 3337-3337 and 3264-3204 cm^{-1} belonged to two stretching vibrations and Fermi resonance band of amino group, respectively.

Strong absorption band in range of 2203-2187 cm^{-1} belonged to nitrile group. Ester functional group was confirmed by absorption bands in regions at 1728-1695 cm^{-1} (C=O ester), 1267-1225 and 1065-1057 cm^{-1} (C-O-C ester). The carbon-carbon double bonds of benzene ring had some absorption bands in regions at 1611-1490 cm^{-1}. Two alkene bonds of pyran ring had absorption bands in regions at 1684-1674 and 1649-1620 cm^{-1}.

The ^{1}H and ^{13}C NMR spectral data of substituted 2-amino-4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyrans (**2a-e**) shown that protons and carbon-13 atoms in these

molecules have proper resonance signals in corresponding spectral regions which are characteristic for each type of atoms (*Figs. 1 and 2*). Aromatic protons had chemical shifts in region at δ = 8.12-7.26 ppm with multiplicities changed in depending on substituted patterns of benzene ring. Resonance signal of amino group on position 6 of pyran ring had signal in range at δ = 7.09-6,91 ppm in singlet. Proton H-4 on pyran ring had chemical shift in region of δ = 5.03-4.30 ppm in singlet.

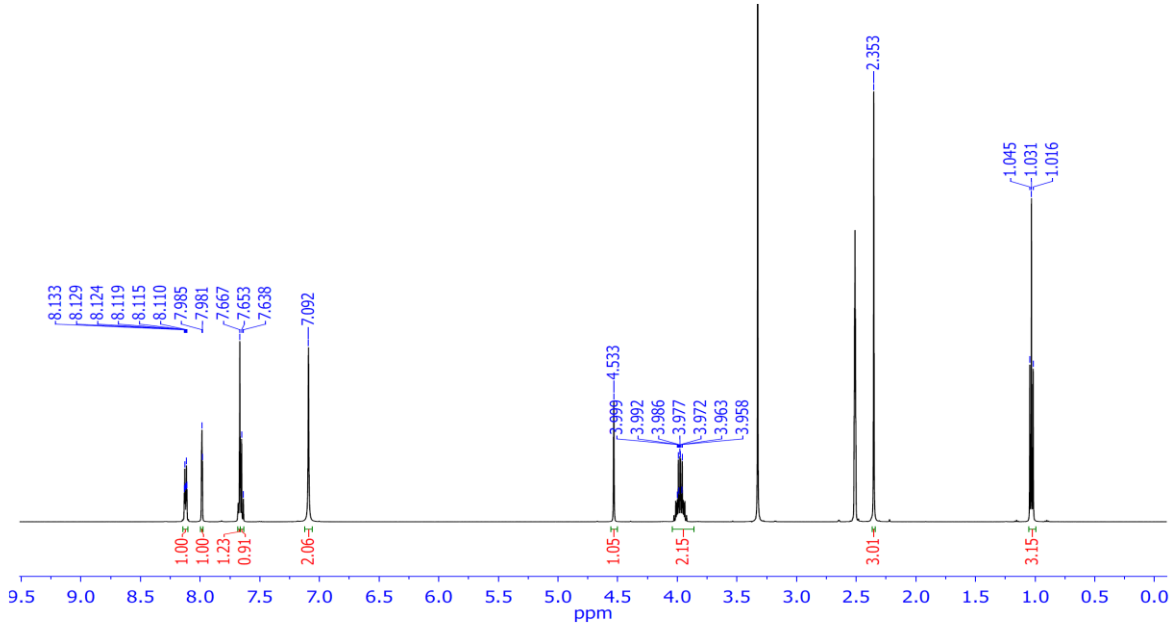


Figure 1. ^{1}H NMR of pyran **2b**.

Carboxyl group of ester had chemical shift in range of δ = 165.92-165.31 ppm. The following evidences confirmed the presence of propargylic group. Chemical shift that occurred in region of δ = 120.19-119.42 belonging to nitrile group on position 5. Methyl group had signal at δ = 2.35-2.27 ppm in singlet pattern in ^{1}H NMR spectra and δ = 18.79-18.59 ppm in ^{13}C NMR spectra.

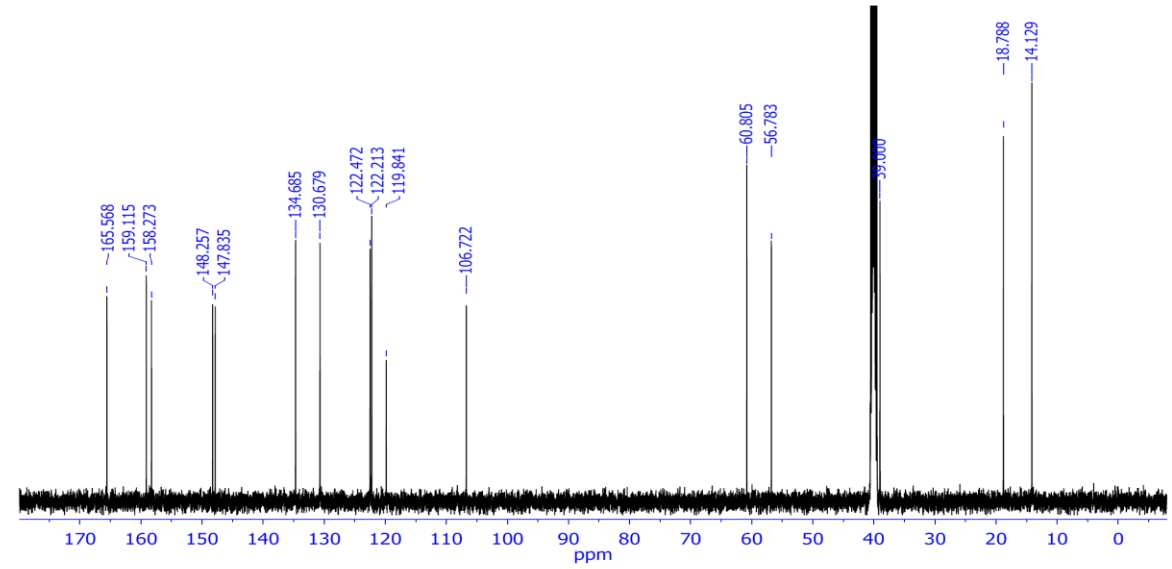


Figure 2. ^{13}C NMR of pyran **2b**.

2-Amino-3-cyano-4*H*-pyrans (**2a-e**) reacted with chloroacetyl chloride. The reaction was carried out in anhydrous DMF at room temperature for 24 hrs. The solution of pyrans **2a-e** became dark brown after chloroacetyl chloride was added. The obtained NMR spectral data showed that the ring-closure take place and 4-oxo-3,5-dihydro-4*H*-pyrano[2,3-*d*]pyrimidines (**3a-e**) were formed. Two stretching vibration bands of amino group were absent in its IR spectra. Strong absorption band of nitrile function did not also find at 2203-2187 cm^{-1} in IR spectra.

Some changes were happened in NMR of these compounds (*Figs. 3 and 4*). Signal in singlet of amino group of compounds **2a-e** that located in range at δ = 7.09-6,91 ppm was disappeared, simultaneously, a new signal in singlet appeared downfield at 13.34-10.70 ppm that belonged to amide NH group in pyrimidin-4(3*H*)-one ring.

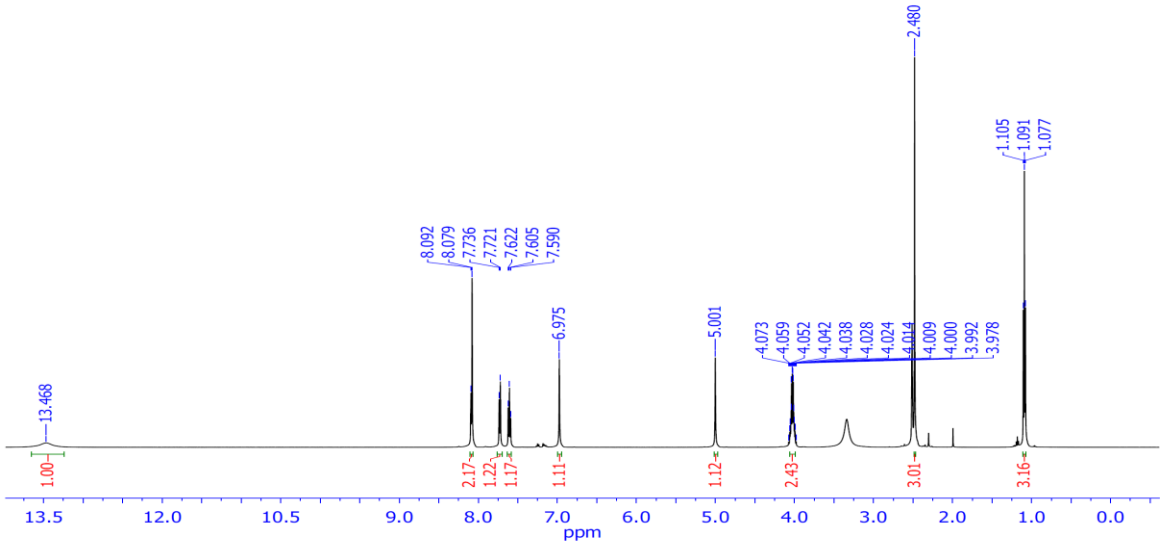


Figure 3. ^{1}H NMR of 4*H*-pyrano[2,3-*d*]pyrimidine **3b**.

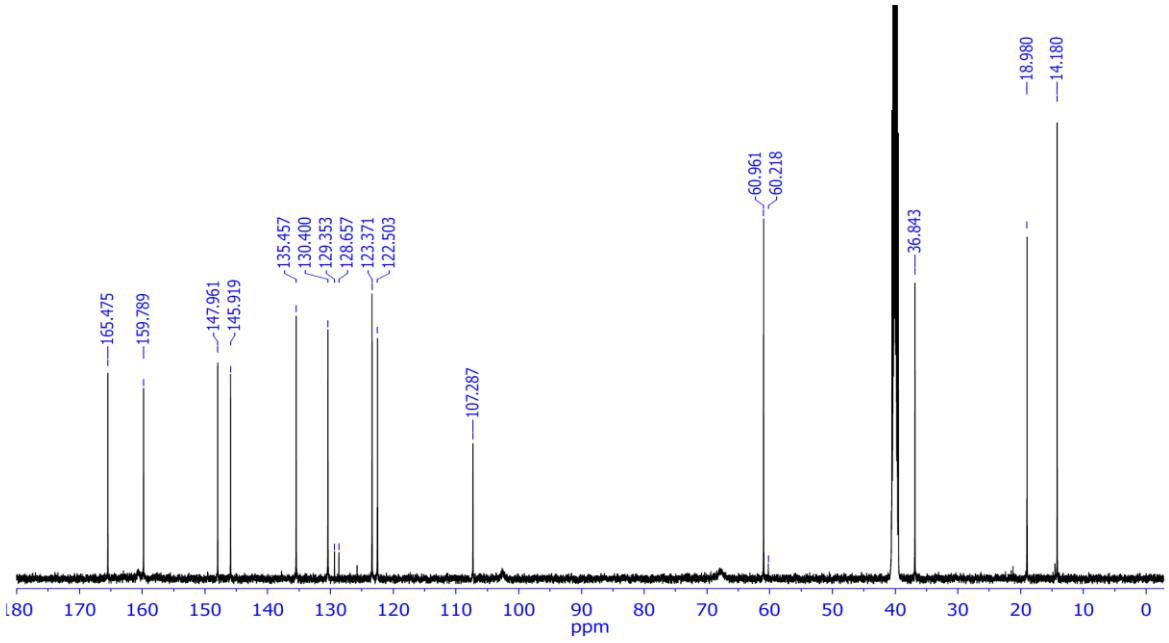


Figure 4. ^{13}C NMR of 4*H*-pyrano[2,3-*d*]pyrimidine **3b**.

All above discursions on spectroscopic characteristics asserted the structure of obtained (**2a-e** and **3a-e**).

In briefly, some substituted 2-amino-4-aryl-3-cyano-5-ethoxycarbonyl-6-methyl-4*H*-pyrans were synthesized by using three-component reaction and converted using reaction with chloroacetyl chloride.

3. Experimental Section

Melting points were determined by open capillary method on STUART SMP3 instrument (BIBBY STERILIN, UK) and are uncorrected. IR spectra (KBr disc) were recorded on an Impact 410 FT-IR Spectrometer (Nicolet, USA), ^{1}H and ^{13}C NMR spectra were recorded on Avance Spectrometer AV500 (Bruker, Germany) at 500 MHz and 125.8 MHz, respectively, using DMSO-d_6 as solvent and TMS as internal standard. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 $WF_{254}S$ (Merck, Germany).

*General procedure for synthesis of ethyl 6-amino-5-cyano-2-methyl-4-(R-phenyl)-4*H*-pyran-3-carboxylates (2)*

To a solution of ethyl acetoacetate (5 mmol), malononitrile (5 mmol) and appropriate substituted benzaldehyde **1** (5 mmol) in 96% ethanol (10 mL) was added appropriate catalyst (5 mol%, exception to NH_4OH). The reaction mixture was stirred at room temperature for 3 h and monitored by TLC on silica gel plates. When the starting materials were disappeared, the separated solid product was filtered, washed by cold 96% ethanol, crystallized from 96% ethanol to afford the title propargyl ester of substituted 4*H*-pyran-3-carbonitriles **2a-e**.

1/ R=H (a)

Yield: 93%. M.p. 195−196°C. ^{1}H NMR , δ (ppm): 7.32 (t, J = 7.5 Hz, 2H, H-3′ & H-5′), 7.23 (d, J = 7.5 Hz, 1H, H-4′), 7.15 (d, J = 7.1 Hz, 2H, H-2′ & H-6′), 6.91 (s, 2H, 6-NH_2), 4.30 (s, 1H, H-4), 4.01−3.94 (m, 2H, O**C**$\mathbf{H_2}$$CH_3$), 2.32 (s, 3H), 1.04 (t, J = 7.0 Hz, 3H, OCH_2**C**$\mathbf{H_3}$). ^{13}C NMR , δ (ppm): 165.92 (C=O ester), 158.95 (C-6), 157.06 (C-2), 145.36 (C-1), 128.91 (C-3′ & C-5′), 127.66 (C-2′ & C-6′), 127.28 (C-4′), 120.19 (C≡N), 107.72 (C-6), 60.61 (O**C**$\mathbf{H_2}$$CH_3$), 57.72 (C-3), 39.30 (C-4), 18.60 (2-CH_3), 14.19 (OCH_2**C**$\mathbf{H_3}$).

2/ R=3-NO_2 (b)

Yield: 72%. M.p. 186−187°C. ^{1}H NMR , δ (ppm): 8.12 (dt, J = 7.25, 2.5 Hz, 1H, H-4′), 7.98 (m, 1H, H-6′), 7.67 (s, 1H, H-2′), 7.65 (t, J = 7.25 Hz, 1H, H-5′), 7.09 (s, 2H, 6-NH_2), 4.53 (s, 1H, H-4), 4.01−3.94 (m, 2H, O**C**$\mathbf{H_2}$$CH_3$), 2.35 (s, 3H, 2-$CH_3$), 1.03 (t, J = 7.25 Hz, 3H, OCH_2**C**$\mathbf{H_3}$). ^{13}C NMR , δ (ppm): 165.57 (C=O ester), 159.12 (C-6), 158.27 (C-2), 148.26 (C-3′), 147.84 (C-1′), 134.68 (C-2′), 130.68 (C-6′), 122.47 (C-5′), 122.21 (C-1′), 119.84 (C≡N), 106.72 (C-3), 60.81 (O**C**$\mathbf{H_2}$$CH_3$), 56.78 (C-3), 39.00 (C-4), 18.79 (2-CH_3), 14.13 (OCH_2**C**$\mathbf{H_3}$).

3/ R=4-Cl (c)

Yield: 89%. M.p. 160−161°C. ^{1}H NMR , δ (ppm): 7.38 (d, J = 8.50 Hz, 2H, H-3′ & H-5′), 7.18 (d, J = 8.50 Hz, 2H, H-2′ & H-6′), 6.96 (s, 2H, 6-NH_2), 4.32 (s, 1H, H-4), 4.03−3.92 (m, 2H, O**C**$\mathbf{H_2}$$CH_3$), 2.32 (s, 3H, 2-$CH_3$), 1.05 (t, J = 7.25 Hz, 3H, OCH_2**C**$\mathbf{H_3}$). ^{13}C NMR , δ (ppm): 165.76 (C=O ester), 158.92 (C-6), 157.46 (C-2), 144.44 (C-1′), 131.82 (C-4′), 129.59 (C-2′ & C-6′), 128.89 (C-3′ & C-5′), 120.02 (C≡N), 107.24 (C-6), 60.70 (O**C**$\mathbf{H_2}$$CH_3$), 57.31 (C-3), 38.76 (C-4), 18.67 (2-CH_3), 14.20 (OCH_2**C**$\mathbf{H_3}$).

4/ R=2-Cl (d)

Yield: 82%. M.p. 180−182°C. ^{1}H NMR , δ (ppm): 7.44 (d, *J* = 8.0 Hz, 1H, H-3′), 7.37 (t, *J* = 7.5 Hz, 1H, H-4′), 7.29 (dd, *J* = 8.0, 1.5 Hz, 1H, H-6′), 7.26 (dt, *J* = 8.0, 1.5 Hz, 1H, H-5′), 6.99 (s, 2H, 6-NH_2), 4.95 and 4.94 (s, 1H, 0.69:0.37, H-4), 4.00−3.94 (m, 2H, O**CH_2**CH_3), 2.41 và 2.40 (s, 3H, 1.85:1.22, 2-CH_3), 1.02 (t, *J* = 7.0 Hz, 3H, OCH_2**CH_3**). ^{13}C NMR , δ (ppm): 165.62 (C=O ester), 158.98 (C-6), 158.32 (C-2), 142.63 (C-1′), 132.47 (C-2′), 130.27 (C-3′), 129.74 (C-4′), 128.85 (C-5′), 128.19 (C-6′), 119.65 (C≡N), 106.47 (C-3), 60.57 (O**CH_2**CH_3), 56.58 (C-5), 35.79 (C-4), 18.59 (2-CH_3), 14.03 (OCH_2**CH_3**).

5/ R=2-NO_2 (e)

Yield: 86%. M.p. 168−170°C. ^{1}H NMR , δ (ppm): 7.87 (dd, *J* = 8.25, 1.25 Hz, 1H, H-3′), 7.71 (td, *J* = 7.5, 1.25 Hz, 1H, H-5′), 7.47 (td, *J* = 8.25, 1.25 Hz, 1H, H-4′), 7.42 (dd, *J* = 7.5, 1.25 Hz, 1H, H-6′), 7.08 (s, 2H, 6-NH_2), 5.03 and 5.02 (s, 1H, 0.50:0.50, H-4), 3.89 (q, *J* = 7.5 Hz, 2H, O**CH_2**CH_3), 2.35 và 2.34 (s, 3H, 1.42:1.48, 2-CH_3), 0.93 (t, *J* = 7.5 Hz, 3H, OCH_2**CH_3**). ^{13}C NMR , δ (ppm): 165.31 (C=O ester), 159.45 (C-6), 158.76 (C-2), 148.99 (C-2′), 140.07 (C-1′), 134.25 (C-5′), 130.93 (C-6′), 128.58 (C-4′), 124.22 (C-3′), 119.42 (C≡N), 106.82 (C-3), 60.77 (O**CH_2**CH_3), 56.37 (C-3), 33.35 (C-4), 18.80 (2-CH_3), 13.96 (OCH_2**CH_3**).

General procedure for synthesis of ethyl 2-(cloromethyl)-7-methyl-5-(R-phenyl)-4-oxo-3,5-dihydro-4H-pyrano[2,3-d]pyrimidin-6-carboxylates (3a-e)

A mixture of compound **2** (5 mmol) and chloroacetyl chloride (0.5 mL, 5 mmol) in dimethylformamide (10 mL) was stirred for 24 h at room temperature, the reaction mixture was poured onto cold water. The obtained solid was crystallized from ethanol to give **3**.

1/ R=H (a)

Yield: 93%. M.p. 228−230°C. ^{1}H NMR, δ (ppm): 13.34 (s, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 4.1 Hz, 2H), 7.21 – 7.17 (m, 1H), 6.97 (s, 1H), 4.86 (s, 1H), 4.08 – 3.99 (m, 2H), 2.45 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ (ppm): 165.81, 158.64, 143.80, 128.72, 128.61, 127.38, 108.43, 60.79, 36.64, 18.82, 14.28.

2/ R=3-NO_2 (b)

Yield: 72%. M.p. 242−244°C. ^{1}H NMR δ (ppm): 13.47 (s, 1H), 8.09 (d, *J* = 6.6 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 6.97 (s, 1H), 5.00 (s, 1H), 4.06 – 3.99 (m, 2H), 2.48 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ (ppm): 165.47, 159.79, 159.07, 147.96, 145.92, 145.42, 135.46, 134.74, 130.40, 129.41, 129.35, 128.66, 126.85, 123.37, 122.89, 122.50, 111.96, 107.29, 60.96, 36.84, 18.98, 14.18.

3/ R=4-Cl (c)

Yield: 89%. M.p. 175−176°C. ^{1}H NMR δ (ppm): 10.70 (s, 1H), 8.05 (dd, *J* = 0.5, 2.75 Hz, 1H), 7.73 (td, *J* = 0.5, 2.75 Hz, 1H), 7.61 (td, *J* = 0.5, 2.75 Hz, 1H), 7.36 (dd, *J* = 0.5, 2.75 Hz, 1H), 5.22-5.17 (m, 3H), 3.98-3.87 (m, 2H), 2.35 (s, 3H), 1.00 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR δ (ppm): 165.67, 158.99, 142.78, 131.97, 130.56, 128.67, 107.92, 60.87, 36.26, 18.88, 14.29.

4/ R=2-Cl (d)

Yield: 82%. M.p. 156−157°C. ^{1}H NMR δ (ppm): 10.61 (s, 1H), 7.52-7.50 (m, 1H), 7.34-7.31 (m, 2H), 7.16- 7.14 (m, 1H), 5.04 (d, *J* = 7.5 Hz, 1H), 5.00 (d, *J* = 7.5 Hz, 1H), 4.00-3.89

(m, 2H), 2.37 (s, 3H), 1.08 (t, *J* = 7.25 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 165.67, 162.88, 148.86, 136.64, 134.00, 130.17, 130.05, 128.50, 128.26, 115.47, 105.55, 60.28, 37.12, 18.43, 14.32, 14.07.

5/ R=2-NO₂ (e)

Yield: 86%. M.p. 148−150°C.

^{1}H NMR δ (ppm): 10.70 (s, 1H), 8.05 (dd, *J* = 0.5, 2.75 Hz, 1H), 7.73 (td, *J* = 0.5, 2.75 Hz, 1H), 7.61 (td, *J* = 0.5, 2.75 Hz, 1H), 7.36 (dd, *J* = 0.5, 2.75 Hz, 1H), 5.22-5.17 (m, 3H), 3.98-3.87 (m, 2H), 2.35 (s, 3H), 1.00 (t, *J* = 7.0 Hz, 1H). δ (ppm): 165.47, 162.90, 149.29, 149.22, 134.89, 134.32, 129.90, 128.74, 125.48, 115.55, 104.89, 60.34, 35.13, 18.57, 14.17.

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