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GLYCEROL PROMOTED SYNTHESIS OF TETRAHYDROCYCLOPENTA[*B*]PYRAN VIA A MULTICOMPONENT-TANDEM STRATEGY UNDER CATALYST FREE CONDITIONS

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Abstract :The development of aone pot, multicomponent-tandem, catalyst free, facilesynthesis of cyclopenta[*b*]pyranand its derivatives is reported.Thekey feature of the reported method is the use of glycerol, as an inexpensive, eco-sustainable,biodegradable and reusablebiomolecule as a solvent cum promoter making ita useful green method.

Keywords: Cyclopenta[*b*]pyran,multicomponent, catalyst free, green synthesis, glycerol, carbocycles

Introduction

The design of novel synthetic strategies for the synthesis of carbocycles having five-membered ring are of great interest due to theirabundantdistributionin biologically important naturally occurring molecules.[i]Among five-membered carbocycles,cyclopenta[*b*]pyran are of great interest due to their interesting biological properties and their presence as a key structural feature in a number of the natural products.[ii]Recently, the isolation of two cyclopenta[*b*]pyran based natural products and their antimicrobial and anticancer activities have been described by Ueda et al.[iii]

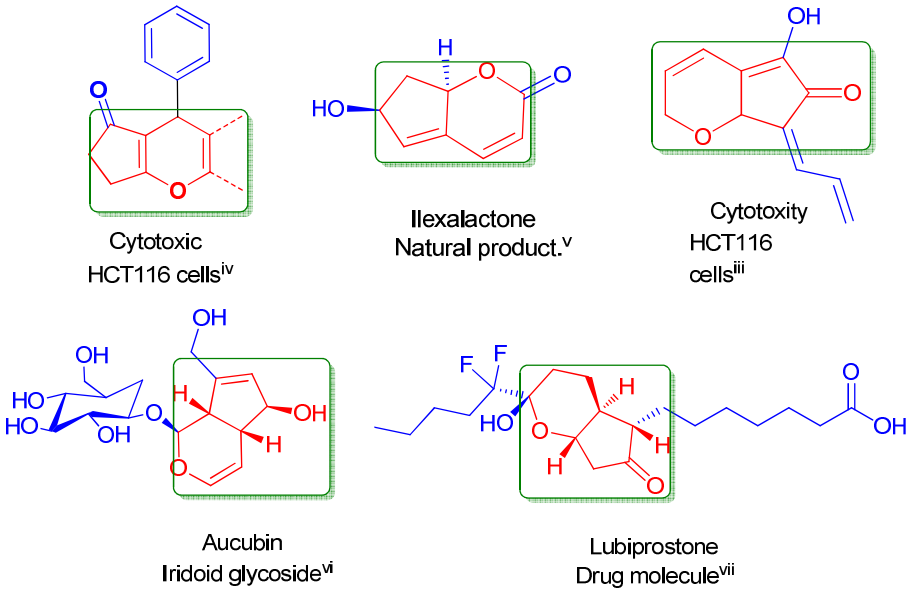
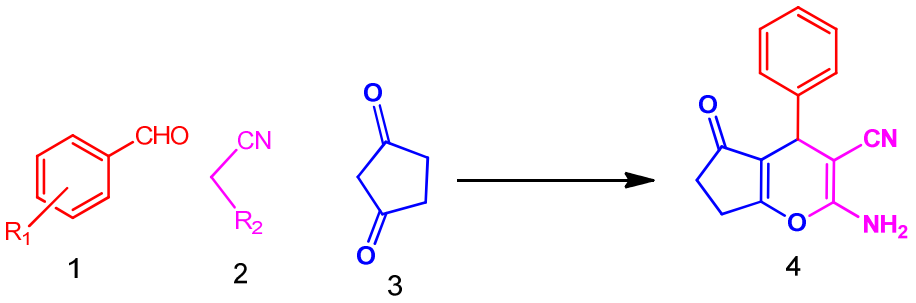


Figure 1. Examples of some cyclopenta[*b*]pyranbased bioactive molecules and natural products

Surprisingly in spite of the potential biological importance of cyclopenta[*b*]pyrans,only a handful of methods for their synthesis have been reported so far.[iib,iii,iv,viii] Moreover the reported methods suffer from one or more drawbacks such as low yields, long reaction times, harsh reaction conditions, tedious work-up procedures, use of toxic and expensive catalysts, use of hazardous solvents and non-recyclability of catalysts and solvents. Consequently the development of more efficient routes to access existing as well as novel cyclopenta[*b*]pyran derivatives remains an important goal for organic chemists.

In the past decade numerous solvents[ix-xiv] have been used as potential substitutes to conventional organic solvents.Although some interesting results have been reported, their use usually involves one or more limitations, such ashigh prices or expensive apparatus,[xv, xvi]difficulty in product separation[xvii] andinsufficient satisfactory data about their toxicity and bio-compatibility.[xviii]In this backdrop glycerol has emerged as an interesting alternative solvent. It combines the benefits of both water and ionic liquids,[xix] is biodegradable, renewable, cheap, non-toxic and easily available. Because of these unique properties, glycerol is finding increasing application as a cheap, convenient and eco-friendly solvent in organic transformations.[xx]

Consequently as part of our continuing efforts towards the development of green synthetic routes to important heterocyclic molecules,[xxi]we herein report the development of a new catalyst free, clean and efficient, one pot synthesis of cyclopenta[*b*]pyran using glycerol as a green promoting media.



Scheme 1. General synthetic strategy

Result and discussion

Initially, the reaction between 4-nitrobenzalaldehyde (1a), malononitrile (2a) and cyclic 1,3-diketone (3a) was investigated in different solvents. Only trace amount of product formation was detected in toluene, DMF, DMSO, n-butyl acetate and in neat conditions (Entries 1-4). Although the reaction was successful in water, it tooktoo much time with the formation of the product in low yield (Entry 5). When the reaction was conducted in ethanol andethanol:water / 1:1 mixture(Entries 6-7) although there was a moderate increase in the yield of the product the reaction proceeded very sluggishly.A further increase in yield was noticedin polyethylene glycol (Entry8). Encouraged by the observed determinant effect of polar protic solvents on the reaction, we decided to investigate the efficacy of glycerol as a solvent for this reaction. As expected, the reaction proceeded very smoothly, with the formation of the desired product in 95% under identical conditions (Entry 12). Interestingly, all starting materials are soluble in glycerol. All obtained products were found to be insoluble in glycerol, so with progress of the reaction, slow sedimentation of the product occurred from the reaction mixture.

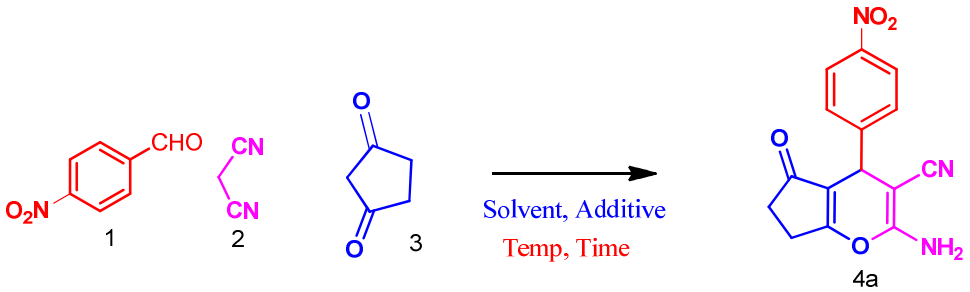


Table 1. Effect of different solvents,and temperature on the yield of product[b]

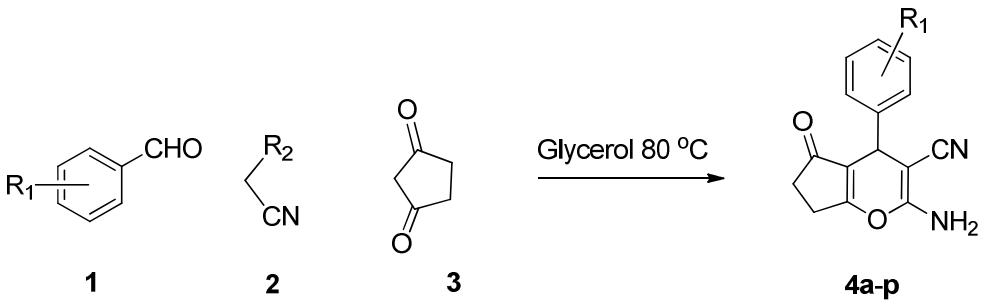
Entry	Solvent	Additive	Temperature	Time	Yield (%)[b]
1	Toluene	None	80 °C	12 h	trace
2	DMF	None	80 °C	12 h	trace
3	DMSO	None	80 °C	12 h	trace
4	n-Butyl acetate	None	80 °C	12 h	trace
5	Water	None	80 °C	12 h	40
6	Ethanol	None	80 °C	6 h	48
7	Ethanol:Water / 1:1	None	80 °C	6 h	56
8	PEG-400	None	80 °C	7h	83
9	Glycerol	None	RT	6h	60

10	Glycerol	None	40 °C	3 h	80
11	Glycerol	None	60 °C	2h	86
12	Glycerol	None	80 °C	1 h	95
13	Glycerol	None	90 °C	1 h	95
14	Glycerol	None	100 °C	1 h	95

[a]All reactions were carried out with **1a** (1 mmol),**2a** (1mmol), **3a** (1mmol),solvent (5 mL) under air.[b]Isolated yields. *This work.

With the optimization results in hand (Table 1), we investigated the scope and limitations of the present method, and the results are listed in table 2. A variety of substrates were used and it was observed that reaction proceeded well and the desired products were formed in good to excellent yields in all the instances(Table 2). Presence of electron withdrawing groups on aromatic aldehydes (Table 2) enhanced the reaction ratewhileelectron releasing groups inhibited the reaction (Table 2).

Table 2. Substrate scope[a]



Entry	R_1	R_2	Product	Time (h)	Yield (%)[b]	Reference
1	2-ClC_6H_4	CN	4b	1.8	88	4
2	C_6H_5	CN	4c	2.5	86	4
3	4-BrC_6H_4	CN	4d	3.0	84	4
4	2-FC_6H_4	CN	4e	1.4	85	4
5	3,4-$Cl_2C_6H_3$	CN	4f	2.5	82	4
6	3-ClC_6H_4	COOEt	4g	5	80	4
7	3,4-$Cl_2C_6H_3$	COOEt	4h	4.6	78	4
8	Thien-2-yl	CN	4i	5	91	4
9	2,4-$Cl_2C_6H_3$	COOEt	4j	5.4	84	4
10	4-ClC_6H_4	CN	4k	1.7	94	8b
11	4-FC_6H_4	CN	4l	1.8	95	8b
12	2,6-$Cl_2C_6H_3$	CN	4m	2.4	93	8b
13	3-FC_6H_4	CN	4n	1.5	92	8b
14	4$CH_3OC_6H_4$	CN	4o	2.3	92	8b
15	2$CH_3OC_6H_4$	CN	4p	3	90	8b

[a]All reactions were carried out , using respective aldehydes (1mmol), active methylene compound (1mmol) and 1,3-diketone(3) (1mmol) at 80[o]Cunder air.[b] Isolated yields

The formation of the desired compound seemed to be initiated by Knoevenagel condensation of the aldehyde and malononitrile to give cyano-olefin **I** followed by Michael type addition between 1,3-diketone and cyano-olefin **I** leading to intermediate **II**. Cyclization resulting through attack of the enolate ion on the nucleophilic nitrile group followed by tautomeric proton shift finally furnishes the tetrahydrocyclopenta[*b*]pyran. It is assumed that the polar amphoteric hydroxyl groups of the glycerol facilitates the interaction of weak acidic and basic components due to the stabilization of the corresponding transition states and intermediates by hydrogen bonding.

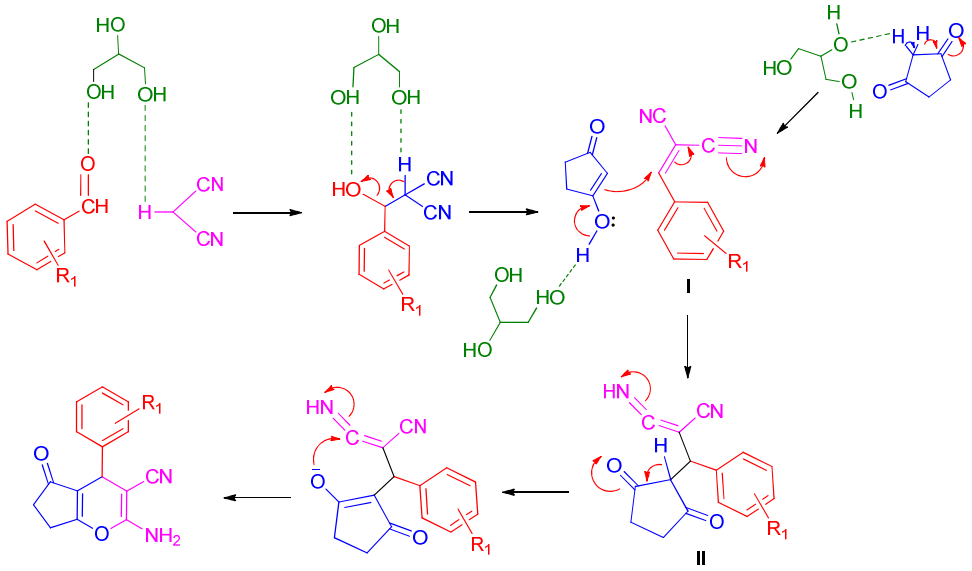
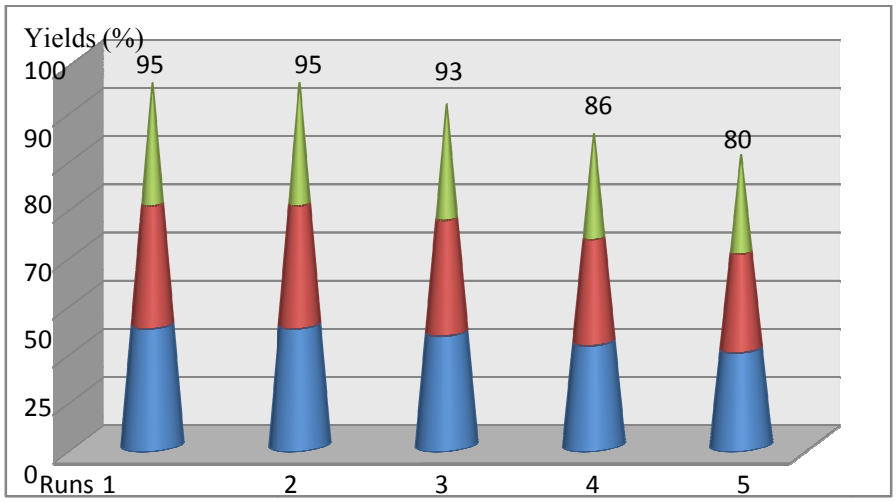


Figure 2. Plausible Mechanism for the synthesis of tetrahydrocyclopenta[b]pyran

Finally we turned our attention towards exploring the recyclability of glycerol (Scheme 2). Due to the highly hydrophilic nature ofglycerol, its separation from product is done by adding hot water. Glycerol easily dissolved in hot water while the product remainedinsoluble.



Scheme 2. Recyclability of glycerol

The solid product was obtained by simple filtration and the filtrate containing glycerol was evaporated *in vacuo* to obtain pure glycerol which was again used for the next cycle.The yield of the product was not significantlyaffected in the first three cycles but there was noticeable reduction in yield in the fourth cycle. Thus recyclability of glycerol makes it an ideal solvent for carrying out this reaction.

Experimental

General Remarks

All the chemicals were reagent grade and purchased from Alfa Aesar, Merck, Aldrich, Qualigensand Spectrochem, and were used as such. The reactions were examined using precoatedAluminium TLC plates of silica G/UV-254 of 0.25 mm thickness (Merck 60 F-254). Column chromatography was performed using silica gel (60-120) and (100-200). NMR spectra were recorded on a Bruker Avance-II 400FT spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C) in DMSO or $CDCl_3$ using TMS as an internal reference. Mass spectra (ESIMS) were obtained on a Waters UPLC-TQD mass spectrometer. IR spectra were recorded on a Thermo Scientific Nicolet iS5 FT-IR spectrometer.Elemental analyses were carried out in a Perkin Elmer2400 CHN Elemental Analyser. Melting points were determined by open glass capillary method and were uncorrected.

General Experimental Procedure

To a round bottom flask containing 5 ml glycerol was added 4-nitro benzaldehyde (1 mmol) and malononitrile (1 mmol) under stirring and the temperature of the reaction was set at 80 ºC. After formation of cyanoolefin, cyclic 1,3-diketone (1 mmol) was added to the reaction mixture and it was allowed to stir till the completion of the reaction (TLC). Now warm water was added to the reaction mixture to dissolve the glycerol and resultinginsoluble solid crude product which was separated by simple filtration was as good as pure compound (^{1}H NMR). The filtrate containing glycerol was extracted with methyl *t*-butyl ether to remove any

organic compounds dissolved in the aqueous layer.The aqueous phase was evaporated *in vacuo* to give pure glycerol which was used for the next cycle.

2-amino-4-(4-nitrophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (4a)M. p. 198-201 ^{o}C; (IR(KBr)): 3386, 2185, 1668, 1231; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)8.12(d,*J*=8.3Hz,2H,), 7.62(d,*J*=8.7Hz, 2H), 7.32(s,2H),4.34(s,1H,ArCH), 2.61-2.78(m,2H,),2.23-2.35 (m,2H).MS (ESI):m/z 297; found 298 $[M+H]^{+}$Anal. calcd for$C_{15}H_{11}N_3O_4$C, 60.61; H, 3.73; N, 14.14; found C, 60.64; H, 3.77; N, 14.17; %.

2-amino-4-(2-chlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile(4b) M. p. 192-196 ^{o}C; IR (KBr): 3463, 2193, 1681, 1631; cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm) 7.31 (d, *J* = 8.1 Hz, 1H), 7.32-7.25 (m, 2H,), 7.21(s, 2H), 7.21 (d, *J* = 7.0 Hz, 1H), 4.57 (s, 1H), 2.80-2.72 (m, 2H), 2.41-2.38 (m, 2H);MS (ESI): m/z: 309; found 310 $[M+H]^{+}$;Anal. calcd for$C_{15}H_{11}ClN_2O_2$: C, 62.84; H, 3.87; N, 9.77; foundC, 62.88; H, 3.89; N, 9.80%.

2-amino-4-phenyl-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile(4c)M. p. 191-193^{o}C; IR ((KBr): 3397, 2289, 1635, 1194 ; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.21 (t, *J* = 7.5Hz, 2H,), 7.12 (t, *J* = 7.1 Hz, 3H,),7.09 (s, 2H,),4.18 (s, 1H,), 2.71-2.64 (m, 2H,),2.31 (t, *J*=4.7Hz ,2H,).MS (ESI): m/z: 252 found253 $[M+H]^{+}$Anal. calcd for$C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10; foundC, 71.44; H, 4.78; N, 11.12%.

2-amino-4-(4-bromophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (4d) M. p. 198-200 ^{o}C; (IR(KBr))(ν, cm^{-1}): 3448, 2185, 1660, 1265 ; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm) 7.40 (d,*J*=8.3Hz,2H), 7.21(s,2H), 7.11(d,*J*=8.1Hz,2H), 4.21(s,1H),2.67-2.80(m,2H),2.31(t,*J*=4.1Hz,2H).MS (ESI):m/z: 330 found331.$[M+H]^{+}$Anal. calcd for$C_{15}H_{11}BrN_2O_2$:C, 54.40; H, 3.35; N, 8.46; found: C, 54.41; H, 3.36; N, 8.47%.

2-amino-4-(2-fluorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile(4e)M. p. 193-195 ^{o}C;IR (IR(KBr))(ν, cm^{-1}): 3328, 2184, 1652, 1232; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.21 (d, *J* = 7.1Hz, 1H), 7.18(s,2H), 7.09-7.18(m,3H),4.38(s,1H), 2.69-2.81 (m,2H,),2.38(t,*J*=3.8Hz,2H).MS (ESI): m/z: 270 found: 271. $[M+H]^{+}$Anal. calcd for$C_{15}H_{11}FN_2O_2$:C, 66.66; H, 4.10; N, 10.37; found:C, 66.67; H, 4.11; N, 10.38%.

2-amino-4-(3,4-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta [*b*]pyran-3-carbonitrile(4f)M. p. 203-206 ^{o}C;(IR(KBr)): 3334, 2187, 1634, 1236, 1218; cm−1; ^{1}H NMR (300MHz DMSO-d_6)(δ, ppm) 7.46(d,*J*=8.1Hz,1H,), 7.38(d,*J*= 1.5Hz,1H,), 7.34(s,2H),7.18(d,*J*=8.1Hz,1H),4.28(s,1H),2.72-2.56(m,2H),2.38(t,*J*=4.3Hz,2H). MS (ESI): m/z: 320 found: 321. . $[M+H]^{+}$Anal. calcd for$C_{15}H_{10}Cl_2N_2O_2$:C, 56.10; H, 3.14; N, 8.72; found:C, 56.11; H, 3.15; N, 8.73%.

Ethyl,2-amino-4-(3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carboxylate (4g) M. p. 140-143 ^{o}C;(IR(KBr):3423, 1736, 1666, 1276; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.74 (s, 2H),7.16 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 10.0 Hz, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 4.26 (s, 1H), 3.88-3.74 (m, 2H), 2.70-2.86 (m, 2H), 2.28 (t, *J* = 2.8 Hz, 2H), 0.76 (t, *J* = 7.2 Hz, 3H)MS (ESI): m/z: 333 found: 334.$[M+H]^{+}$Anal. calcd for$C_{17}H_{16}ClNO_4$:; C, 61.18; H, 4.83; Cl, 10.62; N, 4.20; found:C, 61.19; H, 4.84; N, 4.21%.

Ethyl,2-amino-4-(3,4-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta [*b*]pyran-3-carboxylate (4h) M. p. 140-144 ^{o}C; (IR(KBr)): 3415, 1744, 1637, 1276; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.87(s,2H,), 7.38(d,*J*=4.3Hz,1H), 7.01(s,1H),7.14-7.11(m,1H),4.37(s,1H),3.95-3.82(m,2H), 2.72-2.68(m,2H), 2.36-2.21(m,2H), 0.96 (t, *J* = 6.7 Hz, 3H). MS (ESI): m/z: 367; found: 368 $[M+H]^{+}$Anal. calcd for$C_{17}H_{15}Cl_2NO_4$: C, 55.45; H, 4.11; N, 3.80; found C, 55.46; H, 4.12; N, 3.81%.

2-amino-5-oxo-4-(thiophen-2-yl)-4,5,6,7-tetrahydrocyclopenta[*b*]pyran-3-carbonitrile (4i) M. p. 171-173 ^{o}C; (IR(KBr)): 3301, 2184, 1664, 1234; cm−1; ^{1}H NMR (300MHzDMSO-d_6) (δ,ppm):7.28(dd,J_1=1.5Hz, J_2= 4.1Hz,1H), 7.28(s,2H), 6.87(s,2H), 4.48(s,1H),2.78-2.60(m,2H),2.38(t,*J*=4.8 Hz,2H). MS (ESI): m/z: 258; found: 259.$[M+H]^{+}$Anal. calcd for$C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85; found:C, 60.46; H, 3.91; N, 10.86%.

Ethyl 2-amino-4-(2,4-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta [*b*]pyran-3-carboxylate (4j) M. p. 147-153 ^{o}C;(IR(KBr)): 3331, 1725, 1652, 1267; cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.81(s,2H,), 7.48(d,*J* = 2.2 Hz,) 7.41-7.38 (m,1H,),7.15(d, *J* =8.1Hz,1H,),4.73(s,1H,ArCH),3.88-3.81(m,2H,),2.73-2.63(m,2H,),2.30-2.20(m,2H,), 0.94(t,*J*= 6.1Hz,3H,). MS (ESI): m/z: Calcd. for $[M+H]^{+}$367 found: 368. $[M+H]^{+}$Anal. calcd for$C_{17}H_{15}Cl_2NO_4$: C, 55.45; H, 4.11; N, 3.80; found C, 55.46; H, 4.12; N, 3.82%.

2-amino-4-(4-chlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (4k) M. p. 146-150 ^{o}CIR (KBr, m, cm-1): 3370, 2180, 1630, 1250, cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.98 (d, J = 8.2 Hz, 1H), 7.58(d, J = 8.2 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.6Hz, 2H), 4.10 (s, 1H), 2.96–2.83(m, 4H); MS (ESI): m/z 286 found: 287$[M+H]^{+}$Anal. calcd for$C_{15}H_{11}ClN_2O_2$:C, 62.84; H, 3.87; N, 9.77; found: C, 62.85; H, 3.88; N, 9.76%.

2-amino-4-(4-fluorophenyl)-5-xo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (4l)M. p. 140-143 ^{o}CIR (KBr, m, cm-1): 3346, 2188, 1263 cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm) 7.84(t, J = 5.5 Hz, 2H), 7.46 (t, J = 8.2 Hz, 1H), 7.47 (t, J = 8.2 Hz, 2H), 7.31 (t, J = 8.6 Hz, 1H), 5.37 (s, 1H), 3.87 (s, 1H), 2.95–2.65(m, 3H); MS (ESI): m/z 269found: 270 $[M+H]^{+}$Anal. calcd for$C_{15}H_{11}FN_2O_2$C, 66.66; H, 4.10; F, 7.03; N, 10.37;found C, 66.67; H, 4.11; F, 7.04; N, 10.38%.

2-amino-4-(2,6-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (4m)M. p. 200-206 ^{o}C IR (KBr,cm-1): 3470, 2294, 1773,1133,; cm−1; ^{1}H

NMR(300MHz DMSO-d_6) (δ, ppm)7.46 (d, J = 8.3 Hz, 1H,), 7.68 (s, 1H,), 7.47 (s, 2H),7.40 (t, J = 8.2 Hz, 1H), 4.67 (s, 1H), 2.82 (s, 2H), 2.48 (d,J = 5.4 Hz, 2H); MS (ESI): m/z 320 found: 321 $[M+H]^+$Anal. calcd for$C_{15}H_{10}Cl_2N_2O_2$ C, 56.10; H, 3.14; N, 8.72;found: C, 56.11; H, 3.15; N, 8.73%.

2-amino-4-(3-fluorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (4n)M. p. 180-184 ^{o}CIR (KBr, m, cm-1): 3392, 2193, 1696, 1096, cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm) 7.43–7.35 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H,), 7.11 (t, J = 8.5 Hz,1H,), 4.12 (s, 1H), 3.12–2.92 (m, 4H,); MS (ESI): m/z 270 found: 271$[M+H]^+$Anal. calcd for$C_{15}H_{11}FN_2O_2$C, 66.66; H, 4.10; F, 7.03; N, 10.37;found C, 66.67; H, 4.11; F, 7.04; N, 10.38%.

2-amino-4-(4-methoxyphenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (4o)M. p. 140-142 ^{o}CIR (KBr, m, cm-1): 3411, 2201, 1701, 1199, cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm)7.26(d, J = 8.2 Hz, 1H), 7.41 (s, 2H), 6.90 (d, J = 8.3 Hz), 6.85 (d, J = 12.1 Hz), 4.12 (s, 1H), 3.63 (s, 3H),2.92–2.87 (m, 2H), 2.48 (t, J = 4.3 Hz, 2H); MS (ESI): m/z 282, found: 283 $C_{16}H_{14}N_2O_3$C, 68.07; H, 5.00; N, 9.92;found C, 68.08; H, 5.01; N, 9.93%.

2-amino-4-(2-methoxyphenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (4p) M. p. 144-146 ^{o}CIR (KBr, m, cm-1): 3190, 2289, 1761, 1197, cm−1; ^{1}H NMR (300MHz DMSO-d_6) (δ, ppm) 7.18 (d, J = 7.1Hz, 1H), 7.01 (s, 2H), 6.88 (t, J = 5.4 Hz, 2H), 6.77 (t, J = 7.1 Hz, 1H), 4.61 (s, 1H), 3.66 (s, 3H), 2.72–2.57 (m, 2H), 2.31 (t,J = 4.1 Hz, 2H); MS (ESI): m/z 281 found: 282 $[M+H]^+$Anal. calcd for$C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92; found C, 68.08; H, 5.01; N, 9.93%.

Conclusion

In summary, we have developed a simple, yet highly efficient, one pot, catalyst-free approach to obtain highly functionalized tetrahydrocyclopenta[*b*]pyran using glycerol as an inexpensive, biodegradable and biorenewable,easily available promoting medium.Short reaction times, operational simplicity,easy workup procedures, potential for recycling of the reaction medium,100% atom economy, high yields and finally agreement with green chemistry principles,make the presentapproachan attractive alternativeto existing methods.

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