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Water mediated synthesis, spectral and structural studies of ethyl 6-amino-4-aryl-5-cyano-2-propyl-4*H*-pyran-3-carboxylates: Single crystal X-ray structure of ethyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-propyl-4*H*-pyran-3-carboxylate

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HIGHLIGHTS

- Water mediated synthesis of ethyl 6-amino-4-aryl-5-cyano-2-propyl-4*H*-pyran-3-carboxylates.
- Spectral characterization by IR, 1D and 2D NMR (HSQC and HMBC).
- Single crystal XRD analysis of ethyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-propyl-4*H*-pyran-3-carboxylate.

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ABSTRACT

An efficient and multifunctional three component synthetic protocol was developed to synthesize ethyl 6-amino-4-aryl-5-cyano-2-propyl-4*H*-pyran-3-carboxylates from ethyl 3-oxohexanoate, malononitrile and corresponding aldehydes (**1a–11a**) using K_2CO_3 as a catalyst under water solvent in good yields. The derived compounds have been analyzed by IR and NMR (1D and 2D) spectra. Single crystal X-ray structural analysis of **2a,** evidences the flattened-boat conformation of pyran ring and the phenyl group is nearly perpendicular to the pyran ring.

1. Introduction

Multi Component Reactions (MCR's) involving the simultaneous molecular interaction between three or more components and the issue of selectivity is of particular significance due to the high probability of multi potential parallel reaction pathways leading to different product classes [1,2]. In recent years MCRs have received considerable attention due to their advantages over conventional multistep synthesis [3]. These reactions constitute an especially useful synthetic strategy since they provide mild, easy and rapid access to large libraries of organic molecules with diverse substitution patterns. In addition, multicomponent reactions are more environmentally benign and atom economic as they avoid time-consuming and costly purification processes, as well as protection and deprotection steps [4,5]. Interesting progress has been achieved in areas of selectivity control, connectivity and catalysis, etc. [6,7].

In multistep organic synthesis, several difficult issues arise such as isolation of the products, the corrosive nature of reagents and solvents [8–15]. There is a need for facile, nonpolluting and efficient synthetic procedures that reduce the use of organic solvents, tedious work-up processes and toxic reagents [16]. Although a large number of new synthetic procedures were reported for 4*H*-pyrans, relatively few examples are known for the preparation of substituted 4*H*-pyrans [17–24].

Pyran based heterocyclic compounds are having an important place due to their distinct structures and great potential for further transformations. Active 2-amino-4*H*-pyrans are particularly privileged pharmacological scaffolds among the heterocyclic family members [25]. 2-Amino-4*H*-Pyran derivatives are an important

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class of heterocycles, which have attracted considerable interest due to their useful pharmaceutical and biological properties including antiviral [26], antimicrobial [27], antifungal [28] and cancer therapy [29]. Some new methods for the synthesis of pyrans via MCR's have been reported and several catalysts like $InCl_3$ [30], PEG1000-DAIL/EM [31], Triethanolamine [32], [Bmim] BF_4 [33], Mg/La [34], NH_4OAc [35], Nano ZnO [36–38], Na_2CO_3 [39], Et_3N [40,41], MgO [42], Piperazine [43], S-proline [44], SiO_2 NPs [45], and DMAP [46] have been used for this transformation. However, in most of the cases the synthesis was carried out using toxic solvents or the observed yields are low. Considering the synthetic and therapeutic significance of ethyl 6-amino-4-aryl-5-cyano-2-propyl-4H-pyran-3-carboxylates, it was considered worthwhile to synthesize a series of ethyl 6-amino-4-aryl-5-cyano-2-propyl-4H-pyran-3-carboxylates.

2. Experimental

All chemicals were obtained from commercial suppliers and used without further purification. Melting points were measured in open capillary tubes and are uncorrected. IR spectra were recorded on Avatar Nicolet FT-IR spectrophotometer (range 4000–400 cm^{-1}) as KBr pellets. The ^1H and ^{13}C spectra were recorded at 298 K on a Bruker AMX-400 spectrometer (^1H at 400.13 MHz, ^{13}C at 100.63 MHz) in $CDCl_3$ using TMS as the internal reference. Elemental analyses were recorded on a Thermo Finnegan Flash EA 1112 analyzer. Mass spectra were recorded on VG7070H mass spectrometer.

2.1. General procedure

A mixture of corresponding aldehyde (1.0 mmol), ethyl 3-oxohexanoate (1.0 mmol) and malononitrile (1.0 mmol) in 15 mL saturated K_2CO_3 solution was hand stirred for 3–5 min at 60 °C. After the addition of water (50 mL), the resulting precipitate was collected by filtration and washed with a large portion of cold water to give a pure product for analysis.

2.1.1. Ethyl 6-amino-5-cyano-4-phenyl-2-propyl-4H-pyran-3-carboxylate (**1a**)

Yellow solid, mp: 112–114 °C; yield: 94%; IR (KBr, cm^{-1}): 3402, 3320 (NH_2), 2191 (CN), 1703 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm)δ: 7.31–7.18 (m, 5H, Ar-H), 4.52 (s, 2H, NH_2), 4.45 (s, 1H, (H-4)), 4.03–3.99 (m, 2H, CH_2 (H-8)), 2.81–2.64 (m, 2H, CH_2 (H-10)), 1.70–1.64 (m, 2H, CH_2 (H-11)), 1.09 (t, 3H, J = 10 Hz, (H-9)), 1.00 (t, 3H, J = 14.8 Hz, (H-12); ^{13}C NMR (δ): 165.7, 160.2, 157.6, 143.8, 128.6, 127.5, 127.2, 119.0, 107.9, 62.6, 60.6, 38.8, 33.2, 20.8, 13.8, 13.7. HRMS m/z 313.1. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.14; H, 6.54; N, 8.85%.

2.1.2. Ethyl 6-amino-4-(2-chlorophenyl)-5-cyano-2-propyl-4H-pyran-3-carboxylate (**2a**)

Yellow solid, mp: 118–120 °C; yield:87%; IR (KBr, cm^{-1}): 3440, 3325 (NH_2),2196 (CN), 1703(C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm)δ: 7.35–7.15 (m, 4H, Ar-H), 5.09 (s, 1H, (H-4)), 4.52 (s, 2H, NH_2), 4.03–3.98 (m, 2H, CH_2 (H-8)), 2.84–2.71 (m, 2H, CH_2 (H-10)), 1.73–1.68 (m, 2H, CH_2 (H-11)), 1.07 (t, J = 12 Hz, 3H, (H-9)), 1.03 (t, J = 12 Hz, 3H (H-12)); ^{13}C NMR (δ): 165.4, 161.1, 157.7, 141.1, 133.1, 129.8, 129.7, 128.3, 127.2, 118.5, 106.9, 61.0, 60.6, 35.5, 33.1, 20.7, 13.7, 13.7. HRMS m/z 347.1. Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.48; H, 5.45; N, 8.19%.

2.1.3. Ethyl 6-amino-4-(3-chlorophenyl)-5-cyano-2-propyl-4H-pyran-3-carboxylate (**3a**)

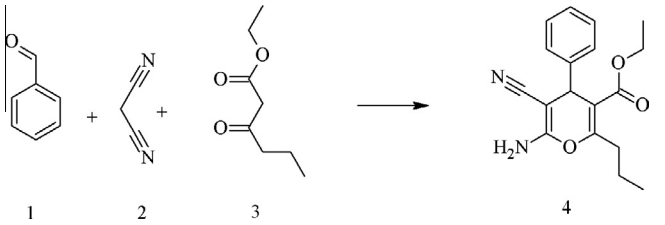
Yellow solid, mp: 116–118 °C; yield:90%; IR (KBr, cm^{-1}): 3391, 3325 (NH_2), 2191 (CN), 1692 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm)δ: 7.28–7.10 (m, 4H, Ar-H), 4.60 (s, 2H, NH_2), 4.45 (s, 1H, (H-4)), 4.08–4.04 (m, 2H, CH_2 (H-8)), 2.76–2.75 (m, 2H, CH_2 (H-10)), 1.69–1.68 (m, 2H, CH_2 (H-11)), 1.14 (t, J = 12 Hz, 3H, (H-9)), 1.01 (t, J = 12 Hz, 3H (H-12)); ^{13}C NMR (δ): 165.4, 160.6, 157.8, 145.9, 134.4, 129.8, 127.7, 127.4, 125.8, 118.6, 107.5, 61.6, 60.7, 38.7, 33.2, 20.7, 13.8, 13.6. HRMS m/z 347.1 Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.19; H, 5.48; N, 8.16%.

2.1.4. Ethyl 6-amino-4-(4-chlorophenyl)-5-cyano-2-propyl-4H-pyran-3-carboxylate (**4a**)

Yellow solid, mp: 146–148 °C; yield: 83%; IR (KBr, cm^{-1}): 3391, 3320 (NH_2), 2191 (CN), 1687 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm)δ: 7.29–7.14 (m, 4H, Ar-H), 4.55 (s, 2H, NH_2), 4.45 (s, 1H, (H-4)), 4.06–4.03 (m, 2H, CH_2 (H-8)), 2.79–2.69 (m, 2H, CH_2 (H-10)), 1.70–1.66 (m, 2H, CH_2 (H-11)), 1.13 (t, J = 12 Hz, 3H, (H-9)), 1.01 (t, J = 12 Hz, 3H (H-12)); ^{13}C NMR (δ): 165.5, 160.4, 157.6, 142.4, 132.9, 128.8, 128.7, 118.6, 107.6, 61.8, 60.7, 38.4, 33.2, 20.7, 13.9, 13.7. HRMS m/z 346.9. Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.46; H, 5.48; N, 7.96%.

2.1.5. Ethyl 6-amino-4-(3-bromophenyl)-5-cyano-2-propyl-4H-pyran-3-carboxylate (**5a**)

Yellow solid, mp: 136–138 °C; yield: 85%; IR (KBr, cm^{-1}):3391, 3325 (NH_2), 2185 (CN), 1692 (C=O); ^1H NMR (400 MHz, $CDCl_3$, ppm)δ: 7.28–7.12 (m, 4H, Ar-H), 4.54 (s, 2H, NH_2), 4.44 (s, 1H, (H-4)), 4.07–4.00 (m, 2H, CH_2 (H-8)), 2.80–2.67 (m, 2H, CH_2 (H-10)), 1.72–1.65 (m, 2H, CH_2 (H-11)), 1.11 (t, J = 12 Hz, 3H, (H-9)), 0.96 (t, J = 16 Hz, 3H (H-12)); ^{13}C NMR (δ): 165.3, 160.7, 157.7, 146.1, 130.6, 130.3, 130.1, 126.3, 122.6, 118.6, 107.4, 61.6, 60.8, 38.6, 33.2, 20.7, 13.9, 13.7. HRMS m/z 390.9. Anal. Calcd for $C_{18}H_{19}BrN_2O_3$: C, 55.26; H, 4.89; N, 7.16. Found: C, 55.72; H, 4.48; N, 7.36%.



Scheme 1. Synthesis of ethyl 6-amino-5-cyano-4-phenyl-2-propyl-4*H*-pyran-3-carboxylate.

Table 1
Effect of reaction conditions on the multicomponent reaction for the synthesis of ethyl 6-amino-4-aryl-5-cyano-2-propyl-4*H*-pyran-3-carboxylate.

Entry	Catalyst (1 mmol)	Solvent	Time	Yield (%)
1	No Catalyst	Water	5 h	0
2	SiO_2	Water	5 h	0
3	TiO_2	Water	5 h	0
4	ZnO	Water	5 h	0
5	$ZnCl_2$	Water	5 h	20
6	p-TSA	Water	5 h	45
7	Na_2CO_3	Water	5 h	75
8	NaOH	Water	5 h	70
9	KOH	Water	5 h	65
10	Et_3N	Water	5 h	40
11	K_2CO_3	Water	3–5 min	94