Novel Pyran Derivative Ornamented with free Amino and Nitrile Functionalities: Synthesis and Spectroscopic Characterization

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Abstract: A novel 4H-pyran derivative tethered with free amino and nitrile groups (1) was synthesized from commercially available meta-bromobenzaldehyde, malononitrile and 2-(methacryloyloxy)ethyl 3-oxobutanoate by adopting a one-step three components reaction strategy. The structure of the synthesized 1 has been established based on physical and spectroscopic methods such as infrared, one dimensional proton and carbon nuclear magnetic resonance as well as two-dimensional HSQC and HMBC spectral techniques.

Keywords: Pyran, MCR, Vibrations, HSQC, HMDC.

I. INTRODUCTION

Multi-component reactions (MCRs), occasionally also called as multi-component assembly processes (MCAPs) and an important sub-class of tandem reactions are nothing but chemical reactions performed with three or more components in a single-step wherein the resulting products must contain components from all the substrates utilized. In recent years, enormous interests have been exposed in the direction of the components from all the substrates utilized. In recent years, enormous interests have been exposed in the direction of the reactions under the category of multi-component in the domains of medicinal chemistry as well as organic synthesis [1-2]. A diverse range of advantages associated with these methodologies includes atom economy, structural diversity, eco-friendliness, high selectivity, solvent-free strategies, and good yields [3-5]. Specifically, synthesis of heterocyclic compounds utilizes multi-component reactions in larger ways [6-8]. Subsequently, development of proficient and green reaction strategies which focus on target chemical entities is a vital noteworthy challenge in synthetic organic chemistry [9,10].

Heterocyclic molecules resembling pyrans add functional variety to the chemical entity and offer prolific area to learn their bio-activity. It is recognized that chemical entities possessing 4H-pyran structural motif are one of the honored heterocyclic ones for the reason that many of their derivatives enjoy useful pharmacological profiles [11,12] and a wide variety of biological properties, which include anticancer, anti-HIV, antimalarial, anti-inflammatory, antibacterial, antifungal, and antimalarial [13-18].

Owing to the importance with respect to biological profile, researchers around the globe have developed diverse strategies for the construction of pyran structural motif by utilizing various catalysts. A few of novel methods include three component reaction utilizing the catalysts such as piperidine, basic ionic liquid, D-proline, Nano-ZnO hydroxyapatite (HAP), and heteropoly acids [19-25]. Although various methodologies have been developed for the construction of pyran ring system, development of a better method with various advantages is highly desired.

In the present piece of research work, an exhaustive exploration results on the synthesis as well as structural characterization of a novel 4H-pyran derivative tethered with free amino and nitrile groups (I) has been disclosed. The structure of the synthesized pyran molecule is established by physical as well as spectroscopic methods such as infrared, one dimensional proton and carbon nuclear magnetic resonance as well as two-dimensional HSQC and HMBC spectral techniques.

II. EXPERIMENTAL SECTION

A. Materials and methodologies

The solvents, starting materials, and reagents were obtained from commercial sources suppliers and utilized as such with no additional purification. Melting point was recorded in open air capillary and is uncorrected. Fourier transform infrared spectrum was measured on an Avatar Nicolet FT-IR spectrometer (frequency range between 4000 and 400 cm⁻¹) for the title molecule in KBr pellets.
The proton and carbon nuclear magnetic spectra were acquired on a Bruker AMX400 spectrometer utilizing tetramethyl silane as the internal reference and CDCl₃ as the solvent. The splitting patterns in the proton NMR are furnished as multiplet (m), doublet (d) and singlet (s).

**B. Synthesis of novel 4H-pyran derivative 1**

In an RB flask with saturated potassium carbonate solution (50 mL), methacryloyloxy substituted ketone (1.0 mmol), 3-bromo benzaldehyde (1.0 mmol) and malononitrile (1.0 mmol) were taken and it was stirred at ~80 °C for 7 min. The throw-out precipitate, after the addition of cold-water (100 mL), was separated by filtration. The solid thus obtained was further washed well with a large quantity of water and eventually purified by recrystallization from ethanol/chloroform (3:1) to acquire the 4H-pyran derivative 1 in pure form. Yield 82 %, MP: 140-142 °C. IR (cm⁻¹, KBr): 3391, 3314, 3195, 3192, 3187, 2993, 2964, 2924, 2195, 1722, 1689, 1607, 1564, 1454, 1404, 1378, 1375, 1325, 1303, 1128, 1070, 935, 883, 848, 729, 690, 675, 499, 478, 437. ¹H NMR (400 MHz, CDCl₃, ppm) δ : 7.34-7.32 (2H, d, Ar-H), 7.14-7.13 (2H, d, Ar-H), 6.05 (1H, s, H-16a), 5.60 (1H, s, H-16b), 4.70 (2H, s, NH₂), 4.39 (1H, s, H-4), 4.30-4.20 (4H, m, H-10 & H-11), 2.39 (3H, s, H-18), 1.92 (3H, s, H-17). ¹³C NMR (δ): 167.0, 165.3, 158.2, 157.7, 156.4, 153.9, 146.1, 135.7, 130.5, 130.4, 130.2, 126.3, 122.8, 118.6, 107.0, 62.4, 62.2, 61.5, 38.6 18.7, 18.3.

**III. RESULTS AND DISCUSSION**

**A. Synthesis**

Synthesis of any molecule using water as a medium is the best one as far as synthetic chemistry is concerned. Initially, a mixture of 2-(methacryloyloxy)ethyl 3-oxobutanoate, 3-bromo benzaldehyde, and malononitrile were stirred in a solution of aqueous K₂CO₃ (saturated) at ~80 °C for 7 min. After standard workup and purification of the reaction mixture via recrystallization, the product 4H-pyran derivative 1 was obtained in 82% yield (Scheme 1). Complete characterization involving infrared, one dimensional proton and carbon nuclear magnetic resonance as well as two-dimensional HSQC (Heteronuclear Single Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Correlation) spectral techniques proved the identity of novel 4H-pyran derivative 1.

![Scheme 1](image)

**Scheme 1 Synthesis of 4H-pyran derivative 1**

**B. Infrared spectral analysis of novel 4H-pyran derivative 1**

The experimental infrared spectrum of 4H-pyran derivative 1 is displayed in Fig. 1 and the selected absorptions frequencies are presented in Table 1.

**C. C-H Vibrations**

The vibrations (stretching) of carbon and hydrogen bond in the aromatic ring usually appear nearly from 3100 to 3000 cm⁻¹ [26]. In the Fourier transform Infrared spectrum, the band resulted at ~3100 cm⁻¹ is due to stretching vibration of carbon and hydrogen in the aromatic unit of 4H-pyran derivative 1. The stretching vibrations of carbon and hydrogen in the aliphatic region are experimentally noted at 2993, 2964 and 2924 cm⁻¹.

**D. C=O Vibrations**

In the FT-IR spectrum, the carbonyl group with various environments generally appear as a strong band in the range between 1800-1600 cm⁻¹ [26,27]. In the 4H-pyran derivative 1, the C=O stretching vibrations of the carbonyl group connected to the carbon carrying olefinic functionality as well as methyl moiety and the other C=O group attached to a carbon of pyran nucleus are resulted at 1749 and 1689 cm⁻¹, respectively.

| S.No. | IR frequency (cm⁻¹) | Functional groups |
|-------|--------------------|-------------------|
| 1     | 3195, 3192, 3187   | Ar. C-H (stretch) |
| 2     | 2993, 2964, 2924   | Ali. C-H (stretch) |
| 3     | 2195               | C=O               |
| 3     | 1722               | C=O connected to   |
| 4     | 1689               | olefinic carbon    |
| 5     | 3391, 3314         | pyran ring         |
| 6     | 675                | C-Br               |

**Table 1. Selected IR Absorptions of target molecule.**

**Fig. 1. IR spectrum of target molecule 1**

**E. C≡N Vibrations**

The nitrile groups normally provide unique spectral values and gives intense absorption between 2280 and 2200 cm⁻¹. In the current investigation, the stretching vibration of C≡N integrated at one of the carbons of pyran structural unit noted at 2195 cm⁻¹ in the FT-IR spectrum (experimental).
F. NH₂ Vibrations

In a spectrum of FT-IR, the existence of a primary amino functionality normally shows stretching vibrations of N-H in the range between 3400 and 3300 cm⁻¹. The FT-IR spectrum of 4H-pyran derivative 1 depicts two typical bands at 3391 and 3314 cm⁻¹, confirming the presence of NH₂.

G. C-Br Vibrations

In most of the bromoaryl molecules, the stretching vibrations of C-Br present in the range between 650 and 395 cm⁻¹ [27]. In the FT-IR spectrum, the characteristic band resulted at 675 cm⁻¹ is corresponds to stretching vibrations of carbon - bromo bond.

H. NMR spectral analysis

I. ¹H NMR analysis of 4H-pyran derivative 1

The ¹H NMR spectrum of 4H-pyran derivative 1 is given in Fig. 2. Generally, the aromatic protons present in a molecule appear in the region between 6.8 to 8.5 ppm with various spin multiplicities depends on the nature of the protons and environments. In the ¹H NMR spectrum of the molecule 1, the signals resulted in the region between 7.33 and 7.24 with two one proton integrals as well as a two protons doublet resulted in the region 7.14 ppm with a vicinal coupling constant value 4.8 Hz are considered to be the protons of aromatic moiety attached to the 4-position of the pyran nucleus. The benzylic proton present at C-4 position o the pyran ring exhibited at 4.39 ppm as a singlet while the two protons of NH₂ group resonated at 4.70 ppm as a singlet. The diastereotopic methylene protons (H16) present at the side chain of the 4H-pyran derivative 1 appeared as two singlets at 6.05 and 5.60 ppm. However, another set of diastereotopic methylene protons (H11 and H10) appeared as a group with a multiplet between 4.30 and 4.20 ppm. Since there are four diastereotopic protons present in the later case and there is no much difference in magnetic environment also, it is quite obvious that the signals appear in close proximity and hence they provide multiplet. The protons of the methyl group which is attached to the olefinic carbon of the side chain (H17) appeared as a singlet at 1.92 ppm while the protons o another methyl group which is attached at the carbon adjacent to the oxygen o the pyran scaffold (H18) resonated as a singlet at 2.38 ppm.

J. ¹³C NMR analysis of 4H-pyran derivative 1

The spectrum of ¹³C NMR of the compound 4H-pyran derivative 1 has been put on view in Fig. 3. In the spectrum of ¹³C NMR of target molecule 1, the ester carbonyl group attached to the carbon of pyran nucleus and the other ester carbonyl functionality adjacent to the carbon of olefin unit occurred in the down filed region 165.3 and 167.0 ppm, respectively. The pyran ring carbons C2 and C6 observed at 157.7 and 158.2 ppm, respectively while the carbons C3 and C5 resonated at 107.0 and 62.4 ppm, respectively. The ipso carbon of the phenyl group attached to the pyran ring resonated at 146.1 ppm and bromo substituted ipso carbon exhibited its resonance at 135.8 ppm. The carbons of aromatic moiety (four) are resonated in the region 130.5 ~ 122.8 ppm (130.4, 130.3, 130.1 and 122.8). The carbon of terminal olefin C16 is resonated at 126.3 ppm, while C15 (quaternary carbon) is located at 135.7 ppm. The signal at 118.6 ppm is because of carbon of nitrile moiety (C≡N) at C5. C10 and C11, the methylene carbon, exhibited signals at 62.2 and 61.5 ppm, respectively while the benzylly carbon (C4) emerged at 38.6 ppm. The carbons of methyl moieties, C17 and C18 observed in the upfield area at 18.3 and 18.7 ppm, respectively.

Fig. 2 ¹H NMR spectrum of 4H-pyran derivative 1

Fig. 3 ¹³C NMR spectrum of 4H-pyran derivative 1
K. C. 3. HSQC and HMBC analysis of 4H-pyran derivative 1

Fig. 4 HSQC spectrum of 4H-pyran derivative 1

In the 1H-13C COSY spectrum, as shown in Fig. 4, the carbon signal at 38.6 ppm shows HSQC correlation with benzylic proton at C-4, hence it is assigned to -CH at C-4. The correlation peaks at 62.4, 107.0, 118.6, 146.1 and 157.7 ppm in its HMBC spectrum (Fig. 5) further confirms the same.

Fig. 5 HMBC spectrum of 4H-pyran derivative 1

The peak at 146.1 ppm is because of ipso carbon (C22) of the phenyl motif based on its HMBC correlation with H-4 proton and aromatic protons. The signals of aromatic carbons resonated in the region 122.8-135.7 ppm which is further confirmed by their correlation spectra.

Table 2. HMBC and HSQC correlations of 4H-pyran derivatives 1

| Signals | Correlations in HSQC | Correlations in HMBC |
|---------|----------------------|----------------------|
| (4.39)  | 38.6                 | 62.4 (α), 107.0 (α), 118.6 (β), 146.1 (α), 157.7 (γ). |
| (Benzylic proton) | | |
| C16 (6.05, 5.60) | 126.3 | 135.7 (α), 167.0 (β), 18.7 (β). |
| C17 (1.92) | 18.3 | 135.7 (α), 167.0 (β), 126.3 (β). |
| C18 (2.39) | 18.7 | 157.7 (α), 107.0 (β). |

A group of signals appeared as multiplet between 4.30 and 4.20 ppm exhibits cross peaks with the signals of carbons at 62.2 and 61.5 ppm, suggests the carbon signals are because of C-10 and C-11. The couple of singlets at 2.39 and 1.92 ppm show cross peaks with the signals of carbons at 18.7 and 18.3 ppm, which imply that the signals of carbons are because of C-18 and C-17, respectively. Over all, the peaks in the spectra of 1H and 13C NMR are unequivocally assigned by using HSQC spectral analysis. All the correlations of HSQC and HMBC are furnished in Table 2.

IV. CONCLUSION

We have reported synthesis of an interesting novel 4H-pyran derivative tethered with free amino and nitrile groups (1) by adopting a multicomponent reaction. This reaction proceeds in water, an environmentally green solvent and the duration of the reaction is also shorter. The complete structure of the molecule is unambiguously established based on one dimensional and two-dimensional spectroscopic techniques. Synthesis of a diverse range of this class of molecules besides the preliminary biological activities of the target molecule 1 is under progress.

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