An efficient synthesis of 2-amino-4*H*-chromenes and 2-amino-4*H*-pyrans derivatives via ultrasound assisted one-pot three-component reaction

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Abstract

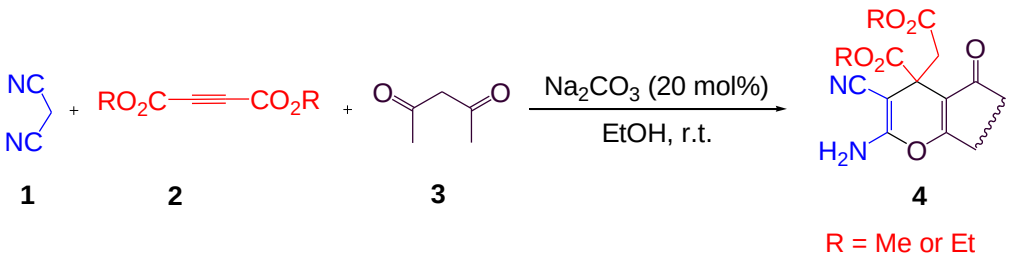
In this research, a new series of substituted 4*H*-pyran and 4*H*-chromene derivatives has been synthesized at ambient temperature in the presence of a catalytic amount of sodium carbonate (20 mol%) *via* one-pot three-component cyclocondensation reactions of malononitrile, dialkyl acetylenedicarboxylates and 1,3-diketones in ethanol under ultrasound irradiation. The synergistic effects of multicomponent reactions and ultrasound irradiation have been successfully demonstrated to offer an easy way for the synthesis of these compounds in excellent yields.

Keywords: 4*H*-pyran, 4*H*-chromene, malononitrile, dialkyl acetylenedicarboxylate, 1,3-diketone, multicomponent reaction, ultrasound irradiation

Introduction

The concept of privileged structures or scaffolds was first introduced in 1988 [1]. A privileged structure was defined as "a single molecular framework able to provide ligands for diverse receptors." Since then, an increasing number of sub-structural frameworks have been described as privileged structures including 4*H*-pyran and 4*H*-chromene [2-5]. These privileged structures have since then been used extensively in medicinal chemistry programs to identify new ligands, and are probably one of the most familiar structural units in naturally occurring compounds. There are many biologically active molecules that contain 4*H*-pyran and 4*H*-chromene moieties [6-9]. Because of their importance in pharmaceuticals, their syntheses have attracted considerable attention [10].

Herein, we wish to present a versatile and new method for the synthesis of substituted 2-amino-4*H*-pyran **4c,d** and 2-amino-4*H*-chromene **4a,b**, as biologically important New Chemical Entities (NCE's), based on a tandem strategy of Michael addition and cyclization between malononitrile **1**, various dialkyl acetylendicarboxylates **2**, and structurally diverse 1,3-diketones **3**, catalyzed by sodium carbonate (Scheme 1). The milder conditions use of catalytic amount of inexpensive environmentally benign sodium carbonate catalyst, high reaction rates, excellent yields, and simple work-up make this procedure an efficient process.



Scheme 1. Synthesis of substituted 4*H*-pyrans **4c,d** and 4*H*-chromenes **4a,b**.

Experimental

1. General

All chemicals and reagents were purchased from Merck and Aldrich and used without further purification. Melting points were determined with an Electrothermal 9100 melting point apparatus and are uncorrected. Infrared spectra were recorded using a Shimadzu FT-IR 8400S instrument. ^{1}H-NMR and ^{13}C-NMR spectra (500MHz) were recorded on a DRX-500 Advance Bruker spectrometer. Ultrasonic apparatus was Hielscher Ultrasonics GmbH UP400S (400W, 24kHz).

2. General Procedure for the Preparation of 4H-pyrans and 4H-chromenes

A mixture of malononitrile **1** (1.0 mmol), dialkyl acetylendicarboxylates **2** (1.0 mmol) and 1,3-diketones **3** (1.0 mmol) in the presence of a catalytic amount of sodium carbonate (0.2 mmol) in 5 ml of ethanol was irradiated in ultrasound apparatus. After completion of the reaction as indicated by TLC, the solvent of the reaction was

evaporated. After that, the mixture was washed with water and purified by recrystallization from hot ethanol.

All of the products were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectral data.

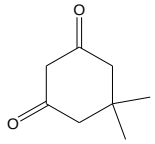
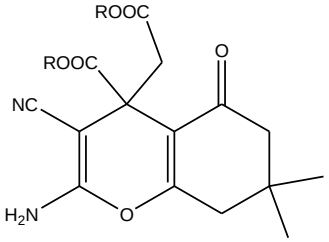
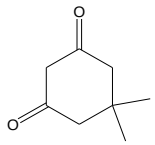
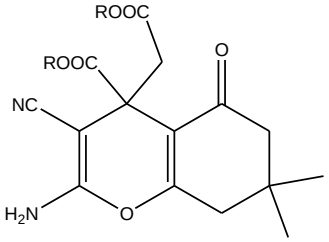
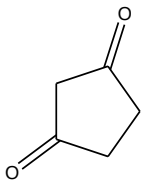
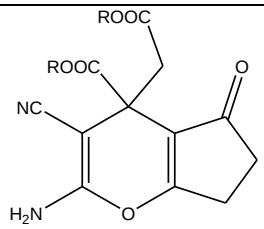
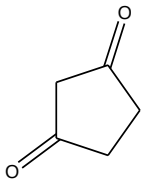
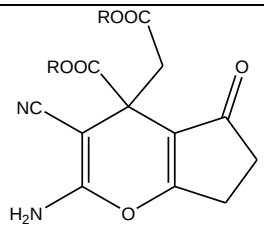
*2.1. ethyl 4-((ethoxycarbonyl)methyl)-2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-4-carboxylate (***4b***)*

IR (KBr), 3365, 3325, 2196, 1733 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 1.04 (3H, s, CH_2), 1.04 (3H, s, CH_3), 1.09 (3H, t, J = 7.1 Hz, CH_3), 1.11 (3H, t, J = 7.1 Hz, CH_3), 2.22 (2H, s, CH_2), 2.42 (2H, s), 2.81 (1H, d, J = 14.9, C(H)HCO_2Et), 2.93 (1H, d, J = 14.9, C(H)HCO_2Et), 4.01 (4H, m, CH_2), 7.26 (2H, s, NH_2); ^{13}C-NMR (125 MHz, DMSO-d_6) δ = 14.8, 14.9, 28.1, 28.2, 32.8, 39.7, 43.6, 50.9, 56.8, 60.7, 61.9, 111.7, 118.3, 160.2, 164.0, 170.5, 171.8, 200.0.

Results and Discussion

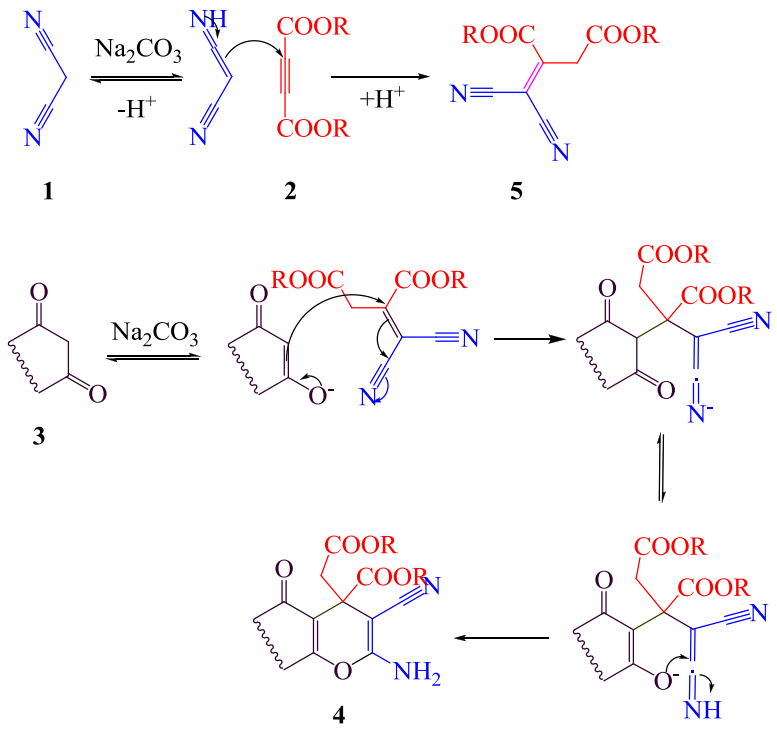
In a pilot experiment, a mixture of malononitrile **1**, diethylacetylenedicarboxylate **2** (DEAD) and cyclohexane-1,3-dione **3** in the presence of a catalytic amount of sodium carbonate was irradiated in ultrasound apparatus in ethanol as a solvent. After that, in order to explore the scope and limitations of the reaction, various dialkyl acetylendicarboxylates and1,3-diketones were used. The results are summarized in **Table 1**.

Table 1. The isolated yield of of 2-amino-4*H*-chromenes and 2-amino-4*H*-pyrans derivatives

Entry	R	Substrate	Product	Time/h	Mp(°C)	Yield/%
1	Me		 **4a**	2:20	180.5-182.5	99
2	Et		 **4b**	2:35	229.5-232	91
3	Me		 **4c**	4:00	199-201	64
4	Et		 **4d**	4:30	207-209	60

A proposed mechanism for the synthesis of 4*H*-pyrans **4c,d** and 4*H*-chromenes **4a,b**, could be explained as following:

We speculate that the initial event is the condensation reaction of malononitrile **1** with diethyl acetylenedicarboxylates **2** in the presence of Na_2CO_3 that leads to the formation of Michael adduct intermediate **5**. The nucleophilic addition of the enolic form of 1,3-diketones to Michael adduct **5** leads to the formation of 4*H*-pyrans **4c,d** and 4*H*-chromenes **4a,b** in 31-91% yield by a tandem addition–cyclization reaction. A plausible mechanism of the reaction is shown in **Scheme 2**.



Scheme 2. Proposed mechanism for the synthesis of 4*H*-pyrans **4c,d** and 4*H*-chromenes **4a,b**.

Conclusion

In summary, highly functionalized 4*H*-pyrans and 4*H*-chromenes has been synthesized through a tandem Michael addition–cyclization process catalyzed by sodium carbonate under sonication at room temperature. The corresponding products,

which have extensive biological and pharmacological activities, can be obtained in moderate to good yields.

Acknowledgment

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