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Etidronic acid promoted an efficient Knoevenagel condensation of 4-oxo-4H-benzopyran-3-carbaldehyde with Meldrum's acid

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Abstract: An efficient synthesis of 2, 2-dimethyl-5- [(4-oxo-4H-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-diones by Knoevenagel condensation of 4-oxo-4H-benzopyran-3-carbaldehydes with Meldrum's acid in presence of etidronic acid at room temperature is reported.

Keywords: Knoevenagel reaction; etidronic acid; 4-oxo-(4H)-1-benzopyran-3-carbaldehyde; Meldrum's acid.

Introduction

Compound having chromone moiety are synthetically versatile molecules with a reactive carbonyl group. They have considerable significance for their biological activities [1] and their reactivity towards nucleophiles, which allow the synthesis of a wide variety of heterocycles. There are number of methods of Knoevenagel condensation between Meldrum's acid and aromatic aldehydes, which gives arylidene derivatives [2]. They are useful intermediates for the synthesis of heterocyclic compounds with potential pharmacological activities [3]. The substrate 4-oxo-4H-benzopyran-3-carbaldehyde has three active sites; the unsaturated carbonyl group i.e. the pyrone ring, a carbon-carbon double bond and a formyl group. Of these, the formyl

group has the highest reactivity towards active methylene compounds. Recently, there have been several methods reported in the literature for the synthesis of 2,2-dimethyl-5- [(4-oxo-4H-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-diones by Knoevenagel condensation reaction [4]. However, some of these methodologies have not been entirely satisfactory, with disadvantages such as long reaction times, harsh reaction conditions and the requirement of expensive catalysts and special apparatus. Therefore, to avoid these limitations, the discovery of a new and efficient process for the synthesis of 2,2-dimethyl-5- [(4-oxo-4H-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-diones derivatives catalyzed by etidronic acid is of prime interest.

Etidronic acid is a phosphonic acid with mild

acidity, is non-volatile and non-corrosive, and is soluble in common organic solvents. It is a white crystalline solid with outstanding physical and chemical properties and is a commercially available cheap chemical. Its applications as a catalyst in organic syntheses were found to be effective in the synthesis of 5-nitro-dihydropyrimidine [6], 5-carboxanilide-dihydropyrimidinones [7], thiiranes [8]. However, there are no examples of the use of etidronic acid as a catalyst for the synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-dione derivatives.

Results and discussion

In continuation of work on Knoevenagel condensation reaction [5] herein, we wish to report an efficient and simple methodology for the synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-diones. In search of an efficient etidronic acid and the best experimental conditions, the reaction of 4-oxo-4*H*-benzopyran-3-carbaldehyde **1a** and Meldrum's acid **2** stirred in THF at room temperature in the presences of different amount of etidronic acid as a catalyst has been considered as the model reaction. The progress of the reaction was monitored by TLC and it was observed that the reaction was complete in 12 minute. It was found that the best result was obtained with 10 mol % of etidronic acid (Table 1)

To select the best solvent for the reaction, the synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-diones. **3a-h** was examined in different solvents (Table 2). As Table 2 indicates, higher yields and shorter reaction times were obtained when the reaction was carried out in THF. Thus, THF was used as reaction media for all reactions. A variety 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-diones were then prepared by simple stirring of **1b-h** and Meldrum's acid **2** at room temperature in THF for the time specified in Table-3. The reaction yields are excellent and the reaction

times are exceedingly short. The products were isolated by washing the reaction mixture with water followed by filtrations. This process is fairly general, and efficient. The experimental process is very simple and environmentally benign.

Conclusion

In conclusion, we developed a simple and practical methodology for the synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-dione from the condensation of substituted 4-oxo-4*H*-benzopyran-3-carbaldehyde with Meldrum's acid in the presence of etidronic acid at room temperature.

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Experimental Section

All chemicals were purchased from Merck, Aldrich and Rankem chemical companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progress of the reactions was monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ¹H NMR spectra were recorded on an 300 MHz FT-NMR spectrometer in CDCl₃ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me₄Si) as an internal standard. The required 4-oxo-4*H*-benzopyran-3-carbaldehydes was prepared by Vilsmeier-Haack reaction [9].

Synthesis of 2, 2-dimethyl-5-[(4-oxo-4*H*-chromen-3-yl) methylene]-1,3-dioxane-4, 6-dione **3(a-h)**:

4-oxo-4*H*-benzopyran-3-carbaldehyde (1 mmol), Meldrum's acid (1 mmol), 5 ml THF and etidronic acid (10 mol%) were taken in a

single neck round bottom flask. The content of flask was stirred at room temperature for the appropriate time given in Table 3. When TLC shows complete disappearance of starting material, the mixture was poured over ice-water and extracted with diethyl ether (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4 . The solvent evaporated under reduced pressure and solid compound was recrystallized from ethyl acetate to afford the corresponding 2, 2-dimethyl-5- [(4-oxo-4H-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-dione **3a** in excellent yield. The structures of the products were confirmed by IR, ^1H NMR and mass spectral data.

Spectral data of compounds

3a) IR (KBr, cm^{-1}): 3062, 2996, 1732, 1670, 1396, 1251. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.8 (6H, s, $2 \times \text{CH}_3$), 7.2-8.1 (4H, m, aromatic), 8.7 (1H, s, olefinic), 9.6 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 301 [M+1].

3b) IR (KBr, cm^{-1}): 3061, 2992, 1730, 1669, 1372, 1296, 797. ^1H NMR (300 MHz, CDCl_3) δ (ppm) = 1.9 (6H, s, $2 \times \text{CH}_3$), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.6 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 335 [M+1].

3c) IR (KBr, cm^{-1}): 3055, 2990, 1710, 1650, 1390, 1280. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 2.5 (3H, s, $\text{Ar}-\text{CH}_3$), 1.9 (6H, s, $2 \times \text{CH}_3$), 7.2-8.2 (3H, m, aromatic), 8.7 (1H, s, olefinic), 9.6 (1H, s, C_2 -H of chromone moiety). EIMS

(m/z , %): = 315 [M+1].

3d) IR (KBr, cm^{-1}): 3065, 2989, 1729, 1674, 1392, 1293, 791. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.9 (6H, s, $2 \times \text{CH}_3$), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.5 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 370 [M+1].

3e) IR (KBr, cm^{-1}): 3060, 2996, 1718, 1649, 1396, 1283, 796. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 2.5 (3H, s, $\text{Ar}-\text{CH}_3$), 1.9 (6H, s, $2 \times \text{CH}_3$), 7.2-7.5 (2H, s, aromatic), 8.6 (1H, s, olefinic), 9.5 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 349 [M+1].

3f) IR (KBr, cm^{-1}): 3084, 3018, 1714, 1662, 1392, 1280, 798. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.8 (6H, s, $2 \times \text{CH}_3$), 7.2-8.3 (2H, s, aromatic), 8.6 (1H, s, olefinic), 9.5 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 370 [M+1].

3g) IR (KBr, cm^{-1}): 3063, 2993, 1735, 1664, 1395, 1280, 805. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.8 (6H, s, $2 \times \text{CH}_3$), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.6 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 380 [M+1].

3h) IR (KBr, cm^{-1}): 3061, 2992, 1730, 1669, 1372, 1296, 797. ^1H NMR (300 MHz, CDCl_3) δ (ppm) = 1.9 (6H, s, $2 \times \text{CH}_3$), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.6 (1H, s, C_2 -H of chromone moiety). EIMS (m/z , %): = 319 [M+1].

Scheme

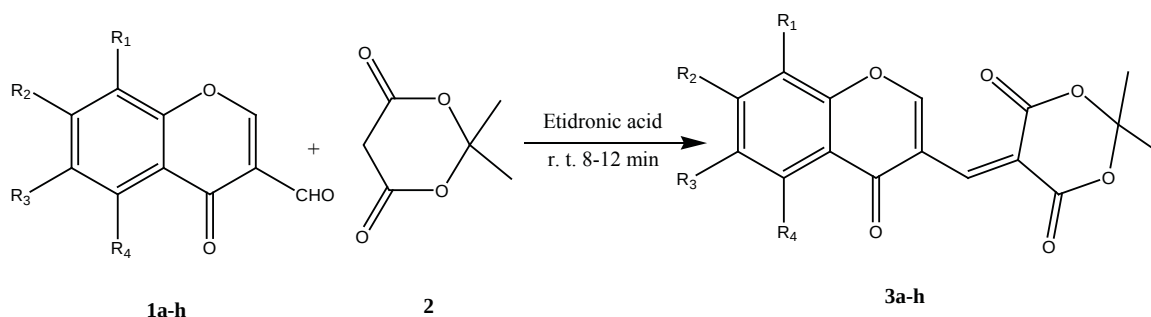


Table 1. The amounts of catalyst optimization for synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-dione^a

Entry	Etidronic acid (mol%)	Time (min.)	% yield ^b
1	0	60	30
2	5	40	68
3	10	12	90
4	15	12	90
5	20	12	88

^aReaction conditions: 4-oxo-4*H*-benzopyran-3-carbaldehyde (1 mmol); Meldrum's acid (1.2 mmol); THF; room temperature. ^bIsolated yield.

Table 2. Solvent optimization for synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-dione^a

Entry	Solvent	Temp. (°C)	Time (min.)	% yield ^b
1	neat	room temp.	30	65
2	C ₂ H ₅ OH	room temp.	30	72
3	CH ₂ Cl ₂	room temp.	30	70
4	CH ₃ CN	room temp.	30	75
5	THF	room temp.	12	90
6	DMF	room temp.	30	62
7	DMSO	room temp.	30	60

^aReaction conditions: 4-oxo-4*H*-benzopyran-3-carbaldehyde (1 mmol); Meldrum's acid (1.2 mmol); etidronic acid (10 mol%). ^bIsolated yield.

Table 3. Synthesis of synthesis of 2, 2-dimethyl-5- [(4-oxo-4*H*-chromen-3-yl) methylene]-1, 3-dioxane-4, 6-dione 3a-h in THF at room temperature

Entry ^a	R ₁	R ₂	R ₃	R ₄	Time(min)	% Yield ^b	M. P
a	H	H	H	H	12	87	182
b	H	H	Cl	H	10	90	198
c	H	CH ₃	H	H	10	90	186
d	Cl	H	Cl	H	08	90	180
e	CH ₃	H	Cl	H	08	92	200
f	H	Cl	Cl	H	08	92	242
g	H	H	Br	H	08	92	205
h	H	H	F	H	08	92	200

^a All the products were characterized by IR, ¹H NMR, spectra.

^b Yield of isolated product.

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