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Synthesis of novel 3-benzylidene chromane-2-one derivatives

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Abstract: New derivatives of (*E*)-3-benzylidene-6, 7-methylene dioxy chromane-4-one, a main group of homo-isoflavonoides (3- benzylidene-4- chromanones), were reported and synthesized by the aldol condensation. The new compounds which includes chalcone functionality, were confirmed by the FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. Chalcones have various biological properties such as antioxidant, fungicide, anti malaria and anticancer activity.

Keywords: Aldol condensation, Antioxidant, Anticancer, Chromanones, Chalcones.

Introduction

The formation of free radicals from the metabolism of fats and sugars in body and their chain reactions can cause damage or death to the cell. Therefore the applying of an agent to terminate these harmful chain reactions would be useful for health [1]. Antioxidants, which are biological molecules, could be effective as inhibiting agent for the oxidation of other molecules via scavenging the free radical intermediates [2, 3]. Antioxidants have widely been investigated for the prevention of vast diseases such as cancer, heart and vascular disease, skin aging and etc. [4]. Many natural and synthetic antioxidants prevent disease progression by decreasing per-oxidation.

It is well known that, cross linking reaction between *α, β*-unsaturated carbonyl moieties (named chalcone or cinnamoyl units) obeys the [2π + 2π] mechanism [5]. Chalcones and their derivatives are of high interest groups because of their versatile biological activities such as anti-inflammatory, antibacterial, antifungal, antitumor and antioxidant properties [6–8]. These pharmacopheres are well known as valuable intermediates in the synthesis of many active pharmaceutical drugs. Various chalcones like naturally occurring butein, sappanchalcone and, licochalcones are reported to exhibit potent scavenging activity.

Isoflavonoids, as plant secondary metabolites, includes 3-phenylchromane skeleton which is derived from 2-phenylchromane functionality of flavonoids. It has been well-established that these materials possess numerous biological activities [9].

Due to the medicinal importance of chalcones, much attention has been devoted to their synthesis. Because of the presence of conjugated *α,β*-unsaturated carbonyl moiety in their structures, it is suggested that the aldol condensation is a suitable manner for this purpose [10]. Aldol condensation is an efficient facile and easy synthetic procedure which required only basic or acidic conditions without any additional reagents and has provided a powerful tool for the carbon-carbon bond formation. Herein, we introduced and synthesized three novel derivatives of 3-benzylidenecroman-2-one with the below structures (Scheme **1**). Analogy with flavonoides and chalcones suggests that (*E*)-3-benzylidene-6, 7-methylene dioxy chromane-4-ones could have anticancer and antioxidant activity as the consequence of radical scavenging.

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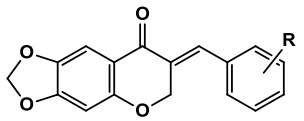


Scheme 1: The structure of (*E*)-3-benzylidene-6, 7-methylene dioxy chromane-4-ones

Aldol condensation between 3,4-methylene dioxy chromane-4-one and different benzaldehyde derivatives in the acidic or basic media was selected as a convenient and fascinating protocol to synthesis -benzylidenecromane-2-one derivatives. Finally we tried to find the most favorable reaction conditions such as temperature, pH and solvent to improve the yields and purity of the products.

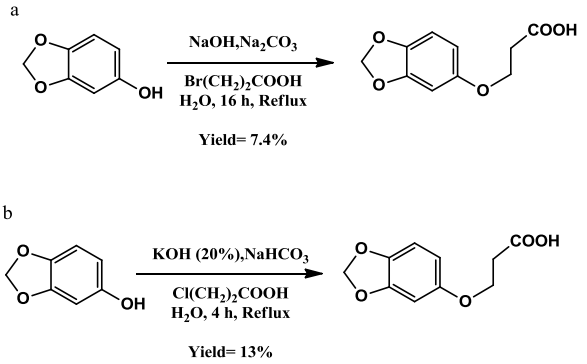
Results and discussion

A) The synthesis of reactants:

1) Synthesis of 3,4- methylene dioxy chromene-4-one:

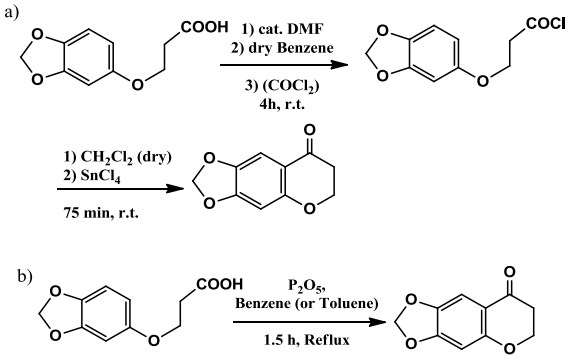
According to the literatures [11], there are two separate steps in the synthesis of *3,4-* methylene dioxy chromane-4-one:

First step was O-alkylation of 3,4-methylene dioxy phenol with 3-bromopropionic acid provided 3-(3,4-methylene dioxy phenoxy) propionic acid, which the yield was low (Scheme **2**) [12]. To improve the yield of the reaction, different bases such as NaOH and KOH were investigated as catalyst and also 3-chloropropionic acid applied instead of 3-bromo propoinic acid as reagent. Solvent, base and temperature didn't show significant improvement in the yield of this reaction. But applying 3-chloropropionic acid instead of 3-bromo propoinic acid as reagent improved the yield (Scheme **2**).



Scheme 2: Synthesis of 3-(3,4- methylene dioxy phenoxy) propionic acid with different reagent.

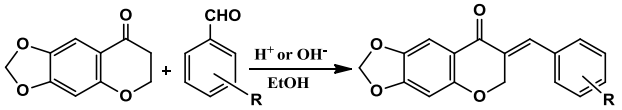
In the second step, 3-(3,4- methylene dioxy phenoxy) propionic acid under Friedel-Crafts acylation gave *3,4-* methylene dioxy chromanone in high yield (Scheme **3a**). In this reaction the high sensitivity to water and toxicity of applied reagents encouraged us to introduce a green and simple method to this purpose. Therefore P_2O_5 was applied as a catalyst to synthesize *3,4-* methylene dioxy chromanone (Scheme **3b**). This method had more advantages versus pervious method like simplicity, clean, low time, fewer reagents, short time and high yield.



Scheme 3: Synthesis of reactant.

B) Aldol condensation between reactants:

To complete the synthesis of target molecules, aldol condensation carried out in acidic or basic conditions (Scheme **4**). Among different solvent, after examination, we found EtOH could be convenient solvent compared to the other ones for this condensation. Its polarity and protic behavior increased the rate of reaction and better proton transfer. Besides, it could solve a vast range of organic and mineral compounds as a nontoxic solvent.

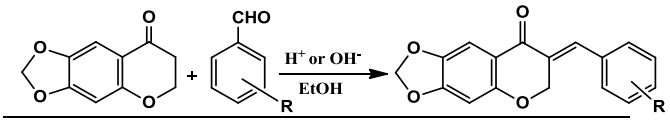


Scheme 4: Aldol condensation to synthesize (*E*)-*3-(benzylidene)-6, 7-methylene dioxy chromene-4-ones*.

In this project, novel chalcones were synthesized via aldol condensation in acidic or basic conditions which this protocol was significantly provided the final products effectively (Scheme **4**). There is no need heating or any additional reagents. The yields of products for all derivatives are shown in (Table **1**):

As shown in Table **1**, the yields in the acidic medium are better compared to the basic conditions noticeably. The plausible explanation was the acidic catalytic (led to protonated carbonyl electrophilic) in the addition of enol to the carbonyl functionality, while there was no catalytic effect in basic condition in the addition process.

Table 1: Synthesis of *(E)-3-(benzylidene)-6, 7-methylene dioxy chromene-4-one.*



Entry	R	Yield (%) [a]	Yield (%) [b]
a	H	48	7.1
b	4-OMe	31	31
c	3-OMe	42	19
d	2-OMe	47	34
e	3,4-methylene dioxy	42	31

[a] Acidic condition
[b] Basic condition

Conclusion

In this study, we introduced and synthesized novel derivatives of (E) -3- benzylidene -6,7-methylene dioxy chromane-4-one, as the new derivatives of chalcones by the aldol condensation in acidic and basic conditions. The acidic condition was appeared more efficiently than basic condition. The introduced protocol was clean and simple to obtain novel chalcones.

Experimental

1) Synthesis of 3-(3,4- methylene dioxy phenoxy) propionic acid:

Method A (with 3-bromopropoinic acid:

To the mixture of 3-bromopropoinic acid 5.51 g (0.036 mol) and 25 ml diluted sodium carbonate in 250 ml water, was added a mixture of 3,4- methylene dioxy phenol 5 g (0.036 mol) and sodium hydroxide 1.45 g (0.036 mol) in 50 ml H_2O. After addition, the reaction mixture was refluxed for 16 hours. Then after cooling, 20 g ice was added to the vessel. The obtained mixture acidified with concentrated hydrochloric acid and extracted with ethyl acetate. The organic layer washed with saturated sodium bicarbonate (3 x 100 ml) and the aqueous phase acidified with concentrated hydrochloric acid again and extracted with EtOAc. The solution was dried by anhydrous Na_2SO_4. Solvent was evaporated in vacuum to yield the desired product which for purification was dissolved in sodium hydroxide solution, filtered and precipitated after acidified. The brown solid product was purified by flash column chromatography with (ethyl acetate: ether) as eluting solvent. 7.4 % yield; mp 149-152°C; ^{1}H NMR (500 MHZ, DMSO-d6): δ 12.32 (s, 1H); 6.79 (d, 1H, *J* = 8.4 Hz); 6.60 (d, 1H, Ar); 6.34 (dd, 1H, *J* = 8.5 Hz); 5.94 (s, 2H); 4.06 (t, 2H, *J* = 6 Hz); 2.63 (t, 2H, *J* = 6 Hz); IR (KBr, cm^{-1}): 2400-3400 (OH), 1694.8 (C=O).

Method B (With 3-chloropropoinic acid):

3,4- methylene dioxy phenol 3.89 g (28.2 mmol) in KOH 20% was added to 3.06 g (28.2 mmol) of 3-chloropropoinic acid and 2.36 g (28.2 mmol) sodium bicarbonate in H_2O. Then the mixture was refluxed for 4 hours. After the completion the time of reaction the product was extracted as the previous method. In the end the product was recrystalized with benzene (13% yield).

2) Synthesis of 6,7-methylene dioxy chromane-4-one:

Method A:

Under argon atmosphere the catalytic amount of dry DMF (10 drops) was added to a mixture of 3-(3,4-methylene dioxy phenoxy) propionic acid 2g (9.5 mol) in dry C_6H_6 (50 ml). Then oxalyl chloride 1.85ml (21 mmol) was added to the obtained mixture and was stirred for 4.5 hours at room temperature. The benzene solvent was evaporated under vacuum, and 30 ml dry CH_2Cl_2 was added to the residue and was cooled to 0 °C. After cooling 1.36 ml (12 mol) of $SnCl_4$ was added to later mixture and permit the mixture was stirred for 1.5 hours at room temperature. At the end of required time, 20 g ice and 30 ml H_2O were added to the obtained mixture, and was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a brown-colored solid as product. 87.5% yield, mp 94-97 °C. ^{1}H NMR (500 MHZ, DMSO): δ 7.11 (s, 1H, Ar); 6.66 (s, 1H, Ar``); 6.09 (s, 2H); 4.47(t, 2H, *J* = 6.1 Hz); 2.69 (t, 2 H, *J* = 6.5 Hz). IR (KBr, cm^{-1}): 1663.5(C=O).

Method B:

0.1 g (0.72 mmol) of 3-(3,4- methylene dioxy phenoxy)propionic acid was reacted with P_2O_5 in dry C_6H_6 (50 ml) under reflux condition for 2 hours. Then the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a brown-colored solid as product. 65% yield, mp 92-97 °C.

3-General procedure for synthesis of E-3-benzylidene-6,7-methylene dioxy chromene-4-ones in acidic condition:

0.73 mmol of different benzaldehyde and 0.1 g (0.52 mmol) of 6,7-methylene dioxy chromane-4-one was dissolved in 2-3 ml absolute EtOH and allowed to stir in a ice-water bath, and then HCl gas was blown for 5 min. After appearance of the reddish-brown color, the blow was stopped and the mixture was stirred in the presence of HCl for 48 hours. The progress of the reaction was confirmed with TLC chromatography. The obtained solid product was filtered and washed with cool EtOH 96% and recrystalized with EtOH and water to achieve yellow solid.

4-General procedure for synthesis of E-3-benzylidene-6,7-methylene dioxy chromene-4-ones in basic condition:

NaOH 50% (0.2 ml) was added to mixture of 0.73 mmol of different benzaldehyde and 0.1 g (0.52 mmol) of 6,7-methylene dioxy chromane-4-one in 1 ml absolute EtOH. After this addition, the produced solid was diluted with 2 ml absolute EtOH and allowed the mixture to stir for 24 hours. The obtained yellow solid product was filtered and washed with Et_2O. To achieve the pure product, the solid was re-dispersed in H_2O and acidified by addition of concentrated HCl, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a yellow solid as product.

Spectral data of novel *E-3-benzylidene-6, 7-methylene dioxy chromene-4-ones:*

a: (E)-3-benzylidene-6,7-methylene dioxy chromene-4-one:

mp 141-144°C. ^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.84 (s, 1H); 7.43-6.41 (m, 7H, Ar); 6.00 (s, 2H); 5.29 (s, 2H). IR (KBr, cm^{-1}): 1664.6(C=O).

b: (E)-3-(4- methoxybenzylidene)-6,7-methylene dioxy chromene-4-one:

mp 169-172°C. ^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.8 (s, 1H); 7.39-6.42 (m, 6H, Ar); 6.00 (s, 2H); 5.32(s, 2H), 3.86(s, 3H). IR (KBr, cm^{-1}): 1665.6(C=O).

c: (E)-3-(3- methoxybenzylidene)-6,7-methylene dioxy chromene-4-one:

mp 157-161°C. ^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.8 (s, 1H); 7.38-6.42 (m, 6H, Ar); 6.00 (s, 2H); 5.29 (s, 2H), 3.84 (s, 3H). IR (KBr, cm^{-1}): 1662.8(C=O).

d: (E)-3-(2- methoxybenzylidene)-6,7-methylene dioxy chromene-4-one:

mp 159-163°C. ^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.96 (s, 1H); 7.4-6.41 (m, 6H, Ar); 6.00 (s, 2H); 5.17 (s, 2H), 3.86 (s, 3H). IR (KBr, cm^{-1}): 1660.7(C=O).

***e**: (E)-3-(3,4- methylene dioxy benzylidene)-6,7-methylene dioxy chromene-4-one:*

mp 141-144°C. ^{1}H NMR (400 MHZ, $CDCl_3$): δ 7.73 (s, 1H); 7.38-6.41 (m, 5H, Ar); 6.03 (s, 2H); 6.00(s, 2H); 5.29 (s, 2H). IR (KBr, cm^{-1}): 1667.7(C=O).

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