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Synthesis of novel 2-benzylidenebenzofuran-3(2*H*)-one derivatives

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Abstract: New derivatives of *Z*-2-benzylidene-4,6-dimethoxy benzofuran-3(2*H*)-ones, a main group of Aurones (2-benzylidenebenzofuran-3(2*H*)-ones), were synthesized by the aldol condensation at first time. Their structures were confirmed by the IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. Aurones have various biological properties and show fungicide activity, antioxidant activity or antilyshmania.

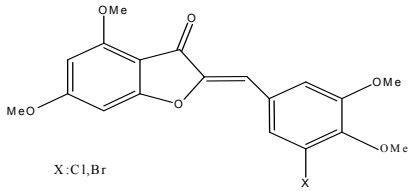
Keywords: Antioxidant, Aurone, Aldol condensation.

Introduction

Antioxidants are effective biological molecules capable of inhibiting the oxidation of other molecules. They have ability to scavenge free radicals, the major cause of oxidation [1]. Radicals are formed from the metabolism of fats and sugars in body [2]. Antioxidants are widely used as ingredients in dietary supplements and have been investigated for the prevention of diseases such as cancer [3]. Also they are used as preservatives in food, cosmetics, rubber or even gasoline [4].

Aurones (2-benzylidenebenzofuran-3(2*H*)-ones) are heterocyclic compounds which contain a benzofuran element associated with a benzylidene linked to furan ring. They are plant flovonoides [5] that are plentiful in the flowers or fruits in the methoxylated, hydroxylated or glycosylated forms and provide yellow color to the flowers of some popular ornamental plants [6]. Analogy with flavonoides suggests that aurones could have anticancer and antioxidant activity as the consequence of radical scavenging [7]. Much attention has been devoted to Aurones synthesis because of their medicinal importance. Due to the presence of conjugated α,β unsaturated carbonyl moiety in their structures, it is suggested that the aldol condensation is a suitable method for their synthesis [8]. Aldol condensation is a facile, efficient and easy synthetic procedure which needs only basic or acidic conditions without any additional reagents and has provided a powerful tool for the aurones synthesis.

Herein, we introduce and synthesize a new derivatives of Aurones, *Z*-2-(3-chloro-5-methoxy-4-methylbenzylidene)-4,6-dimethoxybenzofuran-3 (2*H*)-one and *Z*-2-(3-bromo-5-methoxy-4-methylbenzylidene)-4,6 dimethoxybenzofuran-3(2*H*)-one with the below structures (Scheme **1**).



Scheme 1: Structure of Aurones targeted in this study

Aldol condensation between 4,6-dimethoxy benzofuran-3(2*H*)one and 3-chloro(bromo)-4,5-

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dimethoxybenzaldehyde in the acidic or basic media was selected as a convenient and fascinating method for their synthesis. Finally we try to find the most favorable reaction conditions such as temperature, pH and solvent to improve the yields and purity of products.

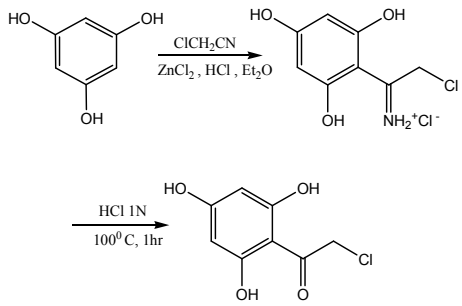
Results and discussion

1) The synthesis of reactants:

1-a) Synthesis of 4,6-dimethoxybenzofuran-3(2H)one:

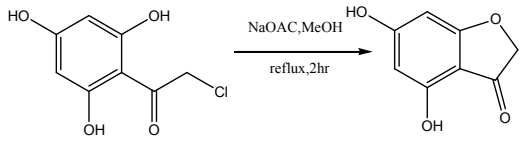
According to the literatures [9], there are three separate steps in the synthesis of 4,6-dimethoxybenzofuran-3(2*H*)one:

1) Hoesch acylation of Phloroglucinol (benzene-1,3,5-triol) with chloroacetonitrile gives iminium salt of 2-(2chloro-1-iminoethyl)benzene-1,3,5-triazole, which hydrolyze readily in the 1 N aqueous hydrochloric acid, provided the 2chloro-1-(2,4,6trihydroxy phenyl)ethanone [10]. The yield is low. Such result is consistent with many side-reactions which are probable in the acidic medium (Scheme **2**).



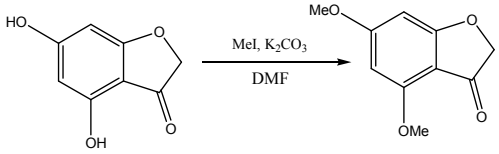
Scheme 2: Synthesis of 2-chloro-1-(2,4,6-trihydroxy phenyl)ethanone

2) Base-catalyzed cyclization of 2-chloro-1-(2,4,6-trihydroxy phenyl) ethanone, gives 4,6- dihydroxy benzofuran-3(2*H*)-one. There is no need to strong bases and drastic conditions and reaction completed by the addition of sodium acetate in methanol as solvent [11] (Scheme **3**).



Scheme 3: Reagents and conditions for synthesis of 4,6-dihydroxybenzofuran-3(2*H*)-one

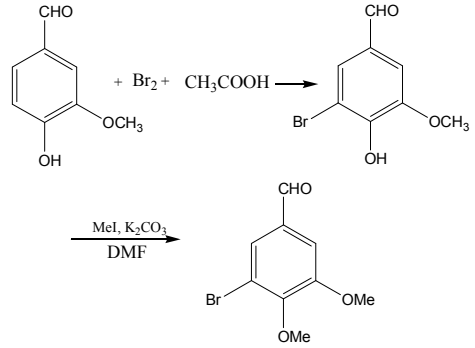
3) To protect phenolic hydroxyls, methylation is required and takes places with methyl iodid in the basic medium. Acidic protons of phenols can prevent the next aldol condensation (Scheme **4**).



Scheme 4: Synthesis of 4,6-dimethoxybenzofuran-3(2*H*)one

1-b) Synthesis of 3-bromo(chloro)-4,5-dimethoxy benzaldehyde:

3-bromo(chloro)-4-hydroxy-5-methoxy benzaldehyde was prepared by direct halogenation of vanillin, with the reaction of vaniline and bromine(or chlorine) in acetic acid. Subsequent methylation of product by methyl iodide in the presence of potassium carbonate yielded the 3-bromo(chloro)-4,5-dimetoxy benzaldehyde (Scheme **5**).

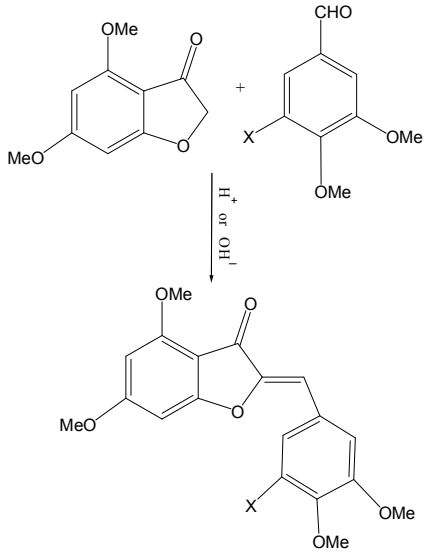


Scheme 5: Synthesis of 3-bromo(chloro)-4-hydroxy-5-methoxybenzaldehyde

2) Aldol condensation between reactants:

In order to complete the synthesis, aldol condensation in acidic or basic conditions is necessary. It was anticipated that ethanol is good solvent compared to the other ones for the condensation. Its polarity and protic nature increase the rate of reaction and permit the better proton transfer. Besides, it can solve both organic and mineral compounds and is not toxic. This idea was confirmed practically. There is no need to heating or any additional reagents. Aldol condensation in acidic or basic conditions was significant, provided the final products effectively. (Scheme **6**) The yields of products for both derivatives are shown in (Table **1**):

The yield in the basic medium is better compared to the acidic conditions noticeably. The plausible explanation is the sensitivity of products, both reactants and their substituent's to the acidic conditions, while there are good stability in the basic ones.



Scheme 6: Aldol condensation between reactants in acidic or basic conditions

Table 1: Percentage yields of products in acidic and basic conditions

Yield	Acidic media	Basic media
X= Cl	22%	52%
X= Br	28%	90%

Conclusion

We synthesize *Z*-2-(3-chloro-5-methoxy-4-methylbenzylidene)-4,6-dimethoxybenzofuran-3 (2*H*)-one and *Z*-2-(3-bromo-5-methoxy-4-methylbenzylidene)-4,6dimethoxybenzofuran-3 (2*H*)-one as the new derivatives of aurones by the aldol condensation in acidic and basic conditions. The yield is better in basic medium due to the stability of products and reactants.

Experimental

1) Synthesis of 2-chloro-1-(2,4,6-trihydroxyphenyl) ethanone:

To the mixture of 15 gr (118 mmol) Phloroglucinol (benzene-1,3,5-triol) and 7.5 ml (119 mmol) chloroacetonitril in 300 ml dry ether, 1.62 gr (0.92 mmol) fused dry powder of zinc chloride was added. The reaction mixture was kept at 0 ^{0}C in ice-water bath and HCl gas was passed through the mixture for 10 minutes. The reaction mixture was refrigerated overnight. Then for second times HCl gas was passed through the mixture. The precipitate was filtered and washed with dry ether. After drying, to the 6 gr (25 mmol) of iminium salt, 100 ml diluted hydrochloric acid (1N) was added and the reaction mixture was refluxed for 1h. After heating, the solution was refrigerated overnight. The precipitate was filtered and washed with water. 38% yield; mp 208-210 ˚c; ^{1}H-NMR (400 MHZ, DMSO): δ 12.08(s,2H); 10.55(s,1H); 5.84(s,2H); 4.94(s,2H). IR (KBr, cm^{-1}): 1642(C=O), 3001-3429(OH)

2) Synthesis of 4,6-dihydroxybenzofuran-3(2H)-one:

1.018 gr (5mmol) 2chloro-1-(2,4,6-trihydroxyphenyl) ethanon was dissolved in 30 ml absolute methanol and 1.14 gr (14 mmol) sodium acetate was added to methanol solution. The solution refluxes for 2hr. Then the solvent was evaporated under reduced pressure. The product was extracted with diethyl ether and the organic layer was successively washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield a pink-colored solid as product. 88% yield; mp 209-210 ˚c. ^{1}H NMR (400 MHZ, DMSO): δ 10.58 (s, 1H); 10.55(s, 1H); 5.90 (s, 2H); 4.54(s, 2H). IR (KBr, cm^{-1}): 1675(C=O); 3320-3550 (OH).

3) Synthesis of 4,6-dimethoxy-benzofuran-3(2H)one:

1gr (6 mmol) 4,6-dihydroxybenzofuran-3(2*H*)-one with 1.65 gr (12 mmol) K_2CO_3 were dissolved in 18 ml DMF and 1ml (17 mmol) methyl iodide was added to the solution. The mixture was stirred for 5hr at room temperature. The reaction mixture was diluted by the water and extracted with ethyl acetate. The solution was dried by anhydrous Na_2SO_4. Solvent was evaporated in vacuum to yielded the desired product which was purified by column chromatography with (hexane:ethylacetate) as eluting solvent. 60% yield; mp 128-130 ˚C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ 6.16 (s, 1H); 6.02 (s, 1H); 4.60 (s, 2H); 3.91 (s, 3H); 3.87 (s, 3H). IR (KBr, cm^{-1}): 1704.6 (C=O).

4) Synthesis of 3-bromo-4-hydroxy-5 methoxybenzaldehyde:

1gr (6.5 mmol) vanillin was dissolved in 6 ml glacial acetic acid. Then solution of 3.15 gr (1 ml) bromine in 6ml acetic acid was added dropwise to the vanillin solution. The reaction mixture was stirred for 1hr at room temperature. The precipitate was filtered, washed with cold glacial acetic acid and dried in air. for high purity, crystallization in absolute ethanol is necessary. 77% yield; mp 163-165 ˚C; ^{1}H NMR (400 MHZ, DMSO): δ 10.7 (S, 1H); 9.7 (S, 1H); 7.71 (S, 1H); 7.41(S, 1H); 3.91(S, 3H).

5) Synthesis of 3-bromo-4,5-dimethoxy benzaldehyde:

2 gr (8.6 mmol) bromovanillin and 1.18 gr (8.5 mmol) K_2CO_3 were solved in 8 ml DMF. To this solution 1.1 ml methyl iodide was added and reaction mixture was stirred for 1hr at 80 ^{0}C. After completion of reaction the reaction mixture was diluted with water and was extracted with Et_2O. The organic layer was washed with water successively, was dried with anhydrous Na_2SO_4. After evaporation of solvent under reduced pressure, the product was obtained as white powder and was purified by crystallization in absolute ethanol. 62 % yield; mp 48-50C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ 9.85 (s, 1H); 7.65 (S, 1H); 7.39 (s, 1H); 3.95 (s, 3H); 3.94 (s, 3H). IR (KBr, cm^{-1}): 1690(C=O).

6) Synthesis of 3-chloro4-hydroxy-5-methoxy benzaldehyde:

Chlorine gas was passed through the solution of 10 gr (65 mmol) vanillin in 30 ml glacial acetic acid at room temperature for 2hr while the solution was stirred. The obtained precipitate was filtered, washed with hexane and dried in air. 66%yield; mp 156-158 °C; ^{1}H NMR (400 MHZ, $CDCl_3$): δ 9.79 (s, 1H); 7.50 (d, 1H, *J*=2); 7.34(s, 1H); 6.50 (s, 1H); 3.99 (s, 3H)

7) Synthesis of 3-chloro-4,5-dimethoxy benzaldehyde:

5 gr (26 mmol) chlorovanillin and 3.68 (26 mmol) K_2CO_3 were solved in 20 ml DMF. To DMF solution, 3.31ml methyl iodide was added and reaction mixture was stirred at 80°C for 3hr. Then 40ml water was poured to the solution and product as precipitate as white solid. The product was filtered and was washed with 400 ml water, dried in air. 89% yield; mp 48-50 ^{0} C; ^{1}H-NMR (400MHz, $CDCl_3$): δ 9.85 (s, 1H); 7.56 (d, 1H, *J*=1.6); 7.39 (d, 1H, *J*=1.6); 3.95 (s, 3H); 3.94 (s, 3H). IR (KBr, cm^{-1}): 1692 (C=O).

8) Aldol condensation between 3-bromo(chloro)-4,5-dimethoxy-benzaldehyde and 4,6-dimethoxy benzofuran-3(2H)one in basic conditions:

0.2 gr (1 mmol) 3-bromo(chloro)4,5-dimethoxy benzaldehyde and 0.2 gr (1 mmol) 4.6-dimethoxy benzofuran-3(2*H*)one was added to 7ml ethanol. Solution of 1 mmol KOH in 0.4 ml water was poured to ethanol solution and reaction mixture was stirred at room temperature for 2hr. 10 ml water was added to resulting solution and product was precipitated as yellow solid. The solid was washed with water and recrystallized in ethanol to produce the pure product. For bromo derivative: 90% yield; mp 198-200 °C; ^{1}H NMR (500 MHZ, $CDCl_3$): δ 7.75 (s, 1H); 7.30 (s, 1H); 6.64 (s, 1H); 6.41 (s, 1H); 6.16 (s, 1H); 3.92-3.97 (m, 12H, OMe). IR (KBr, cm^{-1}): 1692(C=O). For chloro derivative: 52% yield; mp 200-201 °C; ^{1}H NMR (500 MHZ, $CDCl_3$): δ 7.60 (s, 1H); 7.26 (s, 1H); 6.64 (s, 1H); 6.40 (s, 1H); 6.16 (s, 1H); 3.93-3.97 (m, 12H, OMe). IR (KBr, cm^{-1}): 1692(C=O).

9) Aldol condensation between 3-bromo(chloro)- 4,5-dimethoxy benzaldehyde and 4,6-dimethoxy benzofuran-3(2H)one in acidic conditions:

0.5 mmol 3-bromo(chloro)4,5-dimethoxy benzaldehyde and 0.5 mmol 4,6-dimethoxy benzofuran-3(2*H*)one was added in 5 ml ethanol. The reaction vessel was kept at 0 ^{0}C in ice-water bath and was stirred while the HCl gas was entered to the vessel for 6 minute. The vessel was sealed and for 24 hr was kept in contact with HCl gas. After 24 hr, the precipitate was filtered, washed with cold alcohol and recrystallized in hot ethanol, yielded the pure yellow crystals as product 22% yield for chloro derivative and 28% yield for bromo derivative.

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