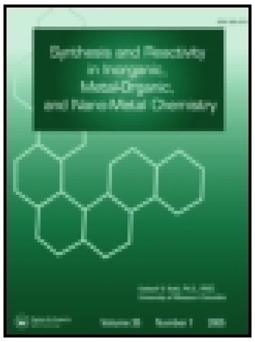

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Efficient One-pot Three-component Synthesis of 3,4,5-Substituted Furan-2(5*H*)-ones Catalyzed Watermelon Juice

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Abstract

A simple, efficient, and environmentally- benign protocol for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones has been achieved using extract of watermelon as a natural catalyst. We found, for the first time, that the extract of watermelon could effectively catalyze The condensation reaction of aldehydes, amines, dialkyl acetylenedicarboxylates to 3,4,5-substituted furan-2(5*H*)-ones in excellent yields under mild conditions. The low cost, easy availability of the catalyst, and simple reaction conditions suggest the possible use of the present method for large scale preparations.

Key word: watermelon juice, dialkyl acetylenedicarboxylates, furan-2(5*H*)-ones, aldehydes

Introduction

New catalytic synthetic methods in organic chemistry which satisfy increasingly stringent environmental constraints are in great demand by the pharmaceutical and chemical industries. In addition, novel catalytic procedures are necessary to produce the emerging classes of organic compounds becoming the targets of molecular and biomedical research. Several types of substances such as enzymes, surfactants, ionic liquids, clays, and supercritical solvents are now widely recognized as practical alternatives to traditional organic synthesis and as convenient solutions to certain intractable synthetic problems. This is due to problems associated with prevailing catalysts, such as hazardous nature, expense, difficult handling, tedious workup, requirements of hazardous organic solvents, elevated temperature conditions, and ,above all, adverse effects on the environment. In an attempt to circumvent these disadvantages, we looked to nature for help. Nature provides a fantastic array of catalysts extremely well suited to support life such as intact plant systems which represent a unique class of potential biocatalysts for the reactions of various organic substrates [1- 3] .

The synthetic transformations are more efficient using these materials and they generate less waste than the conventional chemical methods. More recently, chemical reactions using plant cell cultures and part of plants as biocatalysts have received great attention [4-6]. This crescent interest is due to the wide biotechnological potential of the enzymetic reactions. The biocatalytical transformations using plant root [7,8], plant tubers [9], edible plants [10] and plants` leave [11] extract can be applied in a considerable number of organic reactions. Fruit juice is also naturally occurring used as a biocatalysts in organic synthesis. Fruit juice is now routinely being used in organic synthesis as homogeneous catalysts for various selective transformations of simple and complex molecules.

These interesting properties of aqueous extract of fruit allow us to use watermelon juice as an eco-friendly catalyst for organic synthesis. Considering the widespread utility of furan one derivatives and availability of few literature protocols for the synthesis of furanones and their limitations, in the present work we have successfully developed a synthetic route with minimized drawbacks.

Among the available methods for the construction of furanones, the nucleophilic reaction between zwitterions of amine and dialkyl acetylenedicarboxylates with aldehyde is the most convenient one [12-16]. The three-component condensation of aldehydes, amines and dialkyl acetylenedicarboxylates lead to the formation of 3,4,5-substituted furan-2(5H)-one derivatives (Scheme 1).

Results and discussion

Continuing of our work, following the principles of green chemistry [17-20], we have developed a simple, efficient, and green protocol for the preparation of 3,4,5-substituted furan-2(5*H*)-one using extract of watermelon as a green and inexpensive catalyst as well as solvent. Our approach reduces the use of hazardous organic solvents and it uses simple and mild conditions with inherently lower costs.

Watermelon is one of the main vegetable crops grown and consumed all over the Mediterranean basin. China is the largest producer of watermelon, with 68.9% of the total production. It is much appreciated as an excellent refreshing summer fruit. Besides vitamins, mineral salts and specific amino acids watermelon provide a wide variety of dietary antioxidants such as carotenoids and phenolics. The edible portion contains approximately 6.2 % total sugar and 91.0% water by weight (21-25).

Soluble sugars in content of the watermelon are one of its most important properties, as the value of the watermelon is dependent on this content. The sugars was applied as an efficient and homogenous catalyst for multicomponent reaction in excellent yields (20,26). Our further experiments have been designed to check the activities of some components of watermelon juice on synthesis of 3,4,5-substituted furan-2(5*H*)-one. For this purpose in separate experiments, components with more weight percentage such as sucrose, glucose, fructose, vitamin C, and vitamin B-6 were chosen. Investigations have shown that the reaction has occurred in presence of all above component with good yield. Since the juice contains a substantial number of vitamins, ions and reduces sugars with different ratio and varies, regarding to mentioned experiment, it seems that set of above agents are effective in occurring of these three component reactions.

In the beginning, a test reaction using benzaldehyde **1** (1.0 mmol), aniline **2** (1.0 mmol), and dimethyl acetylenedicarboxylate **3** (1.0 mmol) in 5 mL juice of watermelon at room temperature was performed in order to establish the real effectiveness of the catalyst (solvent), and the product was obtained in good yields.

In order to compare the strength of the juice of watermelon, as a catalyst with juice of various summer fruits, a model reaction was carried out between **1** (1.0 mmol), aniline **2** (1.0 mmol) and dimethyl acetylenedicarboxylate **3** (1.0 mmol) using various juices of fruits as catalysts at room temperature, and the results are summarized in Table 2.

Under the optimized reaction conditions, the generality of the reaction was investigated by the usage of various aldehydes, anilines and dialkyl acetylenedicarboxylate to produce furan-2(5*H*)-one derivatives. The results are summarized in Table 3. These results indicate the effectiveness of electron-withdrawing and electron-donating groups on the time and yield of the reaction. Benzaldehydes with electron-withdrawing groups react with aniline better than electron-donating groups for generation of furan-2(5*H*)-ones in good to high yields. In our research work, aliphatic aldehyde and amine such as propanal and 1-buthylamin did not tolerate the reaction.

The structures of new compounds in Table 3 were deduced on the basis of IR, ^{1}H, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of Compound **4m**, ethyl 4-(3-nitrophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate displayed the molecular ion peak at *m/z* = 368, consistent with the proposed structure. The ^{1}H NMR spectrum of this product, exhibited a triplet at $\delta = 1.22$ ppm and quartet at $\delta = 4.23$ ppm for ethyl protons of the carboxylate group and one sharp singlet arising from benzylic proton at $\delta = 5.83$ ppm. The aromatic protons of product were observed at $\delta = 7.31$-8.34 ppm. A broad singlet for the NH group at $\delta = 9.15$ ppm indicated intra-molecular hydrogen bond formation with the vicinal carbonyl group. The ^{13}C NMR spectrum of this product showed 17 distinct resonances in agreement with the proposed structure. The IR spectrum indicated one sharp peak at 3308 cm^{-1} for NH within product. A proposed mechanism for this transformation can be combination of nucleophilic Michael addition, iminium-enamine tautomerization with γ-Lactonization (27,28).

To compare the applicability and efficiency of watermelon juice with the reported catalysts in the literature for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones, we have tabulated the results of these catalysts in Table 4. As shown in Table 4, watermelon juice can act as an efficient catalyst with respect to reaction time and yield of products.

In conclusion, we have found that the aqueous extract of watermelon is considered as an efficient, economical, and environmentally- friendly catalyst for the synthesis of 3,4,5-substituted furan-2(5*H*)-ones. The high yield of products in a short reaction time along with high purity, mild reaction conditions, and a simple workup procedure makes this procedure attractive. Using watermelon juice as a solvent and biodegradable catalyst is the attractive features of this protocol. Furnishing pure products by simple filtration makes an aqueous approach possible for large scale preparation of furan-2(5*H*)-ones.

EXPERIMENTAL

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on Bruker DRX-400 Avance instruments with $CDCl_3$ as a solvent. Mass spectra were recorded on an Agilent Technology (HP) spectrometer operating at an ionization potential of 70 eV. Samples of fruits were blended using a laboratory electrical blender (Model 32BL79, Waring, USA). All reagents and solvents obtained from Fluka and Merck were used without further purification.

General procedure:

Plant material

Eight fruit samples were purchased from local commercial market, collected between July and August (2013) in the region of South of Sistan and Baluchestan, Iran. After samples were purchased, they were washed and drained. The skins were peeled except Blackberry and the rest of the fruit was cut into 3 cm cubes. The seeds were then removed and all the flesh part was blended using a laboratory electrical blender (Model 32BL79, Waring, USA). The obtained juice was vacuum- filtered and then transferred into a beaker.

General procedure for the synthesis of furan-2(5H)-one derivatives

The mixture of aldehyde (1.0 mmol), amine (1.0 mmol), dialkylacetylenedicarboxylate (1.0 mmol) and 5 mL juice of watermelon were stirred at room temperature. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction products were collected by filtration. After that, the products were washed with water/ethanol (50:50, 3 × 2 mL) to give the corresponding pure compounds. The catalyst remained in the water/ethanol filtrate.

*Ethyl-4-(3-nitrophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate (**4m**)*:

Colorless solid; 0.258 g (70%); mp 208 °C; IR (KBr): 3308, 3093, 2984, 1723, 1686, 1526 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ: 1.22 (t, *J* = 7.2 Hz ,CH_3), 4.23 (q, *J*=7.2 Hz, CH_2), 5.83 (s, 1H, $H_{benzylic}$), 7.31-8.34 (m, 9H, H_{Ar}), 8.341 (s, 1H), 9.158 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1 and 162.9 (ester C=O), 156.2, 148.4, 137.5, 134.1, 129.9, 129.0, 129.0, 127.4, 127.2, 120.0, 115.9, 113.7 (12 C_{Ar} and C_{vinyl}), 61.6 ($C_{benzylic}$), 61.2 (CH_2), 13.9 (CH_3). MS m/z (%): 57 (15), 73 (16), 84 (20), 96 (21), 97 (22), 98 (20), 129 (15), 130 (21), 203 (24), 236 (21), 295 (59), 368 (M^+, 100).

*tert-Butyl-2,5-dihydro-5-oxo-4-(phenylamino)-2-p-tolylfuran-3-carboxylate (**4n**)*:

Colorless solid; 0.268 g (83%); mp 175-178 °C; IR (KBr): 3400, 3020, 2925, 1701, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.38 (s, 9H, CH_3), 2.28 (s, 3H, CH_3), 5.64 (s, 1H, $H_{benzylic}$), 7.04-7.50 (m, 9H, H_{Ar}), 9.29 (br, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1 and 162.9 (ester C=O), 156.7, 138.1, 136.4, 132.1, 129.1, 128.9, 127.4, 125.6, 122.3 and 114.5 (C_{Ar}), 83.2 (C-O), 61.4 ($C_{benzylic}$), 28.0 (3 CH_3), 21.1 (CH_3). MS m/z (%): 57 (44), 77 (33), 91 (27), 115 (58), 144 (99), 189 (100), 264 (61), 291 (19), 309 (94), 365 (M^+, 50).

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Table 1. Some of the chemical composition of watermelon juice

Entry	Soluble sugars	Organic acids	Volatiles	Carotenoids	Vitamins	Minerals
1	Fructose	Oxalic acid	Pentyl-furan	trans violaxanthin	Vitamin A	K
2	Glucose	Malic acid	Limonene	Luteoxanthin	Thiamine	P
3	Sucrose	Tartaric acid	Nonanal	9-cis-Violaxanthin	Riboflavin	Fe
4		Citric acid	1,10-Undecadiene	All-trans lutein	Niacin	Na
5		Quinic acid	(Z)-3-Nonen-1-ol	All-trans zeaxanthin	Ascorbic Acid	Ca
6			(E,Z)-3,6-Nonadien-1-ol	Phytofluene A 3	Vitamin B6	
7			(E)-2-Nonenal	Phytoene		
8			2,6-Nonadien-1-ol	Phytofluene B		
9			3-NO_2-C_6H_4	α-Carotene		
10			Nonanol	ζ-Carotene		
11			Nonanoic acid	β-Carotene		
12			*β*-Ionon	cis-β-Carotene		

Table 2. catalyst screening for the synthesis of furan-2(5*H*)-ones at room temperature.

Entry	Solvent	pH	Time (h)	Yield (%)[a]
1	H_2O	6.8	24	-
2	Melon juice	5.8	6	50
3	Blackberry juice	3.9	15	25
4	Grapes juice	2.9	12	40
5	Pomegranate juice	3	15	25
6	Strawberries juice	3.2	24	-
7	Peach juice	3.30	10	42
8	Verjuice juice	3.5	16	38
9	**Watermelon juice**	**5.6**	**3**	**92**

[a] Isolated yield.

Table 3. **S**ynthesis of furan-2(5*H*)-one derivatives.

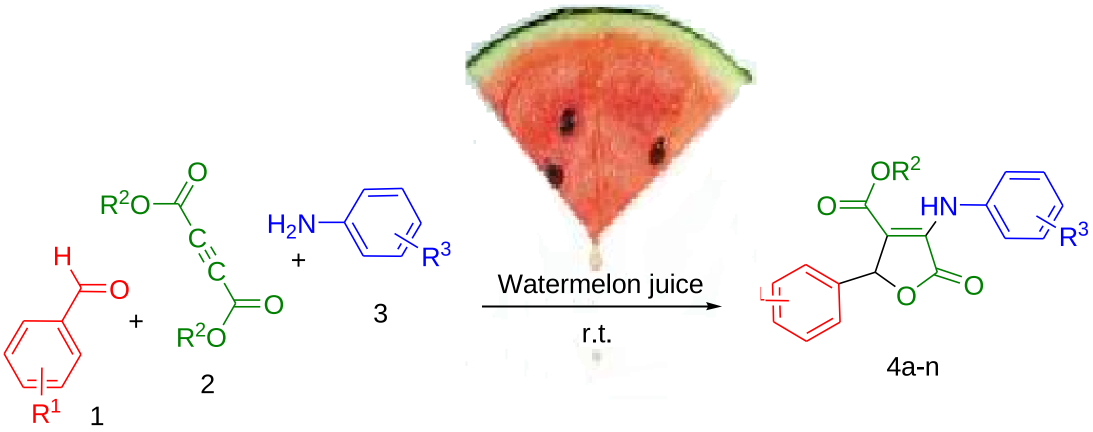
Entry	R^1	R^2	R^3	Time (h)	Yield (%)[a]	Product	Ref.
1	Ph	CH_3	4-F-C_6H_4	2	70	**4a**	13
2	Ph	CH_3	4-Cl-C_6H_4	3	69	**4b**	17
3	Ph	CH_3	3-NO_2-C_6H_4	3	82	**4c**	17
4	4-NO_2-C_6H_4	CH_3	Ph	2	90	**4d**	17
5	Ph	CH_3CH_2	Ph	2	92	**4e**	12
6	4-Me-C_6H_4	CH_3CH_2	Ph	2	88	**4f**	12
7	4-Cl-C_6H_4	CH_3CH_2	Ph	1	85	**4g**	12
8	4-OMe-C_6H_4	CH_3CH_2	Ph	3	85	**4h**	12
9	1- naphtyl	CH_3CH_2	Ph	1	90	**4i**	17
10	Ph	CH_3	3-NO_2-C_6H_4	2	93	**4j**	17
11	4-OMe-C_6H_4	CH_3	Ph	3	60	**4k**	12
12	Ph	CH_3CH_2	4-Me-C_6H_4	3	77	**4l**	12
13	Ph	CH_3CH_2	3-NO_2-C_6H_4	2	80	**4m**	*b*
14	4-Me-C_6H_4	*tert*-buthyl	Ph	2	90	**4n**	*b*
15	Ph	CH_3	Ph	2	90	**4o**	13

[a] Isolated yield.

[b] The new compounds were synthesized in this work. All known products previously reported in the literature were characterized by comparison of m.p., IR and NMR spectra with those of authentic samples.

Table 4 Comparison result of watermelon juice with the reported catalysts in literature for the synthesis of 3,4,5-substituted furan-2(5H)-ones **4o** and **4e**.

Entry	Product	Catalyst	Time	Yield (%)	Ref.
1	**4o**	β-Cyclodextrin	-	-	12
2		Nano-ZnO	2.5 h	94	15
3		$Al(HSO_4)_3$	8 h	84	14
4		$SnCl_2.2H_2O$	6.5 h	90	13
5		AcOH	-	-	17
6		$[Bu_4N][HSO_4]$	5 h	92	18
7		PPA/SiO_2	1 h	90	19
8		Sucrose	9 h	97	25
9		watermelon juice	2h	90	This work
10	**4e**	β-Cyclodextrin	12 h	85	12
11		Nano-ZnO	-	-	15
12		$Al(HSO_4)_3$	9 h	77	14
13		$SnCl_2.2H_2O$	-	-	13
14		AcOH	1 h	95	17
15		$[Bu_4N][HSO_4]$	2 h	90	18
16		PPA/SiO_2	1 h	91	19
17		Sucrose	4.5 h	85	25
18		watermelon juice	2h	92	This work



Scheme 1. Synthesis of furan-2(5*H*)-one derivatives.