Volume 6, Issue 4, 2016, 1401-1405 ISSN 2069-5837

Biointerface Research in Applied Chemistry

www.BiointerfaceResearch.com

Original Research Article Open Access Journal

Received: 25.04.2016 / Revised: 26.06.2016 / Accepted: 30.06.2016 / Published on-line: 20.07.2016

Catalytic comparison of maleic acid and fumaric acid as green catalysts for one-pot synthesis of 3,4,5-substituted furan-2(5*H*)-ones via a multicomponent approach

Malek Taher Maghsoodlou [1],*, Amir Bagheri [1], Mojtaba Lashkari [2], Belgheis Adrom [1], Nourallah Hazeri [2], Razieh Doostmohammadi [1]

[1]Department of Chemistry, Faculty of Science, University of Sistan and Baluchestan, P. O. Box 98135-674 Zahedan, Iran
[2]Faculty of Science, Velayat University, Iranshahr, Iran

*corresponding author e-mail address: ***mt_maghsoodlou@chem.usb.ac.ir , mt_maghsoodlou@yahoo.com***

ABSTRACT

An expeditious one-pot synthesis has been developed to obtain 3, 4, 5-substituted furan-2(5*H*)-ones via a multicomponent approach. The reaction of aldehydes with amines and dialkyl acetylenedicarboxylates in the presence of maleic and fumaric acids in aqueous media afforded 3, 4, 5-trisubstituted furan-2(5*H*)-ones. Use of aqueous medium, green catalyst, operational simplicity, non-chromatographic purification technique, excellent yield and short reaction time makes this approach an attractive protocol for the synthesis of 3, 4, 5-trisubstituted furan-2(5*H*)-ones. Also, in the presence of maleic acid, products were synthesized with greater efficiency. The structures of compounds were deduced on the basis of IR, ^{1}H, and ^{13}C NMR spectroscopies and mass spectrometry.

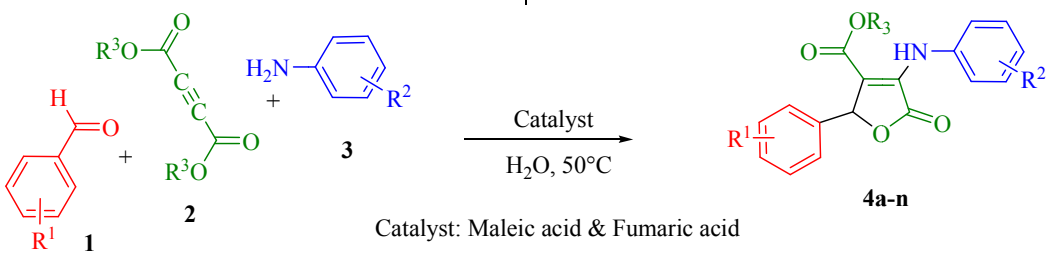
KEYWORDS: *Green protocol, Multi-component reaction, Dialkyl acetylenedicarboxylates, Furan-2(5H)-ones, Maleic acid, Fumaric acid.*

1. INTRODUCTION

The so-called multicomponent reactions (MCRs) are one-pot processes in which at least three or more different simple substrates react for the preparation of target materials [1]. These reactions, which have gained much attention during the past years, are frequently occurring not through a single-step procedure but rather by several sequential steps or multicomponent cascade or domino reactions [2]. Simplicity, greater efficiency, and atom economy with generation of molecular complexity and diversity in the one-pot transformation are some of the advantages of these reactions.

Highly substituted furans play an important role in organic chemistry, not only as the key structural units in many natural products, common subunits in pharmaceuticals [3–8] and flavors [9] but also as useful building blocks in synthetic chemistry [10–14]. The preparation of 3, 4, 5 trisubstituted furan-2(5*H*)-ones can be carried out by multi-component condensation of aryl aldehydes, amines and dialkyl acetylenedicarboxylates in the presence of Lewis or Brønsted acid catalysts such as $SnCl_2$, KOH, rhodium, palladium, β-cyclodextrin [15-19]. However, some of these catalysts suffer from the drawback of green chemistry such as prolonged reaction times, low yields, toxicity and recovery and reusability of the catalyst. Therefore, introducing clean processes and utilizing eco-friendly and green catalysts which can be simply worked-up at the end of reactions have been under permanent attention. The demand for environmentally benign procedure with green catalyst [20, 21] promoted us to develop a safe alternate method for the synthesis of 3,4,5-trisubstituted furan-2(5*H*)-ones.

Herein, we wish to report a simple, convenient, rapid (30 min) and high-yielding method using of maleic and fumaric acids as an efficient, non-toxic and commercially available catalysts for the synthesis of 3,4,5-trisubstituted furan-2(5*H*)-ones (Scheme 1).



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

2. EXPERIMENTAL SECTION

2.1. General.

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-250 and 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. All reagents and solvents obtained from Fluka and Merck were used without further purification.

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

The mixture of aldehyde (1.0 mmol), amine (1.0 mmol), diethylacetylenedicarboxylate (1.0 mmol), 20 mol % maleic acid and 5 mL of water was stirred at 50 °C. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction products were collected by filtration. 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 (**4n**)

Colorless solid (86%); mp 207-209 °C; IR (KBr): 3308, 3093, 2984, 1723, 1686, 1526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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 (**4o**)

Colorless solid (94%); 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).

3. RESULTS SECTION

As an initial attempt, we selected the reaction of benzaldehyde, aniline and diethyl acetylenedicarboxylate using 10 mol % of catalyst as the model to probe this proposed synthetic method. After heating at 30 °C in H_2O for 1.6 h, we were glad to observe the formation of target product 4e in 60% yield. Finally, increasing the amount of maleic acid showed a positive effect on reaction and satisfactory yield was obtained when 20 % mol of maleic acid was employed (Table 1). The feasibility of this method encouraged us to further investigate the reaction conditions to improve the product yield. First, the change on reaction temperature suggested that 50 °C gave better yield while further increase of temperature to 70 °C led to no further yield enhancement (Table 1).

Table 1. Optimization of reaction conditions in the presence of different amount of A: maleic acid B: fumaric acid as catalysts under different temperatures [a].

Entry	Catalyst/ mol %		Temperature/ °C		Time/ h		Isolated Yield/ %	
	A	B	A	B	A	B	A	B
1	10	10	30	30	1.6	2.8	60	51
2	15	15	30	30	1.5	2.6	79	59
3	20	20	30	30	1.2	2.3	87	**70**
4	25	25	30	30	1.3	2.2	82	**77**
5	30	30	30	30	1.4	2.3	80	64
6	20	25	40	40	0.9	2	89	84
7	**20**	**25**	**50**	**50**	**0.8**	**1.6**	**97**	**89**
8	20	25	60	60	1	1.5	87	83
9	20	25	70	70	1.1	1.3	81	79

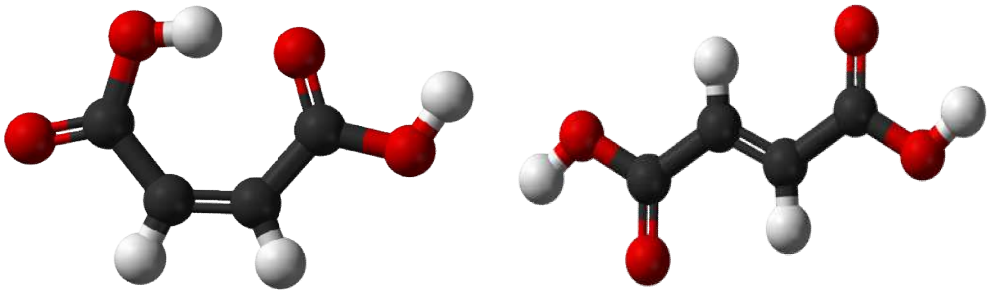
[a] Reaction conditions: Benzaldehyde (1.0 mmol), aniline (1.0 mmol), diethyl acetylenedicarboxylate (1.0 mmol)

Among the entries employing different acids, maleic acid turned out to be a better acid catalyst than fumaric acid (Table 1). The best result for fumaric acid obtained with 25 % mol of catalyst at 50 °C in H_2O (Table 1). Maleic acid is the *cis*-(Z)-2-butenedioic acid and fumaric acid is the *trans*-(E)-2-butenedioic acid (Figure 1). Although maleic and fumaric acids have the same molecular weight and they are both dicarboxylic acids, their pH relationships differ.

The pH of fumaric acid is 2.1 at 4.9 g/L at 20 °C whereas maleic acid has a lower pH. The reason for this difference is that when one proton is removed from the *cis*-isomer (maleic acid) a strong intramolecular hydrogen bond is formed with the nearby remaining carboxyl group. This favors the formation of the maleic acid proton, making maleic acid a stronger acid. In the *trans* isomer, the two carboxyl groups are always far apart, so hydrogen bonding is not observed.

Under the optimized reaction conditions, the generality of the reaction was investigated by the using of various aldehydes, anilines and dialkyl acetylenedicarboxylate to produce furan-2(5*H*)-one derivatives. The results are summarized in Table 2. 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.



Maleic Acid Fumaric Acid

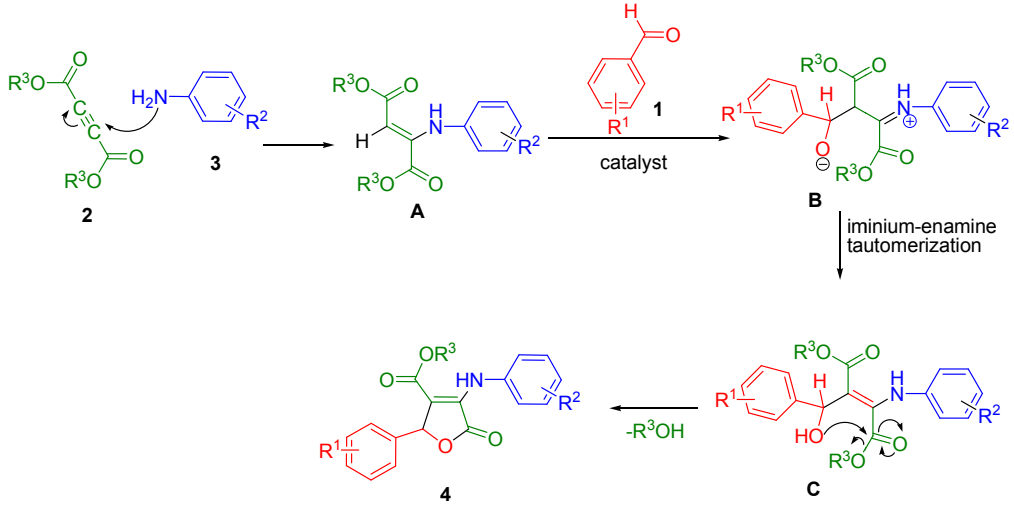
Figure 1. *cis*-(Z)-2-Butenedioic acid (maleic acid) and *trans*-(E)-2-butenedioic acid (fumaric acid).

Table 2. Synthesis of furan-2(5H)-one derivatives in the presence of A: maleic acid B: fumaric acid as catalysts.

Entry	R^1	R^2	R^3	Products	Isolated Yield/ %		Ref.
					A	B	
1	Ph	4-F-C_6H_4	CH_3	**4a**	76	65	[23]
2	Ph	4-Cl-C_6H_4	CH_3	**4b**	74	61	[23]
3	Ph	3- O_2N-C_6H_4	CH_3	**4c**	87	76	[23]
4	4-$O_2NC_6H_4$	Ph	CH_3	**4d**	96	85	[22]
5	Ph	Ph	CH_3CH_2	**4e**	94	85	[22]
6	4-Me-C_6H_4	Ph	CH_3CH_2	**4f**	91	88	[22]
7	4-Cl-C_6H_4	Ph	CH_3CH_2	**4g**	94	86	[22]
8	4-MeO-C_6H_4	Ph	CH_3CH_2	**4h**	91	84	[23]
9	3-O_2N-C_6H_4	Ph	CH_3	**4i**	94	88	[22]
10	Ph	4-Me-C_6H_4	CH_3CH_2	**4j**	82	79	[22]
11	Ph	Ph	CH_3	**4k**	96	84	[27]
12	4-Me-C_6H_4	Ph	CH_3	**4l**	80	74	[27]
13	1-naphtyl	Ph	CH_3CH_2	**4m**	64	63	[19]
14	Ph	3-O_2N-C_6H_4	CH_3CH_2	**4n**	86	81	*a*
15	4-Me-C_6H_4	Ph	*t*-Bu	**4o**	94	85	*a*

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

A suggested mechanism for this transformation is shown in Scheme 2. First, nucleophilic Michael addition of amine **3** to acetylenic ester **2** generates the enaminone **A**. Next, nucleophilic attack of enaminone **A** to the aldehyde **1** would yield iminium–oxoanion intermediate **B**, that can be tautomerized to dialkyl 2-(hydroxy(phenyl)methyl)-3-(arylamino)-2-butenedioate **C**. γ-Lactonization of **C** would produce the alkyl-2,5-dihydro-5-oxo-2-aryl-4-(arylamino)furan-3-carboxylate derivatives **4** [25, 26].



Scheme 2. The suggested mechanism for the formation of furan-2(5*H*)-one derivatives.

The structures of new compounds in Table 2 were deduced on the basis of IR, ^1H, and ^{13}C NMR spectroscopies and mass spectrometry. The mass spectrum of compound **4n**, ethyl 4-(3-nitrophenylamino)-2,5-dihydro-5-oxo-2-phenylfuran-3-carboxylate displayed the molecular ion peak at *m/z* = 368, which is consistent with the proposed structure. The ^1H NMR spectrum

of this product, exhibited a triplet at δ = 1.22 ppm and quartet at δ = 4.23 ppm for ethyl protons of the carboxylate group and one sharp singlet arising from benzylic proton at δ = 5.83 ppm. The aromatic protons of product were observed at δ = 7.31-8.34 ppm. A broad singlet for the NH group at δ = 9.15 ppm indicated intra-molecular hydrogen bond formation with the vicinal carbonyl group. The ^{13}C NMR spectrum of this product was 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.

In order to show the merit of the present work in comparison with reported results in the literature, we compared the reactions of maleic and fumaric acids with β-Cyclodextrin, Nano-ZnO, $Al(HSO_4)_3$, $SnCl_2.2H_2O$, AcOH, $[Bu_4N][HSO_4]$ and PPA/SiO_2 in the synthesis of 3,4,5-substituted furan-2(5*H*)-ones derivatives. As can be seen from Table 3, maleic acid is an efficient catalyst in the formation of 3,4,5-substituted furan-2(5*H*)-ones with high yields and shorter reaction times.

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

Entry	Product	Catalyst	Time	Yield (%)	Ref.
1	**4a**	β-Cyclodextrin	-	-	19
2		Nano-ZnO	2.5 h	94	28
3		$Al(HSO_4)_3$	8 h	84	27
4		$SnCl_2.2H_2O$	6.5 h	90	15
5		AcOH	-	-	22
6		$[Bu_4N][HSO_4]$	5 h	92	24
7		PPA/SiO_2	1 h	90	23
8		Sucrose	9 h	97	29
9		Maleic acid	1h	94	This work
10		Fumaric acids	2h	84	This work
12	**4e**	β-Cyclodextrin	12 h	85	19
13		Nano-ZnO	-	-	28
14		$Al(HSO_4)_3$	9 h	77	27
15		$SnCl_2.2H_2O$	-	-	15
16		AcOH	1 h	95	22
17		$[Bu_4N][HSO_4]$	2 h	90	24
18		PPA/SiO_2	1 h	91	23
19		Sucrose	4.5 h	85	29
20		Maleic acid	1.2	96	This work
21		Fumaric acids	2.3	82	This work

4. CONCLUSIONS

In conclusion, in the present work a new one-step method for the construction of the 3,4,5-trisubstituted furan-2(5*H*)-ones, in very good yields, by using green catalysts (maleic acid and fumaric acid) promoted reaction between aryl aldehydes, amines and dialkyl acetylenedicarboxylates is described. The catalysts shows environmentally friendly characters. Namely, those are inexpensive, clean, safe, nontoxic and easily obtained. Moreover, this method has several other advantages including mild reaction conditions, high yields, operational simplicity, clean and neutral reaction conditions, which makes it a useful and attractive process for the synthesis of a wide variety of biologically active compounds.

5. REFERENCES

[1] Zhu J., Bienayme H., Multicomponent Reactions, *VCH: Weinheim*, **2005.**

[2] Dömling A., Recent developments in isocyanide based multicomponent reactions in applied chemistry, *Chemical Reviews*, 17, 106, **2006.**

[3] Dean F.A., Naturally Occurring Oxygen Ring Compounds, *Butterworth*, London, **1963.**

[4] Katritzky A.R., Advances in Heterocyclic Chemistry, *Academic Press, New York*, 31, **1983.**

[5] Bird C.W., Cheeseman G.W.H., Comprehensive Heterocyclic Chemistry, *Pergamon Press, Oxford*, **1984.**

[6] Lipshutz B.H., Five-Membered Heteroaromatic Rings as Intermediates in Organic Synthesis, *Chemical Reviews*, 86, 795, **1986.**

[7] Bock I., Bornowski H., Ranft A., Theis H., Synthesis of mono- and dialkylfurans, *Tetrahedron*, 46, 1199, **1990.**

[8] Mortensen D.S., Rodriguez A.L., Carlson K.E., Sun J., Katzenellenbogen B.S., Katzenellenbogen J.A., Synthesis and Biological Evaluation of a Novel Series of Furans: Ligands Selective for Estrogen Receptor α**,** *Journal of Medicinal Chemistry*, 44, 3838, **2001.**

[9] Naim M., Zuker I., Zehavi U., Rouseff R.L., Inhibition by thiol compounds of off-flavor formation in stored orange juice. 2. Effect of L-cysteine and N-acetyl-L-cysteine on p-vinylguaiacol formation, *Journal of Agricultural and Food Chemistry*, 41, 9, 1359, **1993.**

[10] Benassi R., Furans and their benzo derivatives: structure, in: Katritzky A.R., Rees, C.W., Scriven E.F.V., Comprehensive Heterocyclic Chemistry II, *Pergamon Press, Oxford*, 2, **1996.**

[11] Heaney H., Ahn J.S., Furans and their benzo derivatives: reactivity, in: Katritzky A.R., Rees C.W., Scriven E.F.V., Comprehensive Heterocyclic Chemistry II, *Pergamon Press, Oxford*, 29, **1996.**

[12] Friedrichsen W., Furans and their benzo derivatives: synthesis, in: Katritzky A.R., Rees C.W., Scriven E.F.V., Comprehensive Heterocyclic Chemistry II, Pergamon Press, Oxford, 2, **1996.**

[13] Katritzky A.R., Rees C.W., Scriven E.F.V., Comprehensive Heterocyclic Chemistry II, *Pergamon Press Oxford*, 2, 395, **1996.**

[14] Trost B.M., Fleming I., Comprehensive Organic Synthesis, *Pergamon Press, Oxford*, 4, 1069, **1991.**
[15] Nagarapu L., Kumar U.N., Upendra P., Bantu R., Simple, Convenient Method for the Synthesis of Substituted Furan2(5H)-one Derivatives Using Tin(II) Chloride, *Synthetic Communications*., 42, 2139, **2012.**
[16] Subburethinam R., Rajagopal N., Efficient One-Pot Multicomponent Synthesis of (Carbazolylamino)furan-2(5H)-one and Carbazolyltetrahydropyrimidine Derivatives, *Synthesis*, 7, 20, 3307, **2011.**
[17] Bassetti M., Annibale A.D., Fanfoni A., Minissi F., Synthesis of α,β-Unsaturated 4,5-Disubstituted γ-Lactones via Ring-Closing Metathesis Catalyzed by the First-Generation Grubbs' Catalyst, *Organic Letters*, 7, 1805, **2005.**
[18] Bellina F., Biagetti M., Carpita A., Rossi R., Selective synthesis of natural and unnatural 5,6-disubstituted 2(2H)-pyranones via iodolactonization of 5-substituted (Z)-2-en-4-ynoic acids, *Tetrahedron*, 57, 2857, **2001.**
[19] Murthy S.N., Madhav B., Kumar A.V., Rao K.R., Nageswar Y.V.D., Facile and efficient synthesis of 3,4,5-substituted furan-2(5H)-ones by using β-cyclodextrin as reusable catalyst, *Tetrahedron*, 65, 5251, **2009.**
[20] Farhadpour F., Hazeri N., Salahi S., Dastoorani P., Doostmohammadi R., Lashkari M., Ghashang M., Maghsoodlou M.T., Maltose as a green catalyst for the synthesis of 3,4,5-substituted furan-2(5H) ones in water, *Iranian journal of catalysis*, 4, 247, **2014.**
[21] Maghsoodlou M.T., Masoumnia A., Mousavi M.R., Hazeri N., Aboonajmi J., Habibi-Khorasani S.M., Kiaee S., A green protocol for synthesis of pyran annulated heterocyclic systems using Na_2SO_4 as an efficient catalyst, *Iranian journal of catalysis*, 5, 169, **2015.**
[22] Doostmohammadi R., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., Acetic acid as an efficient catalyst for the one-pot preparation of 3,4,5-substituted furan-2(5H)-ones, *Research* on *Chemical* Intermediates, 39, 4061, **2009.**
[23] Doostmohammadi R., Hazeri N., Application of Silica Gel-supported Polyphosphoric Acid (PPA/SiO_2) as a Reusable Solid Acid Catalyst for One-Pot Multi-Component Synthesis of 3,4,5-substituted furan-2(5H)-ones, *Letters* in *Organic Chemistry*, 10, 199, **2013.**
[24] Doostmohammadi R., Maghsoodlou M.T., Hazeri N., Habibi-Khorassani S.M., An efficient one-pot multi-component synthesis of 3,4,5-substituted furan-2(5H)-ones catalyzed by tetra-n-butylammonium bisulfate, *Chinese Chemical Letters*, 24, 10, 901, **2013.**
[25] Safaei-Ghomi J., Salimi F., Ramazani A., Zeinali Nasrabadi F., Ahmadi Y., The reaction of dialkyl acetylenedicarboxylates with 2-oxo-2-phenylacetaldehyde in the presence of primary amines: synthesis of alkyl 2-benzoyl-4-alkylamino-5-oxo-2,5-dihydro-3-furan carboxylate derivatives, *Turkish Journal of Chemistry*, 36, 485, **2012.**
[26] Teimouri M.B., Abbasi T., Facile synthesis of oxaspirobicyclic butenolides via a domino Michael addition/aldol reaction/γ-lactonization sequence, *Tetrahedron*, 66, 21, 3795, **2010.**
[27] Mohammad Shafiee M.R., Mansoor S.S., Ghashang M., Fazlinia A., Preparation of 3,4,5-substituted furan-2(5H)-ones using aluminum hydrogen sulfate as an efficient catalyst, *Comptes rendus Chimie*, 17, 131, **2014.**
[28] Tekale S.U., Kauthale S.S., Pagore V.P., Jadhav V.B., Pawar R.P., ZnO nanoparticle-catalyzed efficient one-pot three-component synthesis of 3,4,5-trisubstituted furan-2(5H)-ones, *Journal of the Iranian Chemical Society,* 10, 6, 1271, **2013.**
[29] Hazeri N., Maghsoodlou M.T., Mahmoudabadi N., Doostmohammadi R., Salahi S., Sucrose as an Environmental and Economical Catalyst for the Synthesis of 2(5H) Furanone, *Current Organocatalysis***,** 1, 45, **2014.**

6. ACKNOWLEDGEMENTS

We gratefully acknowledge financial support from the Research Council of the University of Sistan and Baluchestan.

© 2016 by the authors. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).