Application of $Fe_3O_4@SiO_2/(CH_2)_3$-[Imidazolium-SO_3H]Cl as a robust magnetically recoverable solid acid catalyst for the facile preparation of arylbispyranylmethanes

Mohammad Ali Zolfigol,[*1] Mahdiyeh Navazeni,[1] Meysam Yarie[1] and Roya Ayazi-Nasrabadi[1]

Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, PO Box 6517838683, Hamedan, Iran.

Correspondence: Mohammad Ali Zolfigol, Email: zolfi@basu.ac.ir & mzolfigol@yahoo.com, Tel.: +98 811 8282807; fax: +98 811 8380709.

Abstract

In this study, Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl shows robust promoting capability in the synthesis of arylbispyranylmethane derivatives under mild and green conditions. Arylbispyranylmethanes were synthesized *via* efficient three-component reaction of various aromatic aldehydes with 4-hydroxy-6-methyl-2*H*-pyran-2-one. The nanomagnetic core-shell catalyst presented effective potential of at least 8 times recycling applicability in the described synthetic procedure.

Keywords: Magnetically recoverable solid acids, Arylbispyranylmethanes, Multicomponent condensation, Mild and green conditions.

Running Head: Facile preparation of arylbispyranylmethanes

Introduction

Nowadays, growing attentions have been focused on the topic of preparation and application of nanamagnetic core-shell catalysts in the domain of organic functional groups transformations. Heterogenization and solidification of catalytically active agents onto the surface of Fe_3O_4 as a promising magnetic inorganic support lead to generation of stable heterogeneous promoter which inherit several outstanding utilities *viz* highly potential of activity and selectivity as in the case of homogeneous catalysts. Also, they represent good thermal/mechanical stability, nanometer scale, high loading capacity, excellent accessibility and high surface area to volume ratio [1-13].

On the other hand, using one-pot multicomponent reactions (MCRs) as a refine and efficient strategy for carrying out the organic functional groups transformation have appeared as an influential tool in the toolbox of organic methodologists. One-pot multicomponent reactions depict some trustworthy characters such as high degree of atom and step economy, preparation of elaborate target structures and medicinal active compounds and access to molecular library through an eco-compatible route. Moreover, employing of this versatile synthetic tool under solvent free conditions by applying a recoverable nanomagnetic core-shell catalyst can be considered as a branch of green chemistry domain [14-19].

Heterocyclic compounds bearing 4-hydroxy pyran-2-one structural kernels are renowned as influential organic natural products with excellent potent of therapeutic applications in the field of medicinal and biological chemistry. They can be applied as anti-HIV, anti-oxidant, anti-viral, anti-dementia, anti-diabetic, anti-coagulant, anti-inflammatory and anti-platelet aggregative agents [20-24]. Among them, arylbispyranylmethane derivatives are remarkable heterocyclic privileged scaffold as they can be served as building blocks for the synthesis of organic

compounds which possess a broad scope of pharmaceutical activities alike anti-coagulant property and inhibitor for mPGES-1 and 5-LO. Also, 5-substituted pyrimidine nucleoside with arylbispyranylmethane moiety can act as antiviral agent [25-27]. Some bioactive agents bearing 4-hydroxy pyran-2-one structural scaffold are shown in Figure 1.

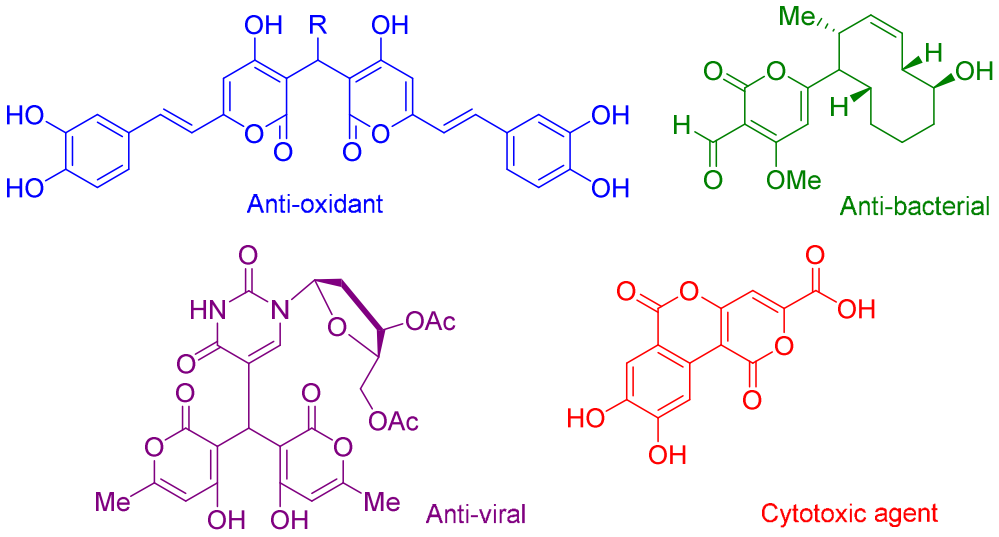
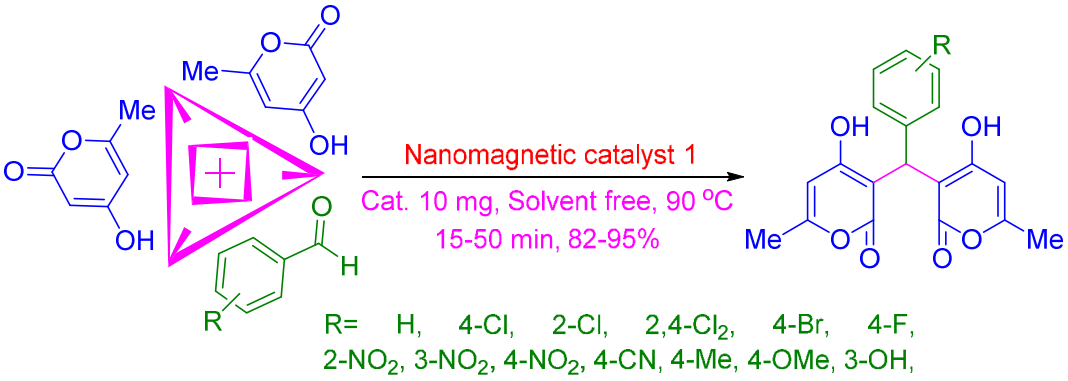


Figure 1: Some bioactive agents which bearing 4-hydroxy pyran-2-one structural scaffold.

Hence, owing to their persuasive prevalent pharmaceutical versatility of the arylbispyranylmethane derivatives [28-30], synthesis and chemistry of them have attracted much attention in recent times. Anyway, most of the reported routes for the construction of these target molecules are connected with some limitations in term of long reaction times, unsatisfactory yields, harsh reaction conditions, tedious work-up, using toxic and unsafe organic solvents. Therefore, presenting of newer methods for the construction of the arylbispyranylmethane derivatives by applying a reusable nanomagnetic catalyst is attractive.

In this report, during the course of our constant research program dedicating of newer and efficient protocols for the synthesis of heterocyclic molecules using silica sulfuric acid [31-33] and nanomagnetic catalysts [34-42], herein, we wish to report the catalytic application of Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl as a nanomagnetic and reusable solid acid catalyst at the preparation of arylbispyranylmethane derivatives. The obtained results have shown in the Schemes 2.



Scheme 2: Synthesis of arylbispyranylmethane derivatives under mild and eco-friendly conditions.

Experimental

General

All materials were obtained from Merck chemical company and used without further purification. The structural verification of the known products was made by comparison of their physical properties and spectral data with those of authentic samples reported in the literature. The reaction progress and purity of the compounds were checked out by using TLC performed with silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker spectrometer. Melting points were recorded with a Buchi B-545 apparatus in open capillary tubes.

General procedure for the construction of two magnetically recoverable solid acids

The construction and structural verification of the applied nanomagnetic based heterogeneous catalyst $Fe_3O_4@SiO_2/(CH_2)_3$-[Imidazolium-SO_3H]Cl was explored in our previously reported method as illustrated in Scheme 3 [43].

General procedure for the synthesis of arylbispyranylmethane derivatives

In a test tube containing a mixture of aromatic aldehydes (1 mmol) and 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol, 0.252 g), 10 mg of $Fe_3O_4@SiO_2/(CH_2)_3$-[Imidazolium-SO_3H]Cl **1** as nanomagnetic catalyst was added. The resulting mixture stirred for proper times under solvent free conditions at 90 ^oC as indicated in Table 2. The progress of the reactions was monitored by TLC skill using *n*-hexane and EtOAc as eluent system. After completion of the reactions, hot ethanol was added to the reaction mixtures to dissolve the desired products and also unreacted starting materials. The nanomagnetic catalyst **1** was not dissolved in used solvent and easily separated from reaction mixture by applying an external magnet, washed with EtOH and preserved for next run. Finally, the pure products were obtained *via* recrystallization from ethanol with good to excellent yields.

Selected spectral data for arylbispyranylmethane derivatives

3,3'-((2-Chlorophenyl)methylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (1c)

Melting point = 156-157 ^oC

FT-IR (KBr): ν (cm^{-1})= 3081, 2990, 1709, 1683, 1619, 1571, 1450, 1408, 1308, 997, 826.

δ_H (400 MHz, DMSO) 11.22 (brs, 2H, OH), 7.30-7.28 (m, 1H, Aromatic), 7.18-7.11 (m, 1H, Aromatic), 5.96 (s, 2H, Olefinic), 5.65 (s, 1H, CH), 2.15 (s, 6H, CH_3).

δ_C (101 MHz, DMSO) 166.4, 164.4, 160.5, 139.2, 132.7, 130.1, 128.6, 127.3, 126.2, 100.6, 100.4, 34.8, 19.1.

3,3'-((3-Hydroxyphenyl)methylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (1d)

Melting point = 226-227 ^oC

FT-IR (KBr): ν (cm^{-1})= 3323, 3188, 3093, 1671, 1618, 1562, 1447, 1271, 995, 794.

δ_H (400 MHz, DMSO) 11.79 (brs, 2H, OH), 9.17 (brs, 1H, OH), 7.02 (t, *J*=8 Hz, 1H, Aromatic) , 6.54 (t, *J*=8 Hz, 1H, Aromatic), 6.44-6.42 (m, 2H, Aromatic), 6.11 (s, 2H, Olefinic), 5.94 (s, 1H, CH), 2.21 (s, 6H, CH_3).

δ_C (101 MHz, DMSO) 168.1, 166.4, 161.3, 157.2, 140.9, 129.1, 117.1, 113.3, 112.7, 101.6, 101.3, 33.6, 19.1.

3,3'-((2,4-Dichlorophenyl)methylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (1e)

Melting point = 234-235 ^oC

FT-IR (KBr): ν (cm^{-1})= 3435, 3216, 1686, 1672, 1633, 1575, 1448, 1409, 1302, 833.

δ_H (400 MHz, DMSO) 11.29 (brs, 2H, OH), 7.50 (d, *J*=4 Hz, 1H, Aromatic), 7.34 (dd, *J*=4 Hz, 1H, Aromatic), 7.18 (d, J=8 Hz, 1H, Aromatic), 6.02 (s, 2H, Olefinic), 5.62 (s, 2H, CH), 2.22 (s, 6H, CH_3).

δ_C (101 MHz, DMSO) 166.2, 163.9, 160.5, 138.8, 133.4, 131.5, 130.7, 127.8, 126.3, 100.2, 100.2, 34.7, 19.4, 19.2.

3,3'-((2-Nitrophenyl)methylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (1h)

Melting point = 235-236 ^oC

FT-IR (KBr): ν (cm^{-1})= 3099, 3027, 2944, 1685, 1611, 1568, 1524, 1417, 1357, 996, 850, 728.

δ_H (400 MHz, DMSO) 11.41 (brs, 2H, OH), 7.82 (d, *J*=8 Hz, 1H, Aromatic), 7.61 (t, *J*=8 Hz, 1H, Aromatic) , 7.47 (t, *J*=8 Hz, 1H, Aromatic), 7.33 (d, *J*=8 Hz, 1H, Aromatic), 6.12 (s, 1H, CH), 6.02 (s, 2H, Olefinic), 2.23 (s, 6H, CH_3).

δ_C (101 MHz, DMSO) 166.5, 164.0, 160.7, 149.4, 135.5, 132.0, 130.0, 126.8, 123.6, 100.2, 100.0, 32.9, 19.2.

4-(Bis(4-hydroxy-6-methyl-2-oxo-2*H*-pyran-3-yl)methyl)benzonitrile (1j)

Melting point = 218-221 ^oC

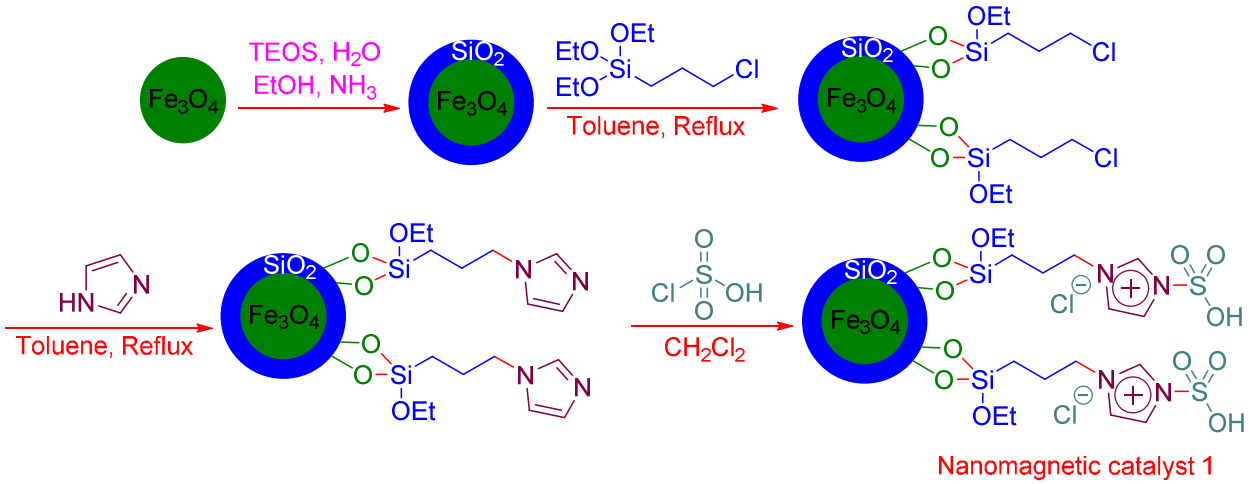
FT-IR (KBr): ν (cm^{-1})= 3448, 3058, 2226, 1687, 1672, 1626, 1445, 1407, 1298, 1000, 827.

δ_H (400 MHz, DMSO) 11.70 (brs, 2H, OH), 7.74 (d, *J*=8 Hz, 2H, Aromatic), 7.28 (d, *J*=4 Hz, 2H, Aromatic), 6.11 (s, 2H, Olefinic), 5.88 (s, 1H, CH), 2.25 (s, 6H, CH_3).

δ_C (101 MHz, DMSO) 167.5, 165.3, 161.3, 147.0, 131.8, 128.0, 119.1, 108.2, 100.9, 100.6, 35.3, 19.1.

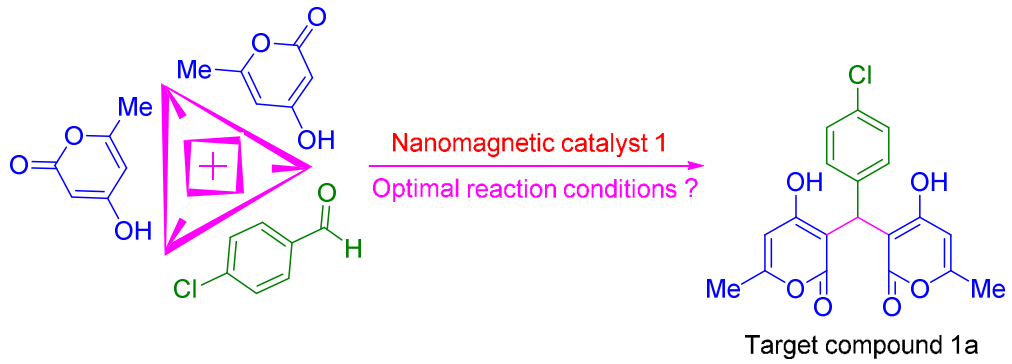
Result and discussion

The preparation and structural confirmation of the employed Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl **1** as a nanomagnetic based heterogeneous catalyst were investigated in our previously reported method as portrayed in Scheme 3 [43].



Scheme 3: The structure of the applied nanomagnetic based heterogeneous catalyst **1**.

In this exploration the catalytic applicability of the Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl **1**, was explored for the synthesis of a series of arylbispyranylmethane derivatives. In the first trial, as in the case of target molecules **1a-m**, variable reaction parameters such as load of catalyst **1**, reaction temperature and solvents were checked out upon the reaction of 4-chlorobenzaldehyde and 2 equivalent of 4-hydroxy-6-methyl-2-pyrone (Scheme 4). The outcome data for optimizing of the reaction conditions are presented in Table 1. The resulting data implied that the best results attained under solvent free conditions in the presence of 10 mg of the nanomagnetic solid acid catalyst **1** at 90 ^{o}C.



Scheme 4: The model reaction for the optimizing of the reaction conditions in the case of 3,3'-((4-chlorophenyl)methylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) **(1a)**.

Table 1: Optimizing of the reaction conditions for the synthesis of 3,3'-((4-chlorophenyl)methylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) (**1a**)[a].

Entry	Solvent	Temperature (˚C)	Load of catalyst (mg)	Time (min.)	Yield (%)[b]
1	-	80	10	47	66
2	-	60	10	45	56
3	-	100	10	40	92
4	**-**	**90**	**10**	**40**	**95**
5	-	90	-	100	40
6	-	90	7	40	90
7	-	90	15	40	90
8	H_2O	Reflux	10	140	85
9	C_2H_5OH	Reflux	10	120	82
10	CH_3CN	Reflux	10	130	40
11	*n*-Hexane	Reflux	10	140	55
12	EtOAc	Reflux	10	120	90

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol, 0.144 g), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol, 0.252 g)., [b] Isolated yields.

In second place, with optimal reaction conditions in hand, the versatility, limitations and scope of the presented synthetic manner to arylbispyranylmethane derivatives, the reaction of several type of arylaldehydes (bearing electron-releasing, electron-withdrawing groups and halogens) and 4-hydroxy-6-methyl-2*H*-pyran-2-one were examined. The collected obtained results in Table 2, illustrated that direct three-component reactions worked well with a variety of arylaldehydes and the target molecules were produced with high to excellent yields in relatively short reaction times.

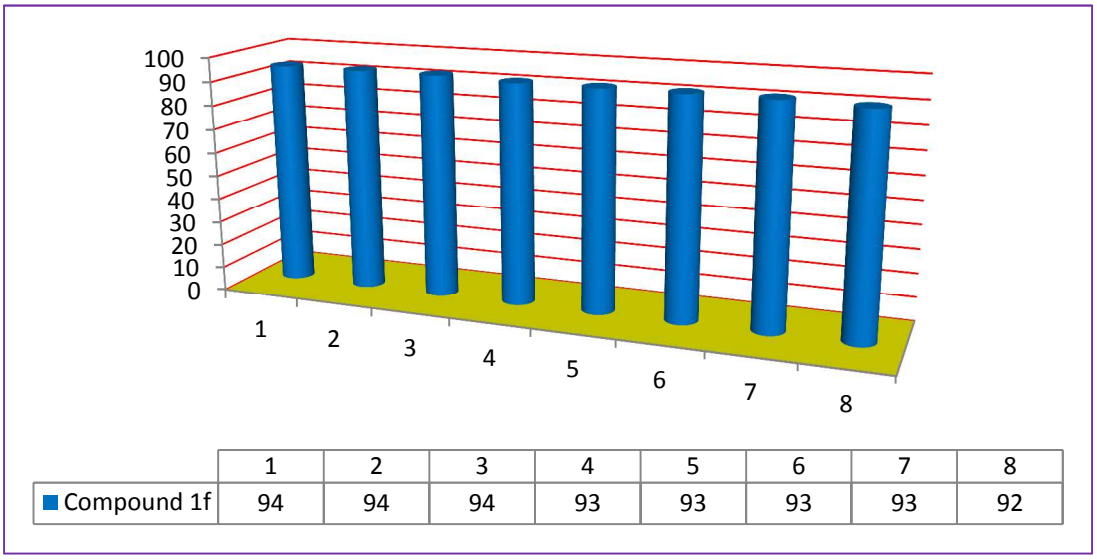
Table 2: Synthesis of target molecules **1a-m** in the presence of nano magnetic catalyst **2**[a].

Entry	**Product**	**R**	Time (min.)	Yield (%)[b]	Melting point (°C), [found]$^{Lit.}$
1	**1a**	**4-Cl**	40	95	223-225 [202-206][37]
2	**1b**	**3-NO_2**	25	91	204-206 [200-204][37]
3	**1c**	**2-Cl**	35	90	156-157 [155-158][37]
4	**1d**	**3-OH**	50	89	226-227 [new]
5	**1e**	**2,4-Cl_2**	40	89	234-235 [244-246][37]
6	**1f**	**H**	15	94	213-215 [213-216][37]
7	**1g**	**4-Me**	20	83	188-190 [183-185][37]
8	**1h**	**2-NO_2**	33	88	235-236 [223-227][30]
9	**1i**	**4-OMe**	30	82	188-190 [174-176][37]
10	**1j**	**4-CN**	50	91	218-221 [223-225][37]
11	**1k**	**4-F**	25	95	199-201 [219-221][37]
12	**1l**	**4-Br**	15	93	217-218 [212-215][37]
13	**1m**	**4-NO_2**	17	86	193-197 [232-234][37]

[a]Reaction conditions: arylaldehyde (1 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol, 0.252 g)., [b] Isolated yields.

In continued, the reusability potential of the Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl as a nanomagnetic catalyst were successfully examined. After completion of each run, in order to separation of nanomagnetic catalyst **1**, hot EtOH was added to the reaction mixture. Afterwards, the catalyst was isolated by using an external magnet, washed with ethanol, weighted and preserved for the following assay. In the presented method for the synthesis of arylbispyranylmethane derivatives, the reaction of benzaldehyde and 4-hydroxy-6-methyl-2-pyrone (target molecule **1f**) was selected as model reaction in the presence of nanomagnetic catalyst Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl. The reusability of the catalyst was

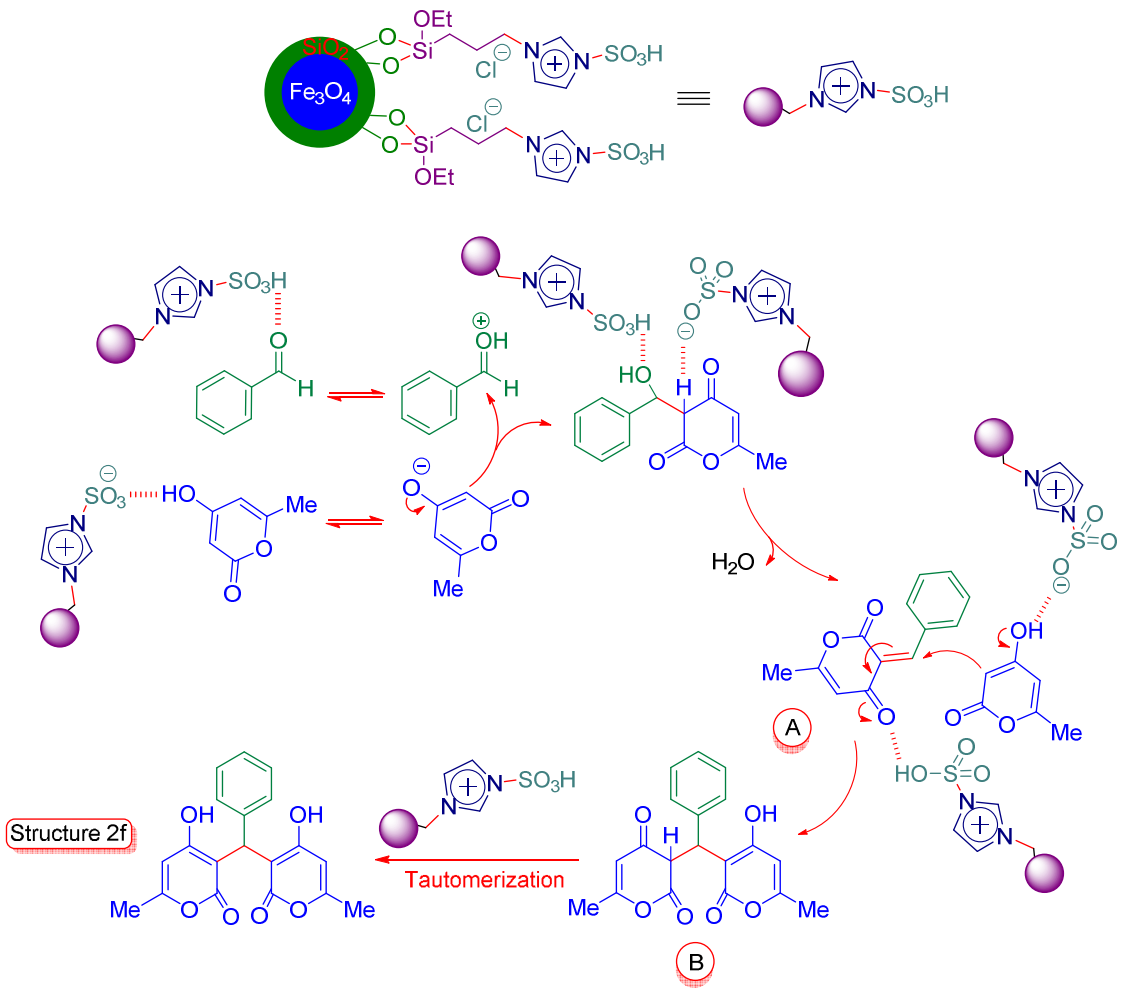
investigated for eight consecutive runs in the period of 15 minutes. The collected data for the multicomponent synthesis of arylbispyranylmethane derivatives is depicted in Figure 2. The achieved data indicated that the used nanomagnetic catalyst Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl shows excellent potential of reusability in the selected reaction.



	1	2	3	4	5	6	7	8
Compound 1f	94	94	94	93	93	93	93	92

Figure 2: Reusability test for both types of the presented multicomponent reactions.

In another assay the plausible mechanistic pathway for the synthesis of 3,3'-(phenylmethylene)bis(4-hydroxy-6-methyl-2*H*-pyran-2-one) **1f** is illustrated in Scheme 5. In first place, 4-hydroxy-6-methyl-2*H*-pyran-2-one attacked to the activated benzaldehyde which was produced intermediate **A** *via* dehydration. In the following step, through the reaction of second mole of 4-hydroxy-6-methyl-2*H*-pyran-2-one with intermediate **A**, intermediate **B** was generated. At last, tautomerization afforded the desired product **1f**.



Scheme 5: Plausible process for the synthesis of target molecule **1f**.

Conclusion

In summary, the catalytic activity of Fe_3O_4@SiO_2/$(CH_2)_3$-[Imidazolium-SO_3H]Cl as a magnetically recoverable solid acids catalyst was explored in the synthesis of arylbispyranylmethane derivatives under mild and green reaction conditions. Arylbispyranylmethanes were synthesized by a highly efficient three-component reaction of varied aromatic aldehydes with 4-hydroxy-6-methyl-2*H*-pyran-2-one. The nanomagnetic core-shell catalyst presented effective potential of at least 8 times recycling in the described synthetic procedure.

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References:

[1] Karimi, B.; Mansouri, F.; Mirzaei, H. M., *ChemCatChem* **2015**, *7*, 1736.

[2] Mokhtary, M. *J. Iran. Chem. Soc*. **2016**, *13*, 1827.

[3] Cheng, T.; Zhang, D.; Li, H.; Liu, G. *Green Chem*. **2014**, *16*, 3401.

[4] Zhang, D.; Zhou, C.; Sun, Z.; Wu, L. Z.; Tung, C. H.; Zhang, T. *Nanoscale* **2012**, *4*, 6244.

[5] Gawande,; M. B.; Luque, R.; Zboril, R. *ChemCatChem* **2014**, *6*, 3312.

[6] Hudson, R.; Feng, Y.; Varma, R. S.; Moores, A. *Green Chem*. **2014**, *16*, 4493.

[7] Polshettiwar, V.; Luque, R.; Fihri, A.; Zhu, H.; Bouhrara, M.; Basset, J. M. *Chem. Rev.* **2011**, *111*, 3036.

[8] Rostamnia, S.; Doustkhah, E. *J. Magn. Magn. Mater*. **2015**, *386*, 111.

[9] Rostamnia, S.; Zeynizadeh, B.; Doustkhah, E.; Baghban, A.; Ojaghi Aghbash, K. *Catal. Commun*. **2015**, *68*, 77.

[10] Doustkhah, E.; Rostamnia, S.; Gholipour, B.; Zeynizadeh, B.; Baghban, A.; Luque, R. *Mol. Catal.* **2017**, *434*, 7.

[11] Baghban, A.; Heidarizadeh, M.; Doustkhah, E.; Rostamnia, S.; Fathi Rezaei, P. *Int. J. Biol. Macromolec*. **2017**, *103*, 1194.

[12] Lamei, K.; Eshghi, H.; Bakavoli, M.; Rostamnia, S.; *Catal. Lett.* **2017**, *147*, 491.

[13] Rostamnia, S.; Doustkhah, E. *Nano. Chem. Res*. **2016**, *1*, 19.

[14] Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin A. K.; *Chem. Rev*. **2014**, **114**, 8323.

[15] Chanda, A.; Fokin, V. V. *Chem. Rev*. **2009**, *109*, 725.

[16] Yanlong, G. *Green Chem*. **2012**, *14*, 2091.

[17] Climent, M. J.; Corma, A.; Iborra, S. *RSC Adv.* **2012**, *2*, 16.

[18] Elnagdi, N. M. H.; Al-Hokbany, N. S.; *Molecules* **2012**, *17*, 4300.

[19] Nielsen, T. E.; Schreiber, S. L. *Angew.Chem. Int. Ed*., **2008**, *47*, 48.

[20] Nicholas, A.; Allan, E. R.; *Drug Metab Rev.*, **2008**, *40*, 355

[21] Jung, J. C.; Park, O. S. *Molecules*, **2009**, *14*, 4790.

[22] Zang, J.; Jiang,Y.; Cao, Y.; Lue, J.; Zheng, D.; Chen, X.; Han, L.; Ziang, C.; Huang, X. *J. Nat. Prod*., **2013**, *76*, 2126.

[23] Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R.; *Nat. Prod. Rep*., **2014**, *31*, 160.

[24] Dhage, G. R.; Thopate, S. R.; Ramteke, S.; Kulkarni, P. *RSC Adv*. **2014**, *4*, 56870.

[25] Rehse, K.; Schinkel, W. *Arch. Pharm*., **1983**, *316*, 988.

[26] Johar, M.; Manning, T.; Kunimoto, D. Y.; Kumar, R. *Bioorg. Med. Chem*. **2005**, *13*, 6663.;

[27] Minassi, A.; Cicione, L.; Koeberle, A.; Bauer, J.; Laufer, S.; Werz, O.; Appendino, G. *Eur. J. Org. Chem*. **2012**, 772.

[28] Zhang, X.; Qu, Y.; Fan, X.; Wang, X.; Wang, J. *J. Chem. Res*. **2009**, 473.

[29] de March, P.; Moreno-Manas, M.; Pi, R.; Trius, A. *J. Heterocycl. Chem*. **1982**, *19*, 335.

[30] Cervera, M.; Moreno-Manas, M.; Pleixats, R. *Tetrahedron* **1990**, *46*, 7885.

[31] Zolfigol, M. A. *Tetrahedron*, **2001**, *57*, 9509.

[32] Salehi, P.; Zolfigol, M. A.; Shirini, F.; Baghbanzadeh, M. *Curr. Org. Chem*. **2006**, *10*, 2171.

[33] Zolfigol, M. A.; Ghaderi, H.; Baghery, S.; Mohammadi, L. *J. Iran. Chem. Soc*. **2017**, *14*, 121.

[34] Aghayee, M.; Zolfigol, M. A.; Keypour, H.; Yarie, M.; Mohammadi, L. *Appl. Organometal. Chem.* **2016**, *30*, 612.

[35] Zolfigol, M. A.; Yarie, M. *RSC Adv*. **2015**, *5*, 103617.

[36] Zolfigol, M. A.; Kiafar, M.; Yarie, M.; Taherpour, A. A.; Saeidi-rad, M.; *RSC Adv*. **2016**, *6*, 50100.

[37] Zolfigol, M. A.; Navazeni, M.; Yarie, M.; Ayazi-Nasrabadi, R. *RSC Adv*. **2016**, *6*, 92862.

[38] Azadbakht, T.; Zolfigol, M. A.; Azadbakht, R.; Khakizadeh, V.; Perrin, D. *New J. Chem*., **2015**, *39*, 439.

[39] Zolfigol, M. A.; Azadbkht, T.; Khakizadeh, V.; Nejatyami, R.; Perrin, D. *RSC. Adv*., **2014**, *4*, 40036.

[40] Zolfigol, M. A.; Khakyzadeh, V.; Moosavi-Zare, A. R.; Rostami, A.; Zare, A.; Iranpoor, N.; Beyzavie, M. H.; Luque, R. *Green Chem*., **2013**, *15*, 2132.

[41] Koukabi, N.; Kolvari, E.; Khazaei, A.; Zolfigol, M. A.; Shirmardi-Shaghasemi, B.; Khavasi, H. R. *Chem. Commun*., **2011**, *47*, 9230.

[42] Safaiee, M.; Zolfigol, M. A.; Afsharnadery, F.; Baghery, S. *RSC Adv*.**, 2015**, *5*, 102340.

[43] Zolfigol, M. A.; Ayazi-Nasrabadi, R.; Baghery, S.; Khakyzadeh, V.; Azizian, S. *J. Mol. Catal. A: Chem.* **2016**, *418*, 54.