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Keggin Heteropoly Acid as a Green and Recyclable Catalyst for One-pot Synthesis of 1,1,3-Triheteroaryl Compounds

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Green and one-pot procedure was reported for the preparation of 1,1,3-triheteroaryl compounds from indoles and α,β-unsaturated carbonyl compounds using heteropoly acid as a reusable heterogeneous catalyst. The desired products were obtained in high yields (60%–80%) at EtOH/H_2O media. Keggin heteropoly acid catalyst can be reused for at least four times without significant loss in the catalytic activity and change of chemical structure. The catalyst recyclability, simplicity, environmental friendliness, and convenient operation of the reaction suggest the potential of the procedure as a real alternative to conventional reaction protocol.

Key words: Keggin heteropoly acid, $H_3PMo_{12}O_{40}$, indole, α,β-unsaturated aldehyde

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Biologically active heterocycles, especially indoles have been reported to possess a wide variety of properties such as anticancer [1], cardiovascular [2] and antibacterial [3]. Furthermore, it was reported that the substitution of heterocyclic moiety at 3-position of the indole ring obviously influence the anti-inflammatory activity [4]. One of the simple and direct methods for the synthesis of 3-substituted indoles involves the conjugate addition of them to α,β-unsaturated carbonyl compounds or reaction of 2 or 3 equiv. of indoles with the carbonyl group in the presence of either Brønsted [5] or Lewis acids [6]. However, these one-pot methods make the use of high-priced catalysts such as $AuCl_3$ [7] and $Zr(OTf)_4$ [8], the dangerous catalyst such as $SbCl_3$ [9], cerium ammonium nitrate (CAN) [10], and $AlCl_3$ [11]. For this reason, cheaper and green acid catalysts with low toxicity are desired. The metal-oxygen clusters specially Keggin-type anions have stimulated much attention over the last few decades due to the strong Brønsted acidity, multi-stage redox activity and remarkable thermal and hydrolytic stability [12]. Among them, the Keggin-type HPAs have long been known to be good catalysts for oxidation reactions [13] and heterogeneous acidic catalysis in green chemistry [14]. Their catalytic properties can be tuned by changing the identity of charge-compensating countercations, heteroatoms and framework metal atoms [15].

In continuation of our work on the synthesis of heterocyclic compounds [16] and catalytic properties of heteropoly acids in the synthesis of organic compounds [17–20], we in this paper studied a convenient and green method for the one-pot preparation of 1,1,3-triheteroaryl compounds from indoles and α,β-unsaturated carbonyl compounds using $H_3PMo_{12}O_{40}$ (3 mol%) as a green, reusable and superior catalyst in a mixture of water and ethanol as a solvent.

EXPERIMENTAL

Material and Methods

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}HNMR spectra were recorded on a Bruker AQS AVANCE-300MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded using KBr disk on the FT-IR Bruker Tensor 27. All products were well characterized by comparison with authentic samples by TLC, spectral and physical data. $H_3PMo_{12}O_{40}$, Al-MCM-41, $Mn(pbdo)_2Cl_2$/MCM-41, $Mn(pbdo)_2Cl_2$/SBA-15 and phenyl phosphonic acid/SiO_2 were prepared in a classical way as described in the literature [21–26]. $MgBr_{2.}$ Et_2O, $NbCl_{5,}$ KAl $(SO_4)_2$.12 H_2O, MCM-41, Nano TiO_2, Phenyl phosphonic acid and Montmorilonit K10 were purchased from Sigma-Aldrich.

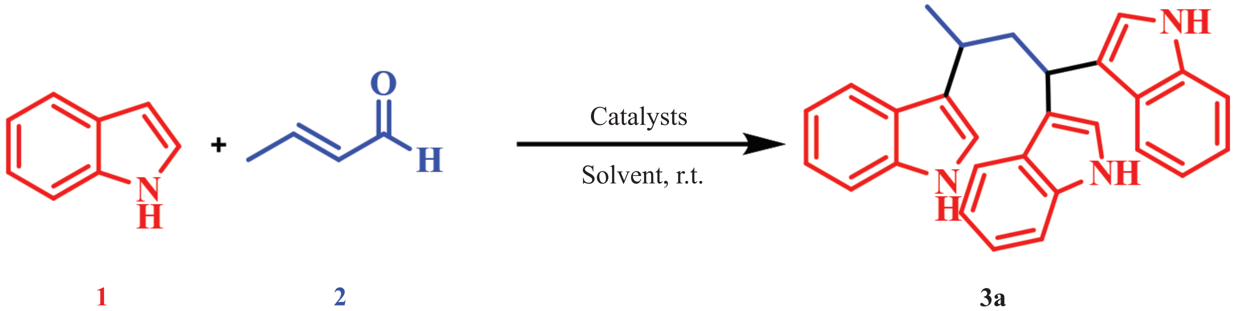
General procedure for synthesis of 1,1,3-triheteroaryl Compounds. $H_3PMo_{12}O_{40}$ (3 mol%) and indole (5 mmol) were dissolved in 6.0 ml of EtOH/H_2O (2/1) mixed solvent. Crotonaldehyde (1 mmol) was added dropwise into the reaction system by a syringe and the reaction mixture was stirred at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the solid product was collected by filtration, washed with cold water and aqueous ethanol and purified by silica gel column chromatography using petroleum ether-ethyl acetate (8:2) as eluent to give 1,1,3-tris(3-indolyl)cyclohexane **3a**.

3a: FT-IR (KBr): 3395, 2920, 1705, 1610, 1455, 1415, 1337, 1235 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (2H, m), 2.95 (2H, t, J = 7.5 Hz), 4.24 (1H, t, J = 7.5 Hz), 6.79 (1H, d, J = 8.1 Hz), 6.88 (2H, d, J = 8.0 Hz), 7.05 (2H, m), 7.20 (5H, m), 7.34 (2H, m), 7.66 (1H, d, J = 7.7 Hz), 7.69 (2H, d, J = 7.8 Hz), 7.86 (3H, br) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 35.1, 36.4, 110.5, 111.6, 117.2, 119.7, 121.5, 121.9, 122.1, 122.5, 122.7, 123.1, 123.3, 125.2, 127.5, 128.0, 136.8, 137.0 ppm.

RESULTS AND DISCUSSION

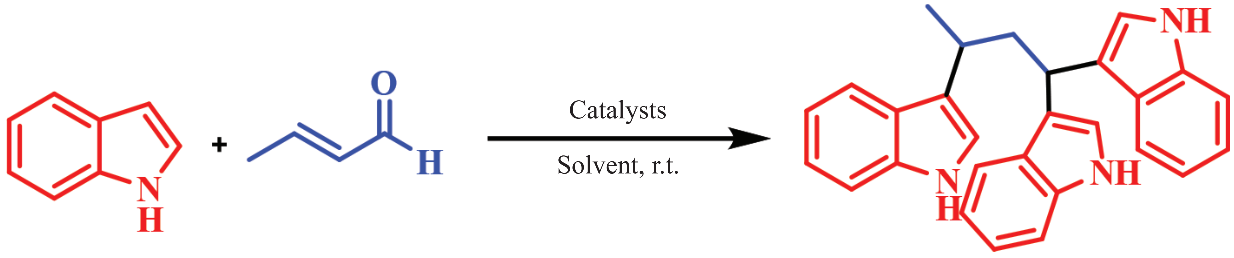
In the initial experiments, indole **1** and crotonaldehyde **2** were used as model substrates to evaluate suitable reaction conditions for the preparation of tris-indole **3a** (Scheme 1).

A wide range of Brönsted and Lewis acids were examined in room temperature. The Lewis acids such as $MgBr_2.Et_2O$, phenyl phosphonic acid and phenyl phosphonic acid/SiO_2 promoted the reaction in 35%–50% yields. (Table 1, entries 2-4). Under the same conditions, montmorilonit K-10 gave **3a** in 55% yield after 5 h (Table 1, entries 5). Nano TiO_2 and $NbCl_5$ did not provide the desired product (Table 1, entries 6, 7). KAl $(SO_4)_2.12H_2O$ gave **3a** in 30% yield after 5 h (Table 1, entry 8). MCM-41 promoted the reaction in 70% yield (Table 1, entry 9). Different mesoporous such as Al-MCM-41, $Mn(pbdo)_2Cl_2$/MCM-41 and $Mn(pbdo)_2Cl_2$/SBA-15 promoted the reaction in 55%–65% yield after 5 h (Table 1, entries 10–12). However, among the catalysts studied for this reaction, $H_3PMo_{12}O_{40}$ was found to be the most effective catalysts since it resulted in the highest conversion to the desired product (Table 1, entry 1). On the other hand, the



Scheme 1. The synthesis of tris-indole **3a**.

Table 1. Effect of catalysts on the preparation of 1,1,3-triheteroaryl compounds.



1 **2** **3a**

Entry	Catalyst	Time (h)	Yield^a (%)
1	$H_3PMo_{12}O_{40}$ (3 mol%)	2	80
2	$MgBr_2$. Et_2O (10 mol%)	5	50
3	Phenyl phosphonic acid (10 mol%)	5	40
4	Phenyl phosphonic acid/SiO_2 (0.1 g)	5	35
5	Montmorilonit K10 (0.05 g)	5	55
6	Nano-TiO_2 (10 mol%)	No reaction	No reaction
7	$NbCl_5$ (10 mol%)	No reaction	No reaction
8	KAl $(SO_4)_2$.12 H_2O (10 mol%)	5	30
9	MCM-41(0.05 g)	3	70
10	Al-MCM-41 (0.05 g)	5	65
11	Mn(pbdo)$_2$Cl$_2$/MCM-41(0.05 g)	5	55
12	Mn(pbdo)$_2$Cl$_2$/SBA-15 (0.05 g)	5	55

[a] The yields refer to isolated products

advantages of $H_3PMo_{12}O_{40}$ as a solid acid catalyst with high activity may include large number of balanced protons and strong bronsted acidity compared with the acidity of usual mineral acids.

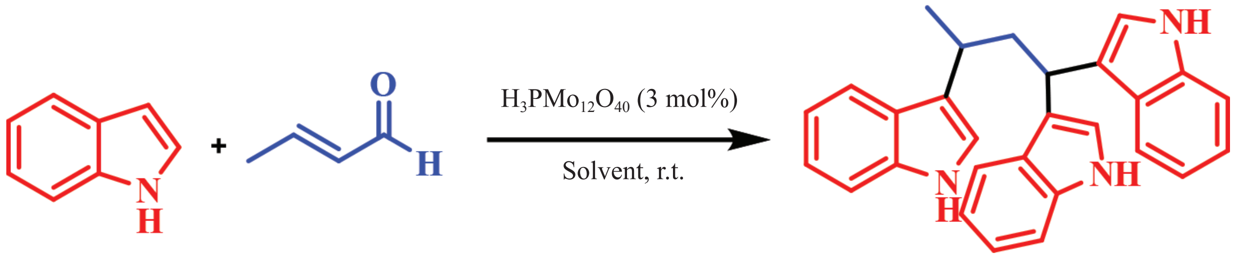
To adjust the amount of catalyst, different experiments were accomplished and it was found that by increasing the amount of catalyst from 1 to 2 and 3 mol%, the yields increased from 70 to 74 and 80%, respectively. The use of 3 mol% $H_3PMo_{12}O_{40}$ was found to be sufficient to push this reaction forward and more catalyst amount (5 mol%) did not improve the yields.

In another experiment, the reaction of indole **1** and crotonaldehyde **2** in the presence of 3 mol% $H_3PMo_{12}O_{40}$ was used as the model system to evaluate the suitability of the media for this reaction. The reaction was performed in various solvents of water, ethanol, chloroform, acetonitrile and ethanol/water. The results are summarized in Table 2. In comparison with other solvents, EtOH/H_2O under room temperature conditions was found to give the best result (Table 2, entry 5).

As shown in Table 3, to establish the generality of the method, a wide variety of suitable substrates were employed. Various α,ß-enals and indols were used and the reactions afforded the corresponding products under the optimized reaction conditions. The reaction afforded a library of 1,1,3-triheteroaryl compounds in good yields.

The plausible mechanism for synthesis of 1,1,3-triheteroaryl compounds is shown in Scheme 2. The 1,4- and 1,2-additions of indole to α,ß-unsaturated aldehyde took place sequentially to give intermediate **A** in the presence of $H_3PMo_{12}O_{40}$ (Scheme 3). It was thought that $H_3PMo_{12}O_{40}$ promoted the reaction by increasing

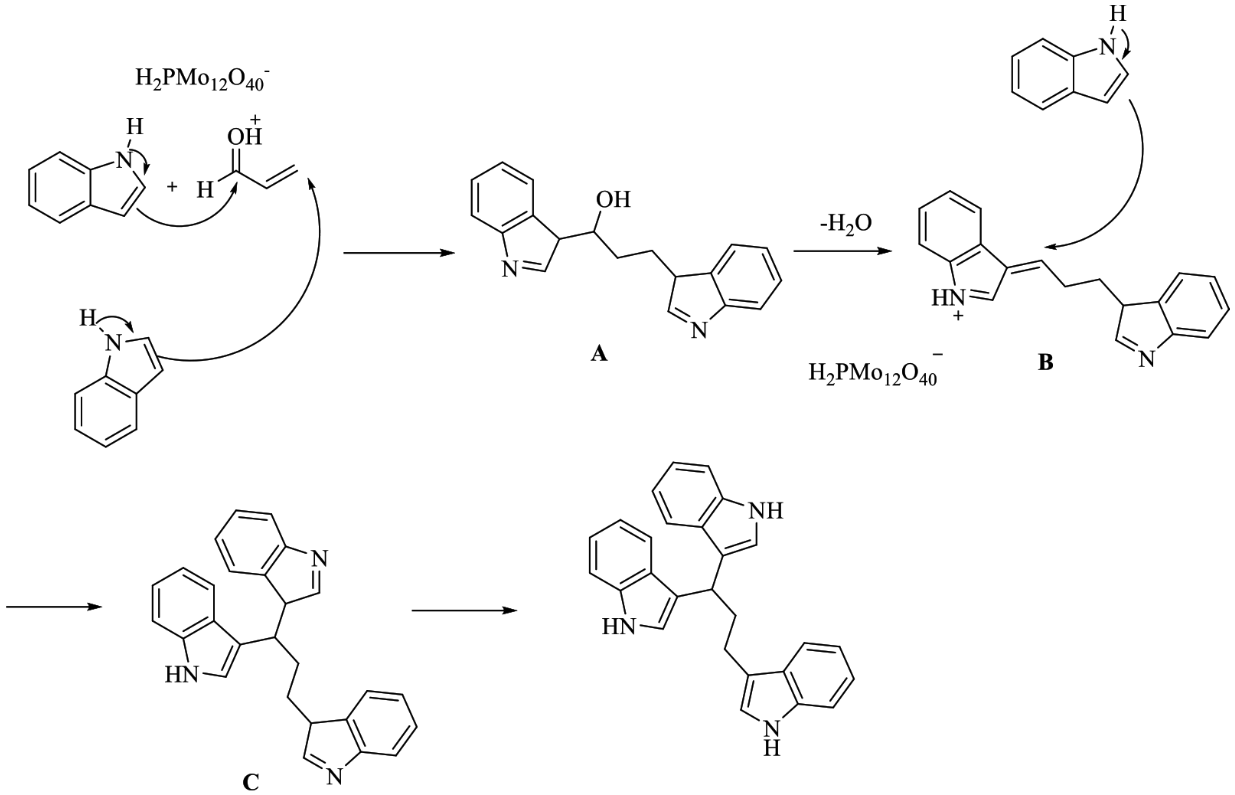
Table 2. Optimization of reaction conditions.



1 **2** **3a**

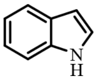
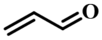
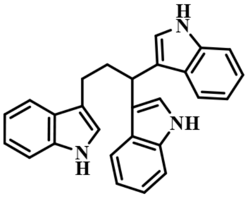
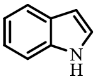
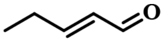
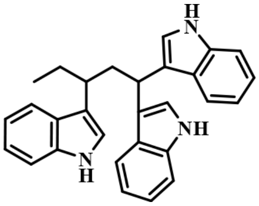
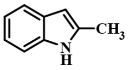
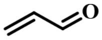
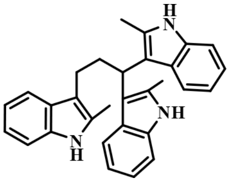
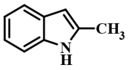
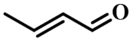
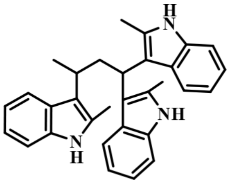
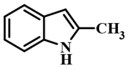
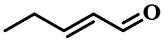
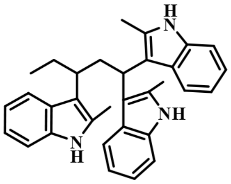
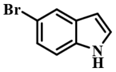
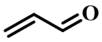
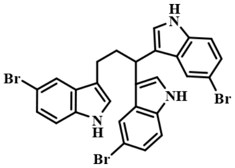
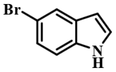
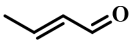
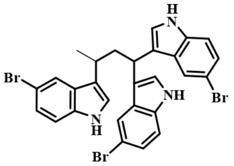
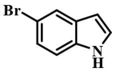
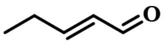
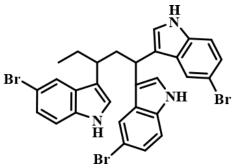
Entry	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]
1	H_2O	r.t.	150	60
2	EtOH	r.t.	120	72
3	$CHCl_3$	r.t.	120	50
4	CH_3CN	r.t.	120	55
5	EtOH/H_2O	r.t.	120	80

[a] Isolated yield

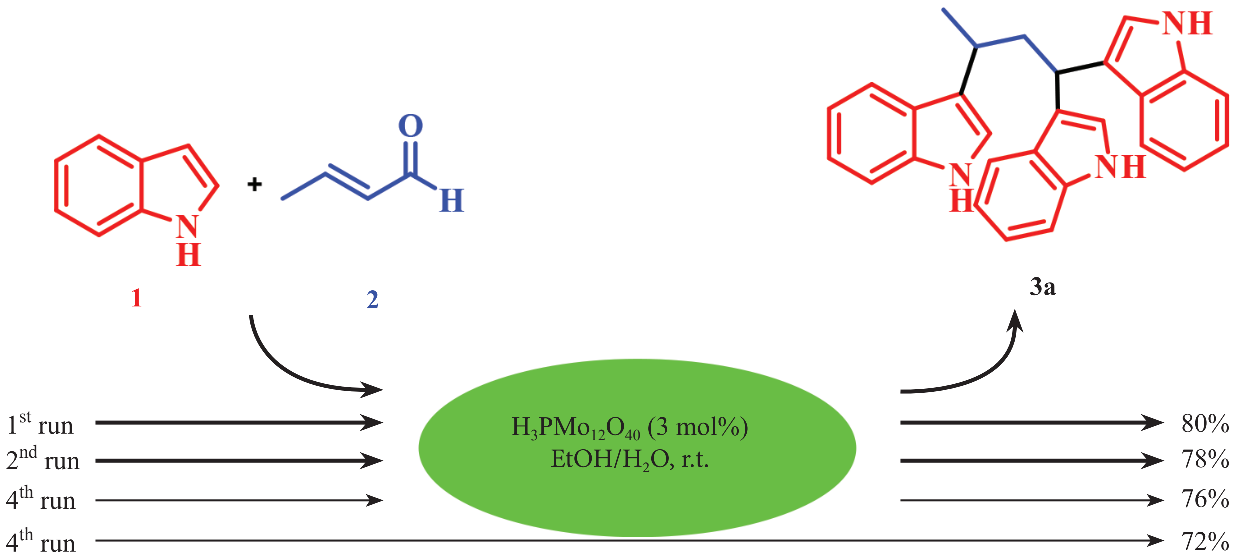


Scheme 2. The plausible mechanism for synthesis of 1,1,3-triheteroaryl compounds.

Table 3. Synthesis of 1,1,3-triheteroaryl derivatives **3** in presence of $H_3PMo_{12}O_{40}$.

Entry	Indole derivatives	α,β-unsaturated aldehydes	Products	Yield[a] (%)	m.p. (°C)	
					Found	Lit.
3a				70	185–187	180–185 [10]
3b				65	138–141	136–141 [11]
3c				65	158–160	158–159 [7]
3d				75	179–180	184–186 [11]
3e				65	177–179	178–179 [10]
3f				60	174–175	170–174 [11]
3g				70	162–165	158–160 [8]
3h				60	167–170	169–171 [11]

[a] The yields refer to isolated products.



Scheme 3. Recycling of the $H_3PMo_{12}O_{40}$ in the synthesis of 3a.

the electrophilic character of the enal. The dehydration of A gave another intermediate B which was further activated by Bronsted acid $H_3PMo_{12}O_{40}$ and served as an electrophile to react with the third molecule of indole, affording intermediate **C**. The corresponding 1,1,3-triindole-incorporated product was subsequently formed from intermediate **C**.

The recovery and reusability of the catalyst, which is very important for industrial purposes and is highly recommended for green processes, was also explored in the model reaction. To test the reusability of the catalyst, after completing the reaction, the products were removed by filtration. The catalyst was recovered by evaporation of solvent and washed with diethyl ether. Subsequently, the catalyst was dried in a vacuum at 60°C–70 °C. The results showed that the heteropoly acid could be used at least four times with about 10% reduction in the yield of the reaction (Scheme 3).

CONCLUSIONS

We have successfully developed a green and mild procedure for the synthesis of 1,1,3-triheteroaryl compounds in the presence of a catalytic amount of $H_3PMo_{12}O_{40}$ in $EtOH/H_2O$. The non-toxicity of the catalyst and solvent, simple experimental procedure, heterogeneous and recyclability of the catalyst and good yields of the products are advantages. This catalyst can be reused for four times without significant loss in the catalytic activity and change of chemical structure. Therefore, it is hoped that these eco-efficient and green protocols are of great value for both synthetic and medicinal chemistry for academic research and practical applications.

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REFERENCES

1. Lee, C-H, Yao, C.F., Huang, S.M., Ko, S., Tan, Y.H., Lee-Chen, G.J. and Wang, Y.C. (2008) Novel 2-step synthetic indole compound 1,1,3-tri(3-indolyl)cyclohexane inhibits cancer cell growth in lung cancer cells and xenograft models, *Cancer* **113**, 815–25.
2. Kumar, A., Kumar, A., Saxena, K.A. and Shanker, K. (1988) 1-Acetyl-5-aryl-3-[(substituted indole-3-yl-methylene-amino) phenyl]-4-pyrazolines as anti-inflammatory agent, *Pharmazie*, **43**, 45–46.

3. Dandia, A., Sehgal, V. and Singh, P. (1993) Synthesis of fluorine containing 2-aryl-3-pyrazolyl/pyranyl/ isoxazolinyl indole derivatives as antifungal and antibacterial agents. *Indian J. Chem.*, **32B**, 1288–1291.
4. Verma, M., Tripathi, M., Saxena A.K. and Shanker, K. (1994) Antiinflammatory activity of novel indole derivatives, *Eur. J. Med. Chem.*, **29**, 941–946.
5. Reddy, A.V., Ravinder, K., Reddy, V.L.N., Goud, T.V. and Ravikanth, V. (2003) Zeolite-catalyzed synthesis of bis(indolyl)methanes. *Synth. Commun*., **33**, 3687–3694.
6. Babu, G., Sridhar, N. and Perumal, P.T. (2000) A convenient method of synthesis of bis(indolyl)-methane indiumtrichloride catalyzed reactions of indole with aldehydes and schiff bases, *Synth. Commun.*, **30**, 1609–1614.
7. Mi, X., Luo, S., He, J. and Cheng, J.P. (2004) Dy(OTf)3 in ionic liquid: an efficient catalytic system for reactions of indole with aldehydes/ ketones or imines, *Tetrahedron Lett.*, **45**, 4567–4570.
8. Nair, V., Vidya, N. and Abhilash, K.G. (2006) Gold(III) chloride promoted addition of electron-rich heteroaromatic compounds to the C=C and C=O bonds of enals, *Tetrahedron Lett.*, **47**, 2871–2873.
9. Shi, M., Cui, S.C. and Li, Q.J. (2004) Zirconium triflate-catalyzed reactions of indole, 1-methylindole, and pyrrole with α,β-unsaturated ketone, *Tetrahedron*, **60**, 6679–6684.
10. Kundu, P. and Maiti, G. (2008) A mild and versatile synthesis of bis(indolyl)methanes and tris(indolyl) alkanes catalyzed by antimony trichloride, *Indian J. Chem.*, **47B**, 1402–1406.
11. Ko, S., Lin, C., Tu, Z., Wang, Y.F., Wang, C.C. and Yao, C.F. (2006) CAN and iodine-catalyzed reaction of indole or 1-methylindole with α,β-unsaturated ketone or aldehyde, *Tetrahedron Lett.*, **47**, 487–492.
12. Shiri, M., Zolfigol, M.A. and Ayazi-Nasrabadi, R. (2010) $AlCl_3$ as a powerful catalyst for the one-pot preparation of 1,1,3-triheteroaryl compounds, *Tetrahedron Lett.*, **51**, 264–268.
13. Kozhevnikov, I.V. (1998) Catalysis by heteropoly acids and multicomponent polyoxometalates in liquid- phase reactions, *Chem. Rev.*, **98**, 171–198.
14. Keggin, J.F. (1933) Structure of the molecule of 12-phosphotungstic acid, *Nature*, **131**, 908–909.
15. Misono, M. (1987) Heterogeneous catalysis by heteropoly compounds of molybdenum and tungsten, *Catal. Rev. Sci. Eng.*, **29**, 269–321.
16. Okuhara, T., Mizuno, N., and Misono, M. (1996) Catalytic chemistry of heteropoly compounds, *Adv. Catal.*, **41**, 113–252.
17. Zakeri, M., Nasef, M.M. and Abouzari-Lotf, E. (2014) Eco-safe and expeditious approaches for synthesis of quinazoline and pyrimidine-2-amine derivatives using ionic liquids aided with ultrasound or microwave irradiation, *J. Mol. Liq.* **199**, 267–274.
18. Zakeri, M., Heravi, M.M. and Abouzari-Lotf, E. (2013) A new one-pot synthesis of 1,2,4-oxadiazoles from aryl nitriles, hydroxylamine and crotonoyl chloride, *J. Chem. Sci.*, **125**, 731–735.
19. Heravi, M.M., Zakeri, M. and Moharami, A. (2012) Versatile three-component procedure for combinatorial synthesis of spiro-oxindoles with fused chromenes catalysed by L-proline, *J. Chem. Sci.*, **124**, 865–869;
20. Zakeri, M, Nasef, M.M. Abouzari-Lotf, E., Moharami, A. and Heravi, M.M. (2015) Sustainable alternative protocols for the multicomponent synthesis of spiro-4H-pyrans catalyzed by 4-dimethylaminopyridine, *J. Indus. Engine. Chem.*, **29**, 273–281
21. Zakeri, M., Heravi, M.M., Oskooie, H.A. and Bamoharram, F.F. (2010) Catalytic performance of heteropolyacids as efficient and eco-friendly catalysts for the one-pot synthesis of benzopyran derivatives, *Synth. React. Inorg. Met.-Org. Nano-Metal Chem.*, **40**, 916–921.
22. Abouzari-lotf, E., Nasef, M.M. Ghassemi, H., Zakeri, M., Ahmad, A. and Abdollah. Y. (2015) Improved methanol barrier property of Nafion hybrid membrane by incorporating nano fibrous interlayer self-immobilized with high level of phosphotungstic acid, *ACS Appl. Mater. Interfaces*, **7**, 17008−17015.
23. Rocchiccioli-Deltcheff, C., Fournier, M., Franck, R. and Thouvenot, R. (1983) Vibrational investigations of polyoxometalates. Evidence for anion-anion interactions in molybdenum (V1) and tungsten (V1) compounds related to the keggin structure, *Inorg. Chem.*, **22**, 207–216.

24. Heravi, M.M., Daraie, M., Farahnaz K., Behbahani, F.K. and Malakooti, R. (2010) Green and novel protocol for one-pot synthesis of β-acetamido carbonyl compounds using Mn(bpdo)2Cl2/MCM-41 catalyst, *Synth. Commun.*, **40**, 1180–1186.

25. Manolov, S., Nikolova, S. and Ivanov, I. (2013) Silica-supported polyphosphoric acid in the synthesis of 4-substituted tetrahydroisoquinoline derivatives, *Molecules*, **18**, 1869–1880.

26. Ko, A.N., Hung, C.H., Chen, C.W., and Ouyang, K.H. (2001) Mesoporous molecular sieve Al-MCM-41 as a novel catalyst for vapor-phase Beckmann rearrangement of cyclohexanone oxime, *Catal. Lett.*, **71**, 219–224.