http://dx.doi.org/10.5012/bkcs.2013.34.5.1508

A Fast, Highly Efficient and Green Protocol for One-Pot Synthesis of 2,4,5-Trisubstituted Imidazoles Catalyzed by $[TBA]_2[W_6O_{19}]$ as a Reusable Heterogeneous Catalyst

Mozhgan Ashrafi, Abolghasem Davoodnia,* and Niloofar Tavakoli-Hoseini

*Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran. *E-mail: adavoodnia@mshdiau.ac.ir*
Received February 11, 2013, Accepted February 28, 2013

A simple and efficient synthesis of 2,4,5-trisubstituted imidazoles was achieved *via* a one-pot three-component cyclocondensation of benzil, aromatic aldehydes, and ammonium acetate in the presence of a catalytic amount of tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$ as a heterogeneous catalyst under thermal solvent-free conditions. The key features of this methodology are operational simplicity, high yields, short reaction times, and a recyclable catalyst with a very easy work up.

Key Words : Heterogeneous catalysis, Solvent-free conditions, Tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$, 2,4,5-Trisubstituted imidazoles

Introduction

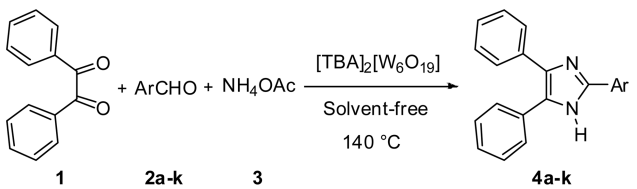
Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity.[1-4] MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery.[5,6] The development of new MCRs and improvement of the known MCRs are an area of considerable current interest. One such reaction is the synthesis of imidazoles.

The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds,[7,8] and plays important roles in biochemical processes.[9] Multisubstituted imidazoles, in particular, 2,4,5-trisubstituted imidazoles are biologically active and occur in structures of a number of antibacterial,[10] analgesic[11] and glucagon receptor antagonism.[12] This core also has been utilized in diverse pharmaceutical applications such as *anti*-tumor,[13] antithrombotic, and vasodilatory[14] activities agents. Various substituted imidazoles also act as inhibitors of p38 MAP kinase[15] and B-Raf kinase.[16] In addition, recent advances in green chemistry and organometallic catalysis have extended the application of imidazoles as ionic liquids[17-19] and *N*-heterocyclic carbenes.[20] Because of their wide range of biological, industrial, and synthetic applications, they have recently received a great deal of attention.

2,4,5-Trisubstituted imidazoles are generally synthesized *via* a one-pot three-component cyclocondensation of a 1,2-diketone with an aromatic aldehyde and ammonium acetate in the presence of several catalysts such as acetic acid,[21] Wells-Dawson heteropolyacid supported on silica (WD/SiO_2),[22] $InCl_3{\cdot}3H_2O$,[23] zirconium modified silica gel,[24] KH_2PO_4,[25] $KAl(SO_4)_2$,[26] Brønsted acidic ionic liquid,[27] *p*-dodecylbenzenesulfonic acid (*p*-DBSA),[28] $Yb(OTf)_3$,[29] L-proline,[30] and ytterbium perfluorooctanesulfonate ($Yb(OPf)_3$).[31] Methods utilizing microwave irradiation in the presence of Al_2O_3[32] or ultrasonic irradiation using zinc (II) [tetra (4-methylphenyl)] porphyrin ([ZnT(4-CH_3)PP])[33] and ionic liquid[34] as catalyst, have also been reported. In addition, they can also be accessed by the reaction of aryl nitriles and α,α-dilithioarylnitromethanes,[35] or by multistep syntheses.[36] However, some of these methodologies encounter some limitations, such as use of homogeneous catalysts, long reaction times, harsh reaction conditions, and expensive catalysts. Moreover, the synthesis of these compounds is usually carried out in organic solvents such as EtOH, MeOH, AcOH, CH_3CN and CH_2Cl_2, leading to complex isolation and recovery procedures. Thus, to avoid these limitations the discovery of new methodologies using new heterogeneous and reusable catalysts is still in demand.

In recent years, considerable interest has been devoted to finding new methodologies for the synthesis of organic compounds in solvent-free condition.[37,38] The toxicity and volatile nature of many organic solvents have posed a serious threat to the environment. Thus, design of solvent-free catalytic reaction has received tremendous attention in recent times in the area of green synthesis.[39]

As part of our current studies on the development of practical and environmentally friendly procedures for the synthesis of organic compounds using reusable catalysts,[40-45] recently, we investigated the application of the isopolytungstate, tetrabutylammonium hexatungstate $[TBA]_2[W_6O_{19}]$,



Scheme 1. $[TBA]_2[W_6O_{19}]$ catalyzed synthesis of 2,4,5-trisubstituted imidazoles.

as a catalyst for a series of organic transformations. This new reusable heterogeneous catalyst performed well and showed a high level of catalytic activity in the Knoevenagel condensation[46] and Biginelli[47] reactions, as well as in the synthesis of bis-coumarins[48] and 1,8-dioxodecahydroacridines.[49] This fact prompted us to investigate the catalytic activity of this material in the synthesis of 2,4,5-trisubstituted imidazoles **4a-k** under solvent-free conditions (Scheme 1).

Experimental

All chemicals were available commercially and used without additional purification. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker spectrophotometer as KBr disks. The ^{1}H NMR (100 & 400 MHz) spectra were recorded with Bruker 100 & 400 spectrometers.

Preparation of Tetrabutylammonium Hexatungstate [TBA]$_2$[W$_6$O$_{19}$]. A mixture of sodium tungstate dihydrate, $Na_2WO_4{\cdot}2H_2O$ (99%, 33 g, 0.1 mol), acetic anhydride (40 mL), and *N*,*N*-dimethylformamide (DMF, 30 mL) was heated at 100 °C for 3 h to obtain a white cream. A solution of acetic anhydride (20 mL) and 12 mol/L HCl (18 mL) in DMF (50 mL) was then added in a drop-wise manner over a period of time with stirring, and the resulting mixture was filtered to remove the undissolved white solids. A solution of tetrabutylammonium bromide (15.1 g, 0.047 mol) in methanol (50 mL) was then added to the filtrate with rapid stirring to give a white precipitate, and the resulting suspension was stirred for 5 min and the product subsequently collected by filtration. Recrystallization from a minimum amount of hot dimethyl sulfoxide (DMSO) gave the product as colorless diamond-shaped crystals.[50]

General Procedure for the Synthesis of 2,4,5-Trisubstituted Imidazoles 4a-k Using [TBA]$_2$[W$_6$O$_{19}$] as Catalyst. A mixture of benzil **1** (1 mmol), an aromatic aldehyde **2a-k** (1 mmol), ammonium acetate **3** (2 mmol), and [TBA]$_2$[W$_6$O$_{19}$] (0.060 g) was heated in the oil bath at 140 °C for 5-30 min. The reaction was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature, hot ethanol was added and filtered to remove the catalyst. The filtrate was concentrated by half and allowed to stand at room temperature. The precipitated solid was collected by filtration, and recrystallized from ethanol to give compounds **4a-k** in high yields.

Recycling and Reusing of the Catalyst. The catalyst recovered by filtration was washed with hot ethanol, and subsequently dried *in vacuo* at 60 °C for 1 h, and reused. The catalyst could be used at least three times with only a slight reduction in the catalytic activity.

Results and Discussion

To optimize the catalytic system, the reaction of benzil **1** (1 mmol), 4-chlorobenzaldehyde **2e** (1 mmol), and ammonium acetate **3** (2 mmol) for the synthesis of compound **4e** was used as a model reaction. In order to get the effective reaction conditions the reaction was optimized in terms of various parameters like effect of solvent, catalyst amount, and influence of temperature. To choose the most appropriate medium in this cyclocondensation reaction, the model reaction was examined under solvent-free conditions and using EtOH, DMF, CH_3CN and CH_2Cl_2 as solvents (Table 1). Reaction under solvent-free conditions, an approach that is gaining popularity as it eliminates the use of volatile organic solvents in synthesis, afforded the highest yield of the product **4e** (entry 10, 92%). The efficiency of the reaction is affected by the amount of catalyst [TBA]$_2$[W$_6$O$_{19}$]. Low yield of the product **4e** was produced in the absence of the catalyst at 140 °C under solvent-free conditions (entry 1). Increasing the amount of the catalyst increased the yield of the product. The optimal amount of [TBA]$_2$[W$_6$O$_{19}$] was 0.060 g. The effect of temperature was also studied by carrying out the model reaction at different temperatures (100 °C, 120 °C and 140 °C) under solvent-free condition and the best results were obtained at 140 °C.

Next, we examined the generality of the catalytic efficiency of [TBA]$_2$[W$_6$O$_{19}$] by studying the reaction of various aromatic aldehydes with benzil and ammonium acetate under optimized reaction conditions. As shown in Table 2, aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields. The kind of aromatic aldehyde has no significant effect on the formation of final product.

To further evaluate the overall utility of the current methodology, we compared our results with those of the other methods reported for the synthesis of 2,4,5-trisubstituted imidazoles. This comparison is shown in Table 3. It is clear from the data that our method reduces the reaction times significantly and provides high yields of the products.

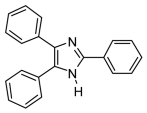
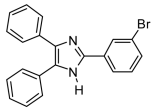
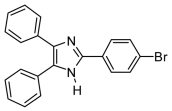
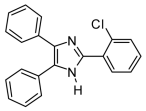
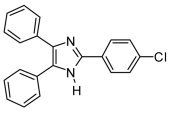
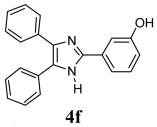
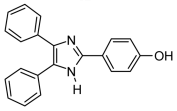
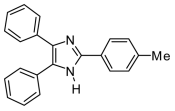
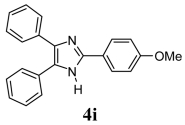
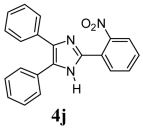
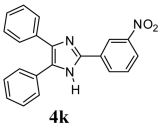
The recycling performance of [TBA]$_2$[W$_6$O$_{19}$] was also

Table 1. Synthesis of compound **4e** in the presence of [TBA]$_2$[W$_6$O$_{19}$] as catalyst in different reaction conditions[a]

Entry	Catalyst (g)	Solvent	T (°C)	Time (min)	Yield (%)[b]
1	None	Solvent-free	140	60	41
2	0.015	Solvent-free	100	25	55
3	0.015	Solvent-free	120	25	68
4	0.015	Solvent-free	140	10	78
5	0.030	Solvent-free	100	20	75
6	0.030	Solvent-free	120	15	78
7	0.030	Solvent-free	140	10	85
8	0.060	Solvent-free	100	20	83
9	0.060	Solvent-free	120	15	85
10	0.060	Solvent Free	140	10	92
11	0.100	Solvent Free	140	15	90
12	0.060	EtOH	Reflux	120	18
13	0.060	DMF	Reflux	120	23
14	0.060	CH_3CN	Reflux	240	Trace
15	0.060	CH_2Cl_2	Reflux	240	Trace

[a]Reaction conditions: benzil **1** (1 mmol), 4-chlorobenzaldehyde **2e** (1 mmol), and ammonium acetate **3** (2 mmol). [b]Isolated yields.

Table 2. Synthesis of 2,4,5-trisubstituted imidazoles **4a-k** using $[TBA]_2[W_6O_{19}]$ as catalyst[a]

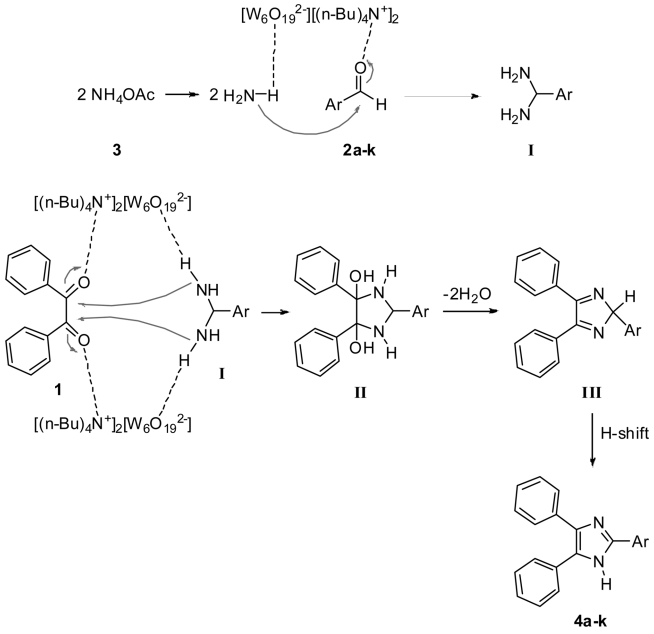
Entry	Ar	Products[b]	Time (min)	Yield (%)[c]	mp ºC		Ref.
					Found	Reported	
1	C_6H_5	 **4a**	5	87	275-276	274-276	22
2	3-BrC_6H_4	 **4b**	5	85	305-306	301-303	33
3	4-BrC_6H_4	 **4c**	10	87	254-256	252-254	26
4	2-ClC_6H_4	 **4d**	20	85	193-194	195-197	25
5	4-ClC_6H_4	 **4e**	10	92	260-261	259-261	26
6	3-HOC_6H_4	 **4f**	15	90	257-258	258-260	30
7	4-HOC_6H_4	 **4g**	20	90	245-247	240-242	29
8	4-MeC_6H_4	 **4h**	20	83	233-234	230-232	25
9	4-$MeOC_6H_4$	 **4i**	30	85	223-224	220-223	30
10	2-$O_2NC_6H_4$	 **4j**	30	78	220-222	230-231	30
11	3-$O_2NC_6H_4$	 **4k**	20	80	311-312	> 300	30

[a]Reaction conditions: benzil **1** (1 mmol), aromatic aldehyde **2a-k** (1 mmol), ammonium acetate **3** (2 mmol), $[TBA]_2[W_6O_{19}]$ (0.060 g) at 140 ºC under solvent-free conditions. [b]All the products were characterized by IR spectral data and comparision of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ^{1}H NMR spectral data. [c]The yields were calculated based on aromatic aldehyde and refer to the pure isolated product.

investigated in the model reaction. After the reaction was complete, the catalyst was recovered as described in the experimental section and was then reused for a similar reaction. We found that the catalyst could be used at least three times with only a slight reduction in activity (92% yield for first use, 90% for second use, and 90% for third use).

Table 3. Comparison of the efficiencies of different catalysts for the the synthesis of 2,4,5-trisubstituted imidazoles

Catalyst	Conditions			Time (min)	Yield (%)	Ref.
	Solvent	T (ºC)	Other			
WD/SiO_2	–	140	–	120	85-90	22
$InCl_3{\cdot}3H_2O$	MeOH	rt	–	500-580	54-82	23
zirconium modified silica gel	CH_3CN	rt	–	285-525	71-89	24
KH_2PO_4	EtOH	reflux	–	35-55	88-94	25
$KAl(SO_4)_2$	EtOH	70	–	150-240	82-94	26
Brønsted acidic ionic liquid	–	100	–	60-180	78-98	27
p-DBSA	H_2O	reflux	–	240	71-89	28
$Yb(OTf)_3$	AcOH	70	–	120	73-97	29
L-proline	MeOH	60	–	510-780	46-92	30
$Yb(OPf)_3$	AcOH	80	perfluorodecalin	360	75-97	31
Al_2O_3	EtOH or CH_2Cl_2	–	MW irradiation	20	67-82	32
([ZnT(4-CH_3)PP])	EtOH	rt	US irradiation	70	90-97	33
Ionic liquid	EtOH	rt	US irradiation	45-90	71-96	34
[TBA]$_2$[W$_6$O$_{19}$]	–	140	–	5-30	78-92	this work



Scheme 2. Plausible mechanism for the formation of 2,4,5-trisubstituted imidazoles in the presence of the [TBA]$_2$[W$_6$O$_{19}$] catalyst.

A mechanistic rationalization for this reaction is provided in Scheme 2. On the basis of our previous reports,[46-49] it is reasonable to assume that [TBA]$_2$[W$_6$O$_{19}$] can play a dual role. Thus, we propose that the tetrabutylammonium ion [(*n*-Bu)$_4$N$^+$] induces the polarization of the carbonyl groups, whereas the terminal oxygen atoms or the bridging oxygen atom in the polyoxometalate anion, $W_6O_{19}^{2-}$, are slightly basic and can promote the necessary reactions. As shown in Scheme 2, we propose that [TBA]$_2$[W$_6$O$_{19}$] facilitates the formation of the intermediates in this reaction. Under these conditions, however, attempts to isolate the proposed intermediates failed even after careful monitoring of the reactions.

Conclusion

In conclusion, we have developed a simple new catalytic method for the synthesis of 2,4,5-trisubstituted imidazoles *via* a one-pot three-component cyclocondensation of benzil, aromatic aldehydes, and ammonium acetate in the presence of a catalytic amount of tetrabutylammonium hexatungstate [TBA]$_2$[W$_6$O$_{19}$] as an efficient, reusable, and green heterogeneous catalyst under solvent-free conditions. Some attractive features of this protocol are good yields, simple procedure, short reaction times, easy work-up, high catalytic activity and recyclability and reusability of the catalyst. The catalyst can be used at least three times without substantial reduction in its catalytic activity.

Acknowledgments. The authors express their gratitude to the Islamic Azad University, Mashhad Branch for its financial support. And the publication cost of this paper was supported by the Korean Chemical Society.

References

1. Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187 and references therein.
2. Domling, A. *Chem. Rev.* **2006**, *106*, 17.
3. Davoodnia, A.; Tavakoli-Nishaburi, A.; Tavakoli-Hoseini, N. *Bull. Korean. Chem. Soc.* **2011**, *32*, 635.
4. Zeinali-Dastmalbaf, M.; Davoodnia, A.; Heravi, M. M.; Tavakoli-Hoseini, N.; Khojastehnezhad, A.; Zamani, H. A. *Bull. Korean Chem. Soc.* **2011**, *32*, 656.
5. Weber, L. *Drug Discov. Today* **2002**, *7*, 143.
6. Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.
7. Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311.
8. Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453.
9. Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182.
10. Antolini, M.; Bozzoli, A.; Ghiron, C.; Kennedy, G.; Rossi, T.; Ursini, A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1023.

11. Ucucu, U.; Karaburun, N. G.; Isikdag, I. *Farmaco* **2001**, *56*, 285.
12. Chang, L. L.; Sidler, K. L.; Cascieri, M. A.; de Laszlo, S.; Koch, G.; Li, B.; MacCoss, M.; Mantlo, N.; Okeefe, S.; Pang, M.; Rolando, A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2549.
13. Wang, L.; Woods, K. W.; Li, Q.; Barr, K. J.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y. H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinsky-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697.
14. Sircar, I.; Steffen, R. P.; Bobowski, G.; Burke, S. E.; Newton, R. S.; Weishaar, R. E.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1989**, *32*, 342.
15. Murry, J. A. *Curr. Opin. Drug Discov. Dev.* **2003**, *6*, 945.
16. Takle, A. K.; Brown, M. J. B.; Davies, S.; Dean, D. K.; Francis, G.; Gaiba, A.; Hird, A. W.; King, F. D.; Lovell, P. J.; Naylor, A.; Reith, A. D.; Steadman, J. G.; Wilson, D. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 378.
17. Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363.
18. Heravi, M. M.; Saeedi, M.; Karimi, N.; Zakeri, M.; Beheshtiha, Y. S.; Davoodnia, A. *Synth. Commun.* **2010**, *40*, 523.
19. Davoodnia, A.; Khojastehnezhad, A.; Bakavoli, M.; Tavakoli-Hoseini, N. *Chin. J. Chem*. **2011**, *29*, 978.
20. Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39.
21. Wang, J.; Mason, R.; VanDerveer, D.; Feng, K.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415.
22. Karimi, A. R.; Alimohammadi, Z.; Amini, M. M. *Mol. Divers.* **2010**, *14*, 635.
23. Das Sharma, S.; Hazarika, P.; Konwar, D. *Tetrahedron Lett.* **2008**, *49*, 2216.
24. Sharma, R. K.; Sharma, C. *Catal. Commun.* **2011**, *12*, 327.
25. Joshi, R. S.; Mandhane, P. G.; Shaikh, M. U.; Kale, R. P.; Gill, C. H. *Chin. Chem. Lett.* **2010**, *21*, 429.
26. Mohammadi, A. A.; Mivechi, M.; Kefayati, H. *Monatsh. Chem.* **2008**, *139*, 935.
27. Shaterian, H. R.; Ranjbar, M. *J. Mol. Liq.* **2011**, *160*, 40.
28. Das, B.; Kashanna, J.; Kumar, R. A.; Jangili, P. *Monatsh. Chem.* **2013**, *144*, 223.
29. Wang, L. M.; Wang, Y. H.; Tian, H.; Yao, Y. F.; Shao, J. H.; Liu, B. *J. Fluorine Chem.* **2006**, *127*, 1570.
30. Samai, S.; Nandi, G. C.; Singh, P.; Singh, M. S. *Tetrahedron* **2009**, *65*, 10155.
31. Shen, M. G.; Cai, C.; Yi, W. B *J. Fluorine Chem.* **2008**, *129*, 541.
32. Usyatinsky, A. Y.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031.
33. Safari, J.; Dehghan Khalili, S.; Banitaba, S. H.; Dehghani, H. *J. Korean Chem. Soc.* **2011**, *55*, 787.
34. Zang, H.; Su, Q.; Mo, Y.; Cheng, B. W.; Jun, S. *Ultrason. Sonochem.* **2010**, *17*, 749.
35. Hayes, J. F.; Mitchell, M. B.; Wicks, C. *Heterocycles* **1994**, *38*, 575.
36. Revesz, L.; Bonne, F.; Makavou, P. *Tetrahedron Lett.* **1998**, *39*, 5171.
37. Khojastehnezhad, A.; Davoodnia, A.; Bakavoli, M.; Tavakoli-Hoseini, N.; Zeinali-Dastmalbaf, M. *Chin. J. Chem*. **2011**, *29*, 297.
38. Davoodnia, A.; Khojastehnezhad, A.; Tavakoli-Hoseini, N. *Bull. Korean Chem. Soc.* **2011**, *32*, 2243.
39. Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
40. Seifi, N.; Zahedi-Niaki, M. H.; Barzegari, M. R.; Davoodnia, A.; Zhiani, R.; Aghaei Kaju, A. *J. Mol. Catal. A Chem.* **2006**, *260*, 77.
41. Tavakoli-Hoseini, N.; Davoodnia, A. *Chin. J. Chem.* **2011**, *29*, 1685.
42. Davoodnia, A. *Asian. J. Chem.* **2010**, *22*, 1595.
43. Davoodnia, A.; Bakavoli, M.; Mohseni, Sh.; Tavakoli-Hoseini, N. *Monatsh. Chem.* **2008**, *139*, 963.
44. Tavakoli-Hoseini, N.; Davoodnia, A. *Asian J. Chem.* **2010**, *22*, 7197.
45. Davoodnia, A.; Zhiani, R.; Tavakoli-Hoseini, N. *Monatsh Chem* **2008**, *139*, 1405.
46. Davoodnia, A. *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.* **2012**, *42*, 1022.
47. Mohammadzadeh-Dehsorkh, N.; Davoodnia, A.; Tavakoli-Hoseini, N.; Moghaddas, M. *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.* **2011**, *41*, 1135.
48. Davoodnia, A. *Bull. Korean Chem. Soc.* **2011**, *32*, 4286.
49. Davoodnia, A.; Zare-Bidaki, A.; Behmadi, H. *Chin. J. Catal.* **2012**, *33*, 1797.
50. Fournier, M. In *Inorganic Synthesis*; Ginsberg, A. P., Ed.; John Wiley: New York, 1990; *27*, 80.