Journal of Molecular Catalysis A: Chemical 356 (2012) 85–89

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Molybdate sulfuric acid as a reusable solid catalyst in the synthesis of 2,3,4,5-tetrasubstituted pyrroles via a new one-pot [2+2+1] strategy

Fatemeh Tamaddon[a,*], Mahnaz Farahi[a], Bahador Karami[b]

[a] Department of Chemistry, Faculty of Science, Yazd University, Yazd 89195-741, Iran
[b] Department of Chemistry, Yasouj University, Yasouj 75918-74831, Iran

ARTICLE INFO

Article history:
Received 17 September 2011
Received in revised form
25 December 2011
Accepted 1 January 2012
Available online 9 January 2012

Keywords:
2,3,4,5-Tetrasubstituted pyrroles
Benzoin
1,3-Dicarbonyls
Ammonium acetate
Molybdate sulfuric acid (MSA)

ABSTRACT

Molybdate sulfuric acid (MSA) has been found as an efficient and reusable solid acid catalyst for the synthesis of new 2,3,4,5-tetrasubstituted pyrroles via a novel [2+2+1] strategy. Thus, one-pot three-component reaction of benzoin derivatives, 1,3-dicarbonyls, and ammonium acetate afforded the desired products in high yield under solvent-free conditions.

1. Introduction

Recently, solid acids have been used as eco- and environmentally friendly catalysts in various organic transformations [1]. The option of reusability of the solid acid catalyst, non toxicity, and easier work up of the reactions catalyzed by these catalysts make them much favorite. Molybdate sulfuric acid (MSA) is a heterogeneous solid acid which has been used as catalyst in organic transformations [2,3]. This Brönsted acid as an efficient proton source is insoluble in most of organic solvents. It is a solid heterogeneous alternative to sulfuric acid. This inexpensive and reusable catalyst can be readily handled and easily separated from the reaction mixture, which these advantages make reactions cleaner and faster with higher yielding.

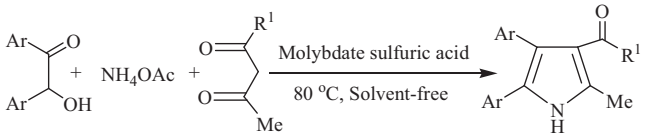
Pyrrole derivatives are certainly one of the most important nitrogen containing heterocyclic compounds which constitute the backbone of many biologically active compounds and natural products such as chlorophyll, hemoglobin, myoglobin, cytochromes, and vitamins [4–6]. A number of clinically used medicines with antibacterial, antiviral, anti-inflammatory, antitumoral or antioxidant properties carry out the pyrrole moiety in their fundamental structures [7]. Substituted pyrroles have also many potential uses as attractive synthetic intermediates in material science and biosynthesis [8–16]. Among the various synthetic approaches to pyrroles, Knorr [10], Paal-Knorr [11], and Hantzsch [12] methods are well-known, while pyrrole derivatives can be also prepared via 1,3-dipolar cycloaddition [14], reductive coupling [15], and aza-Wittig reaction [16].

One-pot multi-component reactions (MCR) play an important role in combinatorial chemistry, so this field remained one of the most interesting areas of researches in recent years [17–23]. During MCR, target compounds are formed with greater efficiency by generating structural complexity in a single step from three or more reactants. Due to the advantages, many four and three-component strategies have been developed for the preparation of pyrrole derivatives which are varied in kind of starting materials [24–29]. Based on the synthetic design and MCR, each component provides the five members of the pyrrole ring with the possible substitutes. This has stimulated interest in further synthetic designs and more simplified catalytic methods for the synthesis of new substituted pyrroles.

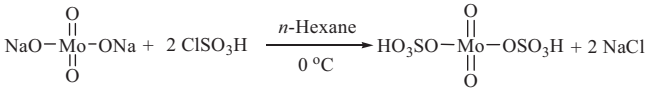
Due to the advantages of MCR and heterogeneous catalysts, in continuation of our researches [30–35], we report herein a new different [2+2+1] strategy for the synthesis of tetrasubstituted pyrroles using molybdate sulfuric acid as an efficient heterogeneous catalyst (Scheme 1).

* Corresponding author. Tel.: +98 3518122666; fax: +98 3518210644.
E-mail addresses: ftamaddon@yazduni.ac.ir (F. Tamaddon), farahimb@yahoo.com (M. Farahi), karami@mail.yu.ac.ir (B. Karami).

1381-1169/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2012.01.003



Scheme 1. MSA catalyzes the synthesis of 2,3,4,5-tetrasubstituted pyrroles.



Scheme 2. Preparation of MSA catalyst.

2. Experimental

2.1. Preparation of catalyst

MSA was prepared via a modified version of the previously reported procedures [2,3] (Scheme 2).

Thus, anhydrous sodium molybdate (20 mmol, 4.118 g) was added to dry *n*-hexane (25 mL) in a 100 mL round bottom flask equipped with ice bath and overhead stirrer. Chlorosulfonic acid (0.266 mL, 40 mmol) was then added dropwise to the flask during 30 min and stirred for 1.5 h. The reaction mixture was gradually poured into 25 mL of chilled distilled water with agitation. The molybdate sulfuric acid was separated as a bluish solid by filtration, washed with cold distilled water five times until the negative test for chloride ion for filtrate, and dried at 120 °C for 5 h. The yield of the obtained bluish acid catalyst was 90%.

2.2. Characterization of catalyst

The prepared catalyst was characterized by determination of decomposition point, FT-IR spectrum, and neutralization titration with standard solution of NaOH.

As a result, the prepared molybdate sulfuric acid which showed good thermal stability decomposed at 354 °C.The overlaid FT-IR spectra of sodium molybdate and molybdate sulfuric acid (MSA) are shown in Fig. 1. As the spectrum of MSA demonstrates, the characteristic bands of both anhydrous sodium molybdate and —OSO_3 group are shifted evidently to the higher wave numbers. The well defined bands at 3600–3000 is related to OH stretching, the band at 1635 cm^{-1} is the H—O—H bending mode of the lattice water, and

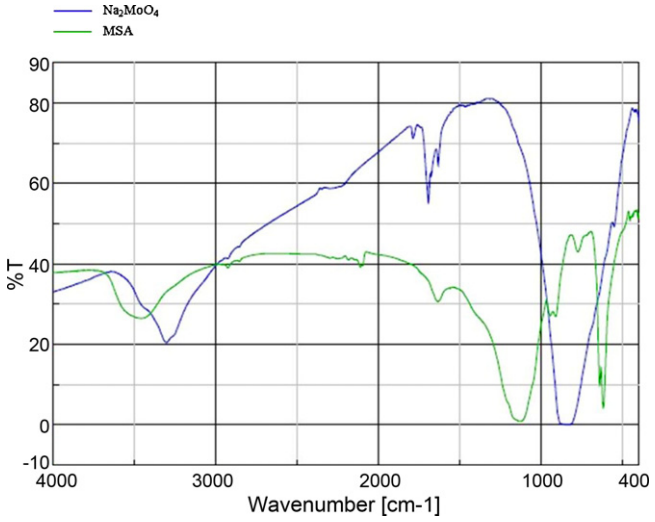


Fig. 1. Overlaid FT-IR spectra of Na_2MoO_4 and $H_3OSO(MoO_2)OSO_3H$ (MSA).

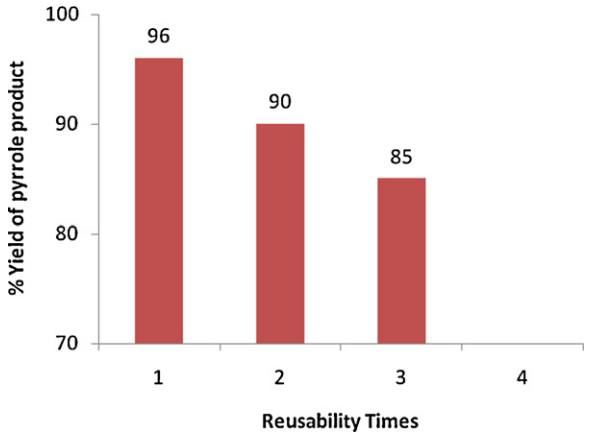
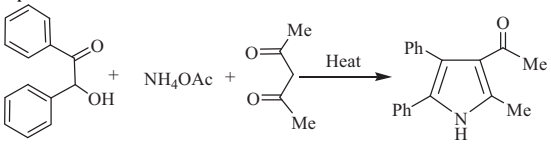


Fig. 2. Reusability of catalyst.

the bands at 1300–1100 cm^{-1} might be the asymmetric and symmetric stretching modes of S=O. A strong band at 827 cm^{-1} in the FT-IR spectrum of sodium molybdate is assigned to the stretching mode of Mo—O. This band is shifted to ~1100 cm^{-1} and appeared as an overlapped band with S=O stretching bands in spectrum of MSA. Broadening of the absorbance band positioned at 3600–3000 cm^{-1} is due to the rapid exchanges of acidic hydrogens via H-bonding and reveals the formation of MSA.

In order to investigate the acid capacity of MSA, a solution of it (0.0805 g) in distilled water (100 mL) was titrated with standard solution of NaOH (0.1 N) in the presence of phenolphthalein as indicator. At the endpoint of titration 5 mL of titrant was consumed. The capacity of MSA was determined according the following equation as 2. $(m/MW) \times n = N_2V_2$, $(0.0805/322) \times n = 0.1 \times 0.005$, thus $n = 2$. Therefore, MSA can be considered as a solid heterogeneous alternative to sulfuric acid.

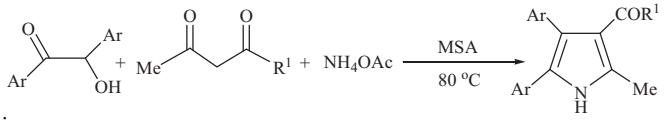
Table 1
Optimization of the reaction. .

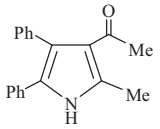
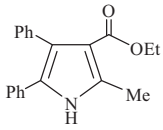
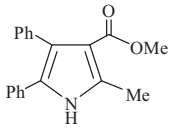
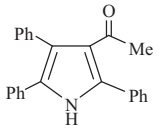
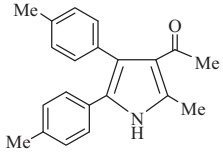
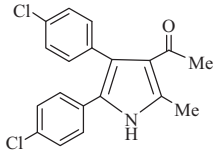
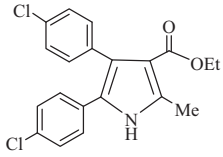
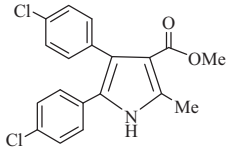
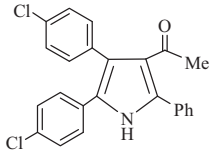


Entry	Solvent	Catalyst loading/temp. (mol%/°C)	Time (min)	Yield (%)[a]
1	None	None/90	300	15
2	None	$ZrOCl_2$ (5)/90	360	81
3	None	$ZnCl_2$ (5)/90	360	75
4	None	$MgBr_2$ (5)/80–90	360	85
5	None	$CuCl_2$ (5)/80–90	400	68
6	None	H_2SO_4 (5)/80–90	60	66
7	None	HCl (5)/80–90	60	37
8	None	Glacial HOAc (5)/80–90	60	57
9	None	MSA (20)/80–90	30	80
10	None	MSA (15)/80–90	30	85
11	None	MSA (10)/80–90	30	90
12	None	MSA (5)/80–90	30	96
13	None	MSA (5)/80	25	96
14	None	MSA (5)/70	55	93
15	None	MSA (5[b])/80	25	85
16	H_2O	MSA (5)/80	60	50
17	EtOH	MSA (5)/80	40	80
18	EtOH	MSA (5)/80	40	80
19	CH_3CN	MSA (5)/80	60	71
20	CH_2Cl_2	MSA (5)/80	60	75

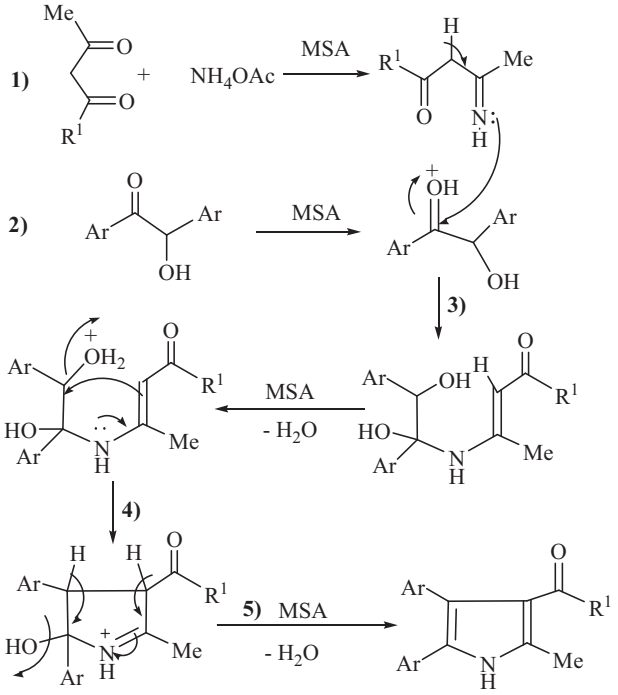
[a] Isolated yields.
[b] The catalyst was reused for run 3.

Table 2
MSA-catalyzed condensation of benzoin, 1,3-dicarbonyls and ammonium acetate.



Entry	Ar	R^1	Time (min)	Product[a]	Yield (%)[b]
1	Ph	Me	25		96
2	Ph	OEt	30		94
3	Ph	OMe	35		90
4	Ph	Me	45		87
5	4-MeC_6H_5	Me	45		87
6	4-ClC_6H_5	Me	30		92
7	4-ClC_6H_5	OEt	45		94
8	4-ClC_6H_5	OMe	40		93
9	4-ClC_6H_5	Me[c]	80		95

[a] All products were fully characterized by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy.
[b] Isolated yield.
[c] Benzoylacetone was used instead of acetylacetone.



Scheme 3. Proposed mechanism for MSA-catalyzed synthesis of tetra-substituted pyrroles.

2.3. General procedure for the synthesis of tetrasubstituted pyrroles

To a mixture of benzoin derivative (2 mmol), 1,3-dicarbonyl compound (2 mmol), and NH_4OAc (3 mmol) was added MSA (5 mol%). The resulting mixture was stirred at 80 °C for the given times (Table 2). After completion of the reaction (as indicated by thin layer chromatography), EtOAc (10 mL) was added and the catalyst was separated by filtration. Evaporation of the solvent under reduced pressure gave the product. Further purification was achieved by recrystallization from EtOH/H_2O (70:30).

2.4. Reusability of catalyst

The recovered catalyst from the model reaction was regenerated by washing with EtOAc and drying at 120 °C for 1 h. Using the recycled catalyst for three consecutive times in the reaction of benzoin, acetylacetone, and ammonium acetate furnished the product with a gradual decreasing of reaction yield (Fig. 2).

2.5. Selected spectral data

2.5.1. 1-(2-Methyl-4,5-diphenyl-1H-pyrrol-3-yl)ethanone (Table 2, entry 1)

Pale yellow solid, mp = 170–172 °C. FT-IR: υ_{max} (KBr) 3177 (NH stretching), 1635 (C=O), 1455, 767, and 698 cm^{-1}. ^{1}H NMR (DMSO-$_{d6}$, 400 MHz) δ: 1.72 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 7.10–7.36 (m, 10H), and 11.61 (br s, 1H, NH) ppm. ^{13}C NMR (DMSO, 100 MHz) δ: 14.32, 30.96, 122.53, 122.58, 126.53, 127.03, 127.33, 128.61, 128.76, 131.22, 132.65, 135.74, 137.57, and 194.95 ppm. Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.85; H, 6.01; N, 5.05.

2.5.2.
1-(4,5-Bis(4-chlorophenyl)-2-methyl-1H-pyrrol-3-yl)ethanone (Table 2, entry 6)

White crystals, mp = 234–235 °C. FT-IR (KBr): υ_{max} (KBr) 3195, 1631, 1576, 1523, 1445, 829, and 798 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.82 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 7.08–7.40 (m, 8H), and 11.73 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.35, 31.10, 121.61, 122.45, 126.21, 128.80, 128.82, 131.17, 131.39, 132.14, 132.93, 136.06, 136.16, and 194.50 ppm. Anal. Calcd for $C_{19}H_{15}Cl_2NO$: C, 66.29; H, 4.39; Cl, 20.60; N, 4.07; O, 4.65%. Found: C, 66.05; H, 4.25; N, 4.05%.

2.5.3. Ethyl
4,5-bis(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (Table 2, entry 7)

Pale yellow crystals, mp = 155–156 °C. FT-IR (KBr): ν_{max} 3286, 1672, 1498, 1481, 831, and 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.58 (s, 3H, CH_3), 4.09 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 6.99–7.26 (m, 8H), and 8.66 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.89, 14.04, 59.45, 112.36, 122.46, 126.50, 127.92, 128.11, 128.73, 130.38, 132.08, 132.47, 134.28, 136.15, and 165.50 ppm. Anal. Calcd for $C_{20}H_{17}Cl_2NO_2$: C, 64.18; H, 4.58; Cl, 18.95; N, 3.74; O, 8.55%. Found: C, 63.96; H, 4.31; N, 3.68%.

2.5.4.
1-(4,5-Bis(4-chlorophenyl)-2-phenyl-1H-pyrrol-3-yl)ethanone (Table 2, entry 9)

Yellow crystals, mp = 247–249 °C. FT-IR (KBr): ν_{max} 3304, 1617, 1595, 1498, 831, and 699 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 7.18–7.48 (m, 13H), and 11.85 (s, 1H, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.21, 121.67, 126.42, 128.28, 128.36, 128.92, 129.31, 131.05, 131.58, 131.97, 132.36, 134.71, 135.11, 140.15, and 192.98 ppm. Anal. Calcd for $C_{24}H_{17}Cl_2NO$: C, 70.95; H, 4.22; Cl, 17.45; N, 3.45; O, 3.94%. Found: C, 70.78; H, 4.37; N, 3.52%.

3. Results and discussion

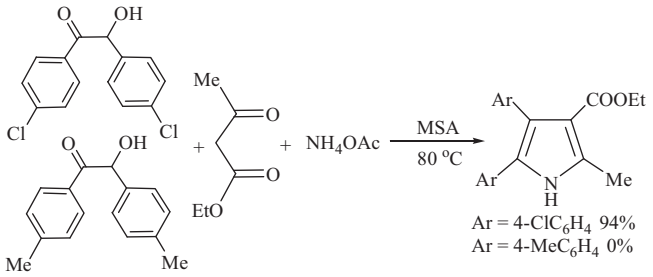
According to our designed synthetic strategy for the preparation of tetrasubstituted pyrroles, reaction of benzoin (1 mmol), acetyl acetone (1 mmol) and NH_4OAc (1.5 mmol) was selected as a model reaction. Use of the higher ratio of NH_4OAc is due to its hygroscopic properties. This reaction was optimized by screening in the presence of various catalysts at different conditions (Table 1).

As can be seen, the best results were obtained by carrying out the reaction in the presence of 5 mol% of molybdate sulfuric acid (MSA) at 80 °C under solvent-free conditions. Molybdate sulfuric acid is an easily prepared and moisture tolerant solid acid which has been used as catalyst in the oxidation of thiols and nitrosation of amines [2,3].

The reusability of catalyst is an important factor for commercial uses. Therefore, the recovery and reusability of MSA was investigated. Hence, MSA was successfully regenerated from the model reaction by washing with EtOAc and drying at 120 °C. Attempts to the reusability of MSA showed that reactivity of the recovered catalyst was efficiently depending on the solvent applied for regeneration of catalyst. However, washing the filtered catalyst from the first run by warm protic solvents such as water and alcohols resulted in the obvious decreasing of reaction yield. In the contrast, the recycled catalyst by EtOAc was reused three times with gradual loss of activity in the model reaction (Table 1, entry 15, and Fig. 2).

Deploying the optimized reaction conditions, the scope of the method was demonstrated using a variety of 1,3-dicarbonyls and benzoins (Table 2).

According to results obtained, benzoins bearing electron-withdrawing groups were reacted with 1,3-dicarbonyls and ammonium acetate faster than those of electron-donating ones. This may be explained according to more positive charge located on carbonyl group of these benzoins, which make them more reactive towards nucleophilic attack of nitrogen of imine intermediate. A proposed mechanism for the formation of pyrrole according to these electronic effects is outlined in Scheme 3. It seems that ketone group of 1,3-dicarbonyl compound reacts initially with NH_4OAc to form an imine intermediate that subsequently condenses with activated benzoin by MSA to produce a cyclic intermediate. Dehydration of this intermediate and elimination of water produces the corresponding tetrasubstituted pyrrole (Scheme 3).



Scheme 4. Chemoselectivity of MSA-catalyzed pyrrole synthesis.

The proposed mechanism was supported by the chemoselectivity of method for electron-deficient benzoins. So, competitive reaction of equal amounts of 4-Me and 4-Cl substituted benzoins with ethylacetoacetate and NH_4OAc in the presence of 5 mol% of MSA showed a high selectivity for 4-cholorobenzoin and the corresponding pyrrole was isolated exclusively in 93% yield (Scheme 4).

4. Conclusion

In conclusion, a new strategy has been developed for the convenient synthesis of tetrasubstituted pyrroles using MSA as a highly efficient catalyst. In the presence of this solid acid a series of tandem condensation and dehydration reactions occurred and resulted in the formation of tetrasubstituted pyrroles in high yields. The advantages of this work are solvent-free conditions, recyclability of catalyst, and availability of starting materials which is capable to design a range of new pyrrole derivatives. The simplicity of the present procedure than the previously reported method of pyrrole synthesis makes this new approach as an interesting alternative to the complex multistep approaches.

Acknowledgments

We acknowledge the research council of Yazd University. We also gratefully thank Dr. Alireza Gorji for his valuable comments about FTIR analysis of inorganic compounds.

References

[1] Wilson, J.H. Clark, Pure Appl. Chem. 72 (2000) 1313–1319.
[2] M. Montazerozohori, B. Karami, Helv. Chim. Acta 89 (2006) 2922–2926.
[3] M. Montazerozohori, B. Karami, M. Azizi, ARKIVOK (2007) 99–104.
[4] V. Estévez, M. Villacampa, J.C. Menéndez, Chem. Soc. Rev. 39 (2010) 4402–4421.
[5] J.-J. Li, E.J. Corey, Name Reactions in Heterocyclic Chemistry, Wiley Interscience, 2005, pp. 301–315 (Chapter 8).
[6] A. Furstner, Angew. Chem. Int. Ed. 42 (2003) 3528–3531.
[7] M. Baumgarten, N. Tyutyulkov, Chem. Eur. J. 4 (1998) 987–989.
[8] A. Deronzier, J.C. Moutet, Curr. Top. Electrochem. 3 (1994) 159–200.
[9] B. Das, K. Damodar, N. Chowdhury, J. Mol. Catal. A: Chem. 269 (2007) 81–84.
[10] L. Knorr, Chem. Ber. 17 (1884) 1635–1642.
[11] C. Paal, Chem. Ber. 18 (1885) 367–371.
[12] A. Hantzsch, Ber. Dtsch. Chem. Ges. 23 (1890) 1474–1476.
[13] F. Berree, E. Marchand, G. Morel, Tetrahedron Lett. 33 (1992) 6155–6158.
[14] A. Furstner, H. Weintritt, A. Hupperts, J. Org. Chem. 60 (1995) 6637–6641.
[15] A. Katritzky, J. Jiang, P.J. Steel, J. Org. Chem. 59 (1994) 4551–4555.
[16] G. Balme, Angew. Chem. Int. Ed. 43 (2004) 6238–6241.

[17] X. Lin, Z. Mao, X. Dai, P. Lu, Y. Wang, Chem. Commun. 47 (2011) 6620–6622.
[18] J.S. Yadav, B.V. Subba Reddy, T. Srinivasa Rao, R. Narender, M.K. Gupta, J. Mol. Catal. A: Chem. 278 (2007) 42–46.
[19] A.R. Bharadwaj, K.A. Scheidt, Org. Lett. 6 (2004) 2465–2468.
[20] D. Tejedor, D. Gonzalez-Cruz, F. Garcia- Tellado, J.J. Marreo-Tellado, M.L. Rodriguez, J. Am. Chem. Soc. 126 (2004) 8390–8391.
[21] N. Isambert, M.D.M. Sanchez Duque, J.-C. Plaquevent, Y. Genisson, J. Rodriguez, T. Constantieux, Chem. Soc. Rev. 40 (2011) 1347–1357.
[22] J.S. Yadav, B.V. Subba Reddy, R. Jain, U.V. Subba Reddy, J. Mol. Catal. A: Chem. 278 (2007) 38–41.
[23] M. Anary Abbasinejad, Kh. Chakhati, H. Anary-Ardakani, Synlett (2009) 1115–1117.
[24] B. Khalili, P. Jajarmi, B. Eftekhari-Sis, M.M. Hashemi, J. Org. Chem. 73 (2008) 2090–2095.
[25] W. Ried, R. Conte, Chem. Ber. 104 (1971) 1573–1579.
[26] E. Ghabraie, S. Balalaie, M. Bararjanian, H.R. Bijanzade, F. Rominger, Tetrahedron 67 (2011) 5415–5420.
[27] S. Ngwerume, J.E. Camp, J. Org. Chem. 75 (2010) 6271–6274.
[28] N. Azizi, A. Khajeh-Amiri, H. Ghafuri, M. Bolourtchian, M.R. Saidi, Synlett (2009) 2245–2248.
[29] L. Ackermann, R. Sandmann, L.T. Kasper, Org. Lett. 11 (2009) 2031–2034.
[30] F. Tamaddon, M.A. Amrollahi, L. Sharafat, Tetrahedron Lett. 46 (2005) 7841–7844.
[31] F. Tamaddon, M. Khoobi, E. Keshavarz, Tetrahedron Lett. 48 (2007) 3643–3646.
[32] F. Tamaddon, F. Tavakoli, J. Mol. Catal. A: Chem. 337 (2011) 52–55.
[33] F. Tamaddon, A. Nasiri, S. Farokhi, Catal. Commun. 12 (2011) 1477–1482.
[34] F. Tamaddon, M.R. Sabeti, A.A. Jafari, F. Tirgir, E. Keshavarz, J. Mol. Catal. A: Chem. 351 (2011) 41–45.
[35] F. Tamaddon, Z. Razmi, A.A. Jafari, Tetrahedron Lett. 51 (2010) 1187–1189.