Res Chem Intermed
DOI 10.1007/s11164-015-2134-y

1, 3-Disulfonic acid imidazolium hydrogen sulphate as an efficient and reusable ionic liquid for the multicomponent synthesis of polyhydroquinoline derivatives under solvent-free conditions

Kamal Mohammadi[1] · **Farhad Shirini**[1] ·
Asieh Yahyazadeh[1]

Received: 14 April 2015 / Accepted: 6 June 2015

Abstract A facile and highly effective one-pot synthesis of polyhydroquinoline derivatives is reported via Hantzsch condensation of aldehydes, 1,3-dicarbonyl compounds, ethyl acetoacetate, and ammonium acetate in the presence of 1,3-disulfonic acid imidazolium hydrogen sulfate as an efficient and recyclable ionic liquid under solvent-free conditions. This methodology offers several advantages such as short reaction times, high yields, environmentally benign, mild reaction conditions, simple work-up procedure, and reusability of the ionic liquid.

Keywords 1, 3-Disulfonic acid imidazolium hydrogen sulfate · Recyclable ionic liquid · Polyhydroquinoline derivatives · Hantzsch condensation · Solvent-free conditions

Introduction

Multicomponent reactions (MCRs) have gained great attention as efficient and attractive synthetic procedures in modern organic synthesis and medicinal chemistry. They are one-pot processes that generate complex products from a combination of three or more substrates simultaneously [1, 2]. Also, MCRs have remarkable benefits in terms of simplicity and synthetic efficiency over formal

---

Electronic supplementary material The online version of this article (doi:10.1007/s11164-015-2134-y) contains supplementary material, which is available to authorized users.

✉ Farhad Shirini
shirini@guilan.ac.ir; fshirini@gmail.com

✉ Asieh Yahyazadeh
yahyazadehphd@yahoo.com

[1] Department of Chemistry, College of Science, University of Guilan, Post Box: 1914, 41335 Rasht, I.R. Iran

chemical reactions [3] and show high atom economy and high selectivity [4, 5]. Therefore, the use of MCRs as well as domino reaction sequences has significantly increased for a large number of products [6].

Recently, an immense interest has been focused on the multicomponent synthesis of 1, 4-dihydropyridines (1, 4-DHPs) because of their wide range of biological and pharmacological properties such as antihypertensive, antitherosclerotic, hepatoprotective, antimutagenic, vasodilator, bronchodilator, antitumor, geroprotective, antimalarial, antibacterial, and antidiabetic activities [7–12]. The 1, 4-DHPs as analogues of NADH coenzymes, such as nifedipine, nicardipine, and amlodipine, are well known as calcium channel blockers for the treatment of cardiovascular disorder including angina, hypertension, and cardiac arrhythmias [13]. Widespread studies have revealed that these compounds show diverse medical applications, which include neuroprotectant, platelet anti-aggregatory activity, and cerebral antischaemic activity in the treatment of Alzheimer's disease and chemosensitizer behavior in tumour therapy [14–17]. These examples clearly indicate the considerable potency of novel DHP derivatives as a source of valuable drug candidates.

In view of the significance of polyhydroquinoline derivatives, several procedures have been reported for their synthesis [18–20]. In 1882, and for the first time, the synthesis of 1, 4-DHPs via the one-pot condensation of aldehydes with ethyl acetoacetate and ammonia in acetic acid or by refluxing in alcohols was reported by Hantzsch [21]. In recent years, several new efficient methods have been developed including the use of TMSCl [22], L-proline [23], polymers [24], $Yb(OTf)_3$ [25], $HClO_4$–SiO_2 [26], heteropoly acid [27], CAN [28], *p*-TSA [29], $InCl_3$ [30], I_2 [31], nanocrystalline TiO_2 [32], Bakers' yeast [33], grinding [34], conventional heating [35, 36], microwave irradiation, and ultrasound [37]. However, some of the reported methods suffer from some drawbacks such as long reaction times, harsh reaction conditions, utilization of volatile and hazardous solvents, high temperature, using expensive and nonreusable catalysts that are harmful to the environment, and low product yields. Therefore, the improvement of a mild and efficient catalytic system for the synthesis of these compounds is still a challenging task for the organic chemists.

The principles of Green Chemistry have been introduced to eliminate or reduce the use or generation of hazardous materials in chemical processes. One of the key areas of green chemistry is the replacement of hazardous solvents with environmentally benign ones or the elimination of solvents altogether [38–40]. In recent years, application of sulfonic acid functionalized ionic liquids (ILs) as "designer solvents" have attracted considerable attention of chemists due to their unique properties such as high thermal stability, negligible vapor pressure, low flammability, environmental compatibility, reusability, greater selectivity, and ease of isolation [41]. They are known as catalysts or as a dual catalyst-solvent for a wide range of chemical reactions such as Hantzsch, Mannich, Biginelli and Friedlander quinoline synthesis [42–45]. The above-mentioned advantages encouraged us to explore the new applications of this IL in organic synthesis.

Experimental

Chemicals were purchased from the Fluka and Merck companies. Melting points were recorded on an electrothermal digital melting point apparatus model IA9100 in open capillary tubes. The IR spectra were run on a Perkin-Elmer model Spectrum One FT-IR Spectrometer. The ^{1}H NMR spectra were recorded on a Bruker AVANCEIII-400 spectrometer using TMS as an internal reference. ^{The} ^{13}C NMR spectra were also recorded on the same instrument at 100 MHz. The purity determination of the substrate and reaction monitoring were accomplished by TLC on silica-gel polygram SIL G/UV 254 plates. Yields refer to isolated products. Products were characterized by their physical constants, comparison with authentic samples, and IR and NMR spectroscopy.

A mixture of the aldehyde (1 mmol), dimedone or 1, 3-cyclohexanedione (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1 mmol), and DSIMHS (0.25 mmol) was heated in an oil bath (70 °C) under stirring. The progress of the reaction was monitored by TLC (*n*-hexane/ethyl acetate, 8:2). After completion, the reaction mixture was washed with water, because DSIMHS is soluble in water, and the product was precipitated with high purity. Then the crude solid product was filtered off and recrystallized from ethanol.

Selected spectral data

Ethyl 2,7,7-trimethyl-4-(4-bromophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylat (Table 2, entry 1): m.p. 254–256 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H), 1.09 (s, 3H), 1.22 (t, $J = 7.2$ Hz, 3H), 2.15–2.37 (m, 4H), 2.40 (s, 3H), 4.08 (q, $J = 7.2$ Hz, 2H), 5.04 (s, 1H), 6.12 (br s,1H), 7.21 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H) ppm; IR (KBr) $v = 3275$, 3190, 3075, 2965, 1703, 1607, 1517, 1492, 1345, 1215, 1167, 1072, 832, 697 cm^{-1}.

Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylat (Table 2, entry 3): m.p. 241–243 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 3H), 1.09 (s, 3H), 1.24 (t, $J = 7.2$ Hz, 3H), 2.13–2.37 (m, 4H), 2.40 (s, 3H), 4.07 (q, $J = 7.2$ Hz, 2H), 5.18 (s, 1H), 6.72 (br s, 1H), 7.51 (d, $J = 8.8$ Hz, 2H), 8.10 (d, $J = 8.8$ Hz, 2H) ppm; IR (KBr) $v = 3275$, 3207, 3078, 2958, 1703, 1648, 1605, 1487, 1381, 1220, 1191 cm^{-1}.

Ethyl 2,7,7-trimethyl-4-(2-chloro-6-fluorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylat (Table 2, entry 12): m.p. 164–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (s, 3H), 1.03 (m, 6H), 1.91 (d, $J = 16$ Hz, 1H), 2.17 (m, 5H), 2.39 (d, $J = 17.2$ Hz, 1H), 3.91 (q, $J = 7.2$ Hz, 2H), 5.44 (s, 1H), 7.04 (m, 1H), 7.14 (m, 2H), 9.15 (s, 1H) ppm; IR (KBr) $v = 3299$, 3080, 2956, 1691, 1649, 1610, 1473, 1217, 1112, 1072, 786 cm^{-1}.

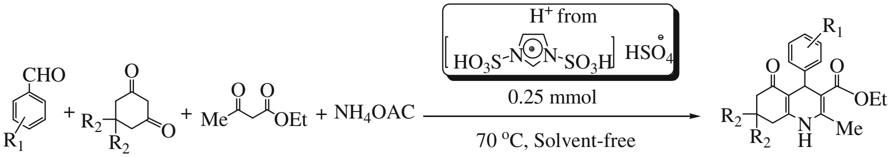
Results and discussion

Very recently we have reported the preparation and application of DSIMHS as a green, efficient, and reusable IL in organic transformations [46–48]. Herein and in continuation of these studies, we wish to report the one-pot Hantzsch condensation of 1, 3-dicarbonyl compounds with various aromatic aldehydes, ethyl acetoacetate, and NH_4OAc in the presence of this IL (Scheme 1).

To find the optimal conditions, the reaction of 4-chlorobenzaldehyde, ethylacetoacetate, dimedone, and ammonium acetate in 1:1:1:1 ratios was chosen as a model. Optimization of the reaction conditions was performed using various amounts of DSIMHS at different temperatures under solvent-free conditions. The results are summarized in Table 1.

As it shown in Table 1, the best result was obtained by carrying out the reaction using 0.25 mmol of DSIMHS at 70 °C (Table 1, entry 5). Increasing the amount of IL and the temperature in this method did not lead to significant improvement in the yields and times (Table 1, entry 4 and 7). In addition, when the mentioned procedure is progressed at room temperature, the yield of the corresponding product was low after 300 min (Table 1, entry 1). Also, Table 1 clearly indicates that without any IL at 70 °C, the product was isolated in poor yield after a long reaction time (Table 1, entry 2).

To show the efficiency and the applicability of this protocol, various substituted aromatic aldehydes were efficiently reacted with dimedone, ethyl acetoacetate, and ammonium acetate in the same conditions. The results are presented in Table 2. It can be seen that both the aromatic aldehydes containing electron-withdrawing groups (such as nitro and halide groups) and electron-donating groups (such as hydroxyl and alkoxy groups) reacted successfully to give the corresponding



Scheme 1 The synthesis of polyhydroquinoline derivatives in the presence of DSIMHS under solvent-free conditions

Table 1 The effect of different amounts of DSIMHS and temperature on the synthesis of ethyl 2, 7, 7-trimethyl-4-(4-chlorophenyl)-5-oxo-1, 4, 5, 6, 7, 8- hexahydroquinoline-3-carboxylate[a]

Entry	DSIMHS (mmol)	Temperature (°C)	Time (min)	Yield (%)[b]
1	0.25	25	300	30
2	–	70	300	12
3	0.15	70	6	78
4	0.25	75	3	93
5	0.25	70	3	93
6	0.25	60	7	90
7	0.35	70	3	94

[a] Reaction condition: 4-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), ethylacetoacetate (1 mmol), and ammonium acetate (1 mmol) at different temperatures under solvent free conditions

[b] Isolated yield

Table 2 Hantzsch synthesis of polyhydroquinolines using DSIMHS under solvent-free conditions[a]

Entry	R_1	R_2	Time (min)	Yield (%)[b]	m.p. (°C)	
					Measured	Reported [Refs.]
1	4-Br	Me	6	92	249–251	252–253 [26]
2	4-Cl	Me	3	93	233–235	233–235 [49]
3	4-NO2	Me	5	91	239–241	241–243 [32]
4	3-NO2	Me	8	89	172–174	174–176 [32]
5	4-OH	Me	10	91	225–227	228–230 [49]
6	4-F	Me	7	89	180–182	184–186 [29]
7	3-Br	Me	8	90	231–233	233–235 [50]
8	4-OCH3	Me	15	88	253–255	255–257 [32]
9	H	Me	5	94	203–205	203–205 [49]
10	4-CH(Me)2	Me	15	92	175–177	179–181 [32]
11	2-Cl	Me	7	92	209–211	206–208 [29]
12	2-Cl-6-F	Me	12	88	164–166	–
13	4-Br	H	5	89	257–259	253–254 [50]
14	4-OH	H	10	90	225–227	221–222 [51]
15	4-NO2	H	8	91	203–206	205–206 [51]
16	4-Cl	H	10	91	248–250	250–251 [32]
17	4-OCH3	H	10	89	209–211	212–215 [32]
18	4-F	H	10	89	246–248	243–244 [51]

[a] All products were characterized by comparison of their mp, IR, 1HNMR spectra with those of authentic samples

[b] Isolated yield

polyhydroquinoline in good to excellent yields and short reaction times. Results have shown that the aromatic aldehydes with electron-withdrawing groups showed an increased reaction rate. Next, we investigated the effect of substitution in the dimedon system using 1, 3-cyclohexanedione. Interestingly, dimedone reacts faster than 1, 3-cyclohexanedione in the presence of DSIMHS as a promoter to afford the corresponding products in excellent yields (Table 2).

Considering the importance of the catalyst recovery, we studied the recyclability and the reusability of DSIMHS from the reaction mixture in the model process. After completion of the reaction, the precipitated mixture was filtered and the solid product was washed with water completely to separate IL from the other materials, because DSIMHS is soluble in water. All water that is collected in this way was washed with CH_2Cl_2 (2 × 10 mL) to remove organic impurities. Then, water was evaporated under reduced pressure and IL was recovered and reused. The obtained results clearly indicated that the recovered IL could be reused directly in the next run without any significant loss of its activity even after the fourth run (Fig. 1).

A possible mechanism for the formation of polyhydroquinoline derivatives in the presence of DSIMHS as a promoter is shown in Scheme 2. On the basis of this mechanism, DSIMHS catalyzes the reaction and polyhydroquinoline 5 may be

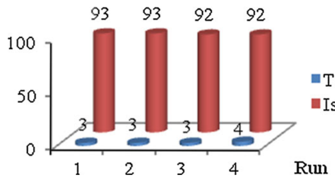
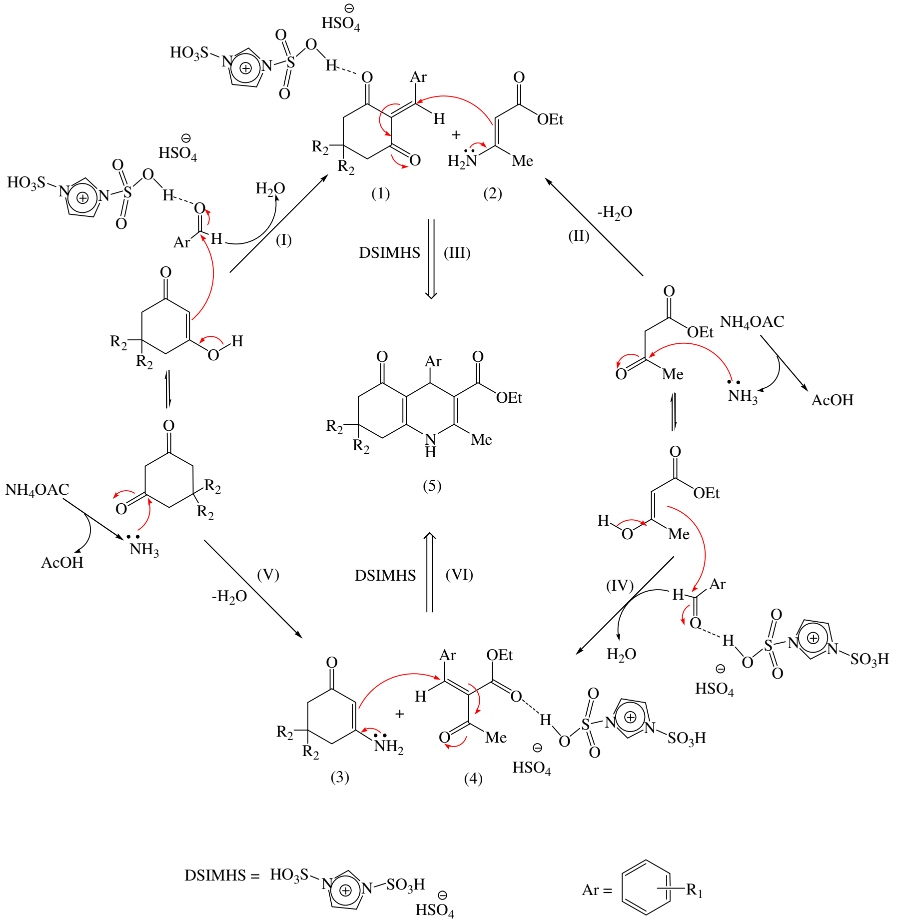


Fig. 1 Results of the reusability of DSIMHS in the synthesis of ethyl 2,7,7-trimethyl-4-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate under solvent-free conditions (Table 3, entry 2)



Scheme 2 Suggested mechanism for the Hantzsch condensation

formed either through steps I–III or through steps IV–VI. The role of DSIMHS comes in steps I and IV, where it catalyzes the Knoevenagel type coupling of aldehydes with active methylene compounds and in steps III and VI, where it catalyzes the Michael type addition of intermediates 1, 2 and 3, 4 to give the product 5.

Table 3 Comparison of the synthesis of polyhydroquinoline in the presence of different catalysts

Entry	Catalyst	Conditions	Time (min)	Yield (%)	[Refs.]
1	DSIMHS (0.25 mmol)	70 °C, solvent-free	3	93	This work
2	*p*-TSA (10 mol %)	EtOH, ambient temp.	120	90	[29]
3	$Hf(NPf_2)_4$ (1 mol %)	60 °C, $C_{10}F_{18}$	120	96	[52]
4	$PPA\text{-}SiO_2$ (30 mg)	80 °C, solvent-free	45	92	[53]
5	$[TBA]_2[W_6O_{19}]$ (7 mol %)	110 °C, solvent-free	20	95	[54]
6	CAN (10 mol %)	EtOH, ambient temp.	150	90	[55]

In order to show the activity of DSIMHS (Table 3, entry 1) in comparisons with other reported catalysts (Table 3, entry 2–6) for the same reactions, we have summarized some of the results in Table 3. The results indicate that the present method is more effective than the other reports in terms of yield and reaction time.

Conclusion

In conclusion, we have successfully developed a simple and efficient procedure for the synthesis of polyhydroquinoline derivatives from the reaction of different aromatic aldehydes, 1, 3-dicarbonyl compounds (dimedone or 1, 3-cyclohexanedione), ethyl acetoacetate, and ammonium acetate in the presence of little amounts of DSIMHS as an eco-friendly and inexpensive catalyst under solvent-free conditions. The present method offers several advantages including short reaction times, high yield of the products, easy work-up, mild reaction conditions, lower catalytic loading, and ease of separation of the used IL. Also, DSIMHS could be easily recovered and reused at least four times without significant loss of activity.

Acknowledgments The authors acknowledge financial support for this work from the Iran National Science Foundation (INSF) (Grant Number 93014856) and partial support of this work by the Research Council of the University of Guilan. F. Shirini and K. Mohammadi also wish to thank the Sobhandarou Company for the partial facilities.

References

1. G. Guillena, D.J. Ramon, M. Yus, Tetrahedron Asymmetry **18**, 693 (2007)
2. A. Domling, I. Ugi, Angew. Chem. Int. Ed. **39**, 3168 (2000)
3. J. Zhu, H. Bienayme (eds.), *Multicomponent Reactions* (Wiley, Weinheim, 2005)
4. I. Ugi, Pure Appl. Chem. **73**, 187 (2001)
5. C.C.A. Cariou, G.J. Clarkson, M. Shipman, J. Org. Chem. **73**, 9762 (2008)
6. L. Yu, B. Chen, X. Huang, Tetrahedron Lett. **48**, 925 (2007)
7. P.N. Kalaria, S.P. Satasia, D.K. Raval, Eur. J. Med. Chem. **78**, 207 (2014)
8. S.C. Karad, V.B. Purohit, D.K. Raval, P.N. Kalaria, J.R. Avalani, P. Thakor, V.R. Thakkar, RSC Adv. **5**, 16000 (2015)
9. P.P. Mager, R.A. Coburn, A.J. Solo, D.J. Triggle, H. Rothe, Drug Des. Discov. **8**, 273 (1992)
10. A. Sausins, G. Duburs, Heterocycles **27**, 269 (1988)
11. R. Manmhold, B. Jablonka, W. Voigdt, K. Schoenafinger, E. Schraven, J. Med. Chem. **27**, 229 (1992)
12. A.C. Gaudio, A. Korokovas, Y. Takahata, J. Pharm. Sci. **83**, 1110 (1994)

13. D.J. Triggle, in *Comprehensive Medicinal Chemistry*, vol. II, ed. by J.C. Emmet (Pergamon, Oxford, 1990)
14. V. Klusa, Drugs Future **20**, 135 (1995)
15. R.G. Bretzel, C.C. Bollen, E. Maeser, K.F. Federlin, Am. J. Kidney Dis. **21**, 53 (1993)
16. R.G. Bretzel, C.C. Bollen, E. Maeser, Drugs Future **17**, 465 (1992)
17. R. Boer, V. Gekeler, Drugs Future **20**, 499 (1995)
18. Z. Zarnegar, J. Safari, Z. Mansouri, Kafroudi. Catal. Commun. **59**, 216 (2015)
19. V.K. Ahluwalia, B. Goyal, U. Das, J. Chem. Res. (s) **7**, 266 (1997)
20. S. Margarita, O. Estael, V. Yamila, P. Beatriz, M. Lourdes, M. Nazario, Q. Margarita, S. Carlos, L.S. Jose, N. Hector, B. Norbert, M.P. Oswald, Tetrahedron **55**, 875 (1999)
21. A. Hantzsch, Ann. Chem. **1**, 215 (1882)
22. G. Sabitha, G.S.K.K. Reddy, C.S. Reddy, J.S. Yadav, Tetrahedron Lett. **44**, 4129 (2003)
23. N.N. Karade, V.H. Budhewar, S.V. Shinde, W.N. Jadhav, Lett. Org. Chem. **4**, 16 (2007)
24. A. Dondoni, A. Massi, E. Minghini, V. Bertolasi, Tetrahedron **60**, 2311 (2004)
25. L.M. Wang, J. Sheng, L. Zhang, J.W. Han, Z. Fan, H. Tian, C.T. Qian, Tetrahedron **61**, 1539 (2005)
26. M. Maheswara, V. Siddaiah, G.L. Damu, C.V. Rao, ARKIVOC **ii**, 201 (2006)
27. M.M. Heravi, K. Bakhtiri, N.M. Javadi, F.F. Bamoharram, M. Saeedi, H.A. Oskooi, J. Mol. Catal. A Chem. **264**, 50 (2007)
28. S. Ko, C.F. Yao, Tetrahedron **62**, 7293 (2006)
29. S.R. Cherkupally, R. Mekala, Chem. Pharm. Bull. **56**, 1002 (2008)
30. G. Babu, P.T. Perumal, Aldrichimica Acta **33**, 16 (2000)
31. S. Ko, M.N.V. Sastry, C. Lin, C.F. Yao, Tetrahedron Lett. **46**, 5771 (2005)
32. F. Shirini, S.V. Atghia, M.A. Khoshdel, Iran. J. Catal. **1**, 93 (2011)
33. A. Kumar, R.A. Maurya, Tetrahedron Lett. **48**, 3887 (2007)
34. S. Kumar, P. Sharma, K.K. Kapoor, M.S. Hundal, Tetrahedron **64**, 536 (2008)
35. J.B. Sainani, A.C. Shah, V.P. Aray, Indian J. Chem. **33B**, 526 (1994)
36. N.K. Ladani, D.C. Mungra, M.P. Patel, R.G. Patel, Chin. Chem. Lett. **22**, 1407 (2011)
37. A. Kumar, R.A. Maurya, Synlett **6**, 883 (2008)
38. P.T. Anastas, J.C. Warner, *Green Chemistry: Theory and Practice* (Oxford University Press, Oxford, 1998)
39. M. Poliakoff, M.J. Fitzpatric, T.R. Farren, P.T. Anastas, Green Chemistry: Science and Politics of change. Science **297**, 807 (2002)
40. I.T. Horváth, P.T. Anastas, Innovations and green chemistry. Chem. Rev. **107**, 2169 (2007)
41. Z. Chen, Q. Zhu, W. Su, Tetrahedron Lett. **52**, 2601 (2011)
42. H.G.O. Alvim, G.A. Bataglion, L.M. Ramos, A.L. de Oliveira, H.C.B. de Oliveira, M.N. Eberlin, J.L. de Macedo, W.A. da Silva, B.A.D. Neto, Tetrahedron **70**, 3306 (2014)
43. H.G.O. Alvim, T.B. de Lima, H.C.B. de Oliveira, F.C. Gozzo, J.L. de Macedo, P.V. Abdelnur, W.A. Silva, B.A.D. Neto, ACS Catal. **3**, 1420 (2013)
44. R. Fu, Y. Yang, W. Lai, Y. Ma, Z. Chen, J. Zhou, W. Chai, Q. Wang, R. Yuan, Synth. Commun. **45**, 467 (2015)
45. J. Akbari, A. Heydari, H.R. Kalhor, S.A. Kohan, J. Comb. Chem. **12**, 137 (2010)
46. F. Shirini, N.G. Khaligh, S. Akbari-Dadamahaleh, J. Mol. Catal. A Chem. **365**, 15 (2012)
47. F. Shirini, N.G. Khaligh, J. Mol. Liq. **177**, 386 (2013)
48. F. Shirini, A. Yahyazadeh, K. Mohammadi, Chin. Chem. Lett. **25**, 341 (2014)
49. M. Tajbakhsh, H. Alinezhad, M. Norouzi, S. Baghery, M. Akbari, J. Mol. Liq. **177**, 44 (2013)
50. M. Nasr-Esfahani, T. Abdizadeh, Orient. J. Chem. **28**, 1249 (2012)
51. X.L. Zhang, S.R. Sheng, X.L. Liu, X.L. Liu, ARKIVOC **xiii**, 79 (2007)
52. M. Hong, C. Cai, W.B. Yi, J. Fluorine Chem. **131**, 111 (2010)
53. A. Khojastehnezhad, F. Moeinpour, A. Davoodnia, Chin. Chem. Lett. **22**, 807 (2011)
54. A. Davoodnia, M. Khashi, N. Tavakoli-Hoseini, Chin. J. Catal. **34**, 1173 (2013)
55. C.S. Reddy, M. Raghu, Chin. Chem. Lett. **19**, 775 (2008)