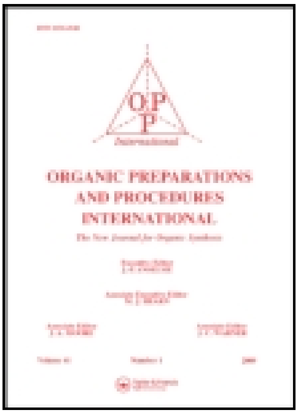


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

Ionic Liquid 3-Methyl-1-sulfonic Acid Imidazolium Chloride as a Novel and Highly Efficient Catalyst for the Very Rapid Synthesis of bis(Indolyl)methanes under Solvent-free Conditions

Mohammad Ali Zolfigol [a], Ardeshir Khazaei [a], Ahmad Reza Moosavi-Zare [a] & Abdolkarim Zare [b]

[a] Faculty of Chemistry, Bu-Ali Sina University, Hamadan, Iran

[b] Department of Chemistry, Payame Noor University (PNU), Iran

To cite this article: Mohammad Ali Zolfigol, Ardeshir Khazaei, Ahmad Reza Moosavi-Zare & Abdolkarim Zare (2010): Ionic Liquid 3-Methyl-1-sulfonic Acid Imidazolium Chloride as a Novel and Highly Efficient Catalyst for the Very Rapid Synthesis of bis(Indolyl)methanes under Solvent-free Conditions, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 42:1, 95-102

To link to this article: http://dx.doi.org/10.1080/00304940903585495

Organic Preparations and Procedures International, 42:95–102, 2010

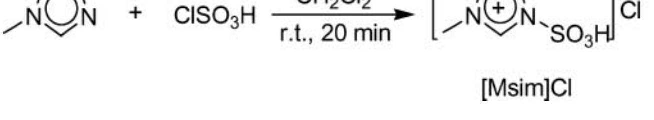
ISSN: 0030-4948 print
DOI: 10.1080/00304940903585495

Ionic Liquid 3-Methyl-1-sulfonic Acid Imidazolium Chloride as a Novel and Highly Efficient Catalyst for the Very Rapid Synthesis of *bis*(Indolyl)methanes under Solvent-free Conditions

Mohammad Ali Zolfigol,[1] Ardeshir Khazaei,[1] Ahmad Reza Moosavi-Zare,[1] and Abdolkarim Zare[2]

[1]Faculty of Chemistry, Bu-Ali Sina University Hamadan, Iran
[2]Department of Chemistry, Payame Noor University (PNU), Iran

The exploitation of ionic liquids as solvents in organic transformations has been reported extensively during the past decade.[1–5] The most useful properties of ionic liquids are the ability to dissolve a wide range of substances, very low vapor pressure, high thermal stability, recyclability, non-flammability, safety and the fact that they can be stored for long times without decomposition.[1–5] Moreover, it is often possible to achieve reactions in ionic liquids that otherwise proceed with great difficulty, or even not at all.[1,2] These green solvents have been also extensively used as catalysts in various organic reactions.[6–17] As part of our ongoing program to extend applications of acidic catalysts and reagents in organic synthesis,[18,19] we have prepared 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} as a new Brønsted acidic ionic liquid, from the simple reaction of 1-methylimidazole with chlorosulfonic acid at room temperature (*Scheme 1*). We believe that this novel ionic liquid can be applied as catalyst in different organic transformations. Herein, we report that *bis*(indolyl)methane derivatives can be very rapidly (nearly immediately) synthesized from indoles and carbonyl compounds in the presence of catalytic amount of [Msim]Cl under solvent-free conditions at room temperature.

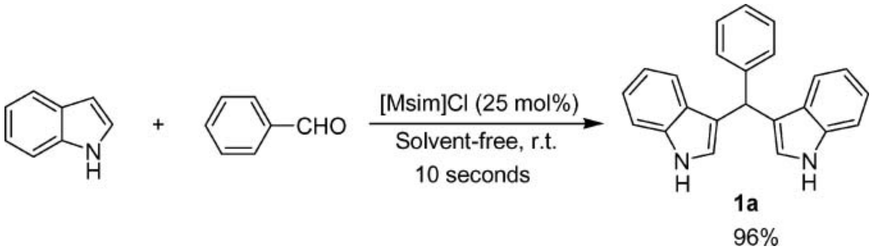


Scheme 1

Solvent-free organic reactions have been used as useful technique in organic synthesis.[20,21] Solid-state protocol often leads to shorter reaction times, higher yields,

Received September 18, 2009; in final form November 27, 2009.
Address correspondence to either Mohammad Ali Zolfigol, Faculty of Chemistry, Bu-Ali Sina University, Hamadan, 6517838683, Iran. E-mail: mzolfigol@yahoo.com or Ardeshir Khazaei, Faculty of Chemistry, Bu-Ali Sina University, Hamadan, 6517838683, Iran. E-mail: Khazaei_1326@yahoo.com

easier work-up, compliance with green chemistry protocols, and may enhance the regio- and stereoselectivity of reactions.[20,21] *bis*(Indolyl)methane derivatives are very important compounds as they display various biological and pharmaceuticals activities.[22–27] Synthesis of *bis*(indolyl)methanes *via* the condensation of indoles with carbonyl compounds is one of the important and well-known transformations in organic synthesis.[28–43] In general, this transformation requires a protic acid[28–32] or a Lewis acid[33–43] to activate carbonyl compounds. For this purpose, several reagents and catalysts such as acetic acid,[28] silica sulfuric acid,[29] $H_3PMo_{12}O_{40}.xH_2O$,[30] HY-Zeolite,[31] $Zn(HSO_4)_2$,[32] $ZrOCl_2.8H_2O$,[33] $AlPW_{12}O_{40}$,[34] $In(OTf)_3$,[35] $Dy(OTf)_3$,[36] $La(PFO)_3$,[37] Zeokarb-225,[38] $MgSO_4$,[39] trityl chloride,[40] P_2O_5/SiO_2,[41] $Zr(DS)_4$[42] and silica chloride[43] have been employed. Moreover, the preparation of *bis*(indolyl)methanes using ionic liquids 1-butyl-3-methylimidazolium bromide (MW, 400 W, 150°C, 6–21 min)[7] and 1-methylimidazolium hydrogen sulfate (or trifluoroacetate) (more than 100 mol% of ionic liquid, r.t., 10–40 min)[8] has been reported. Although various methods on the preparation of *bis*(indolyl)methanes are known, to the best of our knowledge there is no report on the synthesis of these attractive compounds in few seconds. This paper describes the first application of our novel ionic liquid [Msim]Cl as catalyst for the preparation of *bis*(indolyl)methanes *via* the condensation of indoles with aldehydes as well as ketones under solvent-free conditions at room temperature (*Scheme 2*). It is worth noting that this is the first report on the rapid preparation of *bis*(indoly)methanes under extremely mild reaction conditions.



Scheme 2

To optimize the reaction conditions, the synthesis of compound **1a** was selected as a model reaction (*Scheme 2*). Thus to a mixture of benzaldehyde (2 mmol) and 3-methyl-1-sulfonic acid imidazolium chloride (0.5 mmol, 25 mol%) in a mortar was added indole (4.1 mmol), and the resulting mixture was ground vigorously at room temperature; the product was obtained in 96% yield after 10 seconds. Increasing the amount of [Msim]Cl to more than 25 mol% showed no substantial improvement in the reaction results, whereas the yield decreased and the reaction times increased by reducing the amount of the catalyst. To assess the efficiency and the usefulness of [Msim]Cl with respect to known Brønsted acidic ionic liquids, the model reaction was also examined using some of these ionic liquids including $[Hmim]HSO_4$, [Hmim]Tfa, [Hmim]OTs, $[Hmim]BF_4$ and $[Bmim]HSO_4$ as catalysts; the results summarized in Table 1 show that [Msim]Cl afforded **1a** in higher yield and remarkably shorter reaction time.

Indole and 2-methylindole were then treated with structurally diverse aldehydes as well as ketones in the presence of ionic liquid [Msim]Cl under solvent-free conditions at room temperature in order to evaluate the applicability and scope of the catalyst

Table 1

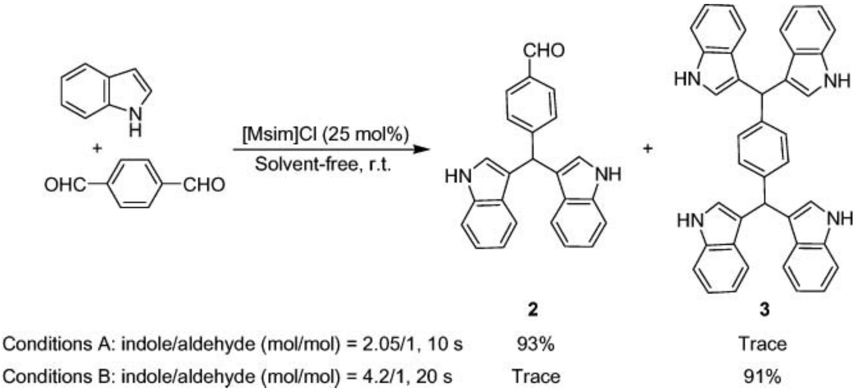
Comparative Condensation of Indole with Benzaldehyde in the Presence of Various Brønsted Acidic Ionic Liquids at Room Temperature

Entry	Ionic Liquid (mol%)	Time	Yield[a] (%)
1	[Msim]Cl (25)	10 sec.	96
2	[Hmim]HSO_4 (111)[8]	15 min.	90
3	[Hmim]HSO_4 (25)	1 hour	78
4	[Hmim]Tfa (102)[8]	10 min.	90
5	[Hmim]Tfa (25)	50 min.	75
6	[Hmim]OTS (25)	5 hrs	65
7	[Hmim]BF_4 (25)	5 hrs.	58
8	[Bmim]HSO_4 (25)	2.5 hrs.	71

[a] Isolated pure product.

(*Table 2*). The data in *Table 2* indicate that indoles were efficiently condensed with all types of aldehydes including aromatic aldehydes bearing electron-withdrawing and electron-releasing substituents, halogens, aliphatic aldehydes as well as ketones, and the desired *bis*(indolyl)methanes were produced in excellent yields within 10–90 seconds.

The condensation of indole with terephthaldehyde was also successfully completed very rapidly in [Msim]Cl. When 2.05 equivalents of indole was treated with terephthalaldehyde, *bis*(indolyl)methane **2** was obtained as the major product while the use of 4.2 equivalents of indole afforded di-*bis*(indolyl)methane **3** as the main product (*Scheme 3*).

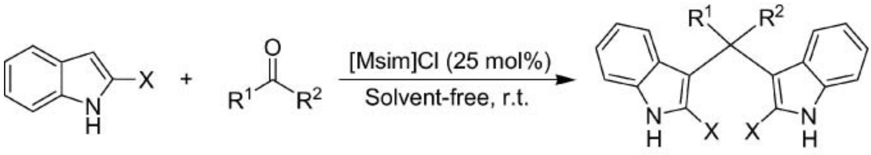


Scheme 3

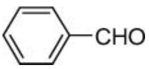
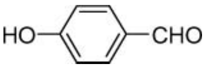
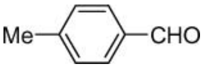
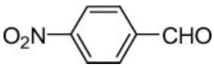
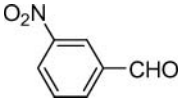
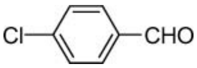
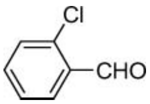
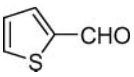
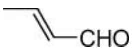
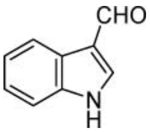
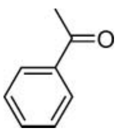
In summary, we have introduced ionic liquid, 3-methyl-1-sulfonic acid imidazolium chloride, as a novel, highly efficient, easily prepared and relatively cheap catalyst in organic synthesis. In this work, this acidic ionic liquid has been used successfully as catalyst for the very rapid synthesis of *bis*(indolyl)methanes *via* the condensation of indoles with aldehydes as well as ketones under solvent-free conditions at room temperature.

Table 2

Synthesis of *bis*(Indolyl)methanes from Indoles and Carbonyl Compounds using [Msim]Cl at Room Temperature



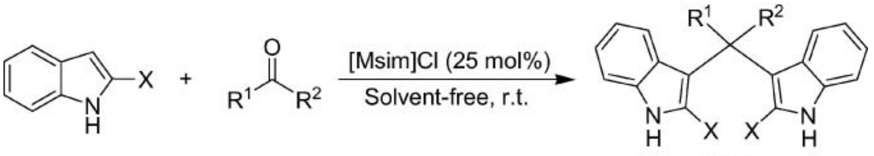
1a-q

Entry	X	Carbonyl Compound	Product[a]	Time (s)	Yield[b] (%)	mp. °C (*lit.*)
1	H		**1a**	10	96	139–141 (140–142)[39]
2	H		**1b**	10	95	119–121 (119–121)[41]
3	H		**1c**	10	93	95–97 (97–99)[29]
4	H		**1d**	10	92	185–187 (178–181)[29]
5	H		**1e**	10	95	217–219 (217–219)[39]
6	H		**1f**	10	90	219–221 (218–220)[39]
7	H		**1g**	10	95	77–79 (78–80)[41]
8	H		**1h**	15	93	74–76 (69–71)[40]
9	H		**1i**	10	94	146–148 (147–149)[41]
10	H		**1j**	15	89	71–73 (71–73)[39]
11	H		**1k**	15	87	127–129 (123–126)[44]
12	H		**1l**	20	91	161, dec. (162, dec.)[41]
13[c]	H		**1m**	90	76	161–164 (165–167)[45]

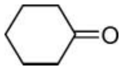
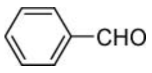
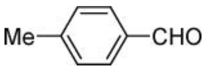
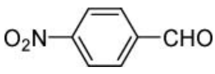
(Continued on next page)

Table 2

Synthesis of *bis*(Indolyl)methanes from Indoles and Carbonyl Compounds using [Msim]Cl at Room Temperature *(Continued)*



1a-q

Entry	X	Carbonyl Compound	Product[a]	Time (s)	Yield[b] (%)	mp. °C (*lit.*)
14[c]	H		**1n**	80	81	163–165 (162–164)[46]
15	Me		**1o**	15	94	245–247 (247–248)[44]
16	Me		**1p**	15	92	175–177 (174–175)[44]
17	Me		**1q**	15	94	239–241 (240–242)[31]

[a] All compounds were identified by comparison of their melting points and NMR data with those in the authentic samples.

[b] Isolated pure product.

[c] This reaction was carried out using 40 mol% of [Msim]Cl.

Experimental Section

All chemicals were purchased from Merck or Fluka Chemical Companies. The progress of the reactions was monitored by thin-layer-chromatography (TLC) using silica gel SILG/UV 254 plates. The ^{1}H NMR (250 MHz) and ^{13}C NMR (62.5 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ) using TMS as an internal standard. Microanalyses were performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Stuart Scientific Apparatus SMP3 (UK) in open capillary tubes.

Procedure for the Preparation of Ionic Liquid [Msim]Cl

A 100 mL round-bottomed flask was charged with 1-methylimidazole (0.410 g, 5 mmol) in dry CH_2Cl_2 (50 mL), and then chlorosulfonic acid (0.605 g, 5.2 mmol) was added dropwise over a period of 5 min at room temperature. Afterward, the reaction mixture was stirred for 20 min, stand for 5 min, and the CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3 × 20 mL) and dried under vacuum to give [Msim]Cl (0.912 g) as a viscous colorless oil.

^{1}H NMR (DMSO-d$_6$): δ 3.77 (s, 3H, CH_3), 7.46 (t, $J = 1.8$ Hz, 1H), 8.84 (t, $J = 1.8$ Hz, 1H), 12.20 (s, 1H), 13.91 (s, 1H); ^{13}C NMR (DMSO-d$_6$): δ 36.5, 120.6, 124.2, 138.6.

Anal. Calcd for $C_4H_7ClN_2O_3S$: C, 24.19; H, 3.55; N, 14.10. Found: C, 24.41; H, 3.69; N, 13.92.

General Procedure for the Synthesis of bis(Indolyl)methanes

To a mixture of carbonyl compound (2 mmol) and [Msim]Cl (0.1 g, 0.5 mmol, 25 mol%) in a mortar was added indole (4.1 mmol), and the resulting mixture was ground at room temperature for 10–90 seconds (*Table 2*). After completion of the reaction, as monitored by TLC, the reaction mixture was extracted with Et_2O (2 × 40 mL). The organic extracts were then combined and washed with saturated solution of $NaHSO_3$ (2 × 30 mL) to remove unreacted aldehyde and then with saturated solution of $NaHCO_3$ (2 × 30 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by recrystallization from EtOAc/petroleum ether (1:2) or plate chromatography on silica gel eluted with EtOAc/petroleum ether (1:2).

Selected Spectral Data of the Products

3-[(1*H*-Indol-3-yl)(phenyl)methyl]-1*H*-indole (1a): Pink solid, mp. 139–141°C (*lit.*[39] 140–142°C); ^{1}H NMR ($CDCl_3$): δ 5.86 (s, 1H, ArCH), 6.66 (s, 2H), 7.11 (t, J = 6.9 Hz, 2H), 7.14–7.22 (m, 3H), 7.28–7.31 (m, 2H), 7.35–7.42 (m, 6H), 7.93 (br, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2.

Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.94; H, 5.82; N, 8.52.

3-[(2-Chlorophenyl)(1*H*-indol-3-yl)methyl]-1*H*-indole (1h): Pink solid, mp. 74–76°C (*lit.*[40] 69–71°C); ^{1}H NMR ($CDCl_3$): δ 6.32 (s, 1H, ArCH), 6.67 (s, 2H), 7.02 (t, J = 7.8 Hz, 2H), 7.10–7.22 (m, 6H), 7.38–7.43 (m, 4H), 7.98 (br, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 37.1, 110.4, 111.6, 119.2, 120.0, 122.4, 123.9, 126.8, 127.3, 128.5, 130.5, 131.4, 135.6, 136.8, 141.5.

Anal. Calcd for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; N, 7.85. Found: C, 77.64; H, 4.94; N, 7.69.

4-[Di(1*H*-indol-3-yl)methyl]benzaldehyde (2): Pink solid, mp. 256°C (dec.) [*lit.*[41] 257°C (dec.)]; ^{1}H NMR ($CDCl_3$): δ 6.08 (s, 1H, ArCH), 6.67 (s, 2H), 6.94–7.01 (m, 4H), 7.21 (d, J = 7.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 7.8 Hz, 2H), 8.02 (br, 2H, NH), 9.68 (s, 1H, O = CH); ^{13}C NMR ($CDCl_3$): δ 36.1, 110.8, 112.4, 119.6, 120.0, 121.5, 124.7, 127.6, 130.0, 130.9, 134.8, 137.9, 146.7, 191.5.

Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 7.99. Found: C, 82.45; H, 5.06; N, 7.83.

Acknowledgements

The authors gratefully acknowledge partial support of this work by the Research Affairs Office of Bu-Ali Sina University (Grant number 32-1716 entitled development of chemical methods, reagent and molecules.), and Center of Excellence in Development of Chemical Method (CEDCM) Hamadan, I.R Iran.

References

1. K. Mikami, “*Green Reaction Media in Organic Synthesis*”, Blackwell Publishing, Oxford, UK, 2005.

2. R. D. Rogers, "*Ionic Liquids As Green Solvents: Progress and Prospects*", American Chemical Society Publication, Washington, 2005.
3. A. Zare, A. Hasaninejad, R. Safinejad, A. R. Moosavi- Zare, A. Khalafi-Nezhad, M. H. Beyzavi, M. Miralai-Moredi, E. Dehghani and P. Kazerooni-Mojarrad, *ARKIVOC*, **xvi**, 51 (2008).
4. A. Zare, A. Hasaninejad, A. R. Moosavi Zare, A. Parhami, H. Sharghi and A. Khalafi-Nezhad, *Can. J. Chem.*, **85**, 438 (2007).
5. A. Zare, A. Hasaninejad, A. Khalafi-Nezhad, A. R. Moosavi Zare and A. Parhami, *ARKIVOC*, **xiii**, 105 (2007).
6. A. Zare, A. R. Moosavi-Zare, A. Hasaninejad, A. Parhami, A. Khalafi-Nezhad and M. H. Beyzavi, *Synth. Commun.*, **39**, 3156 (2009).
7. A. Zare, A. Parhami, A. R. Moosavi-Zare, A. Hasaninejad, A. Khalafi-Nezhad and M. H. Beyzavi, *Can. J. Chem.*, **87**, 416 (2009).
8. M. Dabiri, P. Salehi, M. Baghbanzadeh, M. Shakouri, S. Otokesh, T. Ekrami and R. Doosti, *J. Iran. Chem. Soc.*, **4**, 393 (2007); *Chem. Abstr.*, **150**, 77605 (2009).
9. G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang and D. Sun, *Green Chem.*, **6**, 75 (2004).
10. J. R. Harjani, S. J. Nara and M. M. Salunkhe, *Tetrahedron Lett.*, **43**, 1127 (2002).
11. V. V. Namboodiri and R. S. Varma, *Chem. Commun.*, 342 (**2002**).
12. V. R. Koch, L. L. Miller and R. A. Osteryoung, *J. Am. Chem. Soc.*, **98**, 5277 (1976).
13. D. S. Kim and W. S. Ahn, *Korean J. Chem. Eng.*, **20**, 39 (2003); *Chem. Abstr.*, **139**, 86942 (2003).
14. D. S. Newman, R. E. Winans and R. L. McBeth, *J. Electrochem. Soc.*, **131**, 1079 (1984).
15. C. J. Adams, M. J. Earle, G. Roberts and K. R. Seddon, *Chem. Commun.*, 2097 (**1998**).
16. P. A. Z. Suarez, J. E. L. Dullius, S. Einloft, R. F. de Souza and J. Dupont, *Polyhedron*, **15**, 1217 (1996).
17. H.-P. Zhu, F. Yang, J. Tang, M.-Y. He, *Green Chem.*, **5**, 38 (2003).
18. P. Salehi, M. A. Zolfigol, F. Shirini and M. Baghbanzadeh, *Curr. Org. Chem.*, **10**, 2171 (2006).
19. F. Shirini, M. A. Zolfigol, P. Salehi and M. Abedini, *Curr. Org. Chem.*, **12**, 183 (2008).
20. K. Tanaka, "*Solvent-free Organic Synthesis*", Wiley-VCH, GmbH and KGaA, Weinheim, 2004.
21. A. Loupy, "*Microwave in Organic Synthesis*", Wiley-VCH, Weinheim, 2004.
22. J. J. Michnovicz, H. L. Bradlow, M. J. Huang, T. Osawa, C. T. Ho and R. T. Rosen (editors) "*Food Phytochemicals for Cancer Prevention 1: Fruits and Vegetables*", American Chemical Society, Washington, D.C., 1994.
23. T. Osawa and M. Namiki, *Tetrahedron Lett.*, **24**, 4719 (1983).
24. R. Bell, S. Carmell and N. Sar, *J. Nat. Prod.*, **57**, 1587 (1994).
25. G. Bifulco, I. Bruno, R. Riccio, J. Lavayre and G. Bourdy, *J. Nat. Prod.*, **58**, 1254 (1995).
26. A. Ramirez and S. Garcia-Rubio, *Curr. Med. Chem.*, **10**, 1891 (2003).
27. S. Zhao, X. Liao and J. M. Cook, *Org. Lett.*, **4**, 687 (2002).
28. A. Kamal and A. A. Qureshi, *Tetrahedron*, **19**, 513 (1963).
29. D. M. Pore, U. V. Desai, T. S. Thopate and P. P. Wadgaonkar, *ARKIVOC*, **xii**, 75 (2006).

30. M. A. Zolfigol, P. Salehi and M. Shiri, *Phosphorus, Sulfur, and Silicon*, **179**, 2273 (2004).
31. A. V. Reddy, K. Ravinder, V. L. N. Reddy, T. V. Goud, V. Ravikanth and Y. Venkateswarlu, *Synth. Commun.*, **33**, 3687 (2003).
32. K. Niknam, M. A. Zolfigol, T. Sadabadi and A. Nejati, *J. Iran. Chem. Soc.*, **3**, 318 (2006); *Chem. Abstr.*, **147**, 118094 (2009).
33. H. Firouzabadi, N. Iranpoor, M. Jafarpour and A. Ghadiri, *J. Mol. Cat. A: Chem.*, **253**, 249 (2006).
34. H. Firouzabadi, N. Iranpoor and A. A. Jafari, *J. Mol. Catal. A: Chem.*, **244**, 168 (2006).
35. R. Nagarajan and P. T. Perumal, *Tetrahedron*, **58**, 1229 (2002).
36. X. Mi, S. Luo, J. He and J. P. Cheng, *Tetrahedron Lett.*, **45**, 4567 (2004).
37. L. Wang, J. H. Han, T. Sheng, J. Z. Fan and X. Tang, *Synlett*, 337 (**2005**).
38. C. J. Magesh, R. Nagarajan, M. Karthik and P. T. Perumal, *Applied Catal. A: General*, **266**, 1 (2004).
39. A. Hasaninejad, A. Parhami, A. Zare, A. Khalafi-Nezhad, A. Nasrolahi Shirazi and A. R. Moosavi Zare, *Polish J. Chem.*, **82**, 565 (2008); *Chem. Abstr.*, **150**, 168107 (2009).
40. A. Khalafi-Nezhad, A. Parhami, A. Zare, A. R. Moosavi Zare, A. Hasaninejad and F. Panahi, *Synthesis*, 617 (**2008**).
41. A. Hasaninejad, A. Zare, H. Sharghi, K. Niknam and M. Shekouhy, *ARKIVOC*, **xiv**, 39 (2007).
42. M. A. Zolfigol, P. Salehi, M. Shiri and Z. Tanbakouchian, *Catal. Commun.*, **8**, 173 (2007).
43. A. Hasaninejad, A. Zare, H. Sharghi, M. Shekouhy, R. Khalifeh, A. Salimi Beni and A. R. Moosavi Zare, *Can. J. Chem.*, **85**, 416 (2007).
44. M. L. Deb and P. J. Bhuyan, *Tetrahedron Lett.*, **47**, 1441 (2006).
45. X. Zeng, S. Ji and S. Wang, *Tetrahedron*, **61**, 10235 (2005).
46. J.-T. Li, H.-G. Dai, W.-Z. Xu and T.-S. Li, *Ultrason. Sonochem.*, **13**, 24 (2006).