Journal of Current Chemical & Pharmaceutical Sciences

J. Curr. Chem. Pharm. Sc.: 2(4), 2012, 367-374
ISSN 2277-2871

ONE POT SYNTHESIS OF ANTIMICROBIAL ACTIVE NEW 2-BENZIMIDAZOLESULFONAMIDE DERIVATIVES FROM 2-MERCAPTOBENZIMIDAZOLE

P. B. GOREPATIL, Y. D. MANE, V. S. SURYAWANSHI, V. S. SHINDE and V. S. INGLE*

Research Centre, Department of Chemistry, Shri Chhatrapati Shivaji College,
OMERGA – 413606, Dist-Osmanabad (M.S.) INDIA

(*Received : 06.11.2012; Accepted : 14.11.2012*)

ABSTRACT

The H_2O_2–PCl_5 reagent system has been found to be an efficient reactive reagent for the one pot conversion of 2-mercaptobenzimidazole to 2-benzimidazolesulfonyl chloride with high purity. 2-Benzimidazolesulfonyl chloride on reaction with aromatic amines in the same pot results in the formation of corresponding new2-benzimidazolesulfonamides derivatives in excellent yields and in short reaction time.

Key words: 2-Mercaptobenzimidazole, 2-Benzimidazolesulfonamides, Oxidative–Chlorination, Antimicrobial Activity.

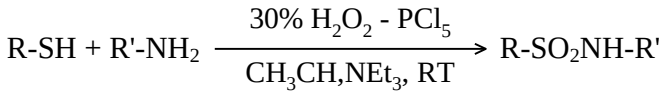
INTRODUCTION

The search of simple, efficient, economical, cascade and eco-friendly chemical processes or methodologies for synthesis of potent organic compounds from easily available reagent is one of the major challenges for an organic chemist. Extensive biochemical and pharmacological studies have confirmed that benzimidazole molecules are effective against various strains of microorganisms[1-7]. Benzimidazole are regarded as a promising class of bioactive heterocyclic compounds that exhibit a wide range of biological activities. Specifically, this nucleus, a constituent of vitamin-B_{12}[8]. 2-mercapto-benzimidazole derivative is one of the most important derivatives of benzimidazole exhibiting a wide variety of interesting biological activities such as antimicrobial[9] and neutropic[10] activities.

The sulfonamide functional group has a long and rich history in organic chemistry and drug discovery. Sulfonamides remain a particularly important class of compound for the treatment of infectious diseases[11-16] and used as anti-inflammatory, anticancer and antiviral agents[17-19]. Over 30 drugs containing this functionality are in clinical use including, antibacterial, diuretics, anticonvulsants, hypoglycemic and HIV protease inhibitors[20]. More recently, sulfonamides have been found to be potent cysteine protease inhibitors, which could possibly extend their therapeutic applications to include conditions such as Alzheimer's disease, arthritis and cancer[21]. Sulfonamides are among the most widely used antibacterial agents in the world, chiefly because of their low cost, low toxicity and excellent activity against common bacterial diseases[22].

Available online at www.sadgurupublications.com
*Author for correspondence; E-mail: gorepatilpratap1986@gmail.com, inglevilas71@yahoo.in, maneyd@gmail.com;
Ph.: +91 9404676129; Fax: +912475 252020

There are various synthetic methods available for the preparation of sulfonamides[23-35]. The most common involve nucleophilic attack by ammonia or primary or secondary amines on sulfonyl chloride in the presence of a base. Although this method is efficient, it is limited by the formation of undesired di-sulfonamides with primary amines and by the need of drastic reaction conditions for less nucleophilic amines such as aniline. It also requires the availability of sulfonyl chlorides, some of which are difficult to store and handle. In view of the above limitations and due to the versatile biological activity of sulfonamides, their synthesis under mild reaction conditions is a field of growing research interest. Here in, we have introduced a useful one-pot method for the synthesis of some benzimidazole derivatives through the conversion of 2-mercaptobenzimidazole into 2-benzimidazole sulfonylchloride and their transformation to a new heterocyclic system such as N-(4-Methoxyphenyl)-1H-benzo[d] imidazole-2-sulfonamide. The route for the synthesis of sulfonamide is as shown below (Scheme 1).



R-SH = 2-Mercaptobenzimidazole

R' = Aryl groups

Scheme 1

EXPERIMENTAL

All used chemicals were of AR grade. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform using tetramethylsilane as an internal standard. IR spectra were acquired on a Bruker FT-IR spectrometer. Elemental analyses were carried out with a Perkin Elmer model 240-C apparatus. The progress of the reactions was monitored by TLC on silica gel GF254 using ethyl acetate as eluent.

General procedure for the synthesis of 2-benzimidazolesulfonamides

A mixture of 2-mercaptobenzimidazole (1 mmole), 30% H_2O_2 (3 mmoles) and PCl_5 (1 mmole) was stirred in acetonitrile at room temperature for an appropriate time. After consumption of the thiol as indicated byvTLC, a solution of aromatic amines (1 mmole) in triethylamine (0.5 mL) was added. The resulting mixture was stirred at room temp. When TLC showed complete disappearance of starting material and then mixture was acidified with 2 N HCl and extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The filtrate was evaporated and the corresponding pure sulfonamides were obtained as a crystalline solid, which on recrystallization from a mixture of ethanol and water affords analytically pure products. The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR. The spectral and analytical data of compounds are as follows.

(1) N-(p-tolyl)-1H-benzo[d] imidazole-2-sulfonamide (Entry 1)

M.P. = 159^{o}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.52 (s, 3H), 5.90 (s, 1H, N-H), 7.04 (d, 2H), 7.08 (d, 2H), 7.17 (d, 2H), 7.14 (d, 2H), 9.26 (S, 1H).

^{13}C NMR (50 Hz, $CDCl_3$) δ 39.30, 122.18, 122, 132.23, 132.23, 143.12.

IR Spectra-1150 cm^{-1}, 1700 cm^{-1}, 1450-1650 cm^{-1}, 3000 cm^{-1}, 3608 cm^{-1}.

Anal. Calculated for $C_{14}H_{13}N_3SO_2$: C- 58.53, H-4.52, N-14.63.

Found: C-58.50, H-4.48, N-14.60.

(2) N-(4-Methoxyphenyl)-1H-benzo[d]imidazole-2-sulfonamide (Entry 2)

M.P. = 205-210^{o}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 4.6 (s, 1H), 5.5 (s, 1H), 6.71 (d, 2H), 6.91 (d, 2H), 7.20 (d, 2H), 7.57 (d, 2H).

^{13}C NMR (50 Hz, $CDCl_3$) δ 55.1, 115.5, 115.2, 122.5, 123.5, 131, 139, 142,152.8

IR Spectra-1145 cm^{-1}, 1710 cm^{-1}, 1420-1610 cm^{-1}, 3100 cm^{-1}, 3508 cm^{-1}.

Anal. Calculated for $C_{14}H_{13}N_3SO_3$: C- 55.45, H-04.30, N-13.86.

Found : C-55.44, H- 04.28, N-13.84.

(3) N-(o-Tolyl)-1H-benzo[d]imidazole-2-sulfonamide (Entry 3)

M.P. = 165-168^{o}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 4.2 (s, 1H), 5.4 (s, 1H), 6.20-7.12 (m, 4H), 7.20 (d, 2H), 7.57 (d, 2H).

^{13}C NMR (50Hz, $CDCl_3$) δ 17.3, 122, 122.2, 138.5, 140.4, 135.7, 125.2, 127.5, 130.3, 133.2

IR Spectra-1147 cm^{-1}, 1705 cm^{-1}, 1450-1650 cm^{-1}, 2950 cm^{-1}, 3350 cm^{-1}.

Anal. Calculated for $C_{14}H_{13}N_3SO_2$: C-58.54, H-04.53, N-14.63.

Found: C-58.53, H-04.53, N-14.62.

(4) N-(4-Bromophenyl)-1H-Benzo[d] imidazole-2-sulfonamide (Entry 4)

M.P. = 162^{o}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 5.90 (s, 1H, N-H), 7.51 (d, 2H, J = 9Hz), 7.65 (d, 2H, J = 9Hz), 7.75 (d, 2H, J = 8Hz), 8.01 (d, 2H, J = 8Hz), 9.28 (s, 1H, -NH).

^{13}C NMR (50 Hz, $CDCl_3$) δ, 122.18, 122, 132.23, 132.23, 140.2, 143.12.

IR Spectra-1145 cm^{-1}, 1715 cm^{-1}, 1450-1650 cm^{-1}, 2800 cm^{-1}, 3008 cm^{-1}.

Anal. Calculated for $C_{13}H_{10}N_3SO_2Br$: C- 44.32, H-2.84, N-11.93.

Found: C-44.1, H-2.7, N-11.80.

(5) N-(2-Nitrophenyl)-1H-benzo[d]imidazole-2-sulfonamide (Entry 8)

M.P. = 180^{o}C. ^{1}H NMR (200 MHz, $CDCl_3$): δ, 6.10 (s, 1H), 7.55 (d, 2H), 7.65 (d, 2H), 6.70-7.95 (m, 4H), 9.21 (S, 1H).

^{13}C NMR (50 Hz, $CDCl_3$) δ 114.3, 118.2, 120.7, 122.9, 124.0, 135.86, 136.7, 138.9, 142.5, 141.8.

IR Spectra-1140 cm^{-1}, 1710 cm^{-1}, 1450-1650 cm^{-1}, 2950 cm^{-1}, 3350 cm^{-1}, 1300-1550 cm^{-1}.

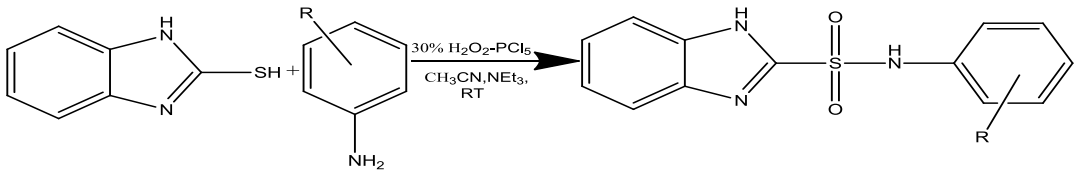
Anal. Calculated for $C_{13}H_{10}N_4SO_4$: C- 49.05, H-3.14, N-17.61.

Found: C-49.01, H-3.10, N-17.50.

RESULTS AND DISCUSSION

Here, it was observed that the H_2O_2-PCl_5 reagent system can be used for the oxidative-chlorination of thiols into sulfonyl chloride, which are important synthetic precursors. Our aim is to develop new route for synthesis of new 2-benzimidazolesulfonamide (Table 1, Entry 01-10). We report here a new, mild, efficient, one pot synthesis of such compounds via the reaction of amines with 2-mercaptobezimidazole in the presence of H_2O_2-PCl_5 reagent system in acetonitrile at room temperature. PCl_5 was used because of its low cost and easily available selective chemical reagent, which play very important roles in organic synthesis, but it has not been studied as promoter in the conversion of thiols to sulfonamides until now. To the best of our knowledge such a reagent system for the preparation of sulfonamides has not been described in the literature.

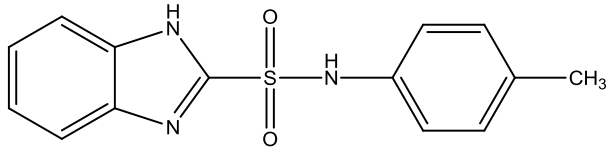
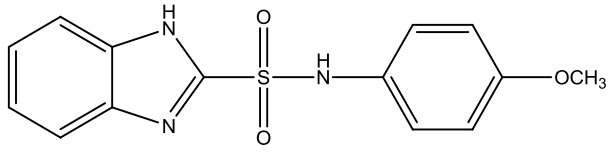
To optimize the reaction conditions, 2-mercaptobenzimidazole and 4-methyl aniline were used as model substrate. Good results were obtained, when reactions was carried out using 3 moles of 30% H_2O_2, 1 mole of 2-mercaptobenzimidazole and 1 mole of PCl_5 at room temperature in acetonitrile solvent. This reagent system was found to be fruitful for both electron donating and electron withdrawing aromatic thiols with high yield and short reaction time (Scheme 2). Some results are shown in Table 1.

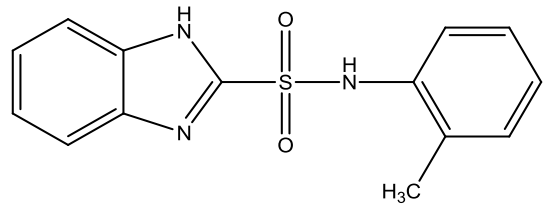
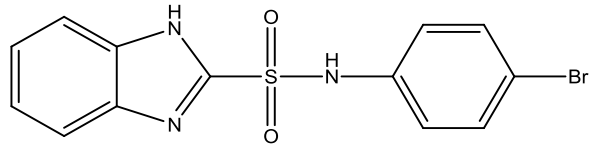


R=Alkyl,Hydroxy,Halide,Methoxy,Niro etc.

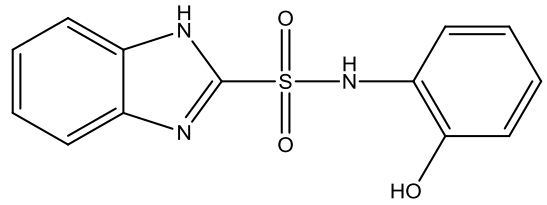
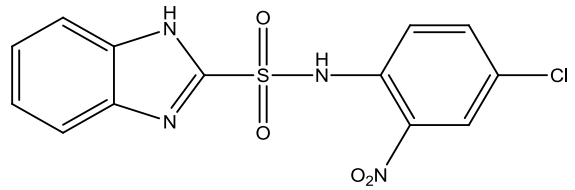
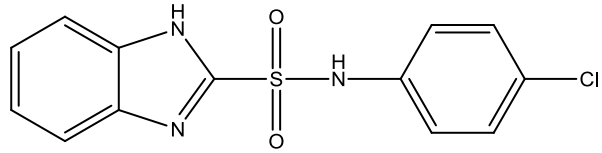
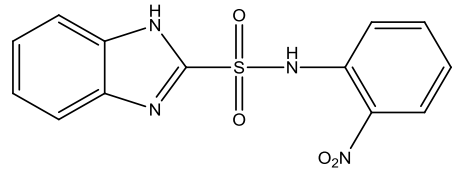
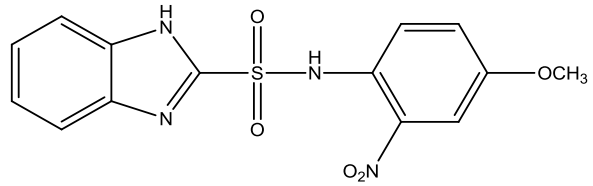
Scheme 2

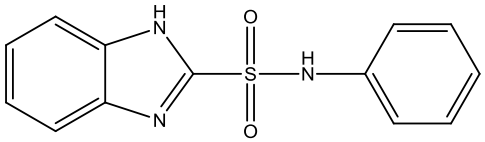
Table 1: Formation of 2-benzimidazolesulfonamides from 2-mercaptobenzimidazole and various aromatic amines

Entry	Structure and name of products	Final product Time (min.)	Yield (%)
1.	 *N*-(*p*-Tolyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	15	94
2.	 *N*-(4-Methoxyphenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	14	98

3.	 *N*-(*o*-Tolyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	17	95
4.	 *N*-(4-Bromophenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	16	97

Cont…

Entry	Structure and name of products	Final product Time (min.)	Yield (%)
5.	 *N*-(2-Hydroxyphenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	15	94
6.	 *N*-(4-Chloro-2-nitrophenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	18	93
7.	 *N*-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	16	96
8.	 *N*-(2-Nitrophenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	19	95
9.	 *N*-(4-Methoxy-2-nitrophenyl)-1*H*-benzo[*d*]imidazole-2-sulfonamide	16	97

10.	 *N*-Phenyl-1*H*-benzo[*d*]imidazole-2-sulfonamide	15	98

* Purity of products was checkedby TLC and all synthesized compounds were characterized by M.P., IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.* Yield refers to pure isolated product

The new 2-benzimidazolesulfonamide derivatives were screened for their antimicrobial activity. The antimicrobial activity was tested by Disc diffusion method by department of Biotechnology sub campus Dr. B. A. M. University, Aurangabad. Compounds were tested at 15 µg/mL concentration and minimum inhibition concentration was determined. Ampicillin was taken as standard for antibacterial screening. After screening five products (Table 1, Entry 1 – 5) out of them, first three sulfonamides show good biological activity against various bacteria. The details are given in Table 2.

Table 2

S. No.	Organisms	Gram nature	Compounds (Diameter of zone of inhibition)				
			1	**2**	**3**	**4**	**5**
1	*Escherichia coli*	Gm –ve	Below 5 mm	6 mm	6 mm	Below 5 mm	Below 5 mm
2	*Salmonella typhi*	Gm –ve	6 mm	7 mm	7 mm	6 mm	6 mm
3	*Azotobacter sp.*	Gm –ve	7 mm	6 mm	Below 5 mm	Below 5 mm	Below 5 mm
4	*Proteus vulgaris*	Gm –ve	6 mm	6 mm	Below 5 mm	Below 5 mm	6 mm
5	*Erwinia sp.*	Gm –ve	Below 5 mm	Below 5 mm	7 mm	Below 5 mm	Below 5 mm
6	*Staph. Aureus*	Gm +ve	6 mm	6 mm	6 mm	6 mm	Below 5 mm
7	*Bacillus sp.*	Gm +ve	Below 5 mm	6 mm	6 mm	Below 5 mm	6 mm

CONCLUSION

We have found simple, efficient, economical and one pot methodology for synthesis of antimicrobial active new 2-benzimidazolesulfonamide derivatives from 2-mercaptobenzimidazole and aromatic amines using H_2O_2-PCl_5. The protocol offers several advantages such as good yield of product and very short reaction times at room temperature. This reaction is very easy to handle, environmentally safe and less costly. Further investigation into the scope and synthetic applications of this reaction is currently under investigation in our laboratory.

ACKNOWLEDGEMENT

One of the author Mr. P. B. Gorepatil is thankful to the CSIR-New Delhi for financial support, Dr. N. D. Shinde (Principal, S. C. S. College, Omerga.) and Dr. Arun Kharat (Director, Dept. of Biotechnology, Dr. B. A. M. University, Sub-campus, Osmanabad) for partial support for this work.

REFERENCES

1. Z. Kazimierczuk, J. A. Upcroft, P. Upcroft, A. Gorska, B. Starosciak and A. Laudy, Acta Biochim. Pol., **49**, 185-195 (2002).
2. H. Goker, C. Kus, D. W. Boykin, S. Yildiz and N. Altanlar, Bioorg. Med. Chem., **10(8)**, 2589-2596 (2002).
3. V. Klimesova, J. Koci, M. Pour, J. Stachel, K. Waisser and J. Kaustova, Eur. J. Med. Chem., **37(5)**, 409-418 (2002).
4. M. Boiani and M. Gonzalez, Mini-Rev. Med. Chem., **5**, 409-424 (2005).
5. K. G. Desai and K. R. Desai, Bioorg. Med. Chem., **14**, 8271-8279 (2006).
6. B. G. Mohammad, M. A. Hussien, A. A. Abdel-Alim and M. Hashem, Arch. Pharm. Res., **29**, 26-33 (2006).
7. O. Ozel Guven, T. Erdogan, H. Goker and S. Yildiz, Bioorg. Med. Chem. Lett., **17**, 2233-2236 (2007).
8. M. J. O'Neil, M. Smith and P. E. Heckelman, The Merck Index, 13th Edition, Merck & Co. Inc., NJ. Monograph Number: 10074 (2001) p. 1785.
9. V. A. Mauro, H. C. Silvia, V. A. Joao and V. N. S. Marcus, J. Sulfur Chem., **28**, 17 (2007).
10. E. V. Bakhareva, M. G. Voronkov, M. S. Sorokin, V. A. Lopyrev, S. B. Seredenin and S. B. Gaidarov, Pharmaceut. Chem. J., **30**, 89-91 (1996).
11. R. Pandya, T. Murashima, L. Tedeschi and A. G. M. Barrett, J. Org. Chem., **68(21)**, 8274 (2003).
12. W. Sneader, Drug Discovery: A History, John Wiley and Sons: West Sussex (2005).
13. W. I. EI-Atrouni, Z. Temesgen, Drugs Today, **43**, 671-679 (2007).
14. D. L. N. G. Surleraux, A. Tahri, W. G. Verschueren, G. M. E. Pille, H. A. De Kock, T. H. M. Jonckers, A. Peeters, S. De Meyer, H. Azijn, R. Pauwels, M. De Bethune, N. M. King, M. Prabu-Jeyabalan, C. A. Schiffer, P. B. T. P. Wigerinck, J. Med. Chem, **48**, 1813-1822 (2005).
15. C. T. Supuran, A. Casini and A. Scozzafava, Med. Res. Rev., **23(5)**, 535 (2003).
16. A. Scozzafava, T. Owa, A. Mastrolorenzo and C. T. Supuran, Curr. Med. Chem., **10**, 925 (2003).
17. A. Kleemann, J. Engel, B. Kutscher, D. Reichert, Eds., Pharmaceutical Substances, Syntheses, Patents, Applications, Thieme, Stuttgart (1999).
18. W. R. Roush, S. L. Gwaltney, J. Cheng, K. A. Scheidt, J. H. McKerrow, E. J. Hansell, Am. Chem. Soc., **120**, 10994 (1998).
19. W. R. Roush, J. Cheng, B. Knapp- Reed, A. Alvarez-Hernandez, J. H. McKerrow, E. Hansell, J. C. Engel, Bioorg. Med. Chem. Lett., **11**, 2759 (2001).
20. N. Ozbek, H. Katırcıoğlu, N. Karacan and T. Baykal, Bioorg. Med. Chem., **15**, 5105 (2007).
21. Y. Gareau, J. Pellicelli, S. Laliberte and D. Gauvreau, Tetrahedron Lett., **44**, 7821 (2003).

22. G. Blotny, Tetrahedron Lett., **44**, 1499 (2003).
23. A. Meinzer, A. Breckel, B. A. Thaher, N. Manicone and H. H. Otto, Helv. Chim. Acta., **87**, 90 (2004).
24. A. Nishiguchi, K. Maeda and S. Miki, Synthesis, 4131 (2006).
25. G. K. S. Prakash, T. Mathew, C. Panja and G. A. Olah, J. Org. Chem., **72**, 5847 (2007).
26. C. Wang, C. Hamilton, P. Meister and C. Menning, Organic Process Researchand Development, **11**, 52-55 (2007).
27. K. Bahrami, M. M. Khodaei and M. Soheilizad, J. Org. Chem., **74**, 9287-9291 (2009).
28. K. Bahrami, M. M. Khodaei and M. Soheilizad, Tetrahedron Lett., **51**, 4843-4846 (2010).
29. J. Humljan and S. Gobec, Tetrahedron Lett., **46(23)**, 4069-4072 (2005).
30. S. W. Wright and K. N. Hallstrom, J. Org. Chem., **71(3)**, 1080-1084 (2006).
31. J. D. Wilden, Synthesis of Functionalized Sulfonamide Libraries: The Application of Microwave Technology to Organic Chemistry (2005).
32. J. D. Bonk, D. T. Amos and S. J. Olson, Synth. Comm., **37(12)**, 2039-2050 (2007).
33. O. Chantarasriwong, D. O. Jang and W. Chavasiri, Tetrahedron Lett., **47**, 7489-7492 (2006).
34. A. R. Massah, S. Sayadi and S. Ebrahimi, RSC Adv., **2**, 6606 (2012).
35. K. Bahrami, M. M. Khodaei and J. Abbasi, Tetrahedron, **68(25)**, 5095-5101 (2012).