An efficient protocol for the synthesis of 4-arylmethylidene-2-phenyl-5(4*H*)-imidazolones using $HClO_4$-SiO_2 as a heterogeneous catalyst under solvent-free conditions

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Abstract: An efficient protocol for the synthesis of 4-arylmethylidene-2-phenyl-5(4*H*)-imidazolones using $HClO_4$-SiO_2 under solvent free conditions is described. The catalyst works under heterogeneous conditions and can be recycled. Antibacterial and antifungal activities performed for the all synthesized compounds.

IndexTerms - Imidazolones, $HClO_4$-SiO_2, heterogeneous recyclable catalyst

INTRODUCTION

Imidazolones have elicited considerable interest among medicinal chemists because these are privileged in many pharmaceutical agents as well as in natural products.[1] The imidazole ring is the key moiety in numerous biologically active compounds because these are importnat in many biological properties such as anti-HIV,[2] Antibacterial,[3] Anti-inflammatory,[1c] antifungal,[4] anticancer,[5] and immunomodulatory activities.[6] Moreover, these scaffolds can also act as intermediates in the synthesis of many natural products, such as biotin,[7] slagenins,[8] axinihydantoins,[9] and oroidin-derived alkaloids.[10] These types of compounds are also known as plant growth regulators and therapeutic agents [11]and act as the chromophores of the some fluorescent proteins.[12] Owing to their significant utility in the fields of medicine, industry, and synthetic organic chemistry, the development of efficient methods for the synthesis of quinolines is highly desirable. The most simple and straightforward method for the synthesis of these compounds is by heating a mixture of 5-oxazolones derivatives with differently substituted aromatic or aliphatic amines in the presence of excess of pyridine for 10-15 h.[13] Various solvents such as benzene, dioxane and acetone used by condensing glycine ester of acetimidic or phenylacetimidic acid,[14] but these methods are associated with harsh reaction conditions and side reactions. Recently, imidazolones were also synthesized by using microwave irradiations.[15] However, most of the methods suffered from certain drawbacks such as drastic conditions, long reaction times, unsatisfactory yields, difficulties in work up, and the use of stoichiometric quantities of the reagents. So although different methods are available for the synthesis of imidazolones, development of an efficient and high-yielding preparation is still of great importance. To the best of our knowledge, no method has been reported for the synthesis of 4-arylmethylidene-2-phenyl-5(4*H*)-imidazolones using silica-supported perchloric acid ($HClO_4$-SiO_2) as a heterogeneous catalyst.

EXPERIMENTAL

Materials and Methods

Melting points were recorded on a Mel-Temp melting point apparatus, in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer BX1 FTIR Spectrophotometer and ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer using TMS as internal standard and the values for chemical shifts (δ) being given in ppm and coupling constants (J) in Hertz (Hz). Mass spectra were recorded on an Agilent 1100 LC/MSD. Acme silica gel G and silica gel (100–200 mesh) were used for analytical TLC and column chromatography, respectively. Other chemicals were purchased from Sigma Aldrich and used without further purification.

Synthesis of 4-arylmethylidene-2-phenyl-5(4H)-imidazolones

A mixture of 4-arylmethylidene-2-phenyl-5(4*H*)-oxazolones (1 mmol), substituted aromatic amines (1.1 mmol) and catalytic amount of $HClO_4$-SiO_2 were stirred at 160 °C for specified time (table 2). The completion of reaction was monitored by TLC. Then the reaction mixture was cooled and poured into cold ethyl alcohol (30 mL). The resultant solids were collected and washed with water. Then the solid was crystallized by ethanol, filtered and on drying to give the desired imidazolones. The characterization data for the selected compounds are given below.

1-(4-Methyl phenyl)-2-phenyl-4 (4'-methoxy benzylidene) – imidazole -5-one (***3c***): [Yield: 90 %]; M. p. 206-208 °C; IR (KBr) $^{\nu}$max / cm^{-1}: 1713, 1638, 1597, 1510, 1374, 1256, 1164, 771. ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 8.27 (2H, d, J = 8.8 Hz), 7.58 (2H, d, J = 7.2 Hz), 7.40 (1H, d, J = 7.6 Hz), 7.32 (2H, dd, J = 7.6, 7.2 Hz), 7.29 (1H, s), 7.21 (2H, d, J = 8.4 Hz), 7.05 (2H, d, J = 8.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 3.87(3H, s), 2.38(3H, s); ^{13}C-NMR (400 MHz, $CDCl_3$, δ, ppm): 21.2, 55.4, 114.4, 127.1, 127.5, 128.2, 129.1, 129.2, 131.0, 132.3, 134.6, 136.9, 138.2, 159.4, 161.6, 170.7; LCMS (*m/z*) 368 [M $^{+}$]; Anal. Calcd. for C_{24} H_{20} N_2O_2: C-78.24; H-5.47; N-7.60; Found: C-78.18; H-5.52; N-7.54.

1-(4-Bromo phenyl)-2-phenyl-4 (4'-methoxy benzylidene) – imidazole -5-one (***3d***): [Yield: 90 %]; M. p. 173-175 °C; IR (KBr) $^{\nu}$max / cm^{-1}: 1713, 1638, 1597, 1490, 1372, 1257, 1166, 769. ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 8.27 (2H, d, J = 8.8 Hz), 7.54 (2H, d, J = 7.2 Hz), 7.53 (2H, d, J = 8.8 Hz), 7.44 (1H, d, J = 7.6 Hz), 7.35 (2H, dd, J = 7.6, 7.2 Hz), 7.31 (1H, s), 7.05 (2H, d, J = 8.8 Hz), 6.98 (2H, d, J = 8.8 Hz), 3.88(3H, s); ^{13}C-NMR (400 MHz, $CDCl_3$, δ, ppm): 55.4, 114.4, 112.0, 127.3, 128.4, 128.8, 128.9, 129.1, 129.9, 131.2, 132.5, 133.9, 134.7, 136.5, 158.7, 161.8, 170.1; LCMS (*m/z*) 433 [M $^{+}$]; Anal. Calcd. for C_{23} $H_{17}BrN_2O_2$: C-63.75; H-3.95; Br-18.44; N-6.47; Found: C-63.69; H-4.09; Br-18.39; N-6.40.

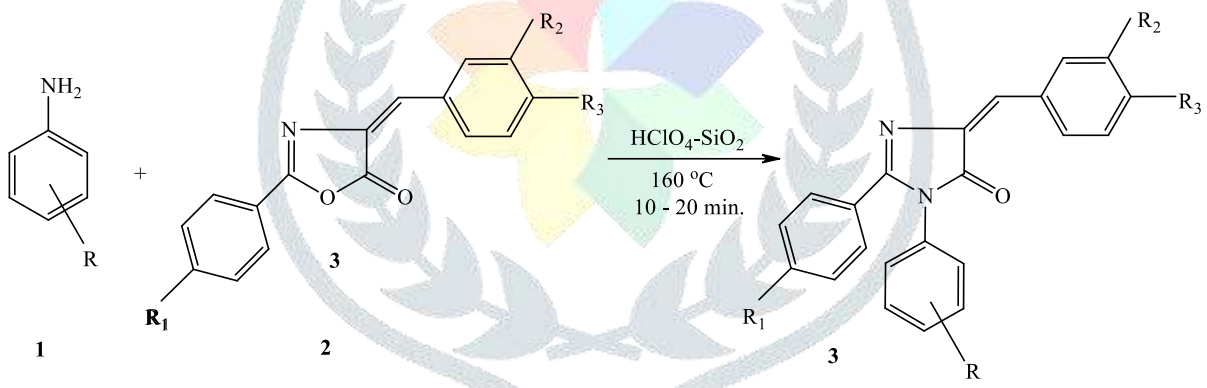
Measurement of antimicrobial activity using Kirby Bauer disc diffusion method: Meuller-Hinton agar media was prepared and poured into sterile petri plates. The plates were inoculated with 100 µl of the test organisms *E. coli* (MTCC 6365), *S. aureus* (MTCC 7443), *B. subtilis* (MTCC 8141) *Proteus vulgaris* (NCIM 2813) *A. niger* (MTCC 6484) and *S. cerevisiae* (MTCC 463) incubated at 37 °C – 24 hrs for bacteria

and 28 °C – 48 hrs for fungi. The diameters of inhibition zones were measured in millimeters. Standard disc of Ampicillin (antibacterial agent) and Fluconazol B (antifungal agent) served as positive controls for activity, but filter disc impregnated with 10 µl of DMSO was used as negative control. Blank paper disks with diameter 8.0 mm were impregnated with 10 µl of test compound and placed on the agar plates. The chemical diffuses from the disc onto the agar. If the organisms is susceptible to the compound it will not grow in the area around the disc is known as " Zone of Inhibition" which is measured.

RESULTS AND DISCUSSION

Chemistry

In recent years the use of heterogeneous catalysts has gained tremendous interest in different areas of organic synthesis.[16] These catalysts are having more advantageous over conventional homogeneous catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be re-used after activation or without activation, thereby making the process more economically viable. As a part our endeavours towards the development of efficient and eco-friendly synthetic methodologies,[17] here, we have reported an efficient silica-supported perchloric acid ($HClO_4$-SiO_2) catalysed synthesis of imidazolones (Scheme 1).



Scheme 1: Synthesis of 4-arylmethylidene-2-phenyl-5(4*H*)-imidazolones using $HClO_4$-SiO_2

In order to investigate the reaction conditions for the synthesis of imidazolones (**3)**, we have chosen the reaction of readily available aniline **(1a)** with 4-(*p*-methoxyphenyl) methylidene-2-phenyloxazol-5(4*H*)-one (**2a)** as a model reaction. A series of 4-arylmethylidene-2-phenyl-5(4*H*)-oxazolones were synthesized by the reported literature procedure.[18] Thus, aniline (1.1 mmol) **(1a)** was treated with 4-(*p*-methoxyphenyl) methylidene-2-phenyloxazol-5(4*H*)-one (**2a)** at 100 °C in the presence of $HClO_4$-SiO_2 under solvent free conditions. It was found that the reaction led to desired **3a** with an yield of 45% after 3 h (Table 1, entry 1). Then we optimized the reaction conditions to increase the yield of the product and to reduce the reaction time. Thus, temperature was initially increased to 120 °C and then to 160 °C, correspondingly yields were

75 and 90% (Table 1, entries 2 & 3), respectively. When the temperature was further increased to 160 °C and 180 °C, no improvement but a slight lowering in the yield was observed (Table 1, entry 4). Further it was observed in our investigations that when the reaction temperature was increased to 160 °C, surprisingly, the reaction was completed within 5 min. In order to determine the potency of $HClO_4$-SiO_2 as catalyst, the same reaction was carried out with various heterogeneous catalysts under similar experimental conditions. The results summarized in Table 1 (entries 5–8) revealed that these heterogeneous catalysts afforded comparatively lower yields of the desired product, even with high catalyst loadings, while very low yield of the product was obtained without any catalyst (Table 1, entry 9). Moreover, $HClO_4$-SiO_2 catalyst was recovered, activated and reused for three consecutive times with only slight variation in the yields of the products (93, 92, and 90%).

Table 1: Effect of reaction conditions

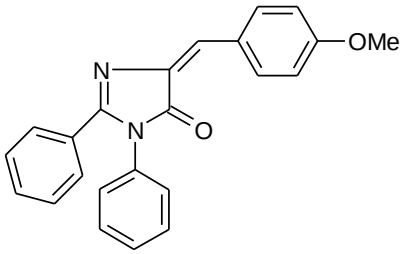
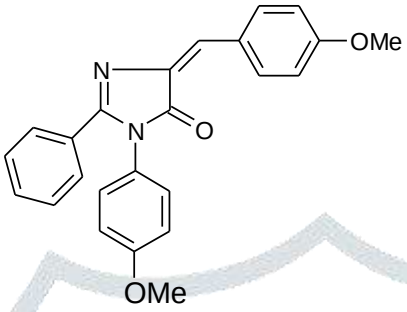
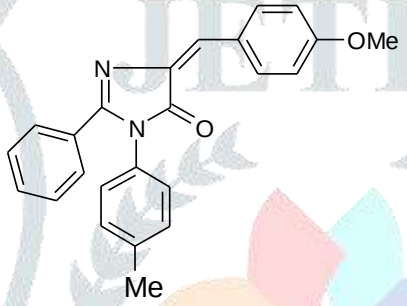
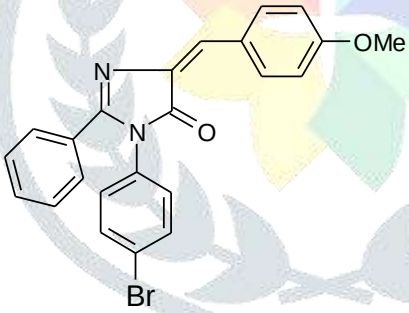
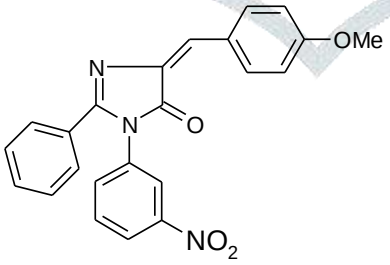
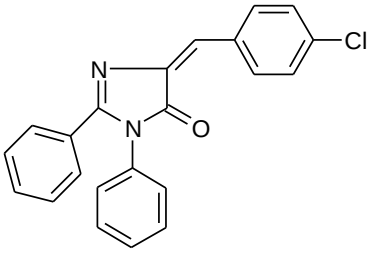
Entry	Catalyst	Amount of Catalyst (mol %)	Temperature (°C)	Time (min)	Yield[a] (%)
1	$HClO_4$.SiO_2	1	100	180	45
2	$HClO_4$.SiO_2	1	120	5	75
3	$HClO_4$.SiO_2	1	160	5	90
4	$HClO_4$.SiO_2	1	180	5	78
5	Activated SiO_2	10	160	5	45
6	$NaHSO_4$.SiO_2	5	160	5	40
7	PTSA.SiO_2	5	160	5	70
8	Amberlyst-15	5	160	5	75
9	-	1	160	180	20

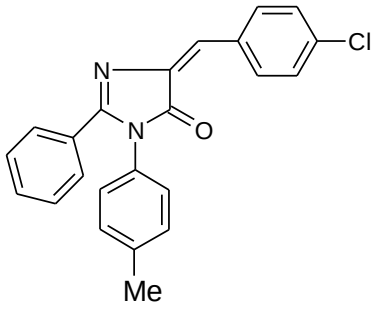
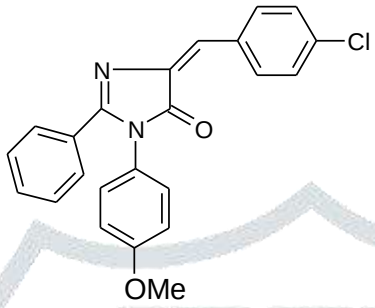
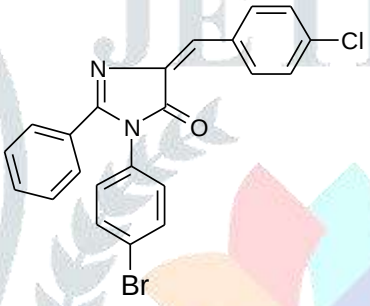
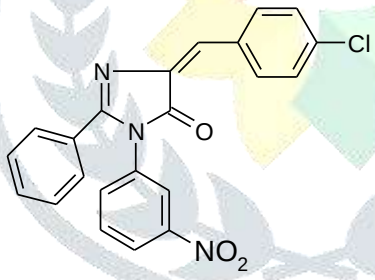
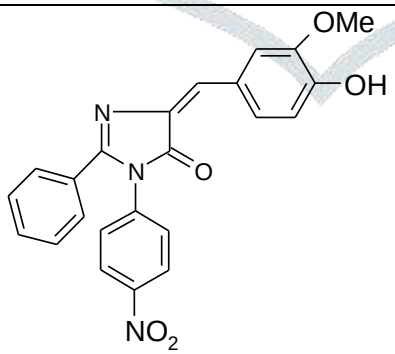
[a]Isolated yield

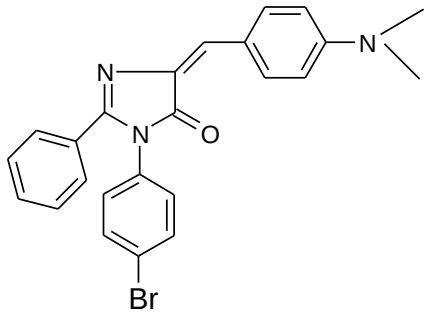
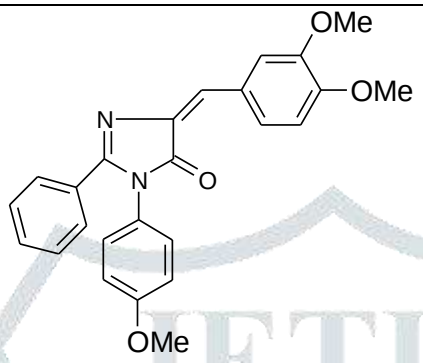
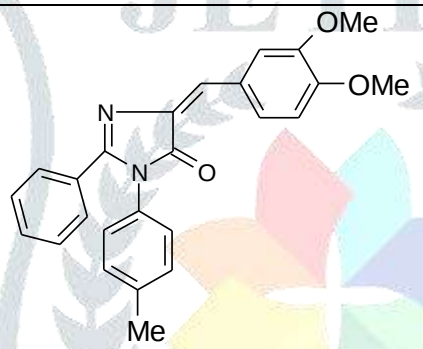
With the optimized conditions in hand, the scope of the reaction substrates was investigated. First, we examined the reaction a variety of aromatic amines possessing both electron donating, electron withdrawing groups and the results are listed in (Table 2). It was found that various substrates were converted into the corresponding products with good yields under the optimized conditions. Aromatic amines having electron-donating and electron withdrawing groups reacted smoothly and gave the good to excellent yields. The structures of the products were determined from their spectral data (IR, ^1H and ^{13}C NMR and LCMS).

Table 2: Synthesis of 4-arylmethylidene-2-phenyl-5(4*H*)-imidazolones using $HClO_4$-SiO_2 under solvent -free conditions at 160 °C .

Entry	Product	Time (min)	Yield (%)

3a		10	90
3b		10	89
3c		10	90
3d		20	85
3e		20	90
3f		20	88

3g		20	90
3h		20	87
3i		15	85
3j		15	90
3k		20	89

3l		20	88
3m		20	90
3n		20	90

Biological Activity

The newly synthesized imidazolones derivatives (3a -3n) were screened for *invitro* antimicrobial activity using Kirby Bauer disc diffusion method. The test organisms used in the study were *E. coli* (MTCC 6365), *S. aureus* (MTCC 7443), *B. subtilis* (MTCC 8141) *Proteus vulgaris* (NCIM 2813) *A. niger* (MTCC 6484) and *S. cerevisiae* (MTCC 463) 100 µl of the microbial suspension was spread onto Meuller-Hinton agar plates and tested for their acitivity. The obtained results are presented in (Table 3). Data in (Table 3) revealed that the target imidazolones compounds 3e, g, j, k, and 3n have shown significant antibacterial and antifungal activities and among them compounds 3e, j, and 3k have shown moderate activity, where as compound 3g and 3n has shown highest activity against bacteria and fungi. The compounds 3a, 3b, 3c, 3d, 3f, 3h, 3i, 3l and 3m showed poor activity.

Entry	*E.coli* MTCC6365	*S. aureus* MTCC7443	*B. subtilis* MTCC 8141	*P. vulgarus* NCIM 2813	*A. niger* MTCC 6484	*S. Cereviciae* MTCC 463
3a	4	2	--	2	2	1
3b	2	3	2	2	1	--
3c	4	4	5	2	3	3
3d	4	3	5	2	2	3
3e	3	4	6	3	3	4
3f	3	2	3	2	2	--
3g	6	5	9	3	6	4
3h	3	5	4	2	4	3
3i	2	3	--	2	--	3
3j	4	5	5	2	3	4
3k	3	4	6	3	3	4
3l	3	2	2	--	2	--
3m	2	--	2	3	3	--
3n	6	4	9	3	6	4

Table 3: Antibacterial and Antifungal activities zones of inhibition in mm

CONCLUSION

In summary, we have developed an efficient and convenient protocol for the synthesis of imidazolones using $HClO_4$-SiO_2 as a heterogeneous recyclable catalyst under solvent-free conditions and their biological activity has been demonstrated. The reaction was eco-friendly, and the reagents were inexpensive. Therefore, this method is an attractive alternative to synthesize imidazolones. The catalyst $HClO_4$-SiO_2 works under heterogeneous conditions and can easily be prepared from readily available $HClO_4$ and silica gel. [18] It can conveniently be handled and removed from the reaction mixture. The catalyst was recycled three times without the loss of activity. It has been applied for the first time to synthesis of oxazolones.

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REFERENCES

1. Wright, W. B.; Brabander, H. J. *J. Org. Chem*. **1961**, *26***,** 4051; (b) Niedbalia, V.; Buettcher, I. *Chem. Abastr*. **1981**, *94*, 15732; (c) Pande, K; Kalsi, K. R.; Bhalla, T. N. *Barthwal Pharmzine*. **1987**, *42***,** 269; (d) Wright, W. B.; Brabander, H. S.; Hardy, R. A.; Osterberg, A. C.; *J. Med .Chem*.

1966, *9*, 852; (e) Luigi, A.; Alfonso, M.; Pierluigi, R.; Afro, G.; Enzo, Z.; Nicola, D. T.; Walter, M. *J. Med. Chem*. **1969**, *12*, 122; (f) Godefroi, E. F.; Platje, J. Th. J. *J. Med. Chem*. **1972**, *15*, 336.

2. Islip, P. J. *British Patent.* **1966**, *675*, 1070.
3. (a) Siddiqui, S. A.; Bhusare, S. R.; Jarikote, D. V.; Pawar, R. P.; Vibhute, Y. B. *Bull. Korean Chem. Soc*. **2001**, *22*, 1033; (b) Saravanan, S.; Selvan, P. S.; Gopal, N.; Kumar Gupta, J. De B. *Archiv der Pharmazie*. **2005**, *338*, 488.
4. Vashi, B. S.; Mehta, D. S.; Shah, V. H. *Ind. J. Pharm. Sci.* **1995**, *57***,** 219.
5. **(**a) Congiu, C.; Cocco, M. T.; Onnis, V. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 989; (b) Kwak, S.-H.; Bang, S-C.; Seo, H-H.; Shin, H-R.; Lee, K-C.; Hoang, L. T. A. *Arch. Pharm. Res.* **2006**, *29*, 721.
6. Mesaik, M. A.; Khan, K. M.; Rahat, S.; Zia, U.; Choudhary, M. I.; Murad, S.; Abdullah, N. R.; Atta-ur-Rahman, A. Ahmad.; Siddiqui, R. A. *Lett. Drug Desig. Discov.* **2005**, *2*, 490.
7. De Clercq, J. P. *Chem. Re*v. **1997**, *97*, 1755.
8. Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 3443.
9. Sosa, A. C. B.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **2002**, *67*, 4498.
10. Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223.
11. Kashyap, S. J.; Sharma, P. K.; Garg, V. K.; Dudhe, R.; Kumar, N. *J. Adv. Sci. Res.* **2011**, *2*, 18
12. Niwa, H.; Inouye, S.; Hirano, T.; Matsuno, T.; Kojima, S.; Kubota, M.; Ohashi, M.; Tsuji, F. I. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93***,** 13617; (b) Kojima, S.; Ohkawa, H.; Hirano, T.; Maki, S.; Niwa, H.; Ohashi, M.; Inouye, S.; Tsuji, F. I. *Tetrahedron Lett.* **1998**, *39*, 5239; (c) Gross, L. A.; Baird, G. S.; Hoffman, R. C.; Baldridge, K. K.; Tsien, R. Y. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 11990.
13. Desai, N. C.; Bhavsar, A. M.; Baldaniya, B. B. *Indian. J Pharm Sci.* **2009**, *71*, 90.
14. (a) Verschave, P.; Vekemans, J.; Hoornaert, G. *Tetrahedron* **1984**, *40*, 2395; (b) Cornforth, J. W. Huang, H. T. *J. Chem. Soc.* 1948, 731; (c) Kjaer, A. *.Acta Chem Scand.* **1953**, *7*, 1030; (d) Lehr, H.; Karlan, S.; Goldberg, M. W. *J. Am. Chem. Soc.* **1953**, *53*, 3640.
15. Fozooni, S.; Tikdari, A. M. *Catal*. *Lett*. **2008**, *120***,** 303.
16. (a) Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett*. **2000**, *41* 8017; (b) Bahulayan, D.; Narayan, G.; Sreekumar, V.; Lalithambika, M.; *Synth. Commun.* 2002, *32*, 3565; (c) Srinivas, K. V. N. S.; Das, B. *Synlett.* **2004**, *10*, 1715.
17. (a) Mangarao, N.; Mahaboob Basha, G.; Ramu, T.; Srinuvasarao, R.; Prasanthi, S.; Siddaiah, V. *Tetrahedron Lett.* **2014**, *55* 177; (b) Siddaiah, V.; Mahaboob Basha, G.; Srinuvasarao, R.; Yessayya, V. *Green Chem. Lett. Rev.* **2012**, *5*, 337; (c) Siddaiah, V.; Mahaboob Basha, G.; Padma Rao, G.; Viplava Prasad, U.; Suryachendra Rao, R. *Synth. Commun.* **2012**, 42 627; (d) Siddaiah, V.; Mahaboob Basha, G.; Padma Rao, G.; Viplava Prasad, U.; Suryachendra Rao, R. *Chem. Lett.* **2010,** *39*, 1127
18. Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 425