Est. 1984

ORIENTAL JOURNAL OF CHEMISTRY

An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2021, Vol. 37, No.(1):
Pg. 250-255

Biocatalytic Oxidation of Sulfides to Sulfones

SHEFALI DHIMAN

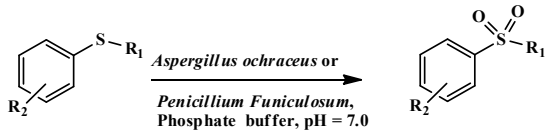
Department of Chemistry, Mehr Chand Mahajan DAV College for Women,
Chandigarh-160017, India.
*Corresponding author E-mail: shefalitac@gmail.com

http://dx.doi.org/10.13005/ojc/370136

(Received: December 05, 2020; Accepted: February 11, 2021)

ABSTRACT

This paper describes a method for the biocatalytic oxidation of sulfides. During the screening of microorganisms using pure cultures of bacteria and fungi for the oxidation of sulfides, it was observed that a number of strains of microorganisms, were able to oxidize various sulfides (1-4), but the desired sulfoxide was either not obtained or obtained only as a minor product. A close observation of the reaction showed complete oxidation and thus sulfone (5-8) formation had occurred in these cases.



1 R_1 = methyl, R_2 = H, **Yield = 90-95%** **5-8**
2 R_1 = ethyl, R_2 = H,
3 R_1 = butyl, R_2 = H,
4 R_1 = methyl, R_2 = 4-chloro

Sulfones are used to stabilize intermediates like α-radicals, α-anions etc. and also used as cationic synthons in many known reactions. This prompted us to explore the sulfone synthesis by biocatalytic route. Approximately 20% of the strains tested (400 bacterial and 200 fungal) showed the formation of sulfone with conversion rate varying from 3 to 100% based on TLC analysis. There were two strains of fungi, *Aspergillus ochraceus* MTCC 5245 and *Penicillium Funiculosum* MTCC 5246 which showed excellent biocatalytic activity for oxidation sulfides to corresponding sulfones in high yield. In all these strains, the product was different from corresponding standard sulfoxide prepared by oxidation with m-chloroperbenzoic acid but well corresponded with the standard sample of sulfone prepared by oxidation of the corresponding sulfides with oxone®. The identity of sulfones in all cases was confirmed by ^{1}H NMR.

Keywords: Biocatalysis, Sulfide oxidation, Sulfone synthesis, Biocatalytic oxidation,

INTRODUCTION

Sulfones have been widely used in organic synthesis to synthesize many popular and complicated molecules.[1]They constitute key skeletal framework of many natural products as well as pharmaceuticals and have attracted considerable attention because of their important biological

properties.[2] A few medicinally privileged compounds containing sulfone as the structural motif are shown in Fig. 1. Many compounds containing sulfonyl group are known to exhibit antibiotic, antitumor, antidepressant, antiresorptive and anticancer properties.[3-5]

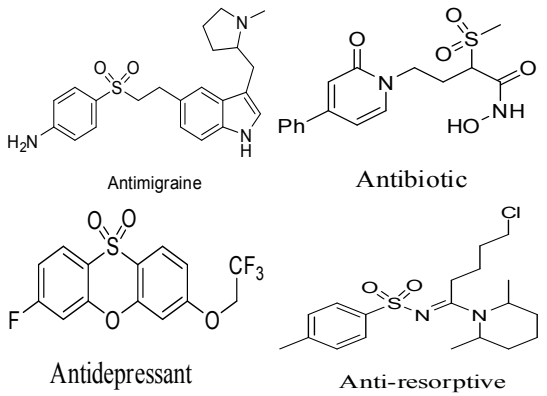


Fig. 1. A few medicinally important Sulfones

Synthesis of sulfoxides or sulfone has attracted a great deal of attention from the researchers. They are used to stabilize intermediates like α-radicals,[6] α-anions[7] etc. They have been also used as cationic synthons in many known reactions.[8] There are many reagents available which can carry out the complete oxidation of sulfides to sulfoxides and sulfones.[9,10] There are many conventional oxidants available like $NaBO_3$,[11] $NaClO_4$,[12] $Ca(ClO)_2$,[13] H_5IO_6/[Mn^{IV}-Mn^{IV}-(μ-O)$_3$L$_2$] $(PF_6)_2$,[14] $KHSO_5$,[15] HNO_3,[16] $(NH_4)_2Ce(NO_3)$[6,17] $NaIO_4$,[18] MnO_2,[19] $KMnO_4$,[20] RuO_4,[21] CF_3CO_3H,[22] dimethyldioxirane,[23,24] *t*-$C_4H_9O_2H$,[25] 4-Methyl morpholine is used with OsO_4,[26] 3-$ClC_6H_4CO_3H$[27] and [(n-$C_4H_9)_4N$]-HSO_5[28] which result in oxidation. The major drawback of most of the above mentioned reagents is that they were not effective for medium- to large-scale synthesis. The major factors which contribute to this are low content of effective oxygen available which would cause the desired oxidation, high cost of production and formation of unwanted side products which is not industry friendly. Singlet oxygen[29] or molecular oxygen combined with reagents like $CH_3CH(CH_3)CHO$[30] or $CH_3CH(CH_3)CH_2CHO$ and $Co(acac)_2$[31] have also been widely employed. It has been observed that aqueous hydrogen peroxide having a concentration of 60% is a versatile reagent as it forms negligible side products, is industry friendly and can be transported easily.[32] These added advantages have led to the development of various H_2O_2 based oxidation methods, which primarily uses tungsten (W) as catalyst systems such as H_2WO_4,[33] [C_5H_5N(n-$C_{16}H^{33}$)]$_3PO_4$$^-$[W(O)$(O_2)_2$]$_4$,[34] Na_2WO_4+[(n-$C_4H_9)_4N$]Cl,[35] as well as CH_3ReO_3,[36] CH_3ReO_3,[37] 2-$NO_2C_6H_4SeO_2H$[38] and hemoglobin.[39]

The oxidation of various sulfides was carried out using a mixture containing 30% H_2O_2 and a buffer solution of $NaHCO_3$ in the presence of a catalyst $MnSO_4.H_2O$.[40]A number of sulfides which contained different functional groups were subjected to oxidation (Table 1). Aromatic sulfides such as diphenyl sulfide showed complete oxidation without the use of any catalyst using both solvents acetonitrile and DMF (Table 1, Entries 1-3). The use of benzyl phenyl sulfide as a substrate to carry out the oxidation showed that acetonitrile was the best solvent for the reaction (Table 1, Entries 4 and 5). The oxidation of p-anisyl methyl sulfide showed that the rate of the reaction was much faster in DMF than CH_3CN without the use of any catalyst. (Table 1, Entries 6-9).

However, many other examples showed acetonitrile as a better solvent to get complete oxidation product sulfone (Table 1, Entries 10-18). It was observed that both vinyl and allyl containing sulfides were completely oxidized to the corresponding sulfones (Table 1, Entries 20-23).

Another strange observation was that even reactive tri-substituted olefin containing moieties were quite inert under these strong oxidation conditions and produced the completely oxidized sulfone (Table 1, Entries 24 and 25).

Alonso *et al.,* have demonstrated the best oxidation of various sulfides to their corresponding sulfoxides or sulfones. The oxidant that was used was 30% hydrogen peroxide without the use of any solvent.[41]

Table 1: Chemical Oxidation of Various Sulfides

Entry	Sulfide	H_2O_2	Solvent	Time (h)	Yield (%)
1	PhSPh	3	CH_3CN	0.25	100(94)
2	PhSPh	3	DMF	0.25	100(94)
3	PhSPh	2[b]	CH_3CN	0.25	100
4	PhSCH2Ph	5	DMF	24	55
5	$PhSCH_2Ph$	5	CH_3CN	0.25	100 (99)
6	$4\text{-}OMeC_6H_4SMe$	5	DMF	0.25	100 (70)
7	$4\text{-}OMeC_6H_4SMe$	5[b]	DMF	0.25	100
8	$4\text{-}OMeC_6H_4SMe$	3.5	CH_3CN	24	63
9	$4\text{-}OMeC_6H_4SMe$	3.5[b]	CH_3CN	24	98
10	$PhSCH_2CH_2OH$	5	DMF	0.25	72
11	$PhSCH_2CH_2OH$	5	CH_3CN	0.25	100 (88)
12	$PhSCH_2CH_2OTHP$	5	DMF	0.25	80
13	$PhSCH_2CH_2OTHP$	5	CH_3CN	0.25	100 (85)
14	$PhSCH_2CH_2OTBDMS$	5	DMF	0.25	72[c]
15	$PhSCH_2CH_2OTBDMS$	5	CH_3CN	0.25	100 (86)
16	$3,5\text{-}(CF_3)\ 2C_6H_3SCH_2CH_2OH$	5	CH_3CN	0.25	100[d]
17	$PhSCH_2CO_2CH_2Ph$	5	DMF	0.25	80[e]
18	$PhSCH_2CO_2CH_2Ph$	5	CH_3CN	0.25	100[d]
19	$3\text{-}CF3C_6H_4SCO_2CH_2Ph$	5	CH_3CN	24	100 (93)
20	$PhSCH=CH_2$	5	CH_3CN	0.25	100 (80)
21	$PhSCH_2CH=CH_2$	5	CH_3CN	0.25	95
22	$(CH_2=CH\ CH_2)_2S$	5	CH_3CN	0.25	100 (94)
23	$PhCH_2\ SCH_2CH=CH_2$	5	CH_3CN	0.25	100 (90)
24	$PhSCH_2CH=C(CH_3)_2$	5	DMF	0.25	100 (87)
25	$PhSCH_2CH=C(CH_3)CH=C(CH_3)_2$	5	CH_3CN	0.25	100

The rate of conversion rate has been determined by spectroscopic analysis. In brackets are mentioned isolated yields after working up the reaction

b. There has been no use of the catalyst for the reaction.

c. It clearly shows sulfoxide yield in the reaction.

d. Only sulfoxide was formed as the oxidation product. No sulfone formation occurred.

e. The yield of the sulfoxide as by-product was only 20%.

MATERIALS AND METHODS

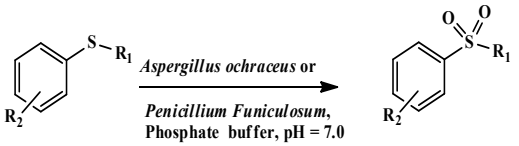
During the initial screening of microorganisms, it was noticed that a number of strains of microorganisms, were able to oxidize simple sulfides like butyl phenyl sulfide and benzyl phenyl sulfide. It was observed that the desired sulfoxide was either not obtained or obtained only as a minor product. In order to select a strain of micro-organisms which would cause complete oxidation of sulfide to sulfone required extensive screening of a library of microorganisms. To begin with, small molecules containing sulfides like butyl phenyl sulfide was chosen as a substrate to oxidize using different strains of micro-organisms. The bacterial cultures chosen after the initial screening were grown in a medium containing Peptone (0.5%), beef extract (0.2%), yeast extract (0.1%) and Sodium Chloride (0.5%) at a pH 7.0-7.5 for 18-24 hours. The medium used for selected strains of Fungi was Peptone M (0.2%), beef extract (0.2%) and KH_2PO_4 (0.2%) at a pH of 6.0-6.5 for 48-72 hours.[42] The bacterial or fungal cells were isolated by centrifugation, followed by their washing with phosphate buffer having a pH 7.0 The cells were subjected to a bio-catalytic reaction using 2 mg of butyl phenyl sulfide at 200 rpm in a shaker for 12 hours. The supernatant was extracted with 4 mL of organic solvent (ethyl acetate). The standard reagents butyl phenyl sulfoxide and sulfone were prepared by chemical oxidation with reagents like m-chloroperbenzoic acid and oxone® respectively. The bio-catalyzed butyl phenyl sulfoxide prepared was analyzed using Thin Layer Chromatography (TLC) by running parallel standard samples of sulfoxide and sulfone. The final confirmation of sulfone was done by ^{1}H-NMR spectroscopy. The same reaction was repeated at a larger scale using 4 g of bacterial or fungal cells and 20 mM substrate concentration.

Approximately 20% of the strains tested (400 bacterial and 200 fungal) showed the formation of sulfone with conversion rate varying from 3-100% based on TLC analysis. A number of strains (such as BNI0011N, BNI0047N, BNI0025N, BNI0018N, BNI0029N and BNI0044N) isolated from sea water and grown in the presence of 5% NaCl produced sulfone at 10-60% conversion rate. Two strains designated as PF7 and PF9 were selected for further studies.

RESULTS AND DISCUSSION

Two fungal Strains PF7 and PF9 have been previously described in connection with enantioselective oxidation of β-keto esters.[42] The identification of the strains has already been reported as *Aspergillus ochraceus* and *Penicillium funiculosum*, respectively by MTCC, IMTECH. The strains have been given accession numbers MTCC 5245 and MTCC 5246. *Aspergillus ochraceus* and *Penicillium funiculosum* were grown in fungal medium as described in the experimental section. The mycelia were isolated by filtration and the cells were suspended in phosphate buffer at pH 7.0 at a concentration of 0.5 g/mL and incubated with 2 mg of butyl phenyl sulfide (3) at 200 rpm at 30°C for 12 hours. The supernatant was separated by centrifugation and extracted with ethyl acetate. The formation of the sulfone 7 was confirmed by ^{1}H NMR for which the biotransformation was repeated at 50 mg scale using 20 mM substrate concentration and 6 g washed cells. The product was assigned structures sulfone based on its ^{1}H NMR spectral data which showed presence of methyl group as triplet (J = 7.27 Hz) at δ 0.89, two of the methylene protons as multiplet at δ 1.35-1.45 and δ 1.64-1.79 and the methylene attached to sulfur atom at δ 3.00 as triplet (J = 7.99 Hz). The aromatic protons appeared as multiplet at δ 7.51-7.88. The NMR spectral data was different from NMR data of sulfoxide prepared by oxidation with m-chloroperbenzoic acid. The CH_2SO methylene group in sulfoxide resonated at δ 2.73 as triplet (J = 7.1Hz), approximately 0.27 ppm upfield and aromatic protons resonated at δ 7.43-7.60 approximately 0.15 ppm upfield compared to the biocatalyzed product. The ^{1}H NMR spectral data, however, corresponded well with ^{1}H NMR data of standard sample of sulfone prepared by oxidation of sulfides with oxone®.

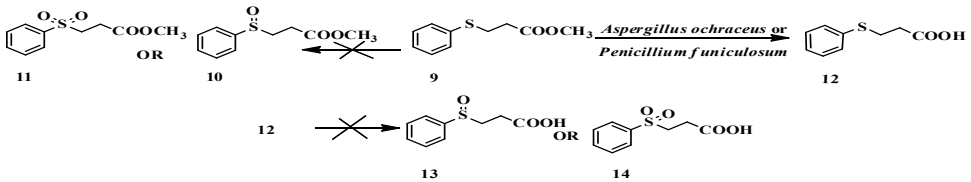
Similarly, *Aspergillus ochraceus* and *Penicillium funiculosum* catalyzed oxidation of methyl phenyl sulfide (1), ethyl phenyl sulfide (2) and 4-Chlorothioanisole (4) produced corresponding sulfones 5, 6 and 8 (Scheme. 1). In all these examples, the product was different from corresponding standard sulfoxide prepared by oxidation with m-chloroperbenzoic acid. In all cases, the proton attached to the α-carbon atom of the biocatalyzed product showed 0.25-0.31 ppm downfield shift and aromatic protons 0.10-0.16 ppm downfield shift compared to standard sulfoxide. NMR spectral data of sulfones corresponded with the standard sample of sulfone prepared by oxidation of the corresponding sulfides with oxone®.



1 R_1 = methyl, R_2 = H, **Yield = 90-95%** **5-8**
2 R_1 = ethyl, R_2 = H,
3 R_1 = butyl, R_2 = H,
4 R_1 = methyl, R_2 = 4-chloro

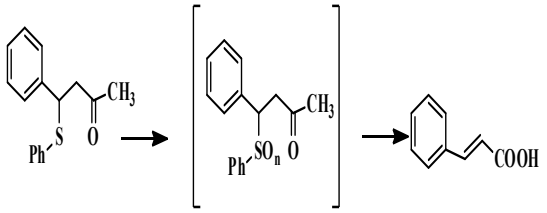
Scheme. 1

Methyl 3-(phenylthio) propionate (9), prepared by conjugate addition of thiophenol on methyl acrylate on biocatalyzed reaction with *Aspergillus ochraceus* and *Penicillium Funiculosum* failed to give the desired sulfoxide 10 or sulfone 11, but TLC showed complete consumption of starting material and formation of a high polarity compound. The NMR spectral data of the isolated product showed absence of ester methyl protons, instead a broad singlet was present at δ 11.12. The aromatic protons resonated at δ 7.13-7.33 as multiplet and methylene protons as a triplet (J = 7.47 Hz) each at δ 2.62 and δ 3.10. The product was therefore assigned the structure 12 (Scheme. 2). No sulfoxide or sulfone of ester, 9 or acid, 12 could be isolated from the reaction mixture.



Scheme. 2

4-phenyl-4-(phenylsulfonyl)butan-2-one 15 also failed to produce any sulfoxide or sulfone, but instead gave a product, which was identified as trans-cinnamic acid 17 based on ^{1}H NMR spectral data. In all probabilities the trans-cinnamic acid was produced via oxidation of sulfide to either sulfoxide or sulfone (16). But neither sulfoxide nor sulfone could be isolated from the reaction mixture. Oxidation of 15 with H_2O_2 or oxone® also resulted in the formation of 17, which indicated lability of the sulfoxide/sulfone under the reaction conditions (Scheme. 3).



15 16, n=1 or 2 17

Scheme. 3

CONCLUSION

Two strains of fungi, *Aspergillus ochraceus* MTCC 5245 and *Penicillium funiculosum* MTCC 5246 have been identified which oxidize alkyl aryl sulfides to corresponding sulfones in high yield. The method is environmentally benign as it requires no organic solvents and can be carried under mild reaction conditions. However, methyl 3-(phenylthio)propionate (9) failed to give desired sulfone 11, instead only the hydrolysis of the ester functionality occurred to give acid, 12. Oxidation of 4-phenyl-4-(phenylsulfonyl)butan-2-one (15) occurred, but sulfoxide/sulfone readily eliminated under the reaction conditions to give trans-cinnamic acid (17). In a similar way, *Aspergillus ochraceus* and *Penicillium funiculosum* catalyzed oxidation of substrates such as methyl phenyl sulfide, ethyl phenyl sulfide and 4-Chlorothioanisole produced corresponding sulfones. In all these examples, the product was different from corresponding standard sulfoxide prepared by oxidation with m-chloroperbenzoic acid. In all cases, the proton attached to the α-carbon atom of the biocatalyzed product showed 0.25-0.31 ppm downfield shift and aromatic protons 0.10-0.16 ppm downfield shift compared to standard sulfoxide. NMR spectral data of sulfones corresponded with the standard sample of sulfone prepared by oxidation of the corresponding sulfides with oxone®.

ACKNOWLEDGEMENT

This research is a part of author's PhD research supported by CSIR-IMTECH.

Conflicts of Interest

The author declares that there is no conflict of interest.

REFERENCES

1. Patai, S.; Rappoport, Z.; Stirling, C. The Chemistry of Sulphones and Sulfoxides; *John Wiley & Sons: Chichester.*, **1988**.
2. Liu, K. G.; Robichaud, A. J.; Bernotas, R. C.; Yan, Y.; Lo, J. R.; Zhang, M. Y.; Hughes, Z. A.; Huselton, C.; Zhang, G. M.; Zhang, J. Y.; Kowal, D. M., 2010, *J. of Med. Chem.,* **2010**, *53*(21), 7639-46.
3. Eldehna, W. M.; Al-Ansary, G. H.; Bua, S.; Nocentini, A.; Gratteri, P.; Altoukhy, A.; Supuran, C. T., *Eur. Journal of Med. Chem.,* **2017**, *127*, 521-30.
4. La Regina, G.; Coluccia, A.; Brancale, A.; Piscitelli, F.; Famiglini, V.; Cosconati, S.; Schols, D., *J. of Med. Chem.*, **2012**, *55*(14), 6634-8.
5. Suja, T. D.; Divya, K. V. L.; Naik, L. V.; Kumar, A. R.; Kamal, A. *Coppercatalyzed Bioorganic Med. Chem. Lett.*, **2016**, *26*(8), 2072-2076.
6. Paquette, L.A. *Synlett.*, **2001**, 1-12.
7. Najera, C.; Sansano, J. M. *Recent Res. Devel. Org. Chem.*, **1998**, *2*, 637-83.
8. Chinchilla, R.; Najera, C. *Recent Res. Devel., Org. Chem.,* **1997**, *1*, 437-67.
9. Kirk-Othmer, C. E. Encyclopedia of Chemical Technology; 4th ed.; Kroschwitz, J. I., Howe-Grant, M., Eds.; *Wiley: New York.*, **1997**, *23*, 134-46.
10. Kirk-Othmer, W. R. Encyclopedia of Chemical Technology; 4th ed.; Kroschwitz, J. I., Howe-Grant, M., Eds.; *Wiley: New York.*, **1997**, *23*, 217-32.
11. Mckillop, A.; Sanderson, W.R. *Tetrahedron Lett.*, **1995**, *51*(22), 6145-66.
12. Khurana, J. M.; Panda, A. K.; Ray, A.; Gogia, A. *Org. Prep. Proc.*, **1996**, *28*, 234-237.
13. Weber, J. V.; Schneider, M.; Salami, B.; Paquer, D. *Recl. Trav. Chim. Pays-Bas.*, **1986**, *105*, 99-102.

14. Barton, D. H. R.; Li, W.; Smith, J. A. *Tetrahedron Lett.*, **1998**, *39*(39), 7055-8.
15. Kennedy, R. J.; Stock, A. M. *J. Org. Chem.,* **1960**, *25*, 1901-6.
16. Trost, B. M.; Curran, D. P. *Tetrahedron Lett.*, **1981**, *22*(14), 1287-90.
17. Goheen, D. W.; Bennett, C. F. *J. Org. Chem.,* **1961**, *26*, 1331-3.
18. Ho, Tse- Lok.; Wong, C. M. *Synthesis.*, **1972**, 561-2.
19. Varma, R.S.; Dahiya, R. *Tetrahedron Lett.,* **1998**, *39*(11),1307-8.
20. R. S.; Saini, R. K.; Meshram, H. M. *Tetrahedron Lett.*, **1997**, *38*(37), 6525-8.
21. Edwards, D.; Stenlake, J. B. *J. Chem. Soc.,* **1954**, 32,72-4.
22. Gokel, G. W.; Gerdes, H. M.; Dishong, D. M. *J. Org. Chem.*, **1980**, *45*, 3634-9.
23. Djerassi, C.; Engle, R. R. *J. Am. Chem. Soc.,* **1953**, *75*, 3838-40.
24. Venier, C. G.; Squires, T. G.; Chen, Y.-Y.; Hussmann, G. P.; Shei, J. C.; Smith, B. F. *J. Org. Chem.*, **1982**, *47*, 3773-4.
25. Murray, R. W.; Jeyaraman, R., *J. Org. Chem.,* **1985**, *50*, 2847-53.
26. Adam, W. and Hadjiarapoglou, L. *Tetrahedron Lett.*, **1992**, *33*(4), 469-70.
27. Breton, G. W., Fields, J. D. and Kropp, P. *J. Tetrahedron Lett.*, **1995**, *36*(22), 3825-8.
28. Kaldor, S. W.; Hammond, M. *Tetrahedron Lett.*, **1991**, *32*(38), 5043-6.
29. Paquette, L. A.; Carr, R. V. C. *Org. Synth. Coll.,* **1990**, *7*, 453-6.
30. Trost, B. M.; Braslau, R. *J. Org. Chem.*, **1988**, *53*, 532-7.
31. Hauser, F.M.; Suzanne R.; Ellenberger, Clardy, J.C.; Bass, L.S. *J. Am. Chem. Soc.*, **1984**, *106*(8), 2458-59.
32. Mandal, A.K.; Khanna, V.; Iqbal, J. *Tetrahedron Lett.*, **1996**, *37*(19), 3769-72.
33. Dell'Anna, M. M.; Mastrorilli, P.; Nobile, C. F. *J. Mol. Catal.*, **1996**, *108*(2), 57-62.
34. Sato, K.; Aoki, M.; Noyori, R., **1998**, *281*, 1646-7.
35. Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.*, **1963**, *28*, 1140-2.
36. Ishii, Y.;Tanaka, H.; Nisiyama, Y. *Chem. Lett.,* **1994**, 1-4.
37. Stec, Z.; Zawadiak, J.; Skibinski, A.; Pastuch, G. *Polish J. Chem.*, **1996**, *70*, 1121-123.
38. Adam, W.; Mitchell, C. M.; Saha-Moeller, C. R. *Tetrahedron.*, **1994**, *50*(47), 13121-4.
39. Yamazaki, S. *Bull. Chem. Soc. Jpn.,* **1996**, *69*(10), 2955-9.
40. Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis.*, **1978**, 299-301.
41. Alonso, D. A; Najera, C.; Varea, M. *Tetrahedron Lett.*, **2002**, *43*, 3459-61.
42. Sangar, S.; Pal, M.; Moon, L.S.; Jolly, R.S. *Bioresour. Technol.*, **2012**, *115*, 102-10.