

## Spotlight: Synthesis and applications of sulfones viz $\beta$ -keto-sulfones, $\alpha$ -halo $\beta$ -keto-sulfones $\alpha$ -halo methyl sulphones and $\alpha, \alpha$ -dihalo methyl sulphones

Suryakiran Navath<sup>a\*</sup>

<sup>a</sup>Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Habsiguda, Hyderabad 500007, India.

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### ABSTRACT

The review summarizes an analysis of recent advances and contributions to the methods of synthesis, chemical and spectral properties and application of  $\beta$ -keto sulfones with the main focus on the their increasingly growing demand as starting substrates and intermediates incorporated in the syntheses of various classes of organic compounds and other synthetic applications.

Compiled by Dr. Suryakiran Navath, Ph. D.

Dr. N. Suryakiran. He obtained M.Sc. and Ph. D. in Organic Chemistry from Jawaharlal Nehru Technological University, Hyderabad India, His research interest is organic synthesis of bioactive Natural Products, medicinal chemistry, drug delivery systems and controlled release and development of new synthetic methodologies.

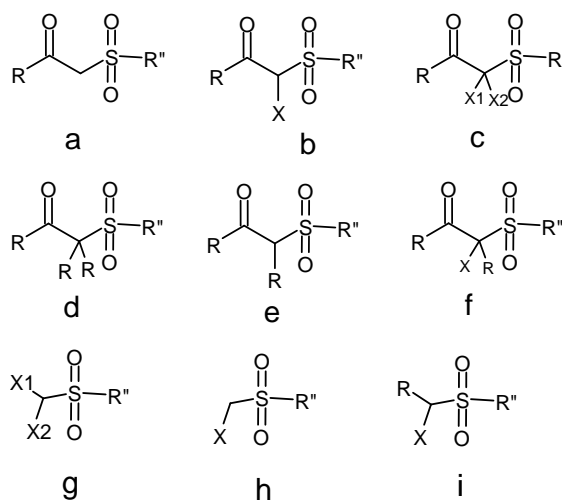
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\*Corresponding author. e-mail: [suryakiran.navath@gmail.com](mailto:suryakiran.navath@gmail.com)

### Introduction

Sulfones are chemical compounds containing a sulfonyl functional group attached to two carbon atoms. The central hexavalent sulfur atom is double-bonded to each of two oxygen atoms and has a single bond to each of two carbon atoms, usually in two separate alkyl or an aryl hydrocarbon substituents. They are very important and fascinating branch of chemistry.<sup>1</sup> The presence of sulfone group, in an organic compound adds variety to its chemical architecture and also enhances the biological activity of the compound. Among sulfones,  $\beta$ -keto-sulfones are very important group of intermediates.  $\beta$ -keto-sulfones are readily obtained from various routes.<sup>2-8</sup> In  $\beta$ -keto-sulfones the presence of both electron withdrawing groups, the methylene group readily enalises in the presence of bases such as piperidine, pyrrolidine, triethylamine, and also in the presence of acids such as acetic acid and ammonium acetate with carbonyl group but not with sulfone group, the effect by sulfone is purely inductive effect only.<sup>9</sup> The  $\beta$ -keto-sulfones are important building blocks in potentially bioactive molecules,<sup>10</sup> and also used as precursors in various organic transformations, such as, Michael and Knoevenagel reactions and in the preparation of allenes, chalcones, polyfunctionalized 4H-pyrans and ketones. In addition,  $\beta$ -keto-sulfones can be converted into synthetically as well as

biologically important optically active  $\beta$ -hydroxy-sulfones and  $\alpha$  halomethyl sulfones and  $\alpha, \alpha$  dihalomethyl sulfones.

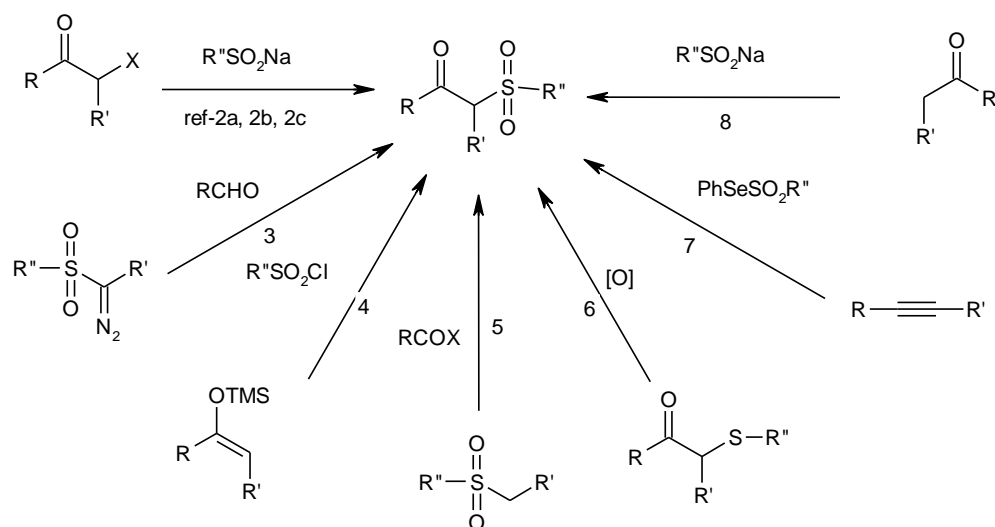


Scheme 1

Makosza<sup>11</sup> have been utilized chloromethyl phenyl sulfones and chloromethyl p-tolyl sulfones in vicarious nucleophilic substitution (VNS) reactions with nitro arenes to afford VNS adducts. These adducts have been elaborated into both 3-sulfonyl substituted indole derivatives and the analogues indazoles.<sup>12</sup> In addition, certain  $\beta$ -keto sulfone derivatives are known to exhibit biological activity. Halo alkyl sulfones are useful preventing aquatic organisms from attaching to fishing nets and shiphulls,<sup>13</sup> in herbicides compositions,<sup>14</sup> bactericidal,<sup>15</sup> anti-fungal,<sup>16</sup> algacides,<sup>17</sup> and insecticides.<sup>18</sup>

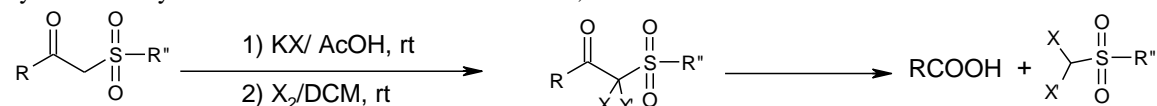
Several methods for the generation of  $\beta$  keto sulfones include nucleophilic addition of methylsulfonyl arenes to acyl chlorides,<sup>2</sup> oxidation of the corresponding  $\beta$  keto sulfides, nucleophilic substitution of  $\alpha$  halo ketones or  $\alpha$  tosyloxy ketones with sodium sulfonates, reactions of diazo sulfones with aldehydes, reactions of sulfonyl chlorides with silyl enol ethers, and. Recently, radical sulfonylation of enol acetates for the preparation of  $\beta$  ketosulfones was reported. For example, Yadav described the synthesis of  $\beta$  ketosulfones through an iron catalyzed sulfonylation of aryl enol acetates with sulfonyl hydrazides. Similarly, methods of synthesis of  $\alpha$ -halo methyl sulfones and  $\alpha$ ,  $\alpha$ -dihalo methyl sulfones have been reported in literature.<sup>19-23</sup> On the other hand, being active methylene substrates,  $\beta$ -keto sulfones are often used as model

(A) As the importance of  $\beta$ -keto-sulfones in organic synthesis, various authors have been reported different routes to synthesis of  $\beta$ -keto-sulfones.<sup>2-8</sup>



**Scheme 2**

(B) The  $\alpha$ -chloro/bromo  $\beta$ -keto-sulfone do not undergo Finkelstein reactions to obtain corresponding  $\alpha$ -iodo  $\beta$ -keto-sulfone. However, the  $\alpha$ -iodo  $\beta$ -keto-sulfone have been synthesized by treatment with iodine monochloride, further on



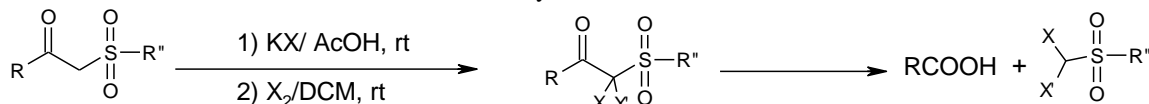
**Scheme 3**

compounds for the studies of the fundamental aspects of reactivity. The chemistry of  $\beta$ -keto sulfones achieved a significant peak of interest during the last decades and nowadays constitutes the whole branch of organosulfur chemistry.

Chemical properties  $\beta$ -keto sulfones are classified by reactions on two key reactive centers, one is methylene group and second one is carbonyl group along with the consideration of the synthetic procedures involving the elimination of sulfonyl group and some other reactions.  $\beta$ -Keto sulfones are stable under acidic or alkaline conditions at room temperature, however  $\alpha$ -halo  $\beta$ -keto sulfones or  $\alpha$ ,  $\alpha$ -di halo  $\beta$ -keto sulfones are base sensitive, it under goes base induced cleavage.  $\beta$ -keto sulfones with  $\alpha'$  primary or secondary protons presence of alkaline conditions under go Ramberg backlund rearrangement.<sup>24</sup> The chemical shift of the  $\alpha$ -protons with mono halo  $\beta$ -keto sulfone compounds, follows the reverse order with the electronegativity of the halogen atoms.  $\alpha$ -Chloro  $\beta$ -keto sulfones of proton has less chemical shift  $\delta$  than the  $\alpha$ -Iodo  $\beta$ -keto sulfones.<sup>25</sup> In many cases, further synthetic application of the products derived from the reactions of  $\beta$ -keto sulfones is also accounted and depicted in schemes, thus emphasizing significance of  $\beta$ -keto sulfones as half-products used in various transformations

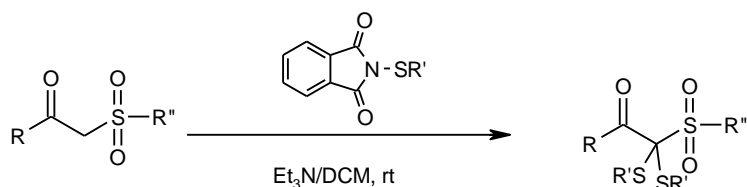
(C) The chemoselective mono halogenation was achieved by treatment with potassium halide in the presence of hydrogen peroxide as an efficient and non polluting halogenation reagent, further on treatment with  $\text{SO}_2\text{Cl}_2/\text{Br}_2$  followed by base induced

cleavage afforded  $\alpha,\alpha$ -symmetrical and asymmetrical dihalo  $\beta$ -keto-sulfone and  $\alpha,\alpha$ -symmetrical and asymmetrical dihalomethyl sulfones respectively.<sup>26</sup>



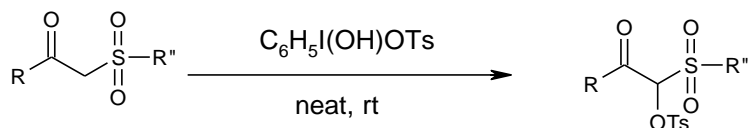
**Scheme 4**

(D) The controlled mono and di sulfenylation of  $\beta$ -keto-sulfone was achieved by on treatment with N-thiophthalimide in the presence of triethyl amine in DCM.<sup>27</sup>



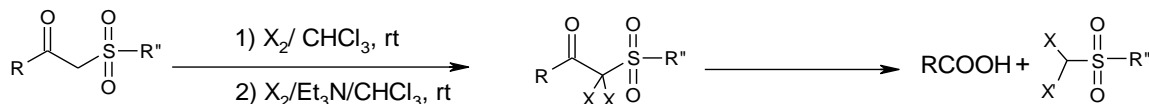
**Scheme 5**

(E) Dalip Kumar *et. al* have been reported the facile synthesis of novel  $\alpha$ -tosyloxy  $\beta$ -keto-sulfone using [hydroxy (tosyloxyiodo)]benzene under solvent free conditions.<sup>28</sup>



**Scheme 6**

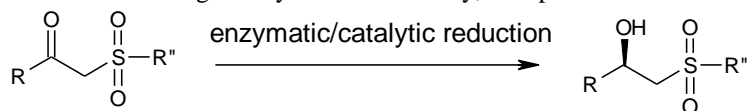
(F) Grossert *et. al.* have been reported the preparation, spectral properties, structures and base-induced cleavage of  $\alpha$ -halo  $\beta$ -keto-sulfones.<sup>29</sup>



**Scheme 7**

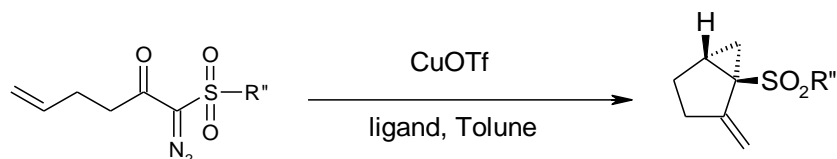
H)  $\beta$ -keto-sulfones on enzymatic or catalytic reduction yield optically active  $\beta$ -hydroxy-sulfones, which are important key constituents in organic synthesis. Recently, compounds of this

class have proved its efficiency as a chiral controller in asymmetric Diels-Alder and alkylation reactions.<sup>30</sup>



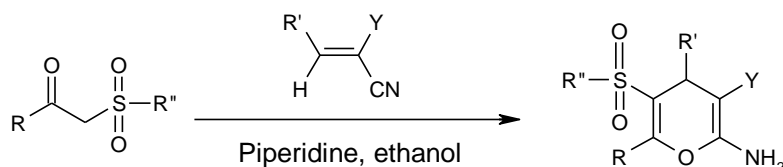
**Scheme 8**

(I) Nakada *et. al.* have been reported asymmetric catalysis on the intramolecular cyclopropanation of  $\alpha$ -diazo  $\beta$ -keto-sulfones.<sup>31</sup>



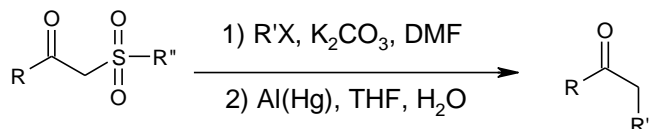
**Scheme 9**

(J)  $\beta$ -keto-sulfones are precursor for Michael reactions;  $\beta$ -keto-sulfones on treatment with substituted acrylonitrile in the presence of piperidine yields sulfonyl substituted amino pyrans.<sup>32</sup>



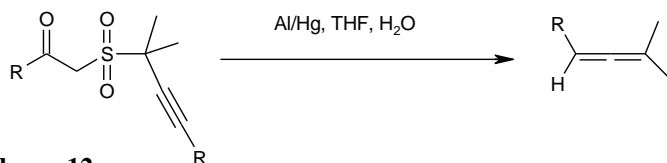
**Scheme 10**

(K)  $\beta$ -keto-sulfones on alkylation followed by facile elimination of sulfone group yields the  $\alpha$ -alkylated ketones.<sup>33</sup>



**Scheme 11**

(L)  $\beta$ -keto-sulfones are useful for the facile synthesis of allenes;  $\alpha,\alpha$ -dialkyl  $\beta$ - acetyleno  $\beta$ -keto-sulfones on treatment with Al(Hg) yields substituted allenes.<sup>34</sup>



**Scheme 12**

## Conclusion

In conclusion a shot review of synthesis and applications of different types  $\beta$ -keto-sulfones, including  $\alpha$ ,  $\alpha$ -dihalo methyl sulfones is reported.

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## References

1. N. S. Simpkins, *Sulfones in organic synthesis*; Ed. J. E. Baldwin, *Peragmon press: Oxford*, **1993**
2. a) Suryakiran, N.; Srikanth Reddy, T.; Asha Latha, K.; Lakshman, M.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, 47, 3853. b) Vennstra, G. E.; Zwaneburg, B. *Synthesis* **1975**, 519.
3. Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, 33, 1131.
4. Kamigata, N.; Udodaira, K.; Shimizu, T. *J. Chem. Soc. Perkin Trans. 1*. **1997**, 783.
5. Field, L.; Lawson, J. E; Mc Fenland, J. W. *J. Am. Chem. Soc.* **1956**, 78, 4389.
6. a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 22, 1287. b) Fan, A. -L.; Cao, S.; Zhang, Z. *J. Heterocycl. Chem.* **1997**, 34, 1657.
7. Hao, Q.; Xian, H. *Synthesis* **2006**, 1934.
8. a) Kumar, D.; Sundaree, S.; Rao, V. S.; Varma, R. S. *Tetrahedron Lett.* **2006**, 47, 4197. b) Xie, Y. -Y.; Chen, Z. -C. *Synth. Commun.* **2001**, 31, 3145.
9. Holst, E. H.; Fernelius, W. C. *J. Org. Chem.* **1957**, 22, 1882.
10. a) Macro, J. -L. *J. Org. Chem.* **1997**, 62, 6575.
11. a) Golinski, J.; Makosza, M. *Tetrahedron lett.* **1978**, 37, 3495. b) Makosza, M.; Chylinska, B.; Mudryk, B. *Ann. Chem.* **1984**, 1, 8. c) Wojciechowski, K.; Makosza, M. *Tetrahedron lett.* **1989**, 62, 4793. d) Wojciechowki, K.; Makosza, M. *Synthesis* **1986**, 8, 651.
12. Takhashi, M.; Suga, D. *Synthesis*, **1998**, 7, 986.
13. Oishi, Y.; Watanabe, T.; Kusa, K.; Kazama, M.; Koniya, K. **1988**, JP. October 7, 63, 243, 067.
14. Shigematsy, S.; Yamada, Y.; Kimura, I. *Herbicidal composition for Rice*. July 30, **1983**, JP 58, 128, 305.z
15. Baker, F.C.; Li, J.P.N. *Substituted male imides in liquid concentrates*. January 27, **1981**, US 4, 247, 559.
16. 10. Eckstein, Z.; Zavistowska, M.; Palut, D.; Polubiec, E. *Aromatic derivatives of chloromethyl sulfones*. *Pol. J. Chem.* **1966**, 45, 314.
17. 11. Ejmocki, Z.; Krassowska, B.K.; Olezak, I.; Eckstein, Z. *Pol. J. Chem.* **1980**, 54, 11-27 and 2153 – 2159.
18. 12. Antane, S.; Bernotas, R.; Li, Y.; David. Mc. R.; Yan, Y. *Synth. Commun.* **2004**, 34, 2443.
19. Middlebos, W.; Strating, J.; Zwanenberg, B. *Tetrahedron Lett.* **1971**, 12, 351
20. Ziegler, W.M.; Conner, R. *J. Amer. Chem. Soc.* **1940**, 62, 2596.
21. Barr, E.; Ziegler, W.M.; Conner, R. *ibid.* **1941**, 63, 106.
22. Kresze, G.; Schram, W. M.; Cleve, G. *Chem. Ber.* **1961**, 94, 2060.
23. Grossert, J. S.; Dubey, P. K.; Gill, G. H.; Cameron, T. S.; Gardner, P. A. *Can. J. Chem.* **1984**, 62, 174.
24. Rigby, J. H.; Warshakoon, N. C. *J. Org. Chem.* **1996**, 61, 7644.
25. Suryakiran, N.; Srikanth Reddy, T.; Suresh, V.; Lakshman, M.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, 47, 4319.
26. Suryakiran, N.; Prabhakar, P.; Srikanth Reddy, T.; Mahesh, K. C.; Rajesh, K. Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, 47
27. Grossert, J. S.; Dubey, P. K.; Elwood, J. *J. Chem. Soc., Chem Commun.* **1982**, 1183.
28. Kumar, D.; Sundaree, S.; Patel, G.; Rao, V. S.; Varma, R. S. *Tetrahedron Lett.* **2006**, 47, 8239.
29. Grossert, J. S.; Dubey, P. K.; Gill, G. H.; Cameron, T. S.; Gardner, P. A. *Can. J. Chem.* **1984**, 62, 798.
30. a) Bertus, P.; Phansavath, P.; Vidal, V. R.; Genet, J. P.; Touati, A. R.; Homri, T.; Hassine, B. B. *Tetrahedron: Asymmetry* **1999**, 10, 1369. b) Svatos, A.; Hun Kova, Z.; Kren, V.; Hoskovec, M.; Saman, D.; Valterova, I.; Vrkoc, J.; Koutek, B. *Tetrahedron: Asymmetry* **1996**, 7, 1285.
31. a) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, 44, 9007. b) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, 125, 2860.
32. Macro, J. L.; Fernandez, I.; Khira, N.; Fernandez, P.; Romero, A. *J. Org. Chem.* **1995**, 60, 6678.
33. a) Sengupta, S.; Sarma, D. S.; Mondal, S. *Tetrahedron* **1998**, 54, 9791. b) Corey E. J.; Chavosky, M. *J. Am. Chem. Soc.* **1964**, 86, 1639.
34. Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Hill, R. L.; Laffey, T. G. *Tetrahedron Lett.* **1995**, 36, 7925.