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A NEW CONVENIENT SYNTHESIS OF γ-KETO-SULFOXIDE

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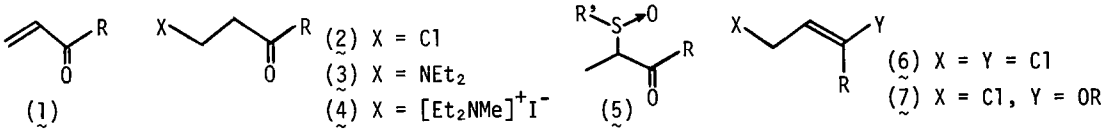
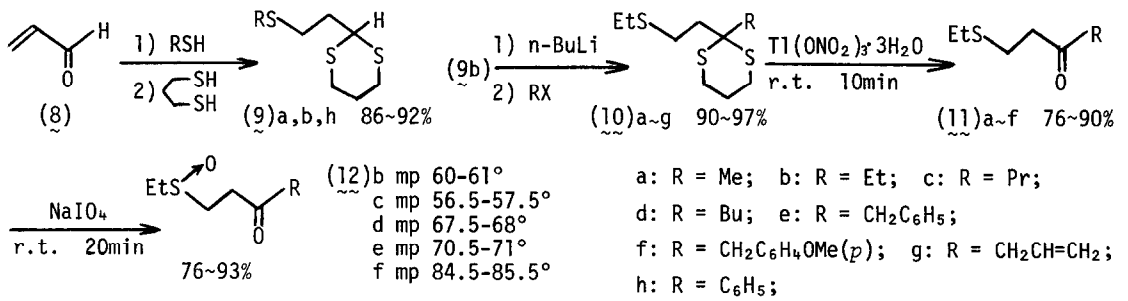
Summary: γ-Keto-sulfoxides have been very conveniently synthesized through a series of reactions from commercially available acrolein. They were obtanined as crystals and shown to be effective as the vinyl ketone equivalents.

Vinyl ketone (1) has been widely used for Michael type addition, Robinson annulation, or Diels-Alder reaction, etc. Because of its versatility, it has been utilized often for construction of the carbocyclic ring in the synthesis of natural products.[1] Actually, however, vinyl ketones are subject to polymerization under the conditions of the C-C bond formation. Hence, its equivlents (2~7) have been elaborated and utilized in many cases.[1]



Among such vinyl ketone equivalents, β-keto sulfoxide (5) was synthesized by Grieco, *et al.*[2] and Yonemitsu, *et al.*[3] using their own procedure. We have investigated an efficient synthetic method of γ-keto sulfoxide (12), an isomer of (5) and the more suitable[4] vinyl ketone equivalent. As the result, we have exploited a new convenient synthetic method of γ-keto-sulfoxides (12b~f) starting from acrolein (8), which is reported here. The sequence is shown in Scheme 1.



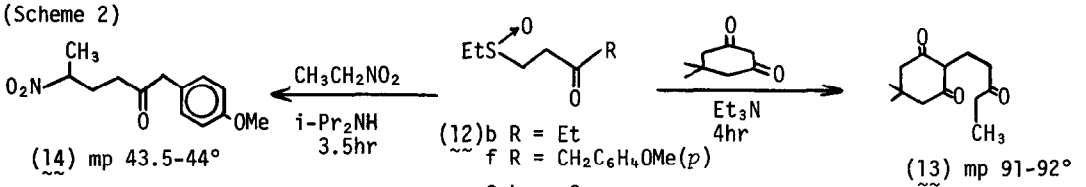
Scheme 1

Acrolein (8) was treated with alkane (or bezene) thiol (1.1eq) and catalytic amount of Et_3N at room temperature in $CHCl_3$ for 2hr. To the reaction mixture were added propane-1,3-dithiol (1.1eq) and BF_3-Et_2O. After stirring at room temperature for further 2hr, a usual work up gave high yields of the desirable thiol adducts (9) as one-pot sulfenylation products. To a solution of (9b) in THF was added dropwise a solution of n-BuLi (1.2eq) in n-hexane at -40°

under stirring in N_2, and the mixture was slowly warmed to -20° over 1hr to give the 2-lithio-1,3-dithiane-derivative. After addition of alkyl halides (1.1eq) at -70° under similar conditions, the mixture was slowly warmed up to -20° over 3hr to give alkylated products (10a~g) in high yields.[5]

Dethioacetalization of (10) was rapidly performed by our method[6] using $Tl(ONO_2)_3 3H_2O$ (2.2eq) in CH_2Cl_2-MeOH to give high yields of ketones (11a~f). The keto-sulfides (11) were allowed to react with aqueous solution of $NaIO_4$ (1.2eq) in MeOH to afford desirable γ-keto-sulfoxides (12b~f) as the crystalline products in high yields.

In order to examine the utility of the vinyl ketone equivalent, γ-keto sulfoxide (12b) was treated with dimedone (1eq) under the presence of Et_3N (1.5eq) in hot MeOH to give the addition product (13) in 79% yield. Similarly, sulfoxide (12f) on treatment with nitroethane (1.1eq)[7] in the presence of diisopropylamine (2.2eq) gave the desired product (14) in 72% yield. (Scheme 2)



Scheme 2

Thus, it was demonstrated that γ-keto-sulfoxide was effective as a synthetically equivalent synthon to the vinyl ketone.

The foregoing γ-keto-sulfoxides (12) can be easily synthesized in a large scale from commercially available acrolein, and they are treated much more conveniently when compared to vinyl ketones themselves, since they are available as the crystalline form.

Furthermore, their gradual conversion into vinyl ketones *in vivo* may be expected, which will be interesting from the point of view for the potential antitumor activity.[8]

Acknowledgement

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References and Notes

1. *Cf.* T. Kametani, H. Nemoto, and K. Fukumoto, *J. Synth. Org. Chem.* (Japan), 35,1009 (1977).
2. P. A. Grieco, D. Boxler, and C. S. Pogonowski, *J. C. S. Chem. Comm.*, 497 (1974).
3. Y. Oikawa, T. Kurosawa, and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), 23, 2466 (1975).
4. Elimination of R-S(→O)-group in γ-keto-sulfoxides should be easier than that of β-keto-sulfoxides.
5. *Cf.* D. Seebach and E. J. Corey, *J. Org. Chem.*, 40, 231 (1975).
6. E. Fujita, Y. Nagao, and K. Kaneko, *Chem. Pharm. Bull.* (Tokyo), 24, 1115 (1976); *idem., ibid.*, 26, 3743 (1978); Y. Nagao, K. Kaneko, K. Kawabata, and E. Fujita, *Tetrahedron Lett.*, 5021 (1978).
7. *Cf.* Y. Nagao, K. Kaneko, and E. Fujita, *Tetrahedron Lett.*, 1215 (1976).
8. E. Fujita and Y. Nagao, *Bioorg. Chem.*, 6, 287 (1977).

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