Pure & Appl. Chem., Vol. 59, No. 8, pp. 1033–1039, 1987.
Printed in Great Britain.

Development of sulfur compounds as synthetic reagents

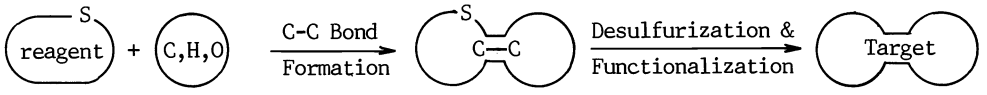
Katsuyuki Ogura

Department of Synthetic Chemistry, Faculty of Engineering, Chiba University

Abstract - Combinations of a thio group and a sulfonyl group have proven to be useful for development of synthetic reagents. Now, I describe organic syntheses using methylthiomethyl p-tolyl sulfone (MT-sulfone) and 3-(methylthio)-2-propenyl p-tolyl sulfone which are prepared from easily obtainable DMSO and 1,3-dichloropropene, respectively.

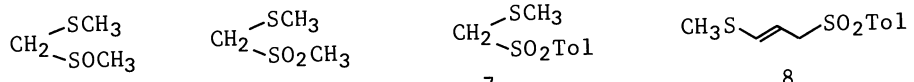
INTRODUCTION

To date, many reports have appeared on using sulfur compounds for organic synthesis, since Corey and Seebach reported the utilization of 1,3-dithiane for preparation of aldehydes and ketones (ref. 1). In general, an organic sulfur compound can be used as a synthetic reagent according to the following scheme, which consists of two processes: (i) formation of a C-C bond between a sulfur reagent (1) and an organic compound (2) to afford an intermediate (3) and (ii) desulfurization of 3 accompanied with creation of a new functional group to produce a desired compound (4).



1 2 3 4

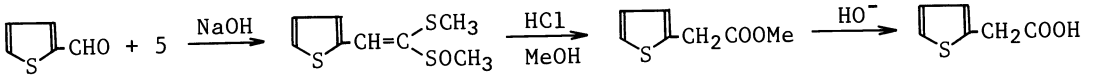
In 1970, our investigation was also initiated in this field, focusing our attention on a combination of two sulfur functionalities, the oxidation states of which are different each other. Hitherto, we have developed four sulfur-containing reagents: methyl methylthiomethyl sulfoxide (FAMSO; 5), methyl methylthiomethyl sulfone (6), methylthiomethyl p-tolyl sulfone (MT-sulfone; 7), and 3-methylthio-2-propenyl p-tolyl sulfone (8).



5 6 7 8

(Tol = p-tolyl)

Methyl methylthiomethyl sulfoxide (5), which possesses methylthio group and methylsulfinyl group on the central methylene carbon, is also named FAMSO by abbreviating another name "formaldehyde dimethyl dithioacetal S-oxide". Oxidation of formaldehyde dimethyl dithioacetal with hydrogen peroxide provides a convenient method.[2] Among many kinds of synthetic methods using FAMSO (5), preparation of (2-thienyl)acetic acid from 2-thiophenecarbaldehyde is performed on a commercial basis. The reason why this method is suitable to the industrial production of (2-thienyl)acetic acid is mainly because FAMSO can be produced in a low cost and because all of the reactions employed proceed in high yields under convenient and mild conditions (ref. 2,3).

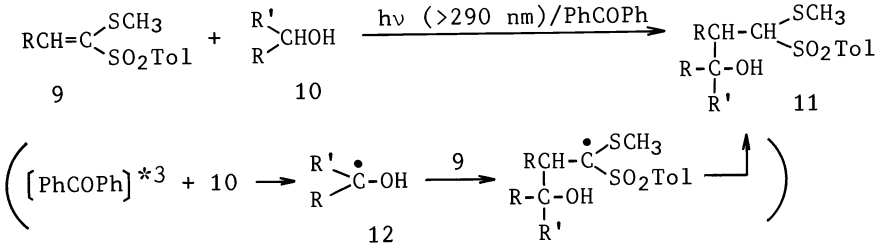


Recently, we found that combinations of a thio group and a sulfonyl group also provides intriguing and useful reagents. Now we would like to describe our research on organic syntheses using 7 and 8.

ORGANIC SYNTHESIS USING METHYLTHIOMETHYL *p*-TOLYL SULFONE (MT-SULFONE) (7)

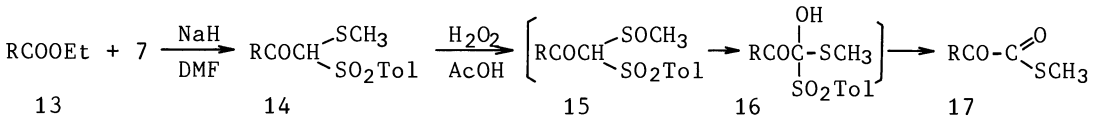
Since a sulfonyl group stabilizes more strongly than the corresponding sulfinyl group, 6 generates an carbanion on their central methylene carbon more easily than 5 does. In fact, 6 undergoes alkylation with an alkyl halide and 50% aqueous sodium hydroxide under the two-

phase reaction conditions using trioctylmethylammonium chloride (TOMAC) as a phase transfer catalyst (ref. 4), which is not applied to alkylation of 5. The Knoevenagel condensation of 6 with an aromatic aldehyde also occurs in the presence of potassium carbonate in refluxing 2-propanol (ref. 5). This combination exhibits another distinct feature that a radical is easily formed on the carbon having both of a thio group (dative group) and a sulfonyl group (captive group).

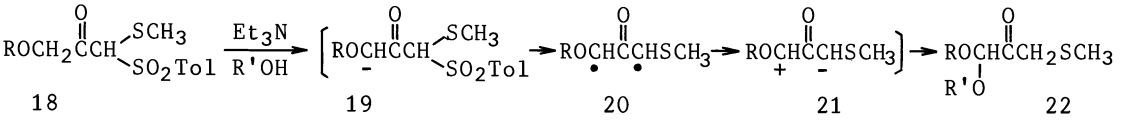


This captodative effect brought about an efficient C-C bond formation in the reaction of a ketene dithioacetal S,S-dioxide (9) with an α-hydroxyalkyl radical (12). Thus irradiation (>290 nm) of 9 in an alcohol (10) containing benzophenone gave an adduct (11) in a high yield, where photochemically excited benzophenone might abstract the α-hydrogen of 10 to produce 12 which smoothly added to 9 (ref. 6).

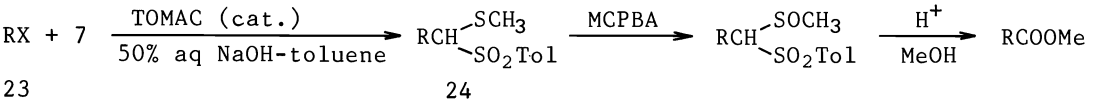
During our investigation to elucidate synthetic methods using 6, we encountered with the trouble that both the central methylene and the sulfonyl methyl of 6 competitively form the corresponding carbanions with a base. Hence we turned our attention to 7 as an alternative reagent. By analogy to the relationship between the pKa values of dimethyl sulfone (31.1) and methyl phenyl sulfone (29.0), the methylene of 7 is estimated to be more acidic by about two pKa units than that of 6. When 7 was subjected to the reaction with a carboxylic ester (13) in the presence of excess NaH in THF, acylation regiospecifically took place to give 14. Under the similar conditions, 6 underwent acylation at the sulfonyl methyl as well as the central methylene. Conversion of the dithioacetal S,S-dioxide group to (methylthio)carbonyl group could be easily achieved by oxidation with hydrogen peroxide in acetic acid at 18 °C followed by slowly warming the reaction system up to 70 °C, which caused a Pummerer-type reaction of the thus obtained sulfoxide (15) and the concurrent elimination of p-toluenesulfinic acid. Thus a new method for synthesizing an S-methyl α-ketocarbothioate (17) was realized by the use of 7 (ref. 7).



To our surprise, the alkoxyacetyl derivative (18) of 7 exhibited an interesting behavior on treatment with such a weak base as triethylamine or sodium acetate. When 18 was treated with triethylamine in an alcohol at an ambient temperature, an acetal (22) of 3-methylthio-2-oxopropanal was produced in an moderate yield (60-70%), probably via a zwitter ion (21) which might be produced by electron transfer from an α-carbanion (19) to the C-SO_2 bond (ref. 8).

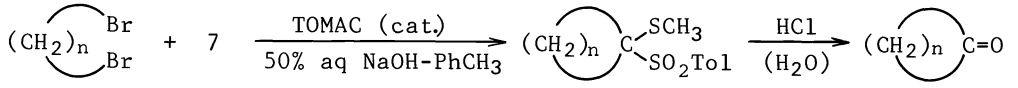


The high acidity of 7 reflected the effectual alkylation. Under the so-called "phase-transfer" conditions using a catalytic amount of trioctylmethylammonium chloride (TOMAC) in toluene-50% aq NaOH, 7 underwent a smooth reaction with an alkyl halide and an alkylated product (24) was afforded in a high yield. The yields were usually higher by 10-20% than those obtained when 6 was employed instead of 7. The product (24) could be transformed into the corresponding methyl ester (12) by oxidation with hydrogen peroxide in acetic acid and the subsequent treatment with hydrogen chloride or sulfuric acid in refluxing methanol (ref. 7).



Under the "phase-transfer" conditions, 1,5-dibromopentane and 1,4-dibromobutane also reacted with 7 to quantitatively give cyclic products (25). A cyclobutanone derivative (25; n = 3) was also obtained under the similar conditions, but its yield was relatively low (45%). The

high yield (85%) of 25 (n = 3) was attained by the reaction of 7 with 1,3-dibromopropane in the presence of NaH in DMF. Since 25 was converted to the corresponding cycloalkanone in a high yield (Table 1), 7 has proven to be useful for the synthesis of six-, five- and four-membered cycloalkanones (ref. 7).



(n = 3, 4, 5) 25

It is noteworthy that the methine proton of the monoalkylated derivative 24 can be cleanly abstracted with NaH in DMF at room temperature to generate the corresponding carbanion, which reacted with an alkyl halide to give a dialkylated product (26). The combination of this fact with the acid-assisted hydrolysis of ketone dithioacetal S,S-dioxides provides a convenient synthetic route leading to symmetrical and unsymmetrical ketones. Table 1 summarized these results. For the preparation of symmetrical ketones, direct dialkylation of 7 with 2 mol-equiv of an alkyl halide and 2 equiv of NaH in DMF is recommended (ref. 9).

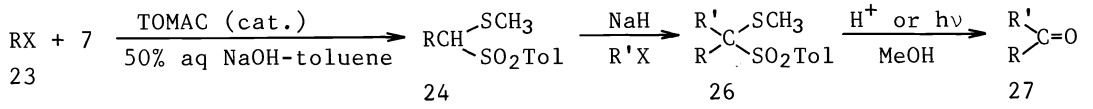
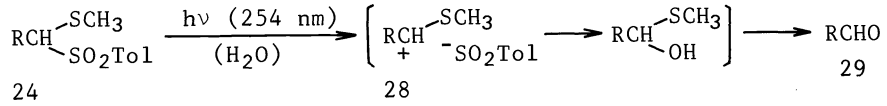


Table 1. Ketone Synthesis Using 7

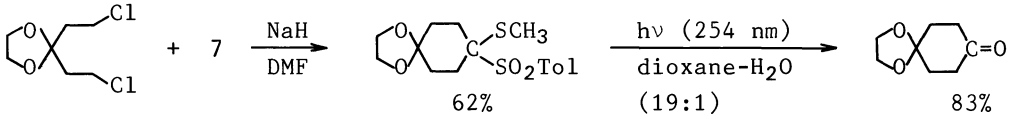
Starting Material	Alkyl Halide (equiv)	Alkylation[a] Temp(°C)/Time(h)	Hydrolysis[b] Temp/Time(h)	Overall Yield
24; R=$PhCH_2$	CH_3I (3.1)	A: rt/19	D: reflux/2	96%
24; R=$PhCH_2$	n-$C_6H_{13}Br$ (2.0)	A: rt/48→50/3	D: reflux/3	92%
24; R=CH_3	$PhCH_2Br$ (1.5)	A: rt/48→60/3	E: reflux/3	85%
24; R=n-$C_{12}H_{25}$	CH_3I (2.4)	A: rt/42	D: reflux/3	90%
1	$PhCH_2Br$ (2.3)	B: rt/48→60/3	E: reflux/3	74%
1	n-$C_{12}H_{25}Br$ (2.6)	B: rt/48→50/3	E: reflux/3	93%
1	$Br(CH_2)_5Br$ (1.0)	C: 60/144	D: reflux/3	91%
1	$Br(CH_2)_4Br$ (1.0)	C: 60/96	D: reflux/5	98%
1	$Br(CH_2)_3Br$ (1.0)	B: -15/6→rt/18	F: 100 °C/20	83%

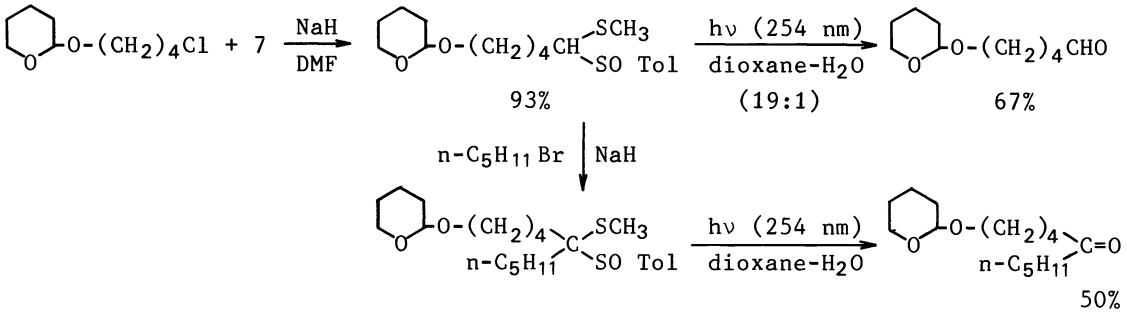
[a] A: with NaH (1.3 equiv)/DMF; B: with NaH (2.5 equiv)/DMF; C: with TOMAC (0.02 equiv)/toluene-50% aq NaOH. [b] D: with conc HCl/MeOH (0.3-1/10 v/v); E: with conc H_2SO_4/MeOH (0.5-1/10 v/v); F: with conc HCl/dioxane (1/10 v/v).

By contrast, the monoalkylated product 24 resisted the above-mentioned hydrolysis. For example, 24 (R = n-dodecyl) was quantitatively recovered even after being heated in conc hydrochloric acid-methanol (1:10) under a reflux for 24 h. Hence, we examined the irradiation of 24 in the presence of water, in expectation of the heterolytic cleavage of the C-SO_2 bond to give an intermediary carbenium ion (28) which led to an aldehyde (29) by capture of water and the subsequent removal of methanethiol.

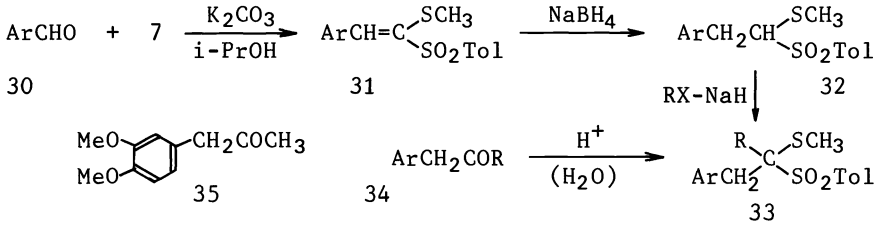


When a solution of 24 (R = n-dodecyl) in dioxane-water (19:1) was irradiated with a low-pressure Hg arc lamp through a Vycor filter, a smooth reaction took place in the presence or absence of a base such as NaHCO or NaOH to give tridecanal (29; R = n-dodecyl). Under the same conditions, 1-methylsulfonyl-1-(methylthio)tridecane remained unchanged, indicating that the photochemical transformation of 24 is initiated by the light absorption of the p-tolyl group. Since the photolytic formation of 29 was not affected by oxygen-bubbling and the employment of ethanol as a solvent produced 1-ethoxy-1-(methylthio)tridecane, the photochemical transformation has proven to involve the cation 28. In the similar manner, the dialkylated derivative (26) underwent photochemical hydrolysis to give the ketones 27. Since this hydrolysis can be conducted under neutral conditions, the present method is suitably applied to preparation of aldehydes and ketones which are susceptible to an acid. A few examples are shown in the following.



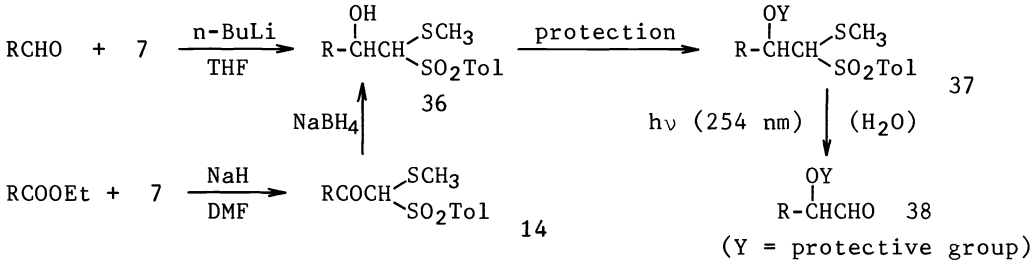


We have found that the C-C double bond of ketene dithioacetal S,S-dioxides is reducible with sodium borohydride. Since arylketene dithioacetal S,S-dioxides (31) are easily prepared by the Knoevenagel condensation of 7 with aromatic aldehydes (30), this fact enables us to conveniently and safely prepare alkyl arylmethyl ketones (34) from 30 according to the following Scheme. The present route is superior to the conventional way, i.e. alkylation of 7 with an arylmethyl halide and a base because the arylmethyl halide, especially the

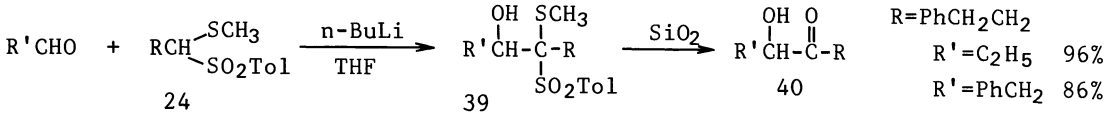


alkoxyl(s)-substituted one, is very unstable and intensely irritant to skin, eyes, and mucous membranes. This provides a convenient route from veratraldehyde to (3,4-dimethoxyphenyl)methyl methyl ketone (35), a synthetic precursor of an antihypertensive drug, methyldopa (ref. 10).

By the use of MT-sulfone (7), we established a simple and general way to produce OH-protected α-hydroxy aldehydes (38). The lithio derivative of 7 reacted with an aldehyde to afford an adduct (36), which was also obtained by the reduction of an acyl derivative (14). Since most of α-hydroxy aldehydes are so unstable as to easily dimerize, the hydroxyl group of 36 must be protected with an easily removable group prior to the hydrolysis. As a result of surveying various conditions, acetyl, tetrahydropyranyl, and methoxymethyl groups were favorably employed without affecting the dithioacetal S,S-dioxide functionality. Irradiation of the OH-protected derivative (37) with a 254 nm light under neutral or basic conditions afforded 38 (ref. 11).

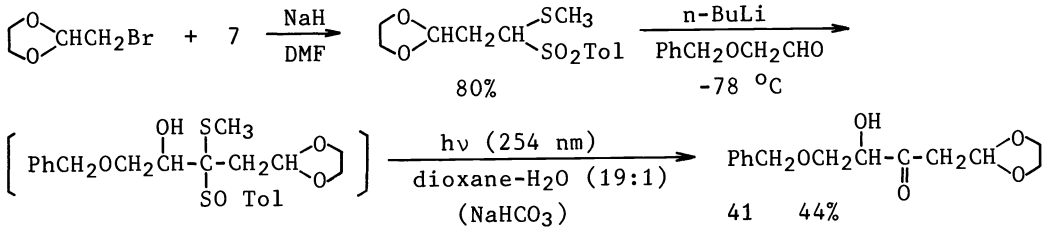


An efficient synthesis of α-hydroxy ketones (40) was also achieved: (i) the addition of the monoalkyl derivative (24) to an aldehyde leading to an adduct (39) and (ii) the subsequent hydrolysis of 39 on silica gel. Isolation of the intermediary 39 is unnecessary and the overall yield of 40 from 24 is excellent. Smooth hydrolysis of 39 on silica gel is an unanticipated result. This may be attributable to the presence of the neighboring hydroxyl group which assists heterolytic dissociation of the C-SO_2 bond of 39.

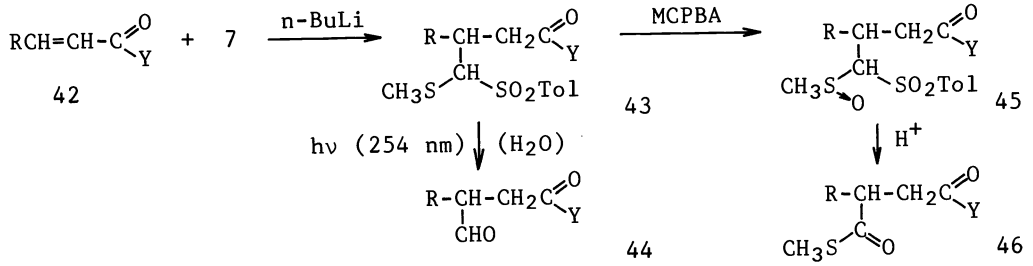


When a silica gel-sensitive functional group is involved in R or R', the photochemical hydrolysis was suitably applied to the transformation of 39 into 40, which was exemplified

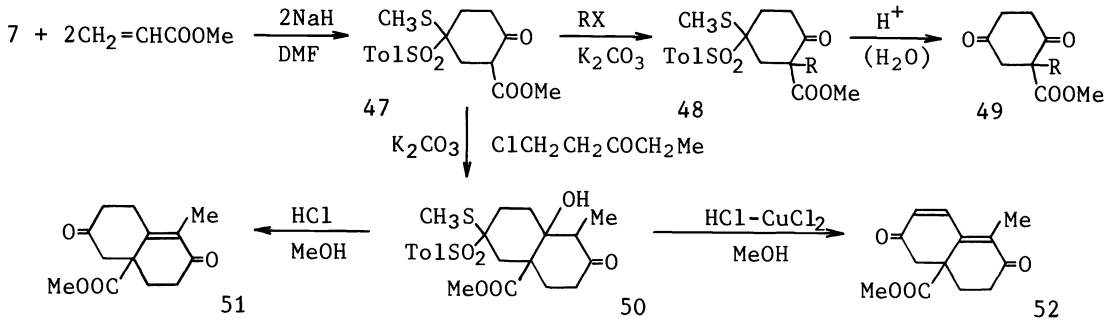
by the synthesis of a precursor (41) of 2-deoxyribose.



As above mentioned, 7 forms a stable carbanion. Hence, the carbanion of 7 is expected to add to α,β-unsaturated carbonyl compounds (42) in a [1,4] fashion. In fact, the lithio derivative of 7 reacted with various 42 to afford the corresponding [1,4] adducts (43) in good to high yields. The introduced (methylthio)(p-tolylsulfonyl)methyl group was easily converted to a (methylthio)carbonyl group or a formyl group (ref. 12).

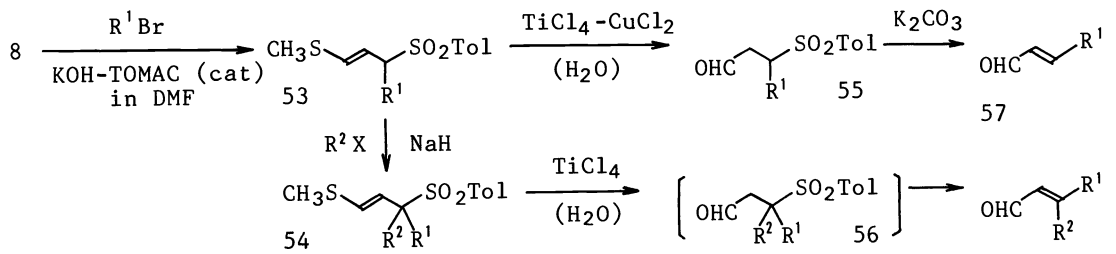


When the reaction of 7 with methyl acrylate was performed with NaH in DMF at an ambient temperature, 2-(methoxycarbonyl)-4-(methylthio)-4-(p-tolylsulfonyl)cyclohexanone (47) was obtained in 81% yield. Furthermore, 47 was shown to be an important intermediate for preparing 2-substituted 2-(methoxycarbonyl)-1,4-cyclohexanediones (49), 6-(methoxycarbonyl)-2-methylbicyclo[4,4,0]dec-1-ene-3,8-dione (51), and 6-(methoxycarbonyl)-2-methylbicyclo-[4,4,0]deca-1,9-diene-3,8-dione (52) (ref. 13).



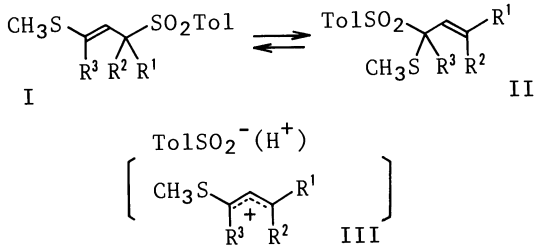
ORGANIC SYNTHESIS USING 3-METHYLTHIO-2-PROPENYL *p*-TOLYL SULFONE (8)

A vinylene homolog of 7, 3-methylthio-2-propenyl p-tolyl sulfone (8), was found to be a novel reagent for making α,β-unsaturated aldehydes (57 and 58): Alkylation of 8 took



place regiospecifically on the carbon α to the sulfonyl group to optionally give a mono- or di-alkylated product (53 or 54), the vinyl sulfide part of which was hydrolyzed by the assistance of titanium chloride and cupric chloride (ref. 14).

During the course of our investigation, we found a facile 1,3-rearrangement of a sulfonyl group in a sulfenyled allylic system such as 54, which is generally represented by the following equation (I ⇌ II) (ref. 15).

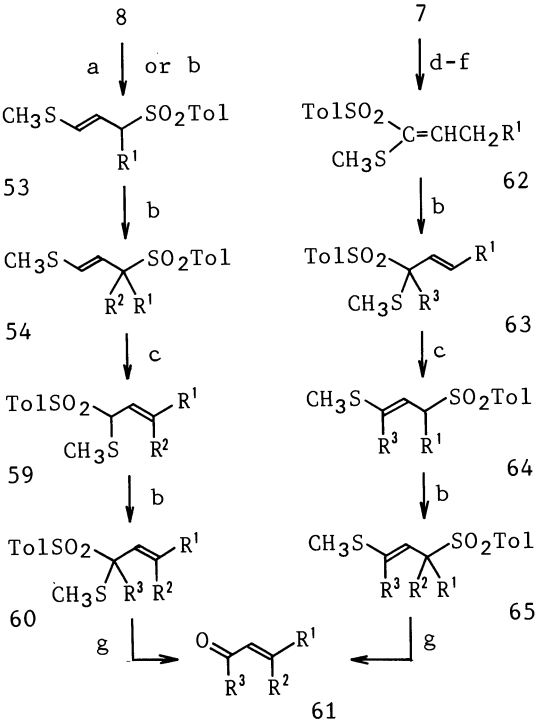


The Equilibrium between I and II

R^1	R^2	R^3	favorable side
alkyl	H	H	I
alkyl	alkyl	H	II[a]
alkyl	H	alkyl	I
H	H	alkyl	I

[a] Except the case of $R^1 = R^2 = Me$

This rearrangement is reversibly attained by the action of a weak acid such as silica gel at an ambient temperature, probably via a cationic intermediate (III). The equilibrium undergoes the significant effect of substituents: When the position α to the sulfonyl group in I is much congested by two alkyls, the equilibrium lies to the side of II. On the other hand, I is thermodynamically stable when R^3 is an alkyl and R^2 is hydrogen. These phenomena are desirable to introducing the third alkyl group to produce a trialkylated I or II ($R^1 = R^2 = R^3$ = alkyl) which realizes a convenient and efficient synthesis of highly substituted α,β-unsaturated ketones (61) starting from 7 and 8.



a: alkyl halide-KOH-TOMAC (cat.) in DMF

b: alkyl halide-NaH in DMF

c: silica gel

d: $R^1CH_2CH_2Br$-TOMAC (cat.) in 50% aq NaOH-$PhCH_3$

e: SO_2Cl_2 in $CHCl_3$

f: heat in $PhCH_3$ (N_2 bubbling)

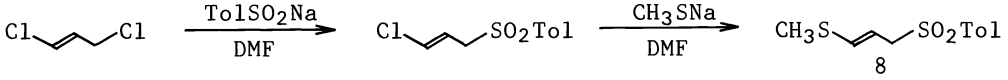
g: $CuCl_2$ in MeOH-H_2O

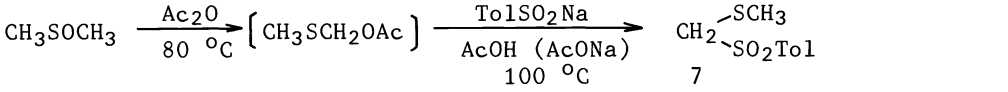
The dialkylated product 54, which was easily obtained from 8, was smoothly transformed into 59 on silica gel. Treatment of the thus-obtained 59 with NaH and an alkyl halide in DMF yielded a trialkylated product (60). Starting from MT-sulfone (7), another trialkylated derivative (65) was also prepared: Alkylation of the alkylidene derivative (62) of 7 followed by treatment with silica gel gave a di-substituted derivative (64), which was further alkylated with an alkyl halide and NaH in DMF to afford 65. When 60 or 65, without any purification, was subjected to the reaction with cupric chloride in methanol-water, hydrolysis of the vinyl sulfide part and dehydrosulfinylation successively occurred to yield 61. The present methods are characterized by the following features: (i) it is widely applicable to making various α,β-unsaturated ketones (61), three substituents of which are optionally and regiospecifically selected; (ii) an inexpensive and easily handled base as NaH or KOH, which enable us to practice these methods on a large scale; (iii) all of the

reactions proceed under mild and convenient conditions. Thus novel synthetic routes to highly substituted α,β-unsaturated ketones (61) by the use of the equilibratory allylic a 1,3-rearrangement of a sulfonyl group, wherein 8 and 7 are utilized as synthetic equivalents of a trianion (O=C-CH=C^{-}) and a dianion (O=C-CH=C-R^{1}), respectively.

SYNTHESIS OF MT-SULFONE (7) AND 3-METHYLTHIO-2-PROPENYL *p*-TOLYL SULFONE (8)

Thus the reagents 7 and 8 have proven to serve as a versatile reagent for making many kinds of organic compounds. Finally we would like to describe convenient methods for preparing these reagents. Although we first synthesized 8 by the reaction of 3-chloro-1-propenyl p-tolyl sulfone with dimethyl sulfide or sodium methanethiolate (ref. 16), we have developed an efficient route from 1,3-dichloropropene to 8: Treatment of 1,3-dichloropropene with sodium p-toluenesulfinate afforded 3-chloro-2-propenyl p-tolyl sulfone, which was subjected to the reaction with sodium methanethiolate to yield 8 (ref. 17).





After examination of various reactions leading to 7, we exploited a convenient method starting from DMSO in one-pot manner: Treatment of DMSO with acetic anhydride followed by the reaction of the resulting acetoxymethyl methyl sulfide with sodium p-toluenesulfinate in acetic acid (ref. 18). Since 7 is so hygroscopic and thermally stable that it can be stored without special care, we hope that MT-sulfone (7) will be utilized as a versatile synthetic reagent in many laboratories (ref. 19).

REFERENCES

1. E. J. Corey and D. Seebach, Angew. Chem. Intern. Ed. Engl., 4, 1075-1077 (1965).
2. K. Ogura and G. Tsuchihashi, Bull. Chem. Soc. Jpn., 45, 2203-2204 (1972).
3. K. Ogura and G. Tsuchihashi, Tetrahedron Lett., 1972, 1383-1386; K. Ogura, Y. Itoh, and G. Tsuchihashi, Bull. Chem. Soc. Jpn., 52, 2013-2022 (1979).
4. K. Ogura, J. Watanabe, and H. Iida, Tetrahedron Lett., 22, 4499-4502 (1981).
5. K. Ogura, J. Watanabe, K. Takahashi, and H. Iida, J. Org. Chem., 47, 5404-5406 (1982).
6. K. Ogura, A. Yanagisawa, K. Takahashi, and H. Iida, an unpublished result.
7. K. Ogura, N. Yahata, K. Takahashi, and H. Iida, Chem. Lett., No. 5, 767-770 (1983).
8. K. Ogura, T. Uchida, K. Takahashi, and H. Iida, an unpublished result.
9. K. Ogura, K. Ohtsuki, M. Nakamura, N. Yahata, K. Takahashi, and H. Iida, Tetrahedron Lett., 26, 2455-2458 (1985).
10. K. Ogura, K. Ohtsuki, K. Takahashi, and H. Iida, Chem. Lett., No. 9, 1597-1598 (1986).
11. K. Ogura, T. Tsuruda, K. Takahashi, and H. Iida, Tetrahedron Lett., 27, 3665-3668 (1986).
12. K. Ogura, N. Yahata, M. Minoguchi, K. Ohtsuki, K. Takahashi, and H. Iida, J. Org. Chem., 51, 508-512 (1986).
13. K. Ogura, N. Yahata, M. Minoguchi, A. Sampei, K. Takahashi, and H. Iida, an unpublished result.
14. K. Ogura, T. Iihama, K. Takahashi, and H. Iida, Tetrahedron Lett., 25, 2671-2674 (1984).
15. K. Ogura, T. Iihama, S. Kiuch, T. Kajiki, O. Koshikawa, K. Takahashi, and H. Iida, J. Org. Soc., 51, 700-705 (1986).
16. K. Ogura, T. Iihama, K. Takahashi, and H. Iida, Bull. Chem. Soc. Jpn., 57, 3347-3348 (1984).
17. K. Ogura, T. Iihama, O. Koshikawa, K. Takahashi, and H. Iida, an unpublished result.
18. K. Ogura, N. Yahata, K. Takahashi, and H. Iida, Bull. Chem. Soc. Jpn., 56, 3543-3544 (1983).
19. Now this reagent (7) is commercially available.