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UTILIZATION OF METHYLTHIOMETHYL p-TOLYL SULFONE IN ORGANIC SYNTHESIS

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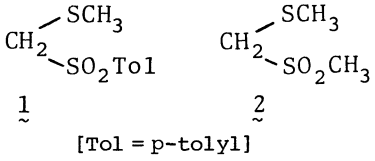
Methylthiomethyl p-tolyl sulfone was found to be one of the useful reagents for preparation of various organic compounds such as S-methyl α-ketocarbothioates, carboxylic esters, five- and six-membered cycloalkanones, and α-methoxy-α-arylacetic esters.

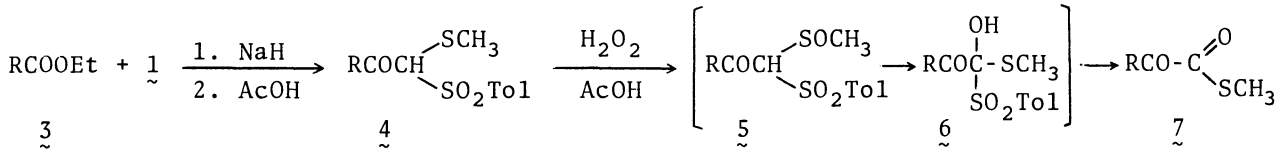
In this paper, we would like to describe that methylthiomethyl p-tolyl sulfone (1)[1] is of considerable value in organic synthesis. Recently, our reports disclosed the usefulness of methyl methylthiomethyl sulfone (2) for making carboxylic esters,[2] acyclic and cyclic ketones,[3] and α-alkoxy-α-arylacetic esters.[4] During our investigation to explore further synthetic utility of 2, we have often encountered with the trouble that both the central methylene and the sulfonyl methyl of 2 competitively form the corresponding carbanions with a base (*vide post*). Hence we turned our attention to the employment of 1 as an alternative reagent on the premise that a carbanion can be regioselectively and efficiently generated at its methylene position. By analogy to the relationship between the pK_a values of dimethyl sulfone (31.1) and methyl phenyl sulfone (29.0),[5] the methylene of 1 is estimated to be more acidic by about two pK_a units than that of 2.



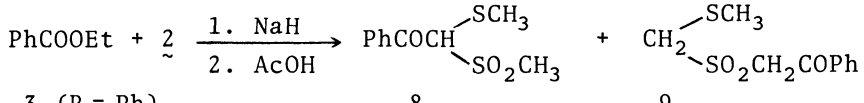
1 2

[Tol = p-tolyl]

When 1 was subjected to the reaction with ethyl benzoate (3, R = Ph) in the presence of excess NaH in THF, benzoylation took place regiospecifically to produce 4 (R = Ph) in 71% yield.[6] This is in sharp contrast with the fact that 2 undergoes the benzoylation on both the methylene and sulfonyl methyl carbons under the similar conditions to afford a mixture of 8 (30%) and 9 (27%). As shown in Table 1, other aromatic and aliphatic carboxylic esters (3) also reacted with 1, and the corresponding acylated products (4) were given in from moderate to good yields.



3 4 5 6 7



3 (R = Ph) 8 9

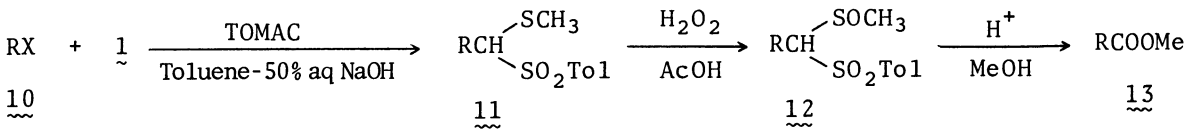
Conversion of the dithioacetal S,S-dioxide group of 4 to methylthiocarbonyl group could be easily achieved by oxidation with hydrogen peroxide in acetic acid at 18 °C followed by warming the reaction system up to 70 °C, which caused a Pummerer-type reaction of 5 leading to 6 and the concurrent elimination of p-toluenesulfinic acid. The results are given in Table 1. Thus a new method for synthesizing an S-methyl α-ketocarbothioate (7) by the use of 1 has been established.[7]

Table 1. Conversion of an Ester (3) to an S-Methyl α-Ketocarbothioate (7)

R	2 → 4[a]				4 → 7[d]		
	3[b]	NaH[b]	Temp./Time	Yield[c]	H_2O_2[e]	Temp./Time[f]	Yield[c]
Ph	1.5	2.1	0 °C/2 h→rt/20 h	71%	1.3	18 °C/70 h→70 °C/4 h	71%
p-ClC_6H_4	1.5	3.0	0 °C/1 h→20 °C/15 h	69%	1.2	18 °C/70 h→70 °C/5 h	64%
p-$MeOC_6H_4$	1.7	3.3	rt/1 h→40 °C/18 h	61%	1.2	18 °C/70 h→70 °C/4 h→90 °C/1 h	80%
p-MeC_6H_4	1.6	3.3	0 °C/1 h→rt/18 h	54%	1.2	18 °C/70 h→70 °C/5 h	62%
m-MeC_6H_4	1.5	3.0	rt/17 h	68%	1.2	18 °C/70 h→70 °C/5 h→90 °C/1 h	70%
n-$C_{11}H_{23}$	1.4	3.3	rt/26 h	71%	1.3	18 °C/52 h→70 °C/2 h	66%

[a] in THF. The reaction was quenched with AcOH. [b] mol equiv. to 1. [c] After addition of water, extraction with dichloromethane, and evaporation of the extract, column-chromatography of the residue on silica gel gave 4. [d] in AcOH. [e] mol equiv. to 4. [f] The temperature was slowly raised from 18 °C to 70 °C over a period of 2 h.

The high acidity of 1 reflected the effectual alkylation. Under the so-called "phase-transfer" conditions using a catalytic amount of trioctylmethylammonium chloride (TOMAC) in toluene-50% aq NaOH, 1 underwent a smooth reaction with an alkyl or 2-alkenyl halide (10), and an alkylated or alkenylated product (11) was produced in a high yield.[9] The yields of 11 were usually higher by 10–20% than those obtained when 2 was employed instead of 1.[2] The product (11) could be transformed into the



10 11 12 13

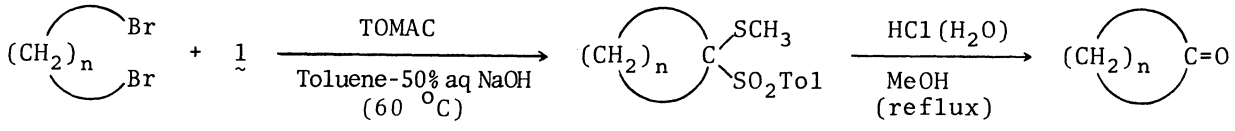
Table 2. Transformation of a Halide (10) into an Ester (13)

RX	10 → 11[a]			11 → 12[c]	12 → 13[e]
	Temp./Time	Yield[b]			
$CH_3(CH_2)_{11}Br$	60 °C/24 h	96%	[84%]	92%	75%
$PhCH_2Br$	rt/48 h	99%	[88%]	69% (96%)[d]	88%
$PhCH_2Cl$	rt/44 h	97%			
$CH_3(CH_2)_6CH=CHCH_2Br$	rt/48 h	93%	[69%]	---[f]	54%[g]

[a] A halide (10, 1.5 mol equiv.) and 1 were stirred with TOMAC (0.02 mol equiv.) in toluene–50% aq NaOH. [b] The yield was based on the used 1. The value in the bracket means the yield obtained when 1.0 mol equiv. of 10 was used. [c] With hydrogen peroxide (1.1 mol equiv.) in AcOH at room temperature for 24 h. [d] The yield based on the unrecovered 11. [e] Treated with HCl (1.7 mol/l) or H_2SO_4 (0.4 mol/l) in refluxing methanol for 6-8 h. [f] Not isolated because the oxidized product was unstable. [g] Overall yield of 13 from 11.

corresponding methyl ester (13) by oxidation with hydrogen peroxide in acetic acid and the subsequent treatment with hydrogen chloride or sulfuric acid in refluxing methanol. Table 2 summarizes these results.

Under the "phase-transfer" conditions, 1,4-dibrompentane and 1,5-dibromobutane also reacted with 1 to give cyclic products (15), which could be further derived into cyclohexanone and cyclopentanone, respectively, in almost quantitative yields by treatment with conc hydrochloric acid (1.2 mol/l) in refluxing methanol. Therefore, 1 has proven to be very useful for synthesis of six- and five-membered cycloalkanones.



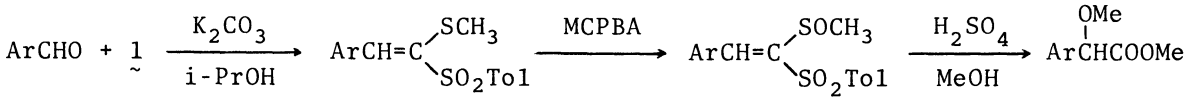
14

n = 5 96%[a]
n = 4 ---[a,b]

n = 5 95%
n = 4 98%[c]

[[a] 1.0 mol equiv. of 14 was used. [b] not isolated. [c] overall yield from 14]

Finally, we wish to report that 1 also is a useful reagent for transformation of an aromatic aldehyde (15) into an α-methoxy-α-arylacetic ester (18), which comprises condensation of 1 with 15 to afford 1-aryl-2-methylthio-2-(p-tolylsulfonyl)-ethene (16), oxidation of 16 leading to 1-aryl-2-methylsulfinyl-2-(p-tolylsulfonyl)-ethene (17), and the acid-catalyzed degradation of 17 in methanol. We have already reported that this sequence could be accomplished by the use of 2 in place of 1.[4] As being apparent from a perusal of Table 3, 1 can be also utilized as a reagent for this transformation. Here it should be emphasized that the K_2CO_3-catalyzed condensation of 15 with 1 gives 16 in a higher yield when compared to the result with 2.[4] This may be attributable to the lower pK_a of 1 than that of 2.



15 16 17 18

Table 3. Conversion of an Aromatic Aldehyde (15) into an α-Methoxy-α-arylacetate (18)

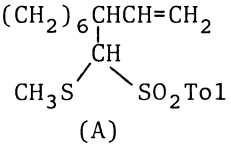
Ar	15 → 16[a] Temp./Time	15 → 16[a] Yield[b]	16 → 17[c,d]	17 → 18[e]
Ph	reflux/43 h	85% (100%)	93% (100%)	74%
3,4-$(MeO)_2C_6H_3$	reflux/45 h	68% (96%)	83% (99%)	74%
2-Thienyl	reflux/48 h	96%	81% (100%)	85%

[a] A solution containing 15 (1.5–1.6 mol equiv.) and 1 in isopropyl alcohol was stirred in the presence of K_2CO_3 (2.0 mol equiv.). [b] The value in the parenthesis is the yield based on the unrecovered 1. [c] With MCPBA (1 mol equiv.) in dichloromethane at -10 °C for 3 h. [d] The value in the parenthesis means the yield based on the unrecovered 16. [e] A solution of 17 in 0.9 mol/l methanolic solution of sulfuric acid was heated under reflux for 18–24 h.

In conclusion, methylthiomethyl p-tolyl sulfone (1) can be preferably employed as a reagent for many kinds of organic syntheses. As compared with 2, the present reagent (1) possesses the following advantageous points: (i) Treatment of 1 with a base forms a carbanion regiospecifically at the methylene position; (ii) the carbanion is generated with a higher efficiency to give an alkylated product or a condensation product in a higher yield in the reaction with an alkyl halide or an aromatic aldehyde, respectively; and (iii) 1 can be conveniently prepared by a manipulative procedure starting from dimethyl sulfoxide.[1] Further synthetic utilities of this reagent are being studied in our laboratory.

References

1) This reagent (1) can be efficiently prepared from dimethyl sulfoxide in one-pot fashion. A mixture of dimethyl sulfoxide (1 mol equiv.) and acetic anhydride (1.3 mol equiv.) was heated at 80 °C for 24 h. After addition of acetic acid (13.4 mol equiv.), sodum acetate (1 mol equiv.), and sodium p-toluenesulfinate (1.5 mol equiv.), the resulting mixture was further heated at 100 °C for 26 h to give 1 in 71% yield. The detail will be reported elsewhere in the near future.
2) K. Ogura, J. Watanabe, and H. Iida, Tetrahedron Lett., 22, 4499 (1981).
3) K. Ogura, M. Suzuki, J. Watanabe, M. Yamashita, H. Iida, and G. Tsuchihashi, Chem. Lett., 1982, 813.
4) K. Ogura, J. Watanabe, K. Takahashi, and H. Iida, J. Org. Chem., 47, 5404 (1982).
5) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, J. Am. Chem. Soc., 97, 7006 (1975).
6) Satisfactory elemental analyses and spectral data have been obtained for all new compounds reported herein.
7) Formylation of 1 with methyl formate in the presence of potassium t-butoxide in THF was reported.[8]
8) G. Ferdinand and K. Schank, Synthesis, 1976, 406.
9) Reaction of 1 with 2-decenyl bromide (10, R = $CH_3(CH_2)_6CH{=}CHCH_2$) in the presence of insoluble K_2CO_3 (2 mol equiv.) in HMPA was very slow, and, even after heating at 60 °C for 48 h, the expected S_N2' product (A) was produced in only 10% yield. Under these conditions, 2 reacted with 2-alkenyl bromide to give the S_N2'-type product in moderate yield.[2]



(A)

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