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# AN EFFICIENT REAGENT FOR SYNTHESIS OF α,β-UNSATURATED ALDEHYDES 3-METHYLTHIO-2-PROPENYL p-TOLYL SULFONE

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*Abstract: Alkylation of 3-methylthio-2-propenyl p-tolyl sulfone (1) with an alkyl halide and a base (NaH or KOH-TOMAC) took place at the position α to the sulfonyl group to give optionally a mono- or dialkylated product (2 or 3), which was converted to β-monosubstituted or β,β-disubstituted α,β-unsaturated aldehyde (6 or 7), respectively, by* $TiCl_4$*-assisted hydrolysis followed by the removal of p-toluenesulfinic acid.*

α,β-Unsaturated aldehydes, which are widely distributed in naturally occurring products, can serve as important intermediates in organic synthesis. We now wish to report a new and convenient method for making α,β-unsaturated aldehydes (6 and 7) by the use of 3-methylthio-2-propenyl p-tolyl sulfone (1),[1] which comprises alkylation of 1 to give optionally a mono- or dialkylated product (2 or 3) and the subsequent acid hydrolysis of the vinyl sulfide part of 2 or 3, followed by the elimination of p-toluenesulfinic acid.

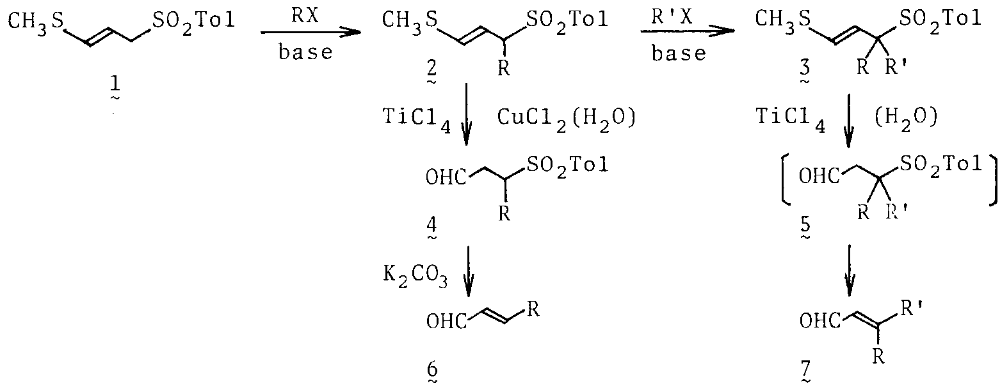


Table 1 summarizes the results for synthesis of β-monosubstituted α,β-unsaturated aldehydes (6). Monoalkylation of 1 can be achieved by treatment with an alkyl halide (RBr or RI) in the presence of KOH-TOMAC (trioctylmethylammonium chloride) or NaH in DMF at -15 °C. For the acid hydrolysis of 2, a combination of $TiCl_4$ and $CuCl_2$ was most effective among the reagents examined herein.[3] Thus, the reaction of 2 with $TiCl_4$ (2 mol-equiv) and $CuCl_2$ (2 mol-equiv) in AcOH-water (9 : 1) at room temperature to 50 °C gave 4, which was treated with $K_2CO_3$(2 mol-equiv) in DME (1,2-di-

Table 1. Synthesis of β-Monosubstituted α,β-Unsaturated Aldehydes (6)

| $1 \longrightarrow 2^a$ | | | $2 \longrightarrow 4^b$ | $4 \longrightarrow 6^c$ | Yield |
|---|---|---|---|---|---|
| RX | Base/Solvent [Temp./Time] | Yield | Temp./Time | Temp./Time | of $6^d$ |
| n-$C_{12}H_{25}Br$ (1.4) | TOMAC(0.03)-50% aq NaOH/$PhCH_3$ [r.t./1 d → 50 °C/2 d] | 32% | r.t./1 d → 50 °C/6 h | r.t./8 h | 73% |
| n-$C_{12}H_{25}Br$ (1.5) | TOMAC(0.05)-KOH (2.0)/DMF [-15 °C/7 h] | 81% | | | |
| n-$C_{12}H_{25}Br$ (1.0) | NaH(1.1)/DMF [-15 °C/4 h] | 55% | | | |
| n-$C_{12}H_{25}I$ (1.0) | NaH(1.2)/DMF [-15 °C/4 h] | 84% | | | |
| n-$C_{12}H_{25}I$ (1.0) | NaH(1.2)/THF-HMPA(9:1) [-15 °C/1.5 h → r.t./2 h] | 70% | | | |
| n-$C_4H_9I$ (1.0) | NaH(1.2)/DMF [-15 °C/2 h] | 91% | r.t./36 h | r.t./12 h | 47% |
| $PhCH_2Br$ (1.0) | NaH(1.2)/DMF [-15 °C/6 h → 0 °C/2 h] | 70%[e] | r.t./18 h → 40 °C/8 h | r.t./15 h | 69% |

[a] ( ) = mol-equiv to 1. [b] with $TiCl_4$ (2.0 mol-equiv) and $CuCl_2$ (2.0 mol-equiv) in AcOH-water (9 : 1). [c] with $K_2CO_3$ (2.0 mol-equiv) in DME. [d] the overall yield from 2. [e] 1 (13%) was recovered unchanged.

methoxyethane) at room temperature to affod 6. It should be noted that the absence of $CuCl_2$ in the acid hydrolysis caused formation of the dimethyl dithioacetal of 4 as a by-product (ca. 20%).

When 2 was subjected to the reaction with an alkyl halide in the presence of NaH in DMF, the second alkylation took place regiospecifically at the position α to the sulfonyl group to yield a dialkylated product (3). Since 3 was sensitive to silica gel, the reaction mixture, without any purification, was hydrolyzed with $TiCl_4$ (2 mol-equiv) in $CH_3CN$-water (9 : 1). Surprisingly, 5 was not obtained in this reaction, but 7 was produced in a good yield as shown in Table 2. The spontaneous removal of p-toluenesulfinic acid from 5 might make the copresence of $CuCl_2$ unnecessary because the capture of methanethiol with p-toluenesulfinic acid.[5] For prepareing 3 (R = R'), direct dialkylation of 1 is desirable. Treatment of 1 with NaH (3.0 mol-equiv) and an alkyl halide (RX) (3.0 mol-equiv) in DMF gave 3 (R = R'). The thus-obtained 3 (R = R') was hydrolyzed with $TiCl_4$ (2 mol-equiv) in $CH_3CN$-water (9 : 1) to afford to the corresponding 7 (R = R'). These results are given in Table 2.

In the reaction of 1,3-dibromopropane with 1, formation of two cyclization products (8 and 9) must be taken into consideration. However, when this reaction was performed by the use of NaH (2.2 mol-equiv) in DMF (-15 °C/3 h → r.t./3 h), the only product (8) was formed in 86% yield.[6] This suggests that the α-carbanion stabilization of p-tolylsulfonyl group overcomes the strain of the four-membered ring of 8. When 8 was subjected to the hydrolysis with $TiCl_4$

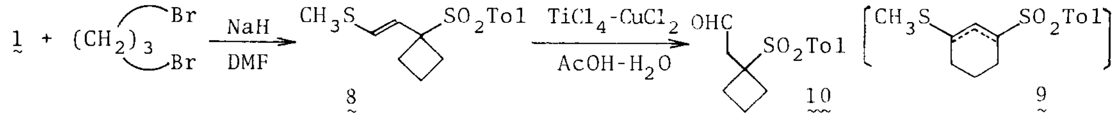


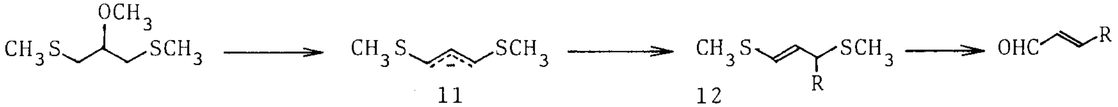
Table 2. Synthesis of β,β-Disubstituted α,β-Unsaturated Aldehydes (7)

| | 1 or 2 $\longrightarrow$ 3 | | | 3 $\longrightarrow$ 7 | Yield |
|---|---|---|---|---|---|
| Substrate | R'X or RX[a] | Method[b] | Temp./Time | Temp./Time[c] | of 7 |
| 2<br>[R = n-$C_{12}H_{25}$] | $CH_3I$ (1.5) | [A] | r.t./1 d | r.t./1 d → 50 °C/6 h | 80%[d,e] |
| | n-$C_4H_9I$ (1.5) | [A] | r.t./12 h | r.t./8 h | 72%[e,g] |
| 1 | n-$C_4H_9I$ (3.0) | [B] | -15 °C/5 h | r.t./8 h | 53%[f] |
| | n-$C_{12}H_{25}I$ (3.0) | [B] | -15 °C/6 h<br>→ r.t./4 d | r.t./7 h | 56%[f] |

[a] ( ) = mol-equiv to 1 or 2. [b] [A] = with NaH (1.2 mol-equiv) in DMF; [B] = with NaH (3.0 mol-equiv) in DMF. [c] with $TiCl_4$ (2.0 mol-equiv) in $CH_3CN$-water (9 : 1). [d] (E) : (Z) = 3 : 2. [e] the overall yield from 2. [f] the overall yield from 1. [g] the (E):(Z) ratio was not determined.

(2.0 mol-equiv) and $CuCl_2$ (2.0 mol-equiv) in AcOH-water (9 : 1) at room temperature for 3 h, 3,3-trimethylene-3-(p-tolylsulfonyl)propanal (10) was produced in 96% yield. This product (10) is a synthetic precursor of 3,3-trimethylenepropanal.[7]

Thus, 3-methylthio-2-propenyl p-tolyl sulfone (1) has proven to be an excellent reagent for the synthesis of β-monosubstituted and β,β-disubstituted α,β-unsaturated aldehydes (6 and 7). As a synthetic equivalent of 2-formylethenyl carbanion ($^-$CH=CHCHO), Corey and his coworkers exploited 1,3-bis(methylthio)-2-propenyl carbanion (11) which was prepared by the action of lithium diisopropylamide (LDA) (2 mol-equiv) on 2-methoxy-1,3-bis(methylthio)propane.[8] Compared with the Corey's procedure, the present method using 1 has some advantageous points: The corresponding carbanion of 1 or 2 can be generated with an easily handled base such as KOH or NaH and the second alkylation (2 → 3) takes place at the position same to that of the first one (1 → 2) to afford 3 with a high regiospecificity. In contrast, further alkylation of the monoalkylated product (12) of 11 is anticipated to give two regioisomeric products (13 and 14) without a high selectivity. Easy generation of the carbanions of 1 and 2 as well as the regiospecificity in the alkylation of 1 and 2 may be attributable to the higher capability of p-tolylsulfonyl group to stabilize an adjacent carbanion than that of methylthio group.[9]



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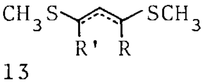

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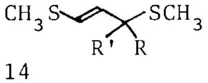

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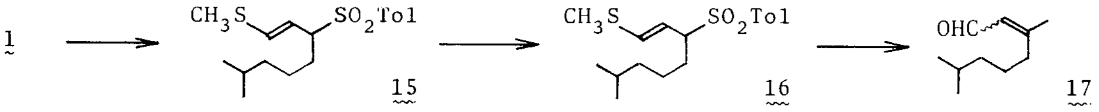
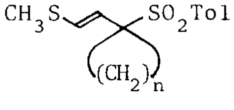
Finally, we would like to describe on the application of the present method to the synthesis of dihydrocitral (17), which also serves as a typical procedure of the present paper. To a solution of 1 (3.63 mmol) in DMF (20 ml), were added 4-methylpentyl bromide (5.54 mmol), TOMAC (0.18 mmol), and pulverized KOH (7.14 mmol), and then the resulting mixture was stirred at -15 °C for 9 h. Then the reaction was quenched by the addition of aqueous $NH_4Cl$ solution and extraced with diethyl ether. The extract was dried over anhydrous $Na_2SO_4$, evaporated, and column-chromatograhed on silica gel [elution with benzene-hexane (2 : 3)] to give a monoalkylated product (15) in 63% yield.[10] To a solution of 15 (1.19 mmol) in DMF (10 ml), were added methyl iodide (1.80 mmol) and NaH (1.78 mmol). The reaction mixture was stirred at room temperature for 24 h. The above mentioned workup was repeated to provide crude 16. Without any purification, this was again dissolved in $CH_3CN$ (18 ml) and the resulting solution was added to the solution prepared by dropwise addition of water (2 ml) to $TiCl_4$ (2.37 mmol) under ice-cooling. The mixture was warmed at 50 °C for 6 h under being stirred. Water was added and the mixture was extracted with diethyl ether. The extract was washed with water, dried, evaporated, and subjected to column chromatography on silica gel using diethyl ether-hexane (1 : 10) as an eluent to give 17[11] in 73% overall yield from 15.



## References and Notes

1. This reagent (1) can be easily prepared by the reaction of sodium methanethiolate or dimethyl sulfide with 3-chloro-1-propenyl p-tolyl sulfone which was obtained by $PdCl_2$-catalyzed chlorination[2] of 2-propenyl p-tolyl sulfone. The detail will be reported elsewhere in the near future.
2. K. Ogura, N. Shibuya, K. Takahashi, and H. Iida, *Tetrahedron Lett.*, 22, 1519 (1981); *Bull. Chem. Soc. Jpn.*, in press.
3. Various conditions (AcOH-water, $HCl/CH_3OH$-water, p-TsOH/$CH_3CN$-water, $CuCl_2/CH_3OH$-water, $HgCl_2/CH_3CN$-water, $AgNO_3/CH_3OH$, $TiCl_4$-$CuCl_2/CH_3CN$-water, and $TiCl_4$/AcOH-water) were also examined. Mukaiyama et al. reported that $TiCl_4$ was effective for the hydrolysis of vinyl sulfides leading to ketones.[4]
4. T. Mukaiyama, K. Kamio, S. Kabayashi, and H. Takei, *Bull. Chem. Soc. Jpn.*, 45, 3723 (1972).
5. J. L. Kice and E. H. Morkved, *J. Am. Chem. Soc.*, 85, 3472 (1963).
6. Under the same conditions, 1,4-dibromobutane and 1,5-dibromopentane also afforded the corresponding cyclization products (18) in 78% and 88% yields, respectively.
7. 10 resisted the elimination of p-toluenesulfinic acid with $K_2CO_3$. Reductive desulfurization is expected to afford 3,3-trimethylene-propanal.



18 (n = 4,5)

8. E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 1970, 311; E. J. Corey, B. W. Erickson, and R. Noyori, *J. Am. Chem. Soc.*, 93, 1724 (1971).
9. Other literatures for the synthon of 2-formylethenyl carbanion: T. Nakai, H. Shiono, and M. Okawara, *Tetrahedron Lett.*, 1974, 3625; K. Kondo and D. Tunemoto, *ibid.*, 1975, 1007.
10. Under these conditions, no formation of the corresponding dialkylated product (3, R = R'= 4-methylpentyl) was observed.
11. (E) : (Z) = 3 : 2.

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