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SYNTHESIS OF α,β-UNSATURATED ALDEHYDES BY MEANS OF 3-METHOXY-1-PHENYLTHIO-1-PROPENE

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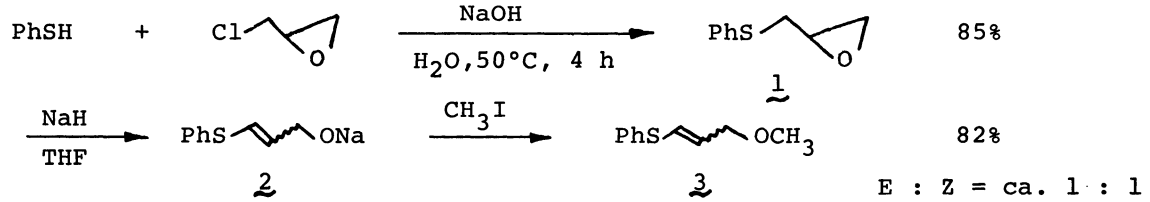
3-Methoxy-1-phenylthio-1-propene (3), obtained by the reaction of 1-phenylthio-2,3-epoxypropane (1) with sodium hydride in tetrahydrofuran (THF) and successive treatment with methyl iodide, was lithiated with lithium diisopropylamide at -78°C. The lithio derivative reacted with alkyl halides regioselectively at the α-position of sulfur atom, and hydrolysis of the products at room temperature in the presence of mercuric chloride afforded the corresponding α,β-unsaturated aldehydes in good yields.

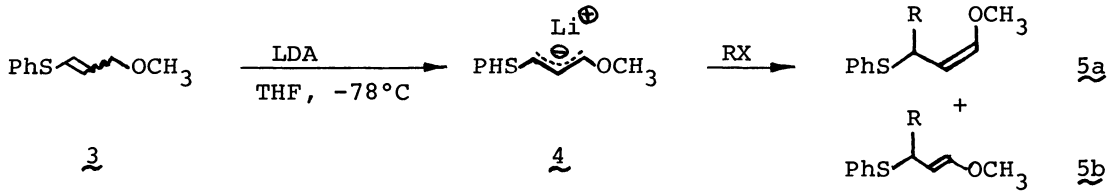
Recently, several synthetic methods of α,β-unsaturated aldehydes or ketones by utilizing organosulfur compounds have been reported.[1] For example, Corey, Erickson, and Noyori revealed that the lithio derivative of 1,3-bis(methylthio)propene served effectively as the equivalent of β-formylvinyl anion, and synthesized a number of α,β-unsaturated aldehydes starting with alkyl halides.[1a]

In this communication, we wish to report that the lithio derivative of 3-methoxy-1-phenylthio-1-propene (3) also serves as a useful β-formylvinyl anion equivalent.

1-Phenylthio-2,3-epoxypropane (1) (bp 111-113°C/4 mmHg, lit.[2] bp 113-114°C/4 mmHg) was synthesized in 85% yield by the reaction of 1-chloro-2,3-epoxypropane and sodium benzenethiolate in water at 50°C for 4 h. The epoxide 1 was found to be transformed into the sodium alcoholate 2 on treatment with sodium hydride in refluxing THF for 30 min, which yielded 3-methoxy-1-phenylthio-1-propane (3) (bp 107°C/5 mmHg) by the reaction with methyl iodide at room temperature.



Lithiation of the methyl ether 3 was performed in THF at -78°C by means of lithium diisopropylamide,[3] and the lithio derivative reacted with alkyl halide to produce a mixture of corresponding alkylated products 5a and 5b in good yield.[4]



3 4

It was found that the alkyl group was introduced regioselectively at the α-position of sulfur atom and no γ-isomer could be detected. The lithium salt 4 reacted also with alkyl tosylate to give 5 though the reaction proceeded more slowly compared with the corresponding alkyl halide. Some of the results are summarized in Table 1.

Table 1 Alkylation of 3-Methoxy-1-phenylthio-1-propene (3)

Entry	3 (mmol)	RX[a]	Reaction Conditions: Lithiation Time (min)	Alkylation Time (h)	5[b] Yield (%)	Bp(°C)/mmHg
1	30	CH_3I	30	0.5	72[c]	102-103/1
2	1.5	CH_3OTs	30	3	62	
3	10	$n\text{-}C_4H_9I$	30	2	80[c]	103/3
4	1.5	$n\text{-}C_6H_{13}Br$	30	2.5	73	
5	1.5	$n\text{-}C_8H_{17}Cl$	30	3	67	
6	1.5	$PhCH_2CH_2Br$	30	2	66	
7	1.5	$PhCH_2CH_2Br$	5	2	73	
8	1.5	$PhCH_2CH_2Br$	30	2	76[d]	
9	2.0	$PhCH_2Br$	30	0.5	70	
10	1.5	$i\text{-}C_3H_7I$	30	4	38	
11	2.0	$CH_2=CHCH_2Br$	30	0.3	70[e]	140-145/1 (bath temp)
12	1.5	$CH_3CH=CHCH_2Cl$	30	1	67	
13	1.5		5	1.5	71	

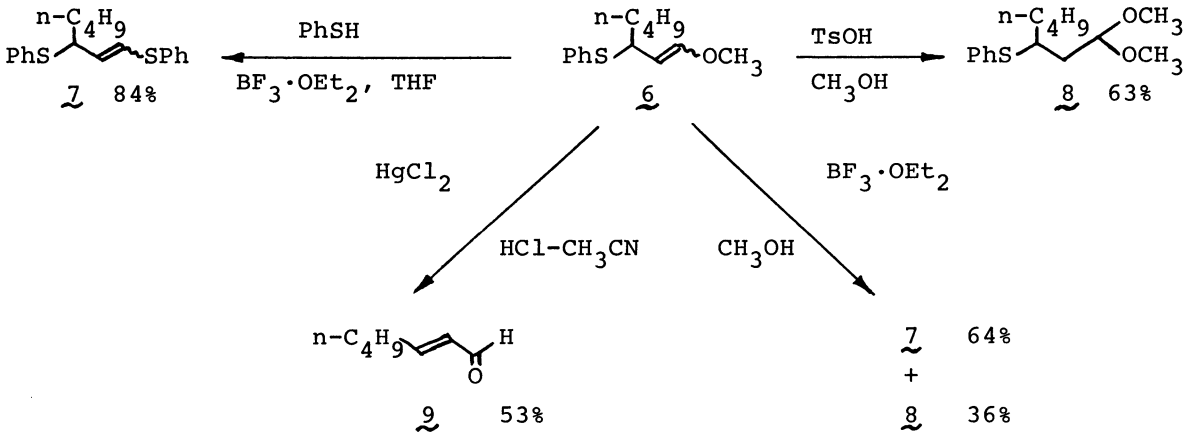
a) The molar ratio of 3, LDA, and RX was 1.0 : ca. 1.5 : 1.05 and yields were based on 3.
b) The products were isolated by silica gel TLC except for entries 1, 3, and 11. Satisfactory IR, NMR, and elemental analyses were obtained for these products.
c) The products were isolated by distillation.
d) The product was separated by using basic silica gel plate (see Text).
e) The product was isolated by bulb to bulb distillation.

A typical procedure of the reaction is as follows; 3-methoxy-1-phenylthio-1-propene (270 mg, 1.50 mmol, in 1.2 ml THF) was added into the solution of lithium diisopropylamide [prepared from diisopropylamine and hexane solution of n- butyl-lithium (1.6 ml; ca. 2.25 mmol)] in 1.5 ml THF at -78°C. After stirring for 30 min at that temperature, THF solution (1 ml) of phenethyl bromide (291 mg, 1.58 mmol) was added and stirred for 2 h at -78°C to complete the reaction. The reaction mixture was quenched with saturated aqueous sodium chloride and the product was extracted with ether. After removal of the solvent under reduced pressure, the residue was subjected to silica gel TLC (benzene : hexane = 1 : 5, Rf 0.5) to afford 1-methoxy-5-phenyl-3-phenylthio-1-pentene (281 mg) in 66% yield.

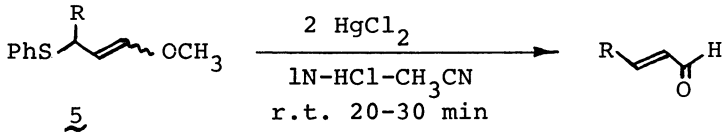
When the lithiation time of 3 was shortened to 5 min in the above reaction, the yield slightly increased (see Entry 7 in Table 1). The isolated product was

sufficiently pure for any synthetic purpose, but it was observed that the product decomposed slowly on silica gel. When the crude alkylated product was separated by using basic silica gel plate prepared from silica gel (Merck PF_{254}) and saturated aqueous sodium bicarbonate, the yield also increased slightly (see Entry 8 in Table 1).

Treatment of 3-phenylthio-1-methoxy-1-heptene (6) (1 mmol) with a catalytic amount of boron trifluoride etherate in methanol produced 1,3-bis(phenylthio)-1-heptene (7) (0.32 mmol, 64%) and 1,1-dimethoxy-3-phenylthioheptane (8) (0.36 mmol, 36%).[5] When p-toluenesulfonic acid was used instead of boron trifluoride etherate in the above reaction, 8 was obtained in 63% yield. The yield of 7 also increased in 84% by the reaction of 6 with benzenethiol in the presence of boron trifluoride etherate in THF.



On the other hand, when 6 was treated with 2 mole of mercuric chloride in acidic acetonitrile-water solution at room temperature, 2-heptenal (9) was isolated in 53% yield. Similarly, the reaction of alkylated products 5 with 2 mole of mercuric chloride furnished the corresponding α,β-unsaturated aldehydes 10 in high yields. Some of the results are summarized in Table 2.



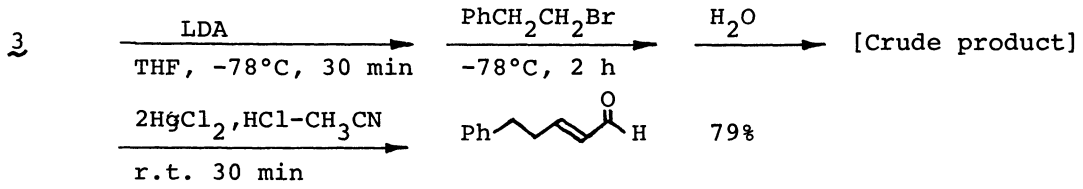
Typical procedure for the hydrolysis is shown in the following; to a solution of 1-methoxy-5-phenyl-3-phenylthio-1-pentene (284 mg, 1 mmol) in acetonitrile-1N-hydrochloric acid (7 : 1, 1 ml), mercuric chloride (0.55 g, 2 mmol) dissolved in the same solvent (6 ml) was added dropwise. Immediately, white voluminous precipitate arised. After stirring for 30 min at room temperature, the reaction mixture was filtered. The precipitate was washed with ether and the latter was combined with the filtrate. The combined solution was washed with phosphate buffer (pH 7.0) and the aqueous layer was extracted with ether. After drying (Na_2SO_4) the combined organic layer, the solvent was evaporated under reduced pressure at room temperature to leave an oil which was purified by silica gel TLC (dichloromethane : hexane = 1 : 1, Rf 0.7) to give 157 mg (98%) of pure 5-phenyl-2-pentenal.

Table 2 Synthesis of α,β-unsaturated aldehydes

Entry	R	Yield of (10)[a] (%)	2,4-Dinitrophenyl hydrazone, Mp(°C)
1	$n\text{-}C_4H_9$-	53	129 ∿ 130
2	$i\text{-}C_5H_{11}$-	69	126 ∿ 128
3	$n\text{-}C_6H_{13}$-	76	123 ∿ 124
4	$n\text{-}C_8H_{17}$-	95	119 ∿ 121
5	$PhCH_2$-	95	172 ∿ 174
6	$PhCH_2CH_2$-	98	169 ∿ 171

a) Structures of products were confirmed by IR and NMR. 2.4-Dinitrophenyl hydrazone of products gave correct elemental analyses.

α,β-Unsaturated aldehyde 10 was also obtained by hydrolysis of the crude alkylated product. After completion of the reaction of 3 with phenethyl bromide, the reaction mixture was quenched with aqueous sodium chloride and extracted with ether. The solvent was removed under reduced pressure and the residue was treated with mercuric chloride in acidic acetonitrile-water solution at room temperature for 30 min. Then, 5-phenyl-2-pentenal was obtained in 79% yield.



In conclusion, the lithio derivative of 3-methoxy-1-phenylthio-1-propene has been shown to serve effectively as the equivalent of β-formylvinyl anion, and it should be noted that the present synthetic method possesses several advantages; 1) the starting material can readily be synthesized, 2) α,β-unsaturated aldehydes are synthesized starting with alkyl halides within only one day because of the ease of hydrolysis of 1-methoxy-3-phenylthiopropene moiety, and 3) aldehydes are obtained in high yields.

References and Notes

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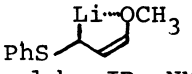
2) A.Allais and P.Girault, Fr. Patent 1444887 (1966); Chem. Abstr., 66,37755p (1967).
3) When n-butyllithium was used as a lithiating reagent, TLC pattern of the reaction mixture was more complex than the case of lithium diisopropylamide and the yield of alkylation became lower.
4) In every cases, 5a was predominant. The ratio of 5a to 5b is about 2∿3:1 except the case of Entry 8 (the ratio is about 9:1). This fact suggests the following allyllithium is the major anionic species in solution.



5) The structures of 7 and 8 were confirmed by IR, NMR and elemental analyses.

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