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Reduction of Ketene Dithioacetal S,S-Dioxides with Sodium Borohydride and Its Application to a Convenient Synthesis of Alkyl Arylmethyl Ketones

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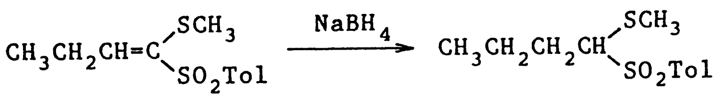
The C-C double bond of a ketene dithioacetal S,S-dioxide was found to undergo reduction with sodium borohydride. This fact provides an efficient synthetic route from an aromatic aldehyde to an alkyl arylmethyl ketone using methylthiomethyl p-tolyl sulfone.

Sodium borohydride is one of easily-handled reducing agents, but most of C-C double bonds are inert to this reagent except that they either conjugate with nitro group1) or cross-conjugate with two electron-withdrawing groups such as carboxylic and cyano groups.2) During the course of our investigation on the reactivity of a ketene dithioacetal S,S-dioxide, we have found that its C-C double bond can be reduced with sodium borohydride. This fact enables an efficient and convenient method for making alkyl arylmethyl ketones (**8**).

When sodium borohydride (2 mol-equiv.) was added to a solution of a ketene dithioacetal S,S-dioxide, 1-methylthio-1-(p-tolylsulfonyl)-1-butene3) (**1**), in ethanol and the resulting mixture was stirred at an ambient temperature, a smooth reduction occurred to give 1-methylthio-1-(p-tolylsulfonyl)butane (**2**). The yield was quantitative.

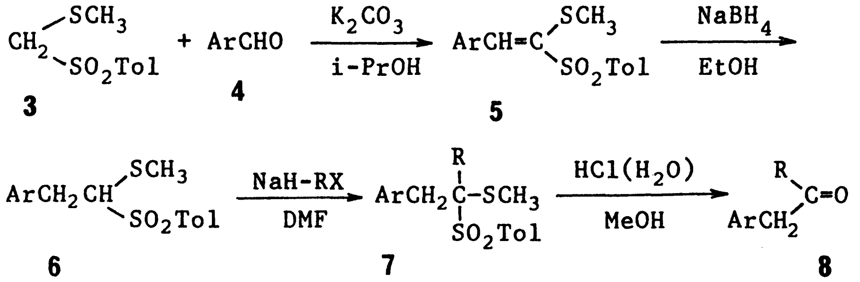


$$CH_3CH_2CH{=}C\begin{smallmatrix}SCH_3\\ SO_2Tol\end{smallmatrix} \xrightarrow{NaBH_4} CH_3CH_2CH_2CH\begin{smallmatrix}SCH_3\\ SO_2Tol\end{smallmatrix}$$

1 (Tol = p-tolyl) **2**

Since we have already reported that arylketene dithioacetal S,S-dioxides (**5**) are easily prepared by the Knoevenagel condensation of methylthiomethyl p-tolyl sulfone (**3**)4) with aromatic aldehydes (**4**) in the presence of potassium carbonate,5) combination of this condensation with the above reduction provides a convenient method for producing the arylmethyl derivative (**6**) of **3**. The present route is superior to the conventional way, i.e. alkylation of **3** with arylmethyl halides and a base5) in the large-scale preparation of **6**, because arylmethyl halides, especially alkoxyl(s)-substituted ones, are very unstable and intensely irritating to skin, eyes, and mucous membranes.

Alkylation of **6** with an alkyl halide and NaH in DMF, followed by hydrolysis with hydrochloric acid in refluxing methanol afforded alkyl arylmethyl ketones (**8**).6) The results are summarized in Table 1, which shows that the present method provides a convenient route from veratraldehyde (**4**c) to (3,4-dimethoxyphenyl)methyl methyl ketone (**8**c; R=CH_3), a synthetic precursor leading to an antihypertensive drug, methyldopa.7)



a: Ar=C_6H_5
b: Ar=4-$MeOC_6H_4$
c: Ar=3,4-$(MeO)_2C_6H_3$
d: Ar=3,4,5-$(MeO)_3C_6H_2$
e: Ar=2-Thienyl

A typical procedure is as follows: To a solution of **5**c[5)] (3.74 mmol) in ethanol (50 ml), was added sodium borohydride (7.5 mmol) and the resulting mixture was stirred at room temperature for 6 h. The usual workup (addition of water, extraction with dichloromethane, and evaporation of the extract) and column chromatography on silica gel gave **6**c. After addition of NaH (1.3 mmol) to a solution of **6**c (1.0 mmol) in DMF (3 ml), the mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. Then methyl iodide (2.0 mmol) was added and the resulting mixture was stirred at from 0 °C to room temperuature for 24 h. Addition of water (50 ml) and extraction with isopropyl ether followed by evaporation of the extract afforded crude **7**c. This was again dissolved in a mixture (5 ml) of methanol-conc hydrochloric acid (9:1) and the reaction mixture was heated under a reflux. The usual workup and column chromatography on silica gel yielded **8**c ($R=CH_3$).

Table 1. Synthesis of Alkyl Arylmethyl Ketones (**8**)

4	**3**→**5**[a)]	**5** → **6**				**6** → **7**[c)]		**7**→**8**[d)]
	Yield/%	$NaBH_4$[b)]	Solvent	Temp(Time/h)	Yield/%	RX	Temp/°C(Time/h)	Yield/%[e)]
4a	85	3.0	EtOH	rt(2)	97	CH_3I	rt(19)	96
						n-$C_6H_{13}Br$	rt(2) → 50 °C(3)	92
4b	56	2.1	EtOH	rt(8)	100	CH_3I	0 °C(6) → rt(18)	79
4c	68	2.0	EtOH	rt(6)	90	CH_3I	0 °C(6) → rt(18)	90
4d	72	2.1	EtOH	rt(6)	95	CH_3I	0 °C(6) → rt(18)	84
4e	96	1.0	EtOH-C_6H_6	50 °C(7)	100	CH_3I	0 °C(6) → rt(18)	59

a) with K_2CO_3 in refluxing i-PrOH (see Ref. 5). b) mol-equiv. to **5**. c) in the presence of NaH in DMF. **7** was not isolated. d) with hydrochloric acid in refluxing MeOH. e) overall yield from **6**.

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