



Pergamon

Tetrahedron Letters 41 (2000) 2121–2124

TETRAHEDRON
LETTERS

A new method for the synthesis of α -thio aldehydes and alcohols from aldehydes with one-carbon elongation

Tsuyoshi Satoh* and Ko-ichi Kubota

Department of Chemistry, Faculty of Sciences, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

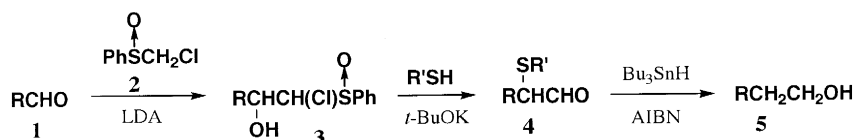
Received 29 November 1999; revised 5 January 2000; accepted 7 January 2000

Abstract

A two-step and high-yield method for the synthesis of α -thio aldehydes from aldehydes with one-carbon elongation is realized by using chloromethyl phenyl sulfoxide as a one-carbon homologating agent. The α -thio aldehydes are easily converted to desulfurized alcohols with Bu_3SnH and AIBN in refluxing benzene in good yield. © 2000 Elsevier Science Ltd. All rights reserved.

The homologation of carbonyl compounds from lower carbonyl compounds by a carbon–carbon coupling reaction is an attractive way for obtaining the desired carbonyl compounds.¹ In addition, the produced carbonyl compounds are easily converted to other compounds useful in organic chemistry.

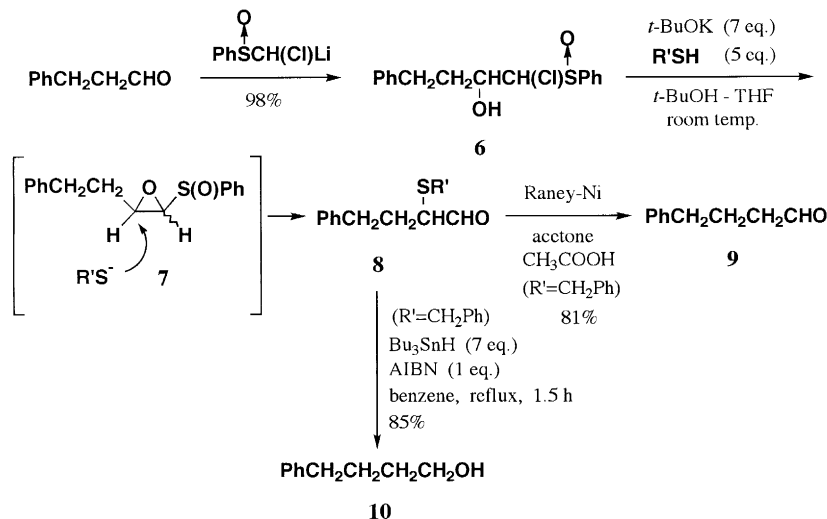
In our laboratory, we have reported some new methods for homologation of carbonyl compounds² by using aryl 1-haloalkyl sulfoxides as acyl anion equivalents.³ In continuation of our work, we report herein a new method for the synthesis of α -thio aldehydes **4** from aldehydes **1** with one-carbon elongation by using chloromethyl phenyl sulfoxide **2** as a one-carbon homologating agent. Moreover, the α -thio aldehydes **4** were easily reduced to one-carbon elongated desulfurized alcohols **5** in good yields.



One-carbon elongation of 3-phenylpropanal is described as a specific example (Scheme 1). Treatment of the lithium carbanion of chloromethyl phenyl sulfoxide with 3-phenylpropanal at -78°C gave the adduct **6** in quantitative yield as a diastereomeric mixture. In order to obtain the sulfinyloxirane **7**, we first treated **6** with several bases;⁴ however, because **7** was very unstable, all the attempts gave a complex mixture. Next, we tried in situ trap of this unstable **7** in the presence of a highly nucleophilic reagent (such as thiolate, selenolate, and amine). Thus, a solution of **6** in THF was added to a mixture of $t\text{-BuOK}$ (7 equiv.) and benzenethiol (5 equiv.) in a mixture of $t\text{-BuOH}$ –THF (2:1) at room temperature. Quite a rapid

* Corresponding author.

reaction took place, and after 10 min the desired α -(phenylthio)aldehyde **8** ($R' = \text{Ph}$) was obtained in 73% yield (see Table 1, entry 1). This reaction is thought to proceed via a sulfinyloxirane **7**.^{1d} We investigated this reaction with other thiols and found that alkyl thiols gave slightly better yield than benzenethiol. The best yield (93%) was obtained with benzyl mercaptan at 0°C (see Table 1, entries 2–4).



Scheme 1.

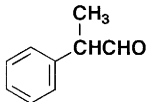
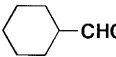
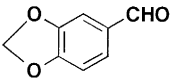
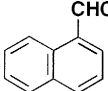
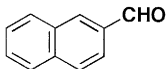
α -Thio aldehydes themselves are very important compounds in organic synthesis;⁵ however, if the α -thio group can be reduced easily to hydrogen, these reactions offer a good method for homologation of aldehydes to one-carbon elongated aldehydes. To this end, reduction of the benzylthio group in **8** ($R' = \text{CH}_2\text{Ph}$) with Raney-Ni in EtOH under several conditions was investigated; this reaction, however, only gave a complex mixture. The reduction in acetone gave some amount of **9**; however, this reaction again usually gave a complex mixture. Finally, we found that the reduction was successful in acetone containing a few drops of acetic acid to give **9** in 81% yield. However, these conditions are still not ideal. Reproducibility of this reaction was variably poor.

As the desulfurization of the α -thio aldehyde was found to be rather difficult, we changed our target to a synthesis of one-carbon elongated alcohols **10**. After some investigation, reduction of **8** ($R' = \text{CH}_2\text{Ph}$) with excess tributyltin hydride in the presence of AIBN⁶ was found to be the conditions of choice. Reduction of **8** with 7 equiv. of tributyltin hydride with 1 equiv. of AIBN in refluxing benzene gave the desired alcohol in 85% yield (Scheme 1 and Table 1, entry 4).

Other representative examples are shown in Table 1, entries 6–12. Entries 1 and 6 show the results with n -alkyl aldehydes. Entries 7 and 8 show the results of the α -branched alkyl aldehydes. Entries 9 to 11 show the results with aromatic aldehydes and entry 12 shows the result with α,β -unsaturated aldehydes. The yields of the adducts **3** of all the aldehydes with the lithium carbanion of chloromethyl phenyl sulfoxide are very high (87–98%). The yields for the reaction with benzyl mercaptan in the presence of $t\text{-BuOK}$ gave again excellent yields of the α -thio aldehydes **4** (89–98%). These results show that this method is quite useful for a one-carbon elongation of aldehydes to α -thio aldehydes.⁷

The reduction of the α -thio aldehydes **4** with Bu_3SnH was examined and the results are shown in Table 1. The yields of the reduction were shown to be somewhat variable. It is important to note that because the α -thio aldehyde in entry 12 was the α,β -(dibenzylthio)aldehyde the alcohol was saturated.

Table 1
One-carbon elongation of aldehydes to α -thio aldehydes and alcohols

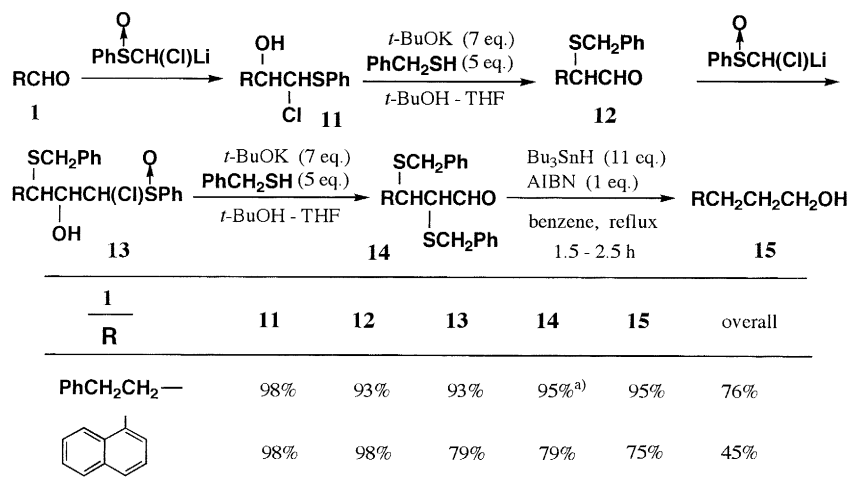
$\text{RCHO} \longrightarrow \text{RCHCH}(\text{Cl})\overset{\text{O}}{\overset{\text{ }}{\text{SPh}}} \xrightarrow[\text{t-BuOK}]{\text{R'SH}} \text{RCHCH}(\text{SR}')\text{CHO} \xrightarrow[\text{AIBN}]{\text{Bu}_3\text{SnH}} \text{RCH}_2\text{CH}_2\text{OH}$ 3 4 5					
Entry	RCHO	3 (Yield / %) ^{a)}	R'SH conditions	4 (Yield / %) ^{a)}	5 (Yield / %) ^{a)}
1	PhCH ₂ CH ₂ CHO	(98)	PhSH r.t., 10 min	(73)	—
2			 r.t., 10 min	(80)	—
3			CH ₃ (CH ₃) ₃ SH r.t., 20 min	(74)	—
4			PhCH ₂ SH 0 °C, 20 min	(93)	(85)
5			HOOCCH ₂ SH 0 °C, 20 min	complex mix.	
6	PhCH ₂ O(CH ₂) ₉ CHO	(94)	PhCH ₂ SH 0 °C, 20 min	(93)	(98)
7		(88)	PhCH ₂ SH 0 °C, 20 min	(95)	(98)
8		(87)	PhCH ₂ SH 0 °C, 20 min	(95)	(89)
9		(87)	PhCH ₂ SH 0 °C, 20 min	(89)	(82)
10		(98)	PhCH ₂ SH 0 °C, 45 min	(98)	(79)
11		(99)	PhCH ₂ SH 0 °C, 40 min	(98)	(91)
12	Ph-CH=CH-CHO	(98)	PhCH ₂ SH 0 °C, 20 min	(73) ^{b)}	Ph(CH ₂) ₄ OH (77)

a) Isolated yield after silica gel column chromatography.

b) The product is 2,3-(dibenzylthio)-4-phenylbutanal.

We next applied the presented method to two-carbon elongation of aldehydes to α,β -dithio aldehydes **14** and alcohols **15**. The overall process and the yields are shown in Scheme 2. All the reactions starting from 3-phenylpropanal gave over 90% yield and the overall yield was 76%. In contrast to this, the yields starting from 1-naphthaldehyde were good but not excellent, and the overall yield was reduced to 45%.

This work was supported by a Grant-in-Aid for Scientific Research No. 11640545 from the Ministry of Education, Science, Sports, and Culture, Japan, which is gratefully acknowledged.



a) A 2:3 diastereomeric mixture.

Scheme 2. Two-carbon elongation of aldehydes **1** to α,β -(dibenzylthio)aldehydes **14** and alcohols **15**

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