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

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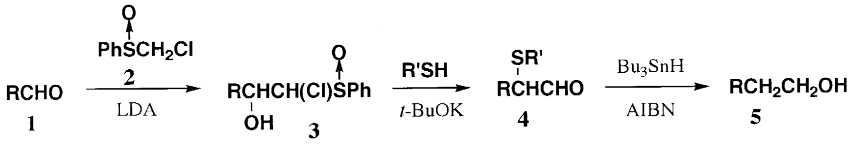
Received 29 November 1999; revised 5 January 2000; accepted 7 January 2000

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 compounds[2] 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*-BuOK (7 equiv.) and benzenethiol (5 equiv.) in a mixture of *t*-BuOH–THF (2:1) at room temperature. Quite a rapid

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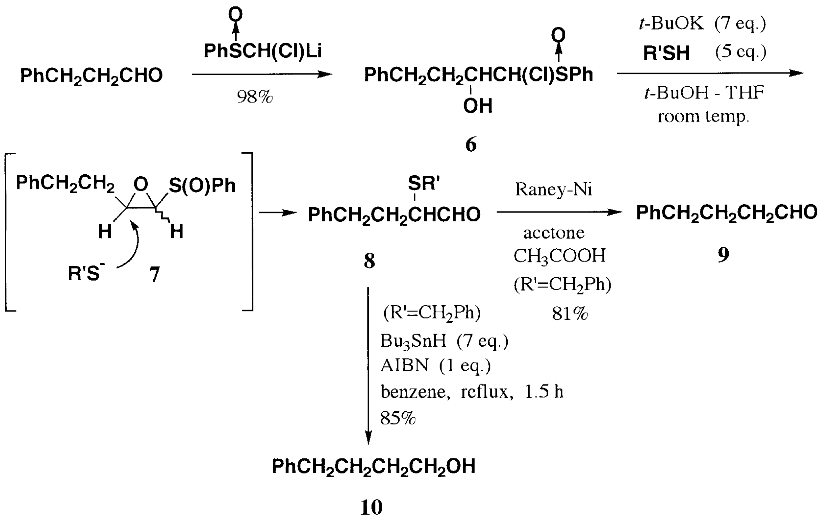
PII: S0040-4039(00)00087-3

reaction took place, and after 10 min the desired α-(phenylthio)aldehyde **8** (R′=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.

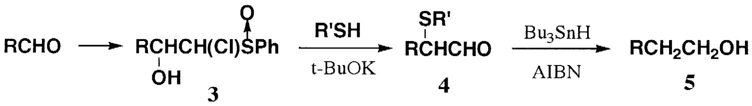
α-Thio aldehydes themselves are very important compounds in organic synthesis;[5] however, if the α-thio group can be reduced easily to hydrogen, these reactions offer a good method for homologation of aldehydes to one-carbon elongated aldehydes. To this end, reduction of the benzylthio group in **8** (R′=CH_2Ph) 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.

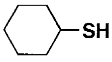
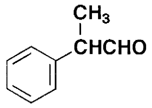
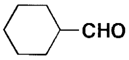
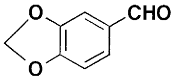
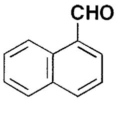
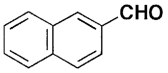
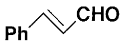
As the desulfurization of the α-thio aldehyde was found to be rather difficult, we changed our target to a synthesis of one-carbon elongated alcohols **10**. After some investigation, reduction of **8** (R′=CH_2Ph) with excess tributyltin hydride in the presence of AIBN[6] was found to be the conditions 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*-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

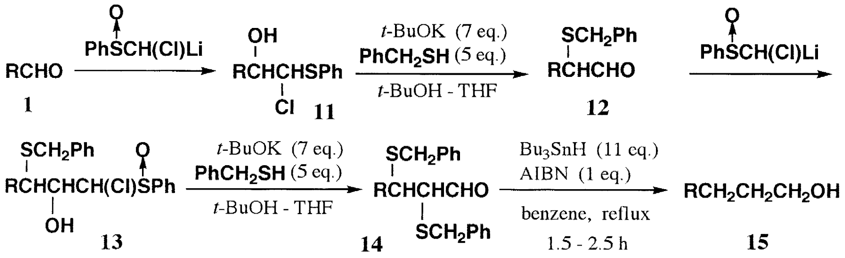


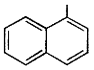
Entry	RCHO	3	R'SH		4	5
		(Yield / %)[a]	conditions		(Yield / %)[a]	(Yield / %)[a]
1	$PhCH_2CH_2CHO$	(98)	PhSH	r.t., 10 min	(73)	——
2				r.t., 10 min	(80)	——
3			$CH_3(CH_3)_3SH$	r.t., 20 min	(74)	——
4			$PhCH_2SH$	0 °C, 20 min	(93)	(85)
5			$HOOCCH_2SH$	0 °C, 20 min	complex mix.	
6	$PhCH_2O(CH_2)_9CHO$	(94)	$PhCH_2SH$	0 °C, 20 min	(93)	(98)
7		(88)	$PhCH_2SH$	0 °C, 20 min	(95)	(98)
8		(87)	$PhCH_2SH$	0 °C, 20 min	(95)	(89)
9		(87)	$PhCH_2SH$	0 °C, 20 min	(89)	(82)
10		(98)	$PhCH_2SH$	0 °C, 45 min	(98)	(79)
11		(99)	$PhCH_2SH$	0 °C, 40 min	(98)	(91)
12		(98)	$PhCH_2SH$	0 °C, 20 min	(73)[b]	$Ph(CH_2)_4OH$ (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.



1 R	**11**	**12**	**13**	**14**	**15**	overall
$PhCH_2CH_2$—	98%	93%	93%	95%[a)]	95%	76%
	98%	98%	79%	79%	75%	45%

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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