Pergamon

Tetrahedron Letters, Vol. 38, No. 34, pp. 5953-5954, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01352-X

A Simple and Efficient Method for Preparation of Unsymmetrical Sulfides

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Abstract: A simple and high efficient method for preparation of unsymmetrical sulfides is described.

The preparation of sulfides (or thioethers) is most often achieved by the thiolate substitution of alkyl halides.[1] The reaction conditions and yields depend on the solvent, the basic catalyst, and the acidity of thiols. Usually harsh conditions (refluxing for long periods) are required.[2] Improved yields can be obtained by phase transfer catalysis,[3] palladium (0) catalytic alkylation,[4] bis(diphenylstannyl)telluride,[5] bis(diphenylphosphino)-methane complex of platinum (II),[6] ligand transfer reactions,[7] and fluorodemetalation.[8]

Here we report that unsymmetrical sulfides can be prepared using mild conditions in excellent yields by reacting thiols with halides in the presence of n-BuLi (Eq. 1). The reactions are rapid (~30 min), quantitative, and can be performed at temperatures from 0 °C to room temperature. In general, no further purification is required. The synthetic yields after preparing 20 sulfides from five different thiols (including alkyl and aryl thiols) and four different halides are shown in Table 1.

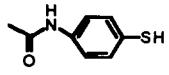
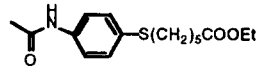
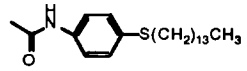
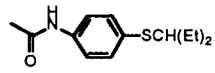
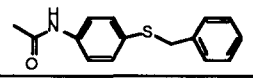
$$R_1SH + R_2Br \xrightarrow[0^0C \text{ -> rt, } 30min]{\text{n-BuLi, THF}} R_1SR_2 \qquad \text{Eq. 1}$$

As shown in Table 1, amide and ester functional groups remained intact under the reaction conditions. The n-BuLi thiolating products can be used without further purification. For example, a one-pot synthesis of sulfur-containing fatty acids can be performed by the thiolation reaction shown in Eq. I followed by alkali hydrolysis without purification of the R_1SR_2 product.

Typical reaction conditions based on Eq. 1 are examplified for the preparation of **2a**. Compound **2a** was prepared by adding 1-octanethiol (10 g, 68.4 mmol) dropwise to a 250 mL r.b. flask which contained 32.8 mL n-BuLi (2.5 M solution in hexanes, 82.0 mmol) and 150 mL dry THF (freshly distilled from sodium) under a nitrogen atmosphere at 0 °C. A white suspension immediately formed. The reaction mixture was allowed to warm to room temperature and stirred for 10 min. Then, ethyl 6-bromohexanoate (15.3 g, 68.4 mmol) was added to the white suspension under a nitrogen atmosphere at rt. The reaction mixture became clear after a few seconds and was stirred for 20 min. Finally the reaction was quenched by addition of water (20 mL) and extracted with hexanes (3 x 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated to give 21.3 g crude product. After flash chromatography, 19.2 g of pure product were obtained in 98.7

% yield. Five of the compounds shown in Table 1 were purified by flash chromatography whereas the other compounds were obtained from extraction.

Table 1. Preparation of sulfides from thiols and halides.

Thiols		Halides	Products	Entry	Yield (%)
$CH_3(CH_2)_2SH$	1	I	$CH_3(CH_2)_2S(CH_2)_5COOEt$	1a	91
		II	$CH_3(CH_2)_2S(CH_2)_{13}CH_3$	1b	98
		III	$CH_3(CH_2)_2SCH(Et)_2$	1c	94
		IV	$CH_3(CH_2)_2SCH_2Ph$	1d	97
$CH_3(CH_2)_7SH$	2	I	$CH_3(CH_2)_7S(CH_2)_5COOEt$	2a	98*
		II	$CH_3(CH_2)_7S(CH_2)_{13}CH_3$	2b	95
		III	$CH_3(CH_2)_7SCH(Et)_2$	2c	98
		IV	$CH_3(CH_2)_7SCH_2Ph$	2d	93*
$CH_3(CH_2)_{15}SH$	3	I	$CH_3(CH_2)_{15}S(CH_2)_5COOEt$	3a	95
		II	$CH_3(CH_2)_{15}S(CH_2)_{13}CH_3$	3b	98
		III	$CH_3(CH_2)_{15}SCH(Et)_2$	3c	92
		IV	$CH_3(CH_2)_{15}SCH_2Ph$	3d	98
PhSH	4	I	$PhS(CH_2)_5COOEt$	4a	95
		II	$PhS(CH_2)_{13}CH_3$	4b	98
		III	$PhSCH(Et)_2$	4c	98
		IV	$PhSCH_2Ph$	4d	94*
	5	I		5a	84*
		II		5b	96
		III		5c	94
		IV		5d	85*

Halides: I, $Br(CH_2)_5COOC_2H_5$; II, $CH_3(CH_2)_{13}Br$; III, $C_2H_5CH(Br)C_2H_5$; IV, $PhCH_2Br$.
*Purified by flash chromatography

Acknowledgments: This work was supported in part by NIH (AI33031).

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(*Received in USA* 5 *June* 1997; *revised* 26 *June* 1997; *accepted* 27 *June* 1997)