Facile Synthesis of Thiols and Sulfides

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Sulfurated sodium borohydride reacts with benzylic halides to give high yields of α-toluenethiol or benzylic polysulfides depending upon the experimental conditions and the mode of hydrolysis.

Aliphatic halides and dibenzylic halides react in the same manner as benzylic halides for a given experimental condition whereas benzylic halides substituted with other groups can be totally or partially reduced depending on the stability of the substituent towards $NaBH_2S_3$.

Halogens directly attached on the aromatic ring do not react with $NaBH_2S_3$.

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La réaction de $NaBH_2S_3$ avec les halogénures benzyliques conduit à une production quantitative d'α-toluènethiol ou de polysulfures benzyliques dépendant des conditions expérimentales employées et du mode d'hydrolyse choisi.

Les halogénures aliphatiques et les halogénures dibenzyliques réagissent de la même manière que les halogénures benzyliques sous des conditions expérimentales similaires, alors que les halogénures benzyliques substitués par d'autres groupes, peuvent être réduit totalement ou partiellement dépendant de la stabilité du deuxième groupe vis-à-vis $NaBH_2S_3$.

Les halogénures directement fixés sur un noyau benzénique ne réagissent pas avec $NaBH_2S_3$.

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Martin and Greco (1) and Tsurugi and Nakabayaski (2) have already reported the synthesis of thiols (1) and sulfides (2) from benzylic halides in very moderate yields. This report describes a significant improvement of the existing synthetic procedures resulting from the use of sulfurated sodium borohydride (3) as a new reagent for the preparation of thiols or sulfides from halogenated compounds.

From Table 1, it can be seen that after treatment with $NaBH_2S_3$, the predominance of a given benzylic sulfurated compound depends largely upon the method of hydrolysis and the experimental conditions used. Considering benzyl chloride as a typical case, we notice that hydrolysis with sodium hydroxide favors greatly the production of sulfides in every case except when a high temperature and an excess of reducing agent are used. At constant temperature, an increase in the molar ratio of the sulfurated hydride increases the production of thiols and the same effect is observed when there is an increase in temperature at constant molar ratio. From these observations it is normal to find very high yields of thiols when an excess of reducing agent and high temperature are used, this effect being independant of the method of hydrolysis. Experimental conditions avoiding large excess of $NaBH_2S_3$ give moderate yields of thiols and sulfides when acidic hydrolysis is used but give high yields of sulfides when hydrolysis is made with a 10% sodium hydroxide solution.

Table 2 shows the reactivity of different organic iodides, chlorides, or bromides and shows that the general trend previously observed with benzyl halides is also verified with other benzylic and aliphatic halides. Methyl iodide reacts the same way as benzyl iodide under similar experimental conditions yielding mainly the corresponding thiol. For aliphatic chlorides, such as *t*-butyl chloride and 2-(chloroethyl)benzene, it appears that the same type of reactivity is obtained except when steric hindrance is important enough to inhibit reaction as seems to be the case with *t*-butyl chloride. 1-(Bromoethyl)benzene reacts in a fashion similar to benzylic bromide yielding similar proportions of the corresponding thiol and polysulfides. *p*-Dibenzylic chlorides give excellent yields of the corresponding dithiols. With substituted benzylic chlorides, such as *p*-nitrobenzyl chloride, the reaction proceeds normally under mild experimental conditions

TABLE 1. Reaction of benzylic halides with $NaBH_2S_3$

					Benzylic thiol and sulfides									
					Hydrolysis with HCl 10%					Hydrolysis with NaOH 10%				
					Thiol	Sulfides				Thiol	Sulfides			
T (°C)	Molar ratio $\frac{NaBH_2S_3}{C_6H_5CH_2X}$	Reaction time (h)	X	$C_6H_5CH_2X$ consumed (%)	—SH	Total	Mono	Di	Poly	—SH	Total	Mono	Di	Poly
20	2:1	66	F	40	7	33	7	7	19					
20	2:1	16	F	42	3	39		6	33					
20	1:1	16	Cl	92	38	54	6	28	20	5	87	9	62	16
20	1:1	16	Br	100	11	89		34	55	7	93	7	64	22
20	1:1	16	I	100	13	87	4	31	52					
20	4:1	65	F	95	22	73	2	22	49					
20	4:1	16	Cl	100	55	45	6	17	22	—	100	19	38	43
20	4:1	16	Br	100	75	25	5	12	8					
20	4:1	16	I	100	85	15	3	12						
65	1:1	16	F	40	25	15	15							
65	1:1	16	Cl	100	78	22	12	10		13	87	59	28	
65	1:1	16	Br	100	62	38	28	7	3					
65	1:1	16	I	100	58	42	34	8						
65	4:1	16	F	100	99	Traces								
65	4:1	16	Cl	100	99	Traces				87	13		13	
65	4:1	16	Br	100	69	31	3	10	18					
65	4:1	16	I	100	95	5	3	2						

TABLE 2. Reactivities of organic halides

Reagent	T (°C)	Molar ratio $\frac{NaBH_2S_3}{\text{reagent}}$	Reaction time (h)	Products	
				Hydrolysis with HCl 10%	
CH_3I	20	4:1	64	Mainly CH_3SH	
	20	1:1	64	CH_3SH (70%) $CH_3S_2CH_3$ (15%) CH_3SCH_3 (15%)	
$(CH_3)_3CCl$	20	4:1	16	No reaction	
	65	4:1	16	Complex mixture of thiols and polysulfides	
$C_6H_5CH_2CH_2Cl$	65	4:1	16	$C_6H_5CH_2CH_2SH$ (90%)	
$C_6H_5CH(Br)CH_3$	65	4:1	16	$C_6H_5CH(SH)CH_3$ (30%)	Polysulfides (70%)
p-$ClCH_2C_6H_4CH_2Cl$	65	8:1	16	$HSCH_2C_6H_4CH_2SH$ (80%)	
p-$NO_2C_6H_4CH_2Cl$	65	8:1	16	p-$NH_2C_6H_4CH_2SCH_2C_6H_4NH_2$ (48%)	Aminated polysulfides (52%)
	20	1:1	16	p-$NO_2C_6H_4CH_2SH$ (53%)	Nitrated polysulfides (47%)
p-$NO_2C_6H_4CH_2Br$	20	4:1	16	p-$NH_2C_6H_4CH_2SCH_2C_6H_4NH_2$ (52%)	Aminated polysulfides (48%)
	20	1:1	16	p-$NO_2C_6H_4CH_2SH$ (traces)	Nitrated polysulfides (90%)
C_6H_5X(F, Cl, Br, I)	65	4:1	16	No reaction	

to give nitrated thiols and polysulfides. With stronger reaction conditions, the reaction proceeds further to transform the nitro group into the amino group.

From the already known selectivity of $NaBH_2S_3$, it can be said that substituted benzylic chlorides would react normally to give the corresponding thiols and sulfides especially if the substituted group is inert to $NaBH_2S_3$, as is the case for ester, acid, ether, or olefinic groups. The same conclusion may be applied to *p*-nitrobenzyl bromide as shown by the results of Table 2.

In conclusion it is important to note that aromatic halides are inert to $NaBH_2S_3$ as shown in Table 2 whereas aliphatic and benzylic halogenated compounds give excellent yields of the corresponding sulfurated products. Actually, the main advantage of sulfurated sodium borohydride over the older reagents for the production of thiols and sulfides from halogenated compounds, is that $NaBH_2S_3$ generally leads to an almost quantitative yield of thiols or sulfides depending essentially upon the choice of the reaction conditions and the mode of hydrolysis, whereas older methods (1, 2) give more moderate yields and call for specific reagents in order to assure the production of thiols or of sulfides.

Experimental

The n.m.r. measurements were made with a Perkin-Elmer R-12A apparatus. The i.r. measurements were made with a Pye Unicam SP 200G spectrophotometer.

Typical Procedures for the Reaction of $NaBH_2S_3$ and Organic Halides

The experimental conditions for the reductions have been described in earlier works (4, 5) and the separation of the reaction products has been made by evaporation or distillation of α-toluenethiol followed by separation over column chromatography using silica gel and a mixture of hexane–CCl_4 as eluant, in order to isolate the sulfides. The identification of these sulfurated compounds has been confirmed by a comparative study of the n.m.r. chemical shifts with the authentic products as mentioned by Grant and Van Wazer (6).

Optimal Conditions for the Reaction of Benzyl Chloride

To a suspension of 0.20 mol (26.40 g) of $NaBH_2S_3$ prepared as described by Lalancette (3) in 200 ml of tetrahydrofuran, 0.05 mol (6.33 g) of benzyl chloride in 100 ml of tetrahydrofuran was added dropwise. The reaction mixture was stirred and refluxed for 16 h and was then evaporated to dryness, under reduced pressure, at room temperature. The residual solid was covered with 200 ml of ethyl ether and 10% hydrochloric acid was added until the p*H* of the reaction mixture was 1.0. The precipitated sulfur was filtered off and the filtrate washed repeatedly with ethyl ether. The organic fraction was then dried over $MgSO_4$ and the evaporation of ether gave a 99% yield of α-toluenethiol. A similar reaction using equimolar quantities of $NaBH_2S_3$ and benzyl chloride at 65° for 16 h was hydrolyzed with a 10% sodium hydroxide solution until the p*H* of the reaction mixture was 11.0. The ethereal fraction was dried over $MgSO_4$ and the evaporation of ether gave a mixture of thiol and sulfides. After evaporation of the α-toluenethiol (13%), the residual solid was analyzed by a column chromatography study using a silica gel column and a mixture of hexane–CCl_4 as eluant. The separation gave 59% of benzyl sulfide and 29% of benzyl disulfide.

The positive identification of all products was made by a comparative n.m.r. study with authentic samples.

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