Reduction of α-Halo Carbonyl Compounds with $NaBH_4$-$SbBr_3$

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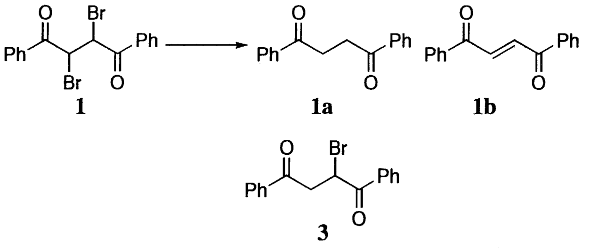
The reagent $NaBH_4$-$SbBr_3$ was found to be chemoselective for the reductive debromination of aromatic α-bromo carbonyl compounds and 2,3-dibromo-1,4-butanediones.

The dehalogenation of α-halo carbonyl compounds has been a useful transformation of organic syntheses.[1] Therefore, a number of methods have been reported.[2] However, the reduction of acid-sensitive α-halo carbonyl compounds with zinc dust was not general because of its acidic conditions. Further, metal hydrides such as $LiAlH_4$ and $NaBH_4$ were not chemoselective for dehalogenation of polyfunctional carbonyl compounds. There have been much interest in mild and chemoselective methods for dehalogenation of α-halo carbonyl compounds. In a previous paper, $LiAlH_4$-$SbCl_3$ was reported to be a good reagent for conjugate reduction of 1,4-disubstituted 2-butene-1,4-diones, in comparison with $LiAlH_4$-other metal halides (e.g., Cu_2I_2, $CuCl_2$, $AlCl_3$, $FeCl_3$).[3] The reagent, $NaBH_4$-antimony halides, has similarly been expected to have a different chemoselectivity in comparison with $NaBH_4$-other metal halides. The reduction of α-halo ketones with $NaBH_4$-antimony halides was carried out to examine the reducing power of these reagents. We would like to report on the results of studies concerning the chemoselective reduction of a variety of α-halo carbonyl compounds with $NaBH_4$-$SbBr_3$.

The reduction of *meso*-2,3-dibromo-1,4-diphenyl-1,4-butanedione (**1**)[4], chosen as a representative α-halo ketone for this study, with $NaBH_4$ (NBH)-$SbBr_3$ in various stoichiometric ratios was carried out in THF-DMSO. The results are summarized in Table 1. At the ratio of bromo diketone **1**, NBH, and $SbBr_3$ (1:2:2 or 1:1:1), a mixture of 1,4-diphenyl-1,4-butanedione (**1a**), trans-1,4-diphenyl-2-butene-1,4-dione (**1b**), and **1** was obtained, accompanied by a small amount of 2-bromo-1,4-diphenyl-1,4-butanedione (**3**). At a stoichiometric ratio of 1:3:3, **1** was reduced to give 1,4-diphenyl-1,4-butanedione (**1a**) in good yield. The optimum conditions for the reduction of **1** to **1a** with NBH-$SbBr_3$ are as follows: i) It needs an equal molar equivalent of $SbBr_3$ over NBH to suppress the 1,2-reduction of diketones. ii) It needs three molar equivalents of $SbBr_3$ and NBH over **1** to give **1a** in high yield.

Table 1. Reduction of *meso*-2,3-Dibromo-1,4-butanedione (**1**) with $NaBH_4$-$SbBr_3$[a]



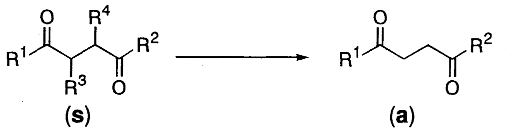
Run	Molar ratio / 1		Products,	Yield / %[b]		
	$NaBH_4$	$SbBr_3$	**1a**	**1b**	**3**	**1**[d]
1	0.5	0.5	-	19	-	21
2	1.0	1.0	15	52	3	73
3	2.0	2.0	55	17	8	95
4	3.0	3.0	91	-	3	100
5	3.0	-	-	-	-	-[c]
6	-	3.0	-	12	-	12

[a] **1**; 0.5 mmol. Temperature; 0-22°C.
Solvent; THF-DMSO (2/1 v/v) 15 ml. [b] Isolated yield.
[c] Mixture of hydroxyl derivatives was obtained.
[d] Conversion (%) of **1** to **1a**, **1b**, and **3**.

The results of NBH-$SbBr_3$ reduction of other halo 1,4-diketones are shown in Table 2. *dl*-2,3-Dibromo-1,4-diphenyl-1,4-butanedione (**2**) and 2-bromo-1,4-diphenyl-1,4-butanedione (**3**) also afforded 1,4-diketone **1a** in good yield. 2-Chloro-1,4-diphenyl-1,4-butanedione (**4**) was recovered unchanged. 2,3-Dibromo-1-phenyl-1,4-pentanedione (**5**), 3,4-dibromo-2,5-decanedione (**6**), and ethyl 3-benzoyl-2,3-dibromopropionate (**7**) afforded the corresponding 1,4-diketones (**5a**-**7a**). These results suggested that the reagent, NBH-$SbBr_3$, was chemoselective for the reductive debromination of α-bromo ketones. The reduction of a variety of aromatic and aliphatic α-bromo ketones with NBH-$SbBr_3$ was carried out to ascertain above-mentioned chemoselectivity. Aromatic α-bromo ketones (**8**-**12**) were reduced to give the corresponding ketones (**8a**-**12a**) in high yields as shown in Table 3. On the other hand, aliphatic α-bromo ketones and α-bromo esters were recovered unchanged. Other halogenated compounds such as 2-chlorocyclohexanone, 2-chloro-2-phenylacetophenone, 2-chloroacetophenone, 1- bromoethylbenzene, and *cis*-2-bromo-1,4-diphenyl-2-butene-1,4-dione were also recovered unchanged in 60-94% yields.

In addition, the following experiments were carried out to clarify the advantage of NBH-$SbBr_3$ for the reductive debromination of α-bromo ketones over that of other reagent such as $LiAlH_4$-$SbCl_3$, NBH-$SbCl_3$, and NBH-other metal halides. At the 1:6:6 molar ratio of **1**, LAH, and $SbCl_3$ in THF, the mixture of **1a** (42%) and enedione (**1b**) (30%) was obtained. On the other hand, **1** was mainly reduced to give **1a** (80%) at the 1:3:3 molar ratio of **1**, NBH, and $SbCl_3$ in THF-DMSO. However, 2-bromo-1,4-diphenyl-1,4-butanedione (**3**) afforded 2-chloro-1,4-diphenyl-1,4-butanedione (**4**) (62%) accompanied by **1a** (18%) at the 1:1:1 molar ratio of **3**, NBH, and $SbCl_3$. Even at the 1:3:3 molar ratio of **3**, NBH, and $SbCl_3$, **4** (6%) was obtained. Therefore, $SbBr_3$ was used insted of $SbCl_3$ to suppress the replacement reaction with chloride ion in NBH-$SbCl_3$ reduction system. The reduction of

Table 2. Reduction of α-Halo diketones with $NaBH_4$-$SbBr_3$[a]

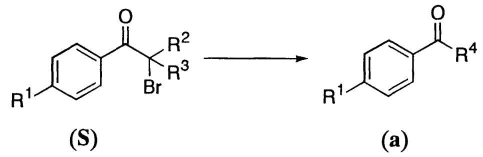


Substrate					Molar ratio / S		Products ,	
R^1	R^2	R^3	R^4	(S)	$NaBH_4$	$SbBr_3$	Yield / %[b]	
Ph	Ph	Br	Br	**1** *(meso)*	3	3	**1a**	91
Ph	Ph	Br	Br	**2** *(dl)*	6	6	**1a**	79
Ph	Ph	Br	H	**3**	5	5	**1a**	96
Ph	Ph	Cl	H	**4**	3	3	**4**	98
n-C_5H_{11}	CH_3	Br	Br	**5**	6	6	**5a**	72
Ph	CH_3	Br	Br	**6**	3	3	**6a**	84
Ph	OEt	Br	Br	**7**	5	5	**7a**	51

[a] α-Halo diketone; 0.5 mmol. Temperature; 0-22°C. Solvent; THF-DMSO (2/1 v/v) 15 ml. Reaction time; 3.5-20 h.

[b] Yield is based on α-halo diketone used.

Table 3. Reduction of Aromatic α-Halo ketones with $NaBH_4$-$SbBr_3$[a]



Substrate				Products			
R^1	R^2	R^3	(S)	R^1	R^4	Yield / %[b]	
H	H	H	**8**	H	CH_3	**8a**	88
H	CH_3	H	**9**	H	C_2H_5	**9a**	87
H	CH_3	CH_3	**10**	H	i-C_3H_7	**10a**	90
Br	H	H	**11**	Br	CH_3	**11a**	90
CH_3O	H	H	**12**	CH_3O	CH_3	**12a**	93

[a] α-Halo ketone; 0.5 mmol. Temperature; 0-22°C. Solvent; THF-DMSO (2/1 v/v) 15 ml. Reaction time; 3.5-20 h. Molar ratio;1:3:3 (halo ketone /$NaBH_4$ / $SbBr_3$).

[b] Yield is based on α-halo ketone used.

1 with NBH-other metal halides (e.g., $NiCl_2$, $CoCl_2$, $CuCl_2$, $AlCl_3$) did not give **1a**. Moreover, it was more mild and convenient to prepare the reagent, NBH-$SbBr_3$, in THF-DMSO in comparison with that of the reagent, LAH-$SbCl_3$, in THF. Thus, the reagent, NBH-$SbBr_3$, provides a selective and convenient procedure for the reductive debromination of α-bromo ketones such as aromatic α-bromo ketones, 2-bromo-1,4-butanediones, and 2,3-dibromo-1,4-butanediones.

The following experimental procedure is illustrative: To a suspension of NBH (54 mg, 1.5 mmol) in THF (6 ml) and DMSO (5 ml) at 0 °C was added $SbBr_3$ (541 mg, 1.5 mmol) dissolved in THF (2 ml). The resulting mixture was stirred for 5 min at 0 °C , and then α-halo ketone (0.5 mmol) in THF (2 ml) was added. After stirring for 3.5-20 h at 0-22 °C, the reaction mixture was treated with 1 M aq $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed by 0.5 M aq $Na_2S_2O_3$ and successively saturated aq NaCl and dried by $MgSO_4$. After removal of solvent *in vacuo*, the residue was purified by column chromatography on silica gel (Wakogel C-200) with CCl_4 and $CHCl_3$ (1:1 v/v). The products (**1a-12a**) were obtained in 51-96% yields.

References

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