2-Halo-2-cyclohexenols from 6,6-Dihalobicyclo-[3.1.0]hexanes and Dimethyl Sulfoxide. Studies towards a Non-basic Hydroxide Equivalent

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A practical, high yielding, cheap and mild method for the synthesis of 2-halo-2-cycloalkenols, especially 2-bromo-2-cyclohexenol, is reported. Direct conversion from a variety of thermally labile n,n-dihalobicyclo$[n-3.1.0]$alkanes to 2-halo-2-cycloalkenols can be achieved without using silver salts by simple heating in DMSO. The intermediate 1,n-dihalocycloalkenes immediately undergo indirect allylic substitution with DMSO to yield the corresponding halocycloalkenols. A possible mechanism for the substitution step comprises nucleophilic attack by DMSO followed by a Pummerer rearrangement and hydrolytic decomposition. Kinetic and mechanistic experiments to verify the course of the reaction are presented.

Dedicated to Professor Lars Skattebøl on the occasion of his 70th birthday

n,n-Dihalobicyclo$[n-3.1.0]$alkanes (1) provide access to a variety of synthetic building blocks and reactive intermediates, usually through ring-opening reactions such as the Doering–Moore–Skattebøl rearrangement, which is by far the best route to cyclic allenes.[1–5] Other versatile building blocks available from the ring opening of bicyclic *gem*-dihalocyclopropanes are 2-halo-2-cycloalkenols (2), especially the cyclohexenols.[6,7] The most common method to synthesize these compounds utilizes soluble silver salts, usually silver nitrate, in the presence of water.[7,8] However, this method is seldom applied in multistep syntheses owing to its cost, sometimes moderate yields, and the possible interference of the silver cations with other functional groups in complex molecules.[9,10] This is in contrast to the ready availability of the starting material, e.g., from the addition of dihalocarbene to cycloalkene.[11–13]

Recently we discovered that simple heating of 6,6-dibromobicyclo[3.1.0]hexane (1a) in dimethyl sulfoxide results in the formation of 2-bromo-2-cyclohexenol (2a) in up to 95% isolated yield, whereas silver nitrate–water gives only 47% product. The reaction starts slowly at ca. 60 °C, is exothermic, and becomes considerably faster if the temperature is increased (Table 1). Quenching of the reaction mixture with water also is strongly exothermic. As by-products the two unsymmet-

rical bromothioanisoles 4 and 5 and 1,6-dibromocyclohexene (3a) are formed, the former preferentially at higher temperatures, the latter at lower ones with incomplete conversion. 6,6-Dichlorobicyclo[4.1.0]hexane (1c) reacts accordingly to give 2-chloro-2-cyclohexenol (2c), but requires either more time or higher temperatures (120 °C).

The extremely sluggish reaction of 7,7-dibromobicyclo[4.1.0]heptane (1b) and the failure of higher homologues to react suggested the thermal ring-opening products, 1,n-dihalocycloalkenes (3), as intermediates and real reaction partners of DMSO (Scheme 2).[14] This could be verified by using the proposed intermediates in a reaction with DMSO. 1,6-Dibromocyclohexene (3a) and 1,7-dibromocycloheptene (3b) reacted almost equally well to the corresponding cycloalkenols (2a/b). Cleaner reactions of either starting material (1 or 3) and higher yields were achieved by adding 2–4 equivalents of water and lowering the temperature; e.g., dibromide 1a gave after 4 h at 80 °C alcohol 2a in 95% isolated yield.

The reaction of 6,6-dibromobicyclo[3.1.0]hexane (1a) in [^{2}H$_6$] DMSO was also followed by NMR spectroscopy (Fig. 1). The experiment clearly showed the initial build up of intermediate 3, which was then followed by product formation in a typical kinetic relationship. The thermal decomposition of bicycle 1a at 90 °C obeyed a first-order rate law with $k = 4.3 \times 10^{-3}$ s^{-1} up to about 80% conversion. At larger conversions the rate increased, probably
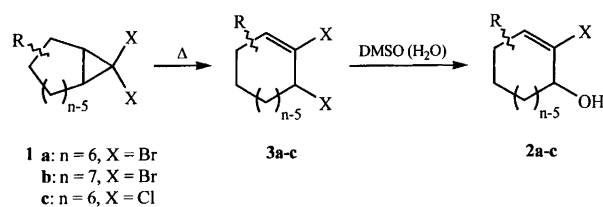
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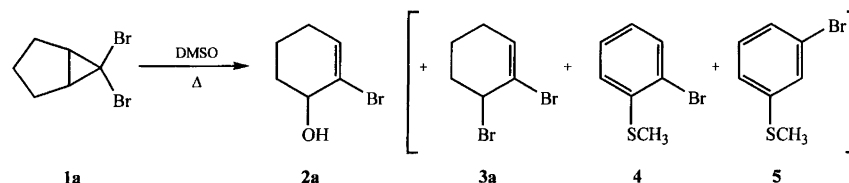
Scheme 1.

Table 1. Influence of temperature and time on the reaction of dibromide **1a** in dry DMSO (cf. Scheme 1).

		Product ratio (%)		
$T/°C$	t/h	**2a**	**3a**	**4+5**
60	3.0	33	67	—
80	3.5	86	14	—
125	0.5	94	4	2

1 a: n = 6, X = Br
  b: n = 7, X = Br
  c: n = 6, X = Cl

Scheme 2.

due to the formation of catalytic amounts of HBr, and possibly other effects emanating from the subsequent substitution reaction. The presence of very small amounts of HBr in the initial phase also cannot be ruled out.[5,15-17] Nevertheless, the acid concentration at this stage should be fairly constant, as DMSO can act as a buffer (reacting in a Pummerer fashion with HBr), and thus an excellent fit is found for first-order kinetics, as indicated by a correlation coefficient of better than 0.999. The rate constant for the cyclohexenol-forming step could not be determined properly in this experiment due to possible secondary and isotope effects (*vide infra*).[18,19]
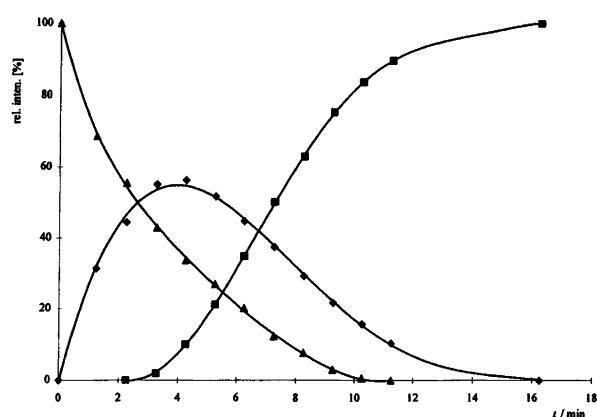

Fig. 1. Kinetics of the reaction of **1a** in [$^2H_6$]DMSO at 90 °C. [Calculated from NMR spectra (lines by polynomial fitting): ▲, 6,6-dibromobicyclo[3.1.0]hexane (**1a**); ◆, 1,6-dibromo-cyclohexene (**3a**); ■, 2-bromo-2-cyclohexenol (**2a**)].

Although addition of water gives cleaner reactions, the reactivity and conversion seemed to depend on DMSO only. To verify this, bicycle **1a**, dissolved in dry DMSO, was divided between two reaction flasks, and 2 equivalents of water were added to one flask. In both cases complete consumption of the bicyclic species was achieved at a similar rate. The reactions differed only in the yields of alcohol **2a** and the side products (cf. Scheme 1). Neither other nucleophiles (cyanide, alcohols, water) nor solvents were able to replace DMSO (Table 2).

Further mechanistic experiments were then performed with 1,6-dibromocyclohexene (**3a**). Other (later) intermediates than compounds **3** could not be detected by NMR spectroscopy. A principal concern in the conversion of **3** into **2** was the possible influence of water and/or DMSO, and experiments to prove or disprove their direct involvement in the substitution step were carried out. With the most reactive compound **3a**, none of the solvents pure water, water in acetone, water in 2-propanol or 2-propanol alone gave similar results to those observed with DMSO. Only trace amounts of the allylic alcohol and/or isopropyl ether were formed with these reagent–solvent systems. Even the Williamson ether synthesis with sodium 2-propanolate resulted in a maximum yield of only 60% of the isopropyl ether of **2a** (4 h, 80 °C).

In contrasting experiments great care was taken to run the reaction in the absence of water. In a typical experiment, and for the conversions achieved, 1–2% of water would have been required in the DMSO used. The certified water content of the commercial dry DMSO was <0.3%. Even with especially dried DMSO, cyclo-

Table 2. Influence of solvents and additives on the reaction of 6,6-dibromobicyclo[3.1.0]hexane (**1a**) and isolated yields of 2-bromo-2-cyclohexenol (**2a**).

Solvent	Additive (mol%)	$T/°C$	t/h	Ratio 3a:2a	Yield of 2a (%)
DMSO	—	80	3.5	86:14	10[a]
DMSO	H_2O (200)	80	3.5	1:100	88
DMSO	MeOH (40)	80	5.0	22:78	47
DMSO	$PhCH_2OH$ (200)	90	24.0	0:100	2.5
DMSO	NaCN (200)	90	24.0	0:100	1[b]
Dioxane	H_2O (200)	80	19.0	86:14	9
Acetone	H_2O (200)	80	3.5	100:0	0
THF	H_2O (200)	65	4.0	100:0	0

[a]Traces of bromothioanisoles **4** and **5** were found as by-products. [b]An undefined dimeric species of **3** was formed in approx. 4% yield.

hexenols were formed as usual. Nevertheless, the reaction was repeated in dry solvents with only 1–4 equivalents of dry DMSO present. In accordance with the ionic transition state proposed below, no reaction was observed in solvents of low polarity such as toluene, chloroform, THF or dioxane. In more polar and protic solvents conversion was either sluggish (isopropyl alcohol, acetonitrile) and/or gave secondary products, e.g., formiates and acetates with DMF and acetic acid, respectively. Of the solvents tested only sulfolane and DMSO proved useful, the latter being the obvious choice for synthetic purposes. Nevertheless, the yields of 2a achieved in sulfolane or DMF would have required much more than 1% water. Most interesting, however, is the fact that mixtures of DMSO with large amounts of water (e.g., 1:1) decreased the conversion (rate) considerably, and that, in general, only small amounts of water (usually 1–4 equiv.) improved the reaction, but were not necessarily required for good conversion.

Thus we are sure that DMSO and not adventitious residual water is the nucleophilic agent and at the very least delivers the oxygen of the introduced alcohol group. Based on the experiments presented we propose the following mechanism (Scheme 3). The first step would be attack by the nucleophilic oxygen of DMSO to form an alkoxysulfonium intermediate 6,[20–22] which is identical with that formed during Pfitzner–Moffatt and Swern oxidations, although these are inverse processes.[23,24] Oxysulfonium salts are known to undergo a Pummerer rearrangement at elevated temperatures, e.g., in a side reaction of Swern oxidations,[22,24] via 7a, to yield O,S-acetals 7b which may be decomposed by the HBr formed, or the water added.[25]
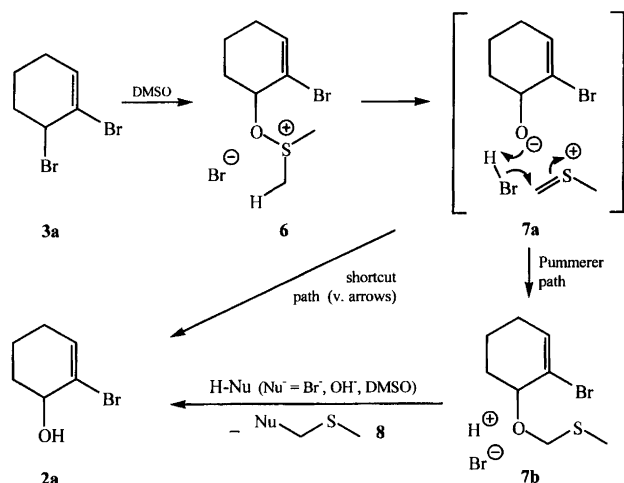
Scheme 3.

However, some uncertainties have still to be clarified. Intermediate 6 or O,S-acetals 7b were never detected in situ (e.g., through NMR spectroscopy in the kinetic study), nor could they be isolated, for instance through basic work-up. Thus other pathways, e.g., nucleophilic attack of the sulfur atom of dimethyl sulfoxide followed

by rearrangements, cannot currently be ruled out. Most likely the short pathway depicted in Scheme 3 (where with 7a, HBr may also be substituted by water, etc.) accounts for the lack of evidence for 7b.[26,27] Finally it should be noted that in contrast to neutral DMSO, DMSO carbanions (dimsyl) monodebrominate n,n-dibromobicyclo[n – 3.1.0]alkanes.[28]

Further investigations regarding the mechanism and attempts to broaden the synthetic aspects of the reaction are underway. In summary, we have presented an unusual variation of an S_N2 reaction with DMSO as a neutral hydroxide equivalent. Non-basic, silver-free methods for the mild and selective conversion of secondary halides into alcohols without significant side reactions, particularly eliminations, are less common than expected.[8,29]

Experimental

The NMR spectra were recorded for samples in $CDCl_3$ with Me_4Si as an internal standard at 300 MHz and 400 MHz (^1H) on Bruker ARX 300 and Varian VXR 400 spectrometers, respectively. n,n-Dihalobicyclo-[n – 3.1.0]alkanes were obtained from the corresponding cycloalkenes and haloform with tert-butoxide[11] or by the phase-transfer method.[12,13,30]

Warning. The following reactions can be exothermic. Although we never experienced problems of reaction control, it should be noted that explosions have been reported for the reaction of DMSO with some alkyl halides.[31] Potentially hazardous halomethyl methyl sulfides may be formed.

Typical procedure for thermal ring opening and subsitution reactions. Reactive n,n-dihalobicyclo[n – 3.1.0]alkane (1), or 1,n-dihalocycloalkene (3), or a mixture of these, (1 mmol, usually n = 6) was dissolved in DMSO (10 ml) with a trace of water (optimum quantity 36 μl, 2 mmol) and heated to a suitable temperature, usually 70–120 °C for bicyclohexane derivatives, or higher (>120 °C) for bicycloheptanes which react only when suitable substituents are present. The reaction was followed by TLC and when complete was quenched with 20 ml of water. The resulting solution was extracted twice with 20 ml of pentane–diethyl ether (1:1). The organic phases were washed three times with water (total of 60 ml) to remove dimethyl sulfoxide, once with ca. 20 ml satd. ammonium chloride solution and dried with Na_2SO_4 or $MgSO_4$. The solvent was removed at reduced pressure in a rotary evaporator. The crude products often had >95% purity (NMR). In other cases the product ratios could be obtained from the NMR spectra. Further purification of these mixtures was attained by flash chromatography on silica gel using mixtures of hexane and ethyl acetate (10:1 to 2:1).

Mechanistic experiments were variations of this procedure as indicated in the main text (cf. Tables 1 and 2) using purified, dry DMSO under argon.

2-Bromo-2-cyclohexenol (**2a**) *from 6,6-dibromo-bicyclo[3.1.0]hexane* (**1a**).[13] According to the general procedure 652 mg (2.7 mmol) of 6,6-dibromobicyclo[3.1.0]hexane (**1a**) and 98 µl of water (5.4 mmol) in 15 ml dry DMSO were kept at 80 °C for 3.5 h. The usual work-up gave 420 mg (88%) 2-bromo-2-cyclohexenol (**2a**).[7,32]

2-Chloro-2-cyclohexenol (**2c**) *from 6,6-dichlorobicyclo-[3.1.0]hexane* (**1c**).[13] According to the general procedure 160 mg (1 mmol) 6,6-dichlorobicyclo-[3.1.0]hexane (**1c**) and 36 µl water (2 mmol) in 5 ml DMSO were kept at 120 °C for 4 h. The usual workup gave 101 mg (76%) 2-chloro-2-cyclohexenol (**2c**).[6,7]

2-Bromo-2-cycloheptenol (**2b**) *from 1,7-dibromocyclo-heptene* (**3b**).[14] According to the general procedure 40 mg (0.16 mmol) 1,7-dibromocycloheptene (**2b**) and 36 µl water (2 mmol) in 12 ml DMSO were kept at 80 °C for 4 h. The usual work-up gave 10 mg (33%) 2-bromo-2-cycloheptenol (**3b**).[7,33]

Kinetic measurements. The kinetic experiments were carried out on a Varian VXR 400 spectrometer (400 MHz) in a standard 5 mm $\varnothing$ NMR tube with 90 mg 6,6-dibromobicyclo[3.1.0]hexane (**1a**) in 0.8 ml [^{2}H$_6$]-DMSO. The compound was purified immediately before the experiment by flash chromatography with petroleum ether. The first spectrum was recorded at 25 °C and, after heating to 90 °C (75 s), spectra were recorded each 60 s for the first 10 min, and thereafter each 5 min for an additional 50 min, with a 1 s accumulation time. The relative concentrations of dibromobicyclo[3.1.0]hexane (**1a**), 1,6-dibromocyclohexene (**3a**) and 2-bromo-2-cyclohexenol (**2a**) were determined by integration of the signals of the bridgehead protons in **1a** (δ 2.23–2.39), and the vinylic proton in **2a** (δ 6.05–6.12) and **3a** (δ 6.19–6.26). [^{2}H$_5$] DMSO (δ 2.49) was the internal standard.

For measurements in sulfolane the solvent was dried with CaH, distilled and kept over molecular sieves (3 Å). For experiments with added HBr, sulfolane was purged with dry HBr gas to give a stock solution (80 mmol l^{-1} HBr by titration). For locking purposes [^{2}H$_6$]benzene was added to give 6 : 1 solutions (v/v), [^{2}H$_5$]benzene being used as internal reference. These solutions (0.7 ml; with or without HBr) were frozen in the NMR tubes by insertion into dry ice, then dibromobicyclohexane **1a** was added on top. DMSO was added likewise (100 µl). After insertion into the spectrometer, samples were heated to 90 °C and scanned as described above. Because of overlap with sulfolane signals quantitative determination of **1a** proved impossible, and only the appearance of product signals (**3a**, **2a**) could be evaluated in relation to [^{2}H$_5$]benzene. However, because of this overlap, the data obtained are not definitive. In cases where DMSO and HBr were added, side reactions occurred before completion of the reaction (Pummerer reaction of DMSO with HBr, HBr-catalyzed water elimination from the product and subsequent aromatization).

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