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Regioselective monohalogenation of 3,3-disubstituted bornane-2-thiones via thione–dihalogen complexes

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Abstract—Reaction of 3,3-disubstituted bornane-2-thiones with Br_2, ICl, or Cl_2 afforded the corresponding 10-bromobornane-2-thiones, 10-iodobornane-2-thiones, or the products originated from skeletal rearrangement of 10-chlorobornane-2-thiones, respectively.

d-Camphor and their derivatives have been widely used as chiral auxiliaries and synthons for organic syntheses. However, few practical methods for functionalization of the bornane skeleton have been reported except for the preparation of *endo*-3-bromocamphor, *d*-camphor-10-sulfonic acid, and their derivatives. It is well known that chalcogenoxo functionalities have a general potentiality to immobilize dihalogen molecules through complexation,[1] and it was naturally expected that dihalosulfurane-type complexes **B**, assumed to be formed by the reaction of thiones (**A**) with an equimolar amount of dihalogen, would result in regioselective monohalogenation at the C-H group closed to the halogen atom of **B**. In line with such expectation, we attempted the treatment of bornane-2-thiones (**2**) with various dihalogens or halogenating agents. In this paper, we describe a novel regioselective monohalogenation of the C-10 position of **2** by treating with Br_2 or ICl.

3,3-Disubstituted ketones **1a–b** were prepared from *d*-camphor (**1c**) according to the reported methods,[2] and, subsequently, ketones **1a–d** were converted into thiones **2a–d** (Table 1) by treating with Lawesson's reagent.[3] When a CH_2Cl_2 or a $CDCl_3$ solution of **2a–b** was treated with Br_2 (1.1 mol amt.) at rt, **2a** or **2b** was converted into the corresponding 10-bromo derivative (**3a–b**, X = Br) in high yields, and no benzylic bromination products were obtained in the case starting from **2b**. The ^1H NMR monitoring of the reaction in $CDCl_3$ at 25°C also showed that **2a–b** were completely converted into **3a–b** (X = Br) as soon as Br_2 was added to the solution of **2**. The structure of **3b** (X = Br) was finally confirmed by X-ray crystallographic analysis,[4] and the ORTEP drawing is shown in Fig. 1. However, a similar treatment of thiofenchone (**2d**) with Br_2 gave **3d** (X = Br) in lower yield along with the formation of unidentified products, and attempted bromination of thiocamphor (**2c**) under similar conditions only gave a

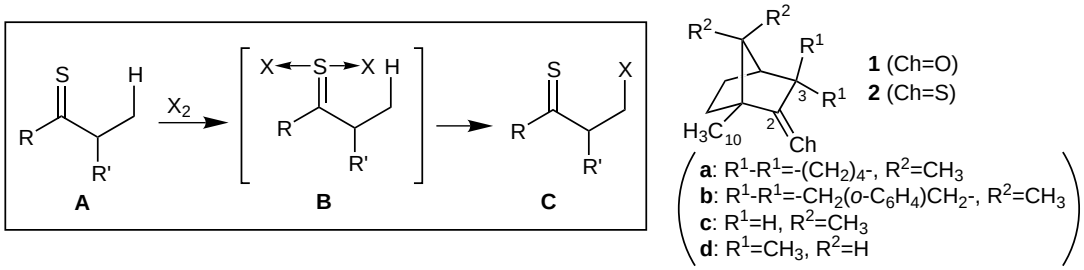

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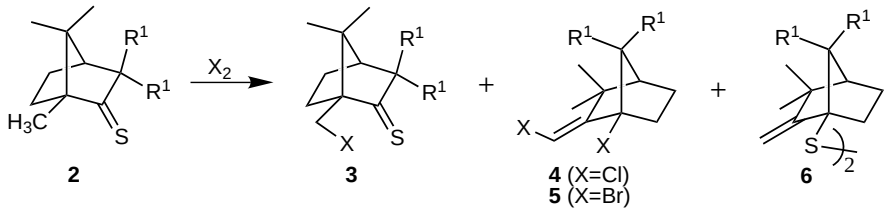
Table 1. Reaction of thiones **2** with a halogenating agent



Substrate **2**	Reagent (mol amt.)	Solvent	Temp.	Time	Yield (%)[a]		
					3	**4**, **5**	**6**
2a	Br_2 (1.1)	CH_2Cl_2	Rt	5 min	87 (**3a**, X = Br)	0	0
2b	Br_2 (1.1)	CH_2Cl_2	Rt	5 min	70 (**3b**, X = Br)	0	0
2b	Br_2 (2.2)	$CDCl_3$	Rt	24 h	0	19 (75,[b] **5b**)	0
2c	Br_2 (1.1)	CH_2Cl_2	Rt	5 min	0	Complex mixture	
2d	Br_2 (1.1)	CH_2Cl_2	Rt	5 min	46 (**3d**, X = Br)	Complex mixture	
2a	I_2 (1.1)	$CDCl_3$	Rt	24 h	0[c]	0	0
2b	I_2 (1.1)	$CDCl_3$	Rt	24 h	0[c]	0	0
2a	ICl (1.1)	CH_2Cl_2	Rt	60 min	14 (**3a**, X = I)[d,e]	0	4 (**6a**)
2a	Cl_2 (excess)	CH_2Cl_2	Rt	60 min	0	36 (60,[b] **4a**)	0
2b	Cl_2 (excess)	CH_2Cl_2	Rt	60 min	0	17 (50,[b] **4b**)	0
2a	*t*-BuOCl (1.1)	$CDCl_3$	Rt	60 min	0	0	85 (**6a**)

[a] Isolated yield.
[b] Estimated by integration of the ^{1}H NMR spectrum of the crude reaction mixture.
[c] Starting material **2** was quantitatively recovered.
[d] The 10-chloro derivative **3a** (X = Cl) was not found at all in the crude reaction mixture.
[e] **2a** was recovered in 56% yield.

complex mixture. A comparative treatment of ketones **1a**–**b** with Br_2 or a reaction of **2a** with anhydrous HBr at rt for 10 min also resulted in the recovery of **1a**–**b** or **2a**, respectively. So, it was clear that the complexation of the thione moiety of **2** with Br_2 was an essential step for the regioselective bromination and that the steric bulkiness around the thione moiety of **2** lacking an α-methylene group was most effective for the reaction in the light of the stabilization of the intermediary complexes. However, a similar treatment of **2a**–**b** with I_2 (1.1 mol amt.) only resulted in the recovery of **2a**–**b** in all cases, even though a CT band ($\lambda = 320$ nm) was observed in the UV–vis spectrum of a mixture solution of an equimolar amount of **2a** and I_2.[1] A similar treatment of **2a** with ICl (1.1 mol amt.) gave 10-iodo derivative **3a** (X = I, 14%) and **6a** (14%) along with the recovery of **2a** (56%). In contrast, treatment of **2a** with *t*-BuOCl (1.1 mol amt.) at rt gave only **6a** in 85% yield.

The NMR monitoring of the reaction of **2a** with Br_2 (1.1 mol amt.) in CD_2Cl_2 at −70°C only showed an approximate 10 ppm up-field shift of the thiocarbonyl carbon signal in the ^{13}C NMR spectrum along with a slight down-field shift of two methyl and one methylene signals of **2a** in the ^{1}H NMR spectrum, and the NMR spectrum at −20°C only showed the signals of **3a** (X = Br). These results indicated that linear 1:1 complexes of **2**-dihalogen were formed at the primary stage and would undergo a facile conversion into **3** at higher temperature. It is well known that the reaction of electronically-stabilized thiones with Br_2 or I_2 afforded T-shaped dibromosulfuranes or linear CT complexes, respectively.[1] The formation of 10-iodo derivative **3a** (X = I) by treating **2a** with ICl, in contrast with the cases of the reactions of **2a**–**b** with I_2, also suggested the formation of chloroiodosulfurane **F** (X, Y = Cl, I). Our results strongly suggested that the regioselective halogenation of **2** would proceed stepwise including the formation of intermediary dihalosulfuranes **F** (X, Y = Cl, Br, I), intramolecular dehydrohalogenation of **F**, and intramolecular halogen transfer from the sulfur atom to the C-10 carbon atom in **G**. The *t*-BuOCl-induced skeletal rearrangement of **2** was also suggested to occur only from chlorosulfonium ions **E** (X = Cl). Further treatment of **3a**–**b** with Br_2 (1.1 mol amt.) at rt for 5 min only gave a recovery of **3a**–**b**, and the reaction of **3b** with Br_2 in $CDCl_3$ in an NMR tube for 72 h gave dibromide **5b** as a major component in the reaction mixture. However, **5b** was gradually decomposed and was isolated only in 19% yield along with unidentified products after the usual workup and purification. It is noteworthy that the further bromination of

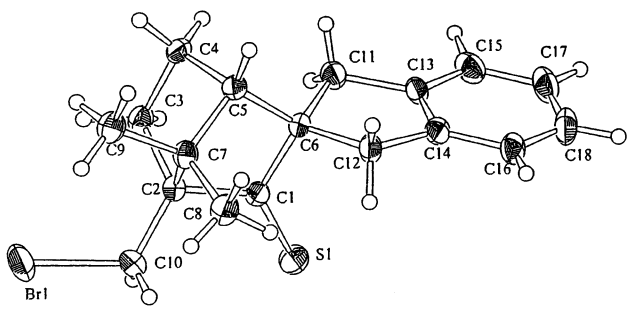
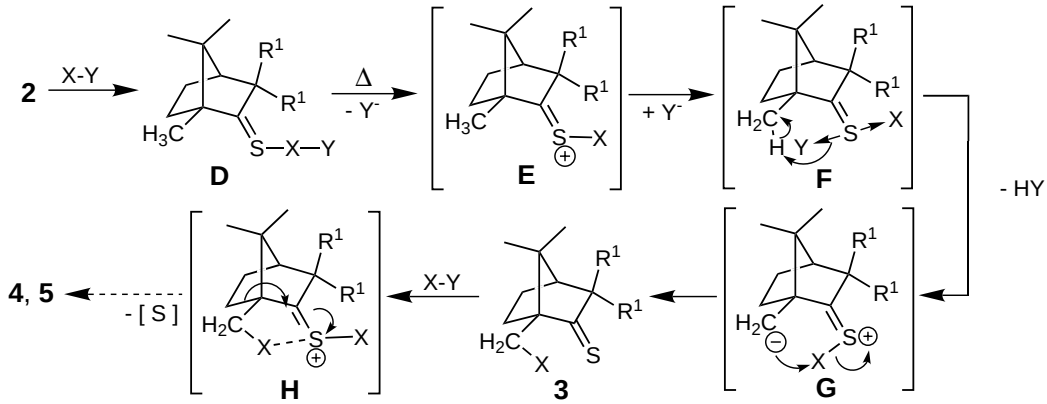


Figure 1. ORTEP drawing of **3b** (X = Br).



Scheme 1. Plausible reaction path for the formation of **3**, **4**, and **5**.

3b was sluggish, and no *gem*-dibromo product was obtained. Treatment of **2a**–**b** with Cl_2 (gas, excess) also gave dichlorides **4a**–**b** in low yields along with unidentified products, and the structure of **4a** was determined by X-ray crystallographic analysis.[5] The similarity in the ^1H NMR and ^{13}C NMR spectral patterns of **4a** to those of **5a** indicated that **5** possessed the same skeleton with the same halogenation pattern as those of **4**, and these results clearly showed that the skeletal rearrangement would proceed exclusively by the further reaction of **3** with halogens. It was assumed that an intramolecular attractive interaction between the halogen atom at the C-10 position and the cationic sulfur center of **H** would prevent the formation of T-shaped dihalosulfuranes like **F**[6] (Scheme 1).

In conclusion, we have achieved a convenient and regioselective monohalogenation of 3,3-disubstituted bornane-2-thiones **2** by treating with 1 molar amount of Br_2 or ICl. Further attempts for detection of intermediary dihalosulfuranes **F** as well as novel synthetic extension of 10-halobornane derivatives **3** as chiral synthons or chiral auxiliaries are in progress in our laboratory.

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4. X-Ray crystallographic data for **3b** (X = Br): $C_{18}H_{21}BrS$, $F_W = 325.31$, red prism, monoclinic, $P2_1$ (#4), $a = 8.863(1)$, $b = 10.6621(9)$, $c = 8.6336(5)$ Å, $\beta = 102.6100(7)°$, $V = 796.2(1)$ Å^3, $Z = 2$, $D_{calcd} = 1.357$ g/cm^3, μ(Mo Kα) = 27.03 cm^{-1}, $R = 0.028$, $R_w = 0.029$.
5. X-Ray crystallographic data for **4a**: $C_{18}H_{20}Cl_2$, $F_W = 307.26$, colorless plate, orthorhombic, $P2_12_12_1$ (#19), $a = 14.004(2)$, $b = 7.4670(5)$, $c = 29.6989(8)$ Å, $V = 3105.5(6)$ Å^3, $Z = 8$, $D_{calcd} = 1.314$ g/cm^3, μ(Mo Kα) = 4.05 cm^{-1}, $R = 0.034$, $R_w = 0.035$.
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