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B-BROMO-9-BORABICYCLO[3.3.1]NONANE. A CONVENIENT AND SELECTIVE REAGENT FOR ETHER CLEAVAGE *

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Summary

In methylene chloride solution, *B*-bromo-9-borabicyclo[3.3.1]nonane (*B*-Br-9-BBN) readily cleaves, in excellent yield, a variety of ethers of representative structural types. The reagent can also be used for selective cleavage of one of the ether groups in a molecule containing more than one such group.

The usefulness of a mild and selective ether cleavage reagent in the synthesis of polyfunctional natural products and biologically active molecules is well recognized. Boron halides have been extensively used for this purpose [1—3]. Of late, boron tribromide has found favor because of its effectiveness under mild conditions [1,4]. However, the presence of three reactive sites in boron tribromide can introduce difficulties with polyfunctional molecules. A monofunctional reagent should permit more selective reaction and better control of reaction conditions. For example, in hydroboration there are significant advantages in the hydroboration of dienes and other polyfunctional molecules with monofunctional disiamylborane and 9-BBN [5]. In cases where a polyfunctional borane yields complex products, these monofunctional hydroborating agents yield clean products. A simple synthesis for the monofunctional reagent *B*-bromo-9-borabicyclo[3.3.1]nonane, *B*-Br-9-BBN, has been developed in this laboratory [6]. It appeared that this reagent might possess significant advantages over boron tribromide for the cleavage of ethers. Accordingly, we undertook to explore the reaction of *B*-Br-9-BBN with representative ethers.

In methylene chloride solution at 25°C, the rate of reaction of *B*-Br-9-BBN (0.58 *M*) and BBr_3 (0.218 *M*) with n-butyl ether (0.623 *M* in both experiments) were measured (Fig. 1). The rates are similar in the initial stages of the reaction.

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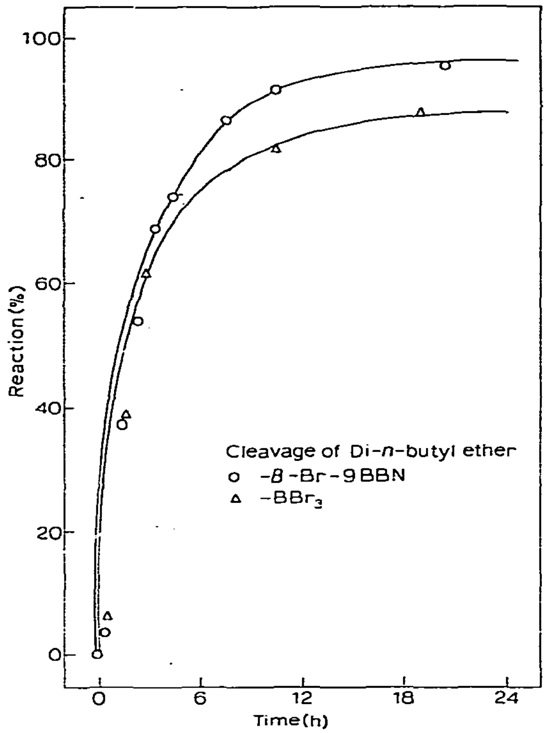
* Dedicated to Professor Herbert C. Brown.

** Visiting Professor, June 1977 to May 1978, on sabbatical leave from Indian Institute of Science, Bangalore-560012 (India).



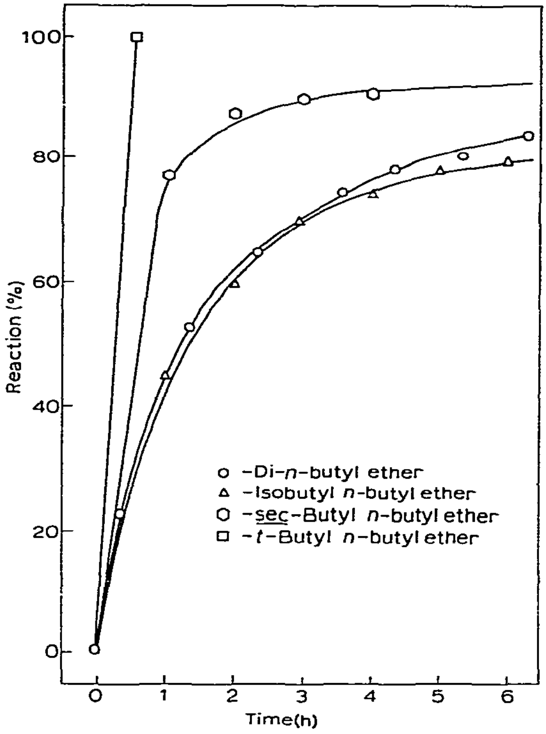


Fig. 1. Comparative rates of cleavage of di-n-butyl ether (0.623 *M*) with *B*-Br-9-BBN (0.58 *M*) and BBr_3 (0.218 *M*) in methylene chloride at 25°C.

Fig. 2. Comparative rates of cleavage of ethers (~*M* solution) with *B*-Br-9-BBN (~*M* solution) in CH_2Cl_2 at room temperature.

However, in the last third of the reaction with BBr_3, the reaction slows down, presumably owing to the slower reactivity of the bromoboronate ester intermediate.

The rates of cleavage of the four isomeric ethers, IV to VII (Table 1) at room temperature in approximately one molar solution in methylene chloride have been studied (Fig. 2). The rate of cleavage of VII was too fast to be measured accurately. Even with considerably reduced concentrations (viz. 0.61 *M B*-Br-9-BBN and 0.51 *M* in VII), the reaction was complete in one-half hour. sec-Butyl n-butyl ether (VI) was the next in the ease of claevage, whereas di-n-butyl ether

TABLE 1

Ether	Bromide formed (GLC yield)
Di-n-butyl ether (IV)	n-Butyl bromide (100)
Isobutyl n-butyl ether (V)	n-Butyl bromide (97) Isobutyl bromide (<3)
sec-Butyl n-butyl ether (VI)	sec-Butyl bromide (100)
t-Butyl n-butyl ether (VII)	t-Butyl bromide (100)

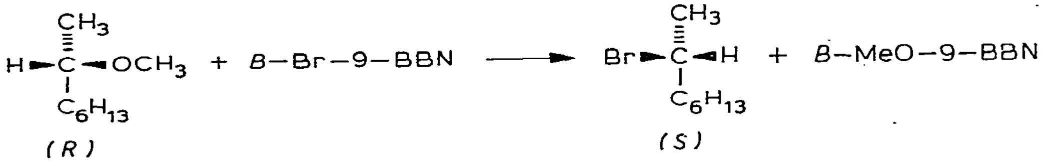
[a] Approximately one molar solutions of reactants were refluxed in methylene chloride for 3 h.

(IV) and isobutyl n-butyl ether (V) were cleaved at approximately similar rates.

The cleavage pattern fits into a simple picture (Table 1). A tertiary alkyl group is converted more readily into the corresponding bromide than a secondary one; the latter more readily than a primary group. Thus VII gives only t-butyl bromide and *B*-n-BuO-9-BBN, whereas sec-butyl n-butyl ether (VI) leads only to sec-butyl bromide and *B*-n-BuO-9-BBN. With di-n-butyl ether (IV) and isobutyl n-butyl ether (V), n-butyl bromide is formed, exclusively in the first case and predominantly in the second.

It is instructive to compare the cleavage pattern of *B*-Br-9-BBN with that reported [3] for BCl_3 *: (i) Only one of the C—O bonds, the same one with both compounds, is cleaved exclusively, in all the compounds studied: (ii) the bromide is formed without rearrangement with *B*-Br-9-BBN. In contrast, V gives a mixture of isobutyl and t-butyl chloride with BCl_3 [3]; and (iii) even with a highly sensitive ether such as allyl phenyl ether, *B*-Br-9-BBN produces allyl bromide as the major product. With BCl_3 allyl phenyl ether undergoes Claisen rearrangement [3].

An insight into the mode of reaction with *B*-Br-9-BBN is provided by the cleavage of *R*-2-octyl methyl ether, $[\alpha]_D^{25}$ −8.14, (76.5% optical purity) to yield *S*-2-octyl bromide, $[\alpha]_D^{25}$ +24.54 (55.6% optical purity). This corresponds to 73% inversion of configuration at the C—O bond. (With BCl_3 it is reported [3] that analogous experiment gave predominantly racemic 2-octyl chloride.)



Relative rates of cleavage of some representative ethers are given in Table 2.

In the case of hydroquinone dimethyl ether, it was possible to cleave one of the methoxy groups using one molar equivalent of *B*-Br-9-BBN at 25°C for 24 h. in molar solution of the reactants in methylene chloride.

An interesting example is provided by the methylenedioxy group. The reaction in molar solution of methylenedioxybenzene and *B*-Br-9-BBN in methylene chloride is imperceptibly slow at 25°C. However, refluxing a solution in the same solvent containing 2 *M* concentration of *B*-Br-9-BBN and 1 *M* in methylenedioxybenzene for 24 h results in complete cleavage. This would mean that it should be possible to selectively cleave methoxy groups without affecting the methylenedioxy group.

Most of the common type of ethers were cleaved quantitatively by refluxing molar solutions for 3 h in methylene chloride. The following procedures are typical.

Recently, the ether cleavage property of trimethylsilyl iodide has been reported [8—10]. Essentially quantitative cleavage of ethers has been claimed [8]. 2-Octyl methyl ether reacts with trimethylsilyl iodide to give after hydrolysis 2-octanol (86%), 2-octyl iodide (7%) and 2-octyl methyl ether (7%). With *B*-Br-9-BBN,

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* Unfortunately, comparable data for BBr_3 are not available.

TABLE 2

RELATIVE RATES OF CLEAVAGE OF ETHERS [a]

Ether	Relative rate
Di-n-butyl ether	1.0
Isobutyl n-butyl ether	0.66
sec-Butyl n-butyl ether	2.3
t-Butyl n-butyl ether	Too fast Complexe in 1/2 h
Anisole (Phenyl methyl ether)	0.14
Phenetole (Phenyl ethyl ether)	0.09
Hydroquinone dimethyl ether	1.0
Phenyl allyl ether	>0.76

[a] One molar solutions of reactants in methylene chloride at room temperature. The rates were followed by titration of the hydrobromic acid liberated by quenching aliquots in ice.

the cleavage products are cleanly 2-octyl bromide (with 73% inversion) and methoxy-9-BBN. Apparently the two reagents could give rise to different products, at least in some cases. Also the selectivity with trimethylsilyl iodide with molecules containing more than one ether linkage has not been reported.

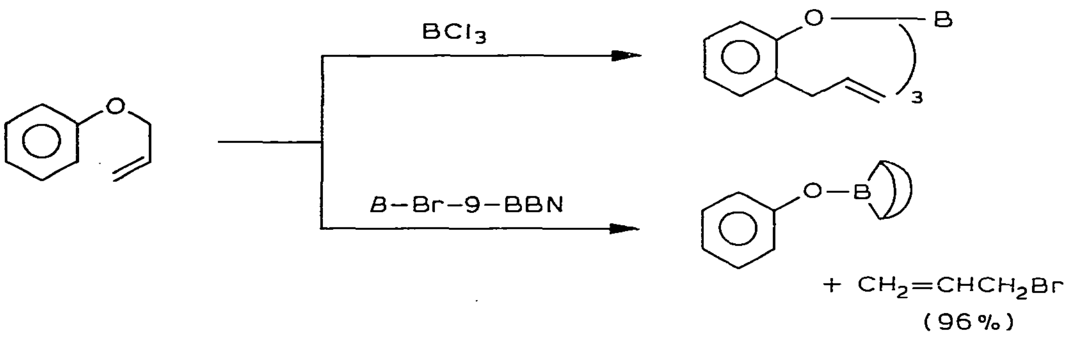
Cleavage of di-n-butyl ether

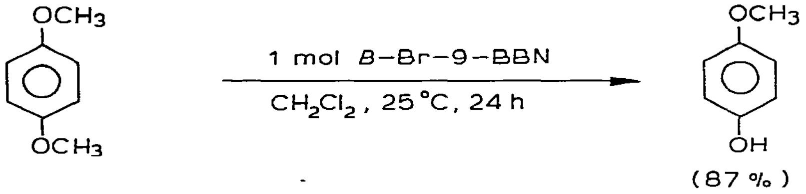
To a dry 200-round bottom flask fitted with a reflux condenser and carrying a spout and septum, and flushed with nitrogen, was transferred through a syringe 20.4 g (102 mmol) of *B*-Br-9-BBN and 68 ml of dry methylene chloride. Then 13.45 g (103 mmol) of dry di-n-butyl ether also was added. The reaction mixture was heated at reflux for 3 h. The solvent was distilled off using a 15 cm Vigreux column. The liquid distilling between 100—103°C/756 mmHg was collected to give 10.0 g (73%) of pure n-butyl bromide, identified by NMR and GLC.

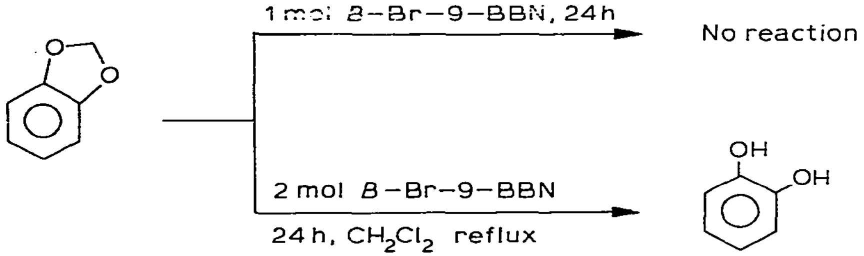
After cooling, the pot material was diluted with 100 ml of pentane, and 2-aminoethanol, (6.6 g, 108 mmol), was carefully added [7]. The white precipitate was filtered and the filtrate was concentrated and distilled. The fraction boiling at 118—121°C/756 mmHg was collected to give 5.49 g (74%) of substantially pure n-butanol (identified by NMR and GLC.

Preparation of p-methoxyphenol

Hydroquinone dimethyl ether (6.9 g, 50 mmol), methylene chloride (35 ml) and *B*-Br-9-BBN (10.3 g, 51 mmol) were mixed in a flask under nitrogen. The reaction mixture was stirred under nitrogen at 27°C for 24 h. Methylene chloride was removed at reduced presssure and the oily residue was diluted with 100—150 ml of pentane. 2-Aminoethanol (3.26 g, 52.6 mmol) was carefully added. The white precipitate which formed was filtered. The filtrate and the solid were shaken with 100 ml of 3 *N* KOH solution. The alkaline extract was acidified and extracted with ether. The ethereal extract, after drying ($MgSO_4$), and removal of the solvent, was distilled at reduced pressure (0.1 to 0.2 mmHg) to yield 5.39 g of colorless crystalline material, m.p. 50—55°C, 87% yield. The NMR spectrum was consistent with the structure of *p*-methoxyphenol.







Preparation of B-Br-9-BBN [6]

A solution prepared from 123.2 g (~1 mol) of 9-BBN and ~1700 ml of dry pentane (dried over molecular sieve) was filtered under nitrogen. The strength of the solution was estimated by hydride analysis. Thus 1670 ml of a solution 0.54 *M* in 9-BBN corresponding to 900 mmol was obtained. To this solution was added 28.5 ml of BBr_3 (300 mmol) and refluxed for 3 h. The solvent was distilled off, the last portion using suction. The residual liquid was distilled under reduced pressure to yield a clear colorless viscous liquid, b.p. 54—59°C/0.3—0.4 mmHg. Yield: 155 g (86%). The ^{11}B NMR spectrum showed a singlet at δ 83.9 ppm.

Acknowledgement

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