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EXCEPTIONALLY MILD AND STEREOSPECIFIC RING FRAGMENTATIONS PROMOTED BY DIMETHYLBORON BROMIDE

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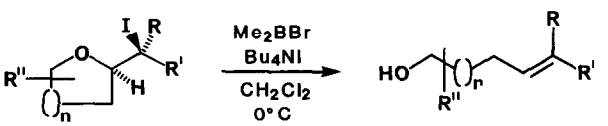
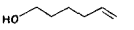
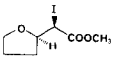
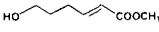
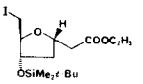
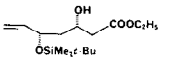
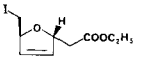
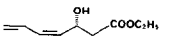
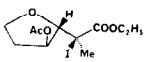
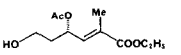
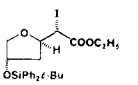
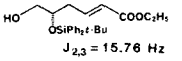
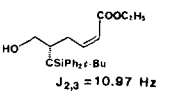
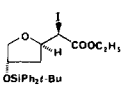
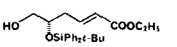
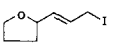
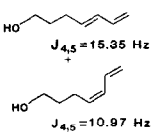
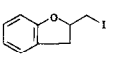
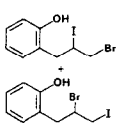
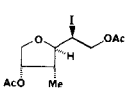
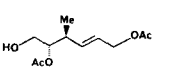
Abstract: A stereospecific and exceptionally mild fragmentation of β-iodoethers and allylic iodoethers by Me_2BBr in the presence of nBu_4NI was developed.

The early work with the reagents of the general formula R_2BBr[2] has stimulated a number of synthetic applications, all of them demonstrating the uniqueness of their reactivity for the cleavage of carbon-oxygen bonds.[3] Some synthetic possibilities afforded were recently exemplified in the efficient preparation of a key intermediate for mevinolin and compactin,[4] and of chiral 1,3 diols.[5] Pivotal to these syntheses is the conversion of simple chiral precursors into stereochemically well defined chiral tetrahydrofurans[6] and their subsequent regiocontrolled ring opening (S_N2 based control) to generate a pair of functional groups. In order to enhance and broaden the synthetic utility of this approach we were seeking a method that would permit a controlled opening of a given tetrahydrofuran without having to depend on base induced rearrangements nor steric factors. The development of a reaction that would be dependent on the presence β to oxygen of a functionality that could participate in an anchimeric way was then envisaged, and the retro-iodoetherification reaction studied.

We now wish to report our preliminary results with the Me_2BBr-promoted fragmentation of cyclic β-iodoethers. Typically, in the past, reductive fragmentations were effected with Zn in boiling alcohols or by treatment of the halogen compound with BuLi,[7] or with excess 2-lithio-1,3-dithian,[8] or with minor variations of these.[9] Most presumably, the reaction proceeds by a single electron transfer, expulsion of bromide ion from the intermediate radical anion followed by a second single electron transfer and a heterolytic fragmentation to form the olefin and release of the oxygen.[7] Taking in account the very potent oxygenophilic character of boron, we reasoned that the reverse iodo-etherification reaction would be possible if Me_2BBr was used together with a nucleophile such as iodide. This hypothesis was successfully verified and the results are presented in the table.



ENTRY	SUBSTRATE	CONDITIONS[1]	PRODUCT[2]	YIELD (%)[3]
1		A		82
2		A		91
3		A		82
4		A		93
5		A		88
6		A	 $J_{2,3}$ = 15.76 Hz	89
7	"	B	 $J_{2,3}$ = 10.97 Hz	76
8		B		73
9		A	 $J_{4,5}$ = 15.35 Hz + $J_{4,5}$ = 10.97 Hz	64
10		C		92
11	"	D		60
12		A		77

		A	B	C	D
1) CONDITIONS:	Et_3N (EQUIV.)	0.1	0.1	0.1	0.1
	$n\text{-}Bu_4NI$ "	3.0	3.0	3.0	0
	Me_2BBr "	2.5	0.95	2.5	2.5
	TIME (HR)	0.5	1	12	1

2) ALL NEW PRODUCTS WERE CHARACTERIZED BY ^{1}H-NMR, I.R. AND MASS SPECTROSCOPY.

3) YIELD BASED ON ISOLATED MATERIAL.

As can be seen from the table, primary, secondary, tertiary, activated or non-activated cyclic β-iodoethers were equally reactive to Me_2BBr in presence of nBu_4NI (e.g. entries 1, 2, 3, 5, 9 and 12) to give in good to excellent yield the corresponding olefins. With the exceptions of entries 10 (less basic oxygen), 6, 7 and 8 (0.95 equiv. of Me_2BBr used) which required longer reaction time, the transformation was complete in ca. 0.5 hr, and the materials obtained after extractive work-up were contaminated only by traces of tetrabutylammonium salts (^1H-250 MHz NMR): filtration through a pad of silica gel delivered the pure products. Other nucleophiles or Lewis acids tested (e.g. TMSCl/nBu_4NI, TMSBr, ZnI_2, BBr_3) were found ineffective in promoting the reaction or potentially incompatible with other functional groups present or generated (e.g. BBr_3 converts alcohols to bromides).

Only β-iodoethers gave rise to the reported fragmentation. For example 2-(bromomethyl)-tetrahydro-2H-pyran was left unchanged (0°C, 6 hours) while 2-(iodomethyl-tetrahydro-2H-pyran (entry 1) reacted completely to give the corresponding olefin. This may reflect the weaker effectiveness of bromide as a neighboring participating group.[10] Unsubstituted tetrahydro-2H-pyran would yield 1-bromopentanol on prolonged treatment with Me_2BBr as previously reported[3].

To further illustrate the possibilities offered by the reaction, substrates bearing olefinic functionalities were considered. As seen in entry 4, a diene could be generated, while preserving the stereochemical integrity of the starting olefin, in excellent yield. An allylic iodoether was also subjected to the conditions of the reactions (entry 9) and the corresponding 4,6-heptadien-1-ol was obtained in excellent yield (Z/E ratio 5:1).

In every respect the reaction can be seen as a retro-iodoetherification.[11] In fact, the isolation (c.a. 60%) of 2-(2'-bromo-3'-iodopropyl)phenol and 2-(2'-iodo-3'-bromopropyl)phenol when no external nucleophile was added (entry 11) strongly suggest the formation of an intermediate iodonium ion subsequently attacked by the halide ion. On treatment with $n\text{-}Bu_4NI$, this intermediate cleanly and quickly collapsed to 2-allylphenol as expected.[12,13] Therefore, use of excess $n\text{-}Bu_4NI$ is desirable to achieve a faster and more complete overall conversion. Furthermore, if the iodonium ion conforms to the microscopic reversibility of the fragmentation/iodoetherification tandem, cis-olefins should be obtained from threo-β-iodoethers (trans, from erythro). When this hypothesis was tested under the proposed typical conditions (A) (entry 6), the product was exclusively of the trans-geometry. However, when only 0.95 equivalent of Me_2BBr was used (entry 7), the cis-geometry was retained almost completely (>95%). This result along with others,[14] indicates that in the first case excess Me_2BBr had probably added to the Michael system and, upon quenching, generated the thermodynamically more stable trans-olefin. As expected, under the same conditions (entry 8) the isomeric erythro β-iodoether yielded only the trans-olefin. Therefore when Michael systems are generated, excess use of Me_2BBr is precluded, while otherwise it effects a faster conversion, especially when the substrate contains other sites of complexation for the reagent.

At the present time, this fragmentation suffers only from it's incompatibility with glycosidic functions (ketals are cleaved with Me_2BBr at -78°C)[3,15] which hinder it's use as a substitute for the well known Vasella reaction for glycosides, but makes it the complement of choice in other systems.

In conclusion, this stereospecific and exceptionally mild fragmentation of β-iodoethers and allylic iodoethers by Me_2BBr in the presence of nBu_4NI adds to the remarkably diversified possibilities offered by boron based reagents.

Typical procedure: To a cold (0°C), stirred solution of the substrate (entry 3) (0.29 mmol) and triethylamine (0.029 mmol, to neutralize traces of free acid) in CH_2Cl_2 (5 cc), under N_2, was added n-Bu_4NI (0.87 mmol) followed by a CH_2Cl_2 solution of dimethylboron bromide (1.81 M, 0.405 mL). After 0.5 h, the dark red reaction mixture was poured into a vigourously stirred 1:1 mixture of 10% $NaHCO_3$ and 10% $Na_2S_2O_3$ (10 cc); after iodine had all been reduced, extractive work-up (ethyl acetate), drying of the organic layer (brine, Na_2SO_4) and removal of the solvent left a residue which was passed through a pad of silica gel to afford, after removal of the solvent, the product (72 mg, 82%).

References

1. Present address: Bio-Mega Inc., 2100 Cunard, Laval, Québec, Canada H7S 2G5
2. Y. Guindon, C. Yoakim and H.E. Morton, Tetrahedron Lett., 24, 2969 (1983).
3. a) Y. Guindon, M. Thérien, Y. Girard and C. Yoakim, J. Org. Chem., in press.
   b) Y. Guindon, H.E. Morton and C. Yoakim, Tetrahedron Lett., 24, 3969 (1983).
   c) Y. Guindon, C. Yoakim and H.E. Morton, J. Org. Chem., 49, 3912 (1984).
   d) H.E. Morton and Y. Guindon, J. Org. Chem., 50, 5379 (1985).
4. Y. Guindon, C. Yoakim, M.A. Bernstein and H.E. Morton, Tetrahedron Lett., 26, 1185 (1985).
5. Y. Guindon, Y. St. Denis, S. Daigneault and H.E. Morton, Tetrahedron Lett., 27, 1237 (1986).
6. For a recent review see: P.A. Bartlett in "Asymetric Synthesis", J.D. Morrison Ed; Vol. 3, Chapter 6, 1984.
7. B. Bernet and A. Vasella, Helv. Chim. Acta., 67, 1328 (1984).
8. H. Redlich, J.B. Lenfers and W. Bruns, Liebigs Ann. Chem., 1570 (1985).
9. a) K. Shishido, K. Hiroya, H. Komatsu, K. Fukumoto and T. Kametani, J. Chem. Soc., Chem. Commun., 904 (1986). b) S.D. Burke, F.J. Schoenen and C.W. Murtiashaw, Tetrahedron Lett., 27, 449 (1986).
10. D.L.H. Williams, E. Bienvenue-Goetz and J.E. Dubois, J. Chem. Soc. (B), 517 (1969).
11. A.R. Chamberlin, R.L. Mulholland, Jr., S.D. Kahn and W.J. Hehre, J. Am. Chem. Soc., 109, 672 (1987).
12. E. Baciocchi in S. Patai and Z. Rappoport, "The Chemistry of Functional Groups, Supplement D", pt. 2, p. 161-201, Wiley, New York, 1983.
13. These observations do not completely rule out other possible concomitant mechanisms.
14. Unpublished results from this laboratory (H.E. Morton).
15. Y. Guindon and P. Anderson, Tetrahedron Lett., 28, 2485 (1987).

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