Tetrahedron Letters, Vol. 33, No. 43, pp. 6439-6442, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

IODINE MONOBROMIDE (IBr) AT LOW TEMPERATURE: A SUPERIOR PROTOCOL FOR DIASTEREOSELECTIVE CYCLIZATIONS OF HOMOALLYLIC CARBONATES

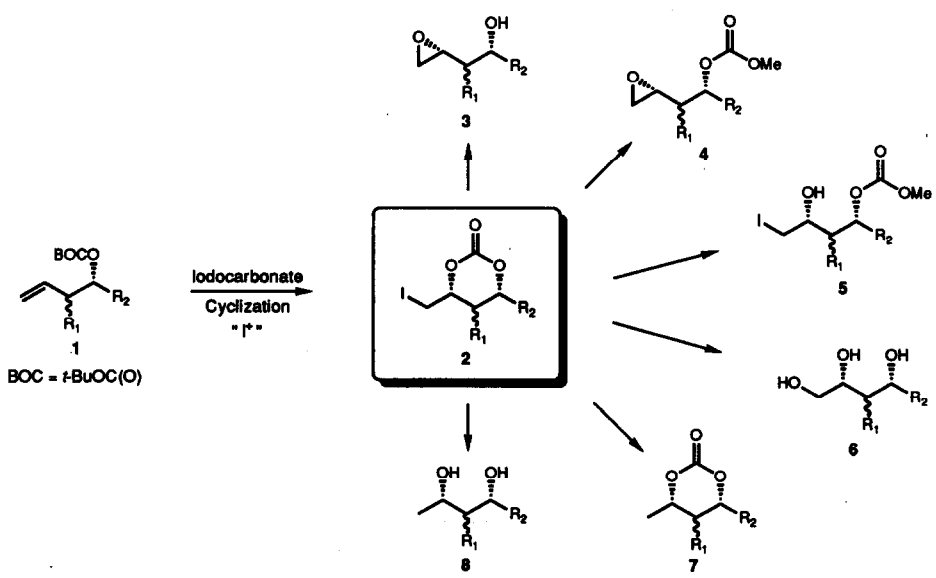
James J.-W. Duan, Paul A. Sprengeler, and Amos B. Smith, III*

Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104, U. S. A.

Summary: Iodine monobromide (IBr) induces efficient electrophilic cyclizations of homoallylic *t*-butyl carbonates in toluene or methylene chloride at low temperature, affording significantly better diastereoselectivity than iodine (I_2) in acetonitrile.

Whereas the stereoselective epoxidation of allylic alcohols has become a cornerstone of modern synthetic methodology,[1] the analogous transformation of homoallylic substrates remains generally unsatisfactory.[2] The iodine-induced electrophilic cyclization of homoallylic *t*-butyl carbonates was introduced as an effective alternative in the early 1980s.[3,4] As illustrated in Scheme I, the resultant six-membered iodocarbonates (**2**) are versatile intermediates which readily furnish epoxy alcohols **3** (3 equiv K_2CO_3, MeOH, or Amberlyst 26-A, OH^- form, MeOH),[3a,4b] methyl carbonate derivatives **4** (1.1 equiv K_2CO_3, MeOH, H_2O),[3a] iodohydrins **5** (1 equiv K_2CO_3, MeOH, 0 °C),[3a] triols **6** (Amberlyst 26-A, CO_3^{2-} form, PhH),[4b] cyclic carbonates **7** (Bu_3SnH),[3a] and diols **8** ($LiAlH_4$).[3a] In connection with our ongoing calyculin synthetic studies, we recently exploited the potent electrophile IBr in an iodocarbonate cyclization for the first time.[5] Herein we report that this reagent provides markedly enhanced diastereoselectivity in low-temperature cyclizations of structurally diverse homoallylic carbonates.

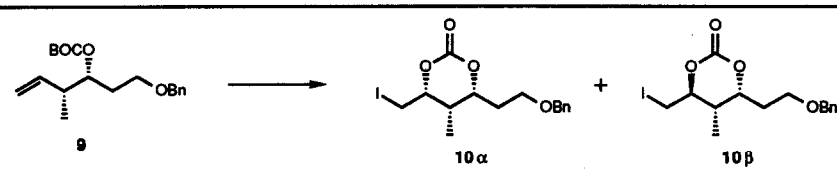
Scheme I



For the calyculin venture, we sought to transform carbonate **9** to iodide **10α**[5] (Table 1). Bartlett's original I_2/CH_3CN protocol[3] furnished the desired epimer **10α**[6,7] with 5.7:1 diastereoselectivity at -20 °C (entry 1). We anticipated that the isomer ratio could be improved by lowering the reaction temperature, but even at -20 °C the cyclization proceeded relatively slowly, suggesting that a more electrophilic reagent might be required. The high melting point of CH_3CN (-48 °C) prompted us to consider alternative solvents as well. However, the I_2 cyclizations reportedly were successful only in CH_3CN; other solvents such as CH_2Cl_2 and CCl_4 afforded low yields of intractable products.[3a]

Iodine monobromide,[8] a potent electrophile toward olefinic bonds,[9] reacted readily with **9** at -20 °C in CH_3CN; indeed, the dramatic rate increase vis-à-vis I_2 led to complete conversion within 15 min (Table 1, entry 2). This result set the stage for investigation of new solvents and lower temperatures. In contrast with molecular iodine, iodine monobromide induced efficient carbonate cyclization in hexane, diethyl ether, 1,2-dimethoxyethane, methylene chloride, and toluene. In methylene chloride, as the temperature was decreased from -20 to -94 °C, the isomer ratio improved from 3.3:1 to 8.7:1 (entries 3-5). Likewise, the diastereoselectivity in toluene increased from 6.7:1 to 14.9:1 as the temperature was lowered from -20 to -85 °C (entries 6 and 7). Although the IBr cyclizations in both CH_3CN and CH_2Cl_2 at -20 °C were less selective than the Bartlett method (3.1-3.3:1 vs 5.7:1, entries 1-3), IBr in toluene proved to be more selective (6.7:1, entry 6). The enhancement achieved with iodine monobromide in toluene at -80 to -85 °C thus derives from both temperature and solvent effects. The modest toluene solubility of IBr at low temperature necessitated a 6-h reaction time for cyclization of 6.2 mmol of **9**.

Table I. Optimization of the IBr Cyclization Protocol

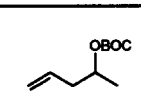
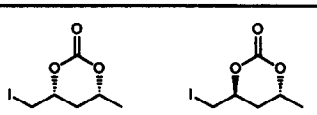
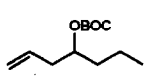
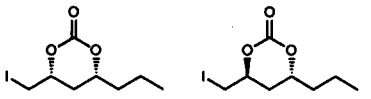
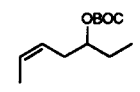
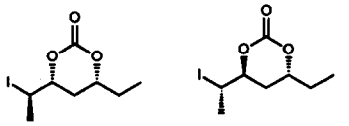
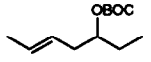
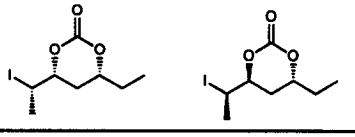
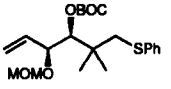
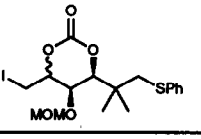
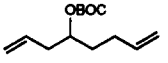
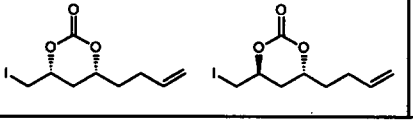


Entry	Conditions	Reaction time	Total yield[a]	Ratio of 10α:10β
1	I_2, CH_3CN, -20 °C	6.5 h	79%	5.7:1[b]
2	IBr, CH_3CN, -20 °C	15 min	67%	3.1:1[c]
3	IBr, CH_2Cl_2, -20 °C	15 min	75%	3.3:1[b]
4	IBr, CH_2Cl_2, -85 °C	15 min	74%	7.7:1[d]
5	**IBr, CH_2Cl_2, -94 °C**	**15 min**	**83%**	**8.7:1[b]**
6	IBr, PhMe, -20 °C	30 min	(e)	6.7:1[b]
7	**IBr, PhMe, -80 to -85 °C**	**6 h[f]**	**80%**	**14.9:1[b]**

Notes: (a) After flash chromatography. (b) Determined by dividing the average 125-MHz ^{13}C NMR integration values for several well-resolved carbons in each isomer. (c) Determined via separation by flash chromatography. (d) Determined by 500-MHz ^1H NMR analysis of crude mixture. (e) Not determined. (f) Reaction time for 6.2 mmol of **9**.

We then compared the IBr/CH_2Cl_2 and IBr/PhMe protocols with the published I_2/CH_3CN procedure for six additional substrates (Table II). The cyclizations were effected with 3 equiv of I_2 in acetonitrile at -20 °C for 5-10 h or with 1.5-2.0 equiv of IBr at -80 to -85 °C,[10] either in methylene chloride for 30 min or in toluene for 0.5-1 h. IBr generally furnished higher diastereomer ratios in toluene than in methylene chloride, whereas iodine in acetonitrile was least selective. The complex, functionalized substrate in entry 5 cyclized readily upon exposure to IBr but did not react with I_2, even at room temperature; the factors responsible for diminished selectivity in this case remain to be elucidated. In contrast with I_2, IBr adds to

Table II. Evaluation of IBr and I_2 for Cyclization of Diverse Homoallylic Carbonates

Entry	Substrate[a]	Products	I^+/Solvent	Yield[b]	Ratio[c]	Ref.
1			I_2/CH_3CN[d]	77%	10:1	
			IBr/CH_2Cl_2	87%	14:1	6,11
			IBr/PhMe	89%	21.1:1	
2			I_2/CH_3CN	90%	8:1	
			IBr/CH_2Cl_2	90%	12:1	6,7
			IBr/PhMe	95%	25.8:1	
3			I_2/CH_3CN[d]	91%	6.5:1	
			IBr/CH_2Cl_2[e]	87%	12:1	6,11
			IBr/PhMe	87%	18.8:1	
4			I_2/CH_3CN[d]	88%	4:1	
			IBr/CH_2Cl_2	89%	6.5:1	6,11
			IBr/PhMe	86%	6.4:1	
5			I_2/CH_3CN	No rxn[f]	---	
			IBr/CH_2Cl_2	86%[g]	1.7:1	6
			IBr/PhMe	69%[g,h]	3.4:1	
6			I_2/CH_3CN[d]	69%	6.5:1	
			IBr/CH_2Cl_2	---[i]	---	6,11
			IBr/PhMe	---[i]	---	

Notes: (a) Substrates were prepared from the corresponding alcohols by treatment with *n*-BuLi/BOC-ON. (b) After flash chromatography. (c) To facilitate comparison with the data reported in reference 3a, the ratios were determined by dividing the average 125-MHz ^{13}C NMR integration values for several well-resolved carbons in each isomer. (d) This result was reported in reference 3a. (e) This reaction was performed at -94 °C. (f) No reaction occurred after 8 h at -20 °C and 1 h at room temperature. (g) The relative configurations of the products were not determined. (h) Some starting material was also recovered. (i) Addition of IBr to the second double bond afforded a complex mixture.

alkenes and thus cannot be employed for cyclizations of polyolefinic substrates (entry 6).

In summary, iodine monobromide at low temperature comprises a highly effective protocol for diastereoselective iodocarbonate cyclizations. We obtained optimal diastereoselectivity in toluene at -80 to -85 °C. A detailed experimental procedure is provided below.[12,13]

Acknowledgments. Support for this work was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033. The authors would like to thank Dr. George Furst, Mr. John Dykins, and Ms. Magda Cuevas for assistance with spectroscopic analyses.

Notes and References

1. (a) For a review of diastereoselective epoxidation of allylic alcohols, see: Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323. (b) For a review of Sharpless asymmetric epoxidation, see: Pfenninger, A. *Synthesis* **1986**, 89.

2. (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Tsuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 989. (c) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690. (d) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707. (e) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 6191.

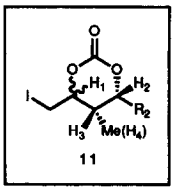
3. (a) Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: Orlando, Florida, 1984; Vol. 3, pp 411-454.

4. For analogous iodine-induced cyclizations of lithium carbonates, see: (a) Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465. (b) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626. (c) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (d) Lipshutz, B. H.; Barton, J. C. *J. Org. Chem.* **1988**, *53*, 4495.

5. Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855. Also see: Smith, A. B., III; Salvatore, B. A.; Hull, K. G.; Duan, J. J.-W. *Tetrahedron Lett.* **1991**, *32*, 4859.

6. All compounds gave satisfactory IR, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry.

7. Product stereochemistry was assigned by analysis of the H_1-H_3, H_2-H_3, and, where applicable, H_1-H_4 and H_2-H_4 coupling constants (cf., **11**, illustrated at right).



11

8. IBr was purchased from Aldrich Chemical Company, Inc. and used without purification.

9. White, E. P.; Robertson, P. W. *J. Chem. Soc.* **1939**, 1509.

10. Although optimal selectivity for IBr/CH_2Cl_2 was obtained at -94 °C (liquid N_2/hexane bath), a Dry Ice/Et_2O bath afforded superior temperature regulation (-80 to -85 °C).

11. Product structure and stereochemistry were determined by appropriate comparison with spectral data reported in reference 3a.

12. **Experimental Procedure.** IBr cyclizations in toluene were performed on 0.08-6.2-mmol scales without noticeable changes in yield or selectivity. A 1.0 M methylene chloride solution of IBr (1.5-2.0 equiv) was added dropwise to a solution of the carbonate in toluene (10 mL/mmol) at -80 to -85 °C (reference 10) under argon. After the reaction was complete, the mixture was stirred at 0 °C and 20% $Na_2S_2O_3$-5% $NaHCO_3$ solution (10 mL/mmol) and Et_2O (15 mL/mmol) were added. The organic phase was separated and washed with brine (10 mL/mmol) and the combined aqueous solutions were then extracted twice with Et_2O (5-mL/mmol portions). The organic solutions were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Following determination of the diastereomer ratio by ^{13}C NMR analysis, the products were separated by flash chromatography and characterized.

13. The iodocarbonates prepared in this study were stored at 0 °C and slowly decomposed over several weeks. We recommend immediate use in a subsequent transformation.

(Received in USA 26 March 1992; accepted 5 August 1992)