Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6347–6350

TETRAHEDRON LETTERS

Fragmentation of carbohydrate anomeric alkoxy radicals: a new synthesis of chiral 1-halo-1-bromo compounds

Concepción C. González, Elisa I. León, Concepción Riesco-Fagundo and Ernesto Suárez*

Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206 La Laguna Tenerife, Spain

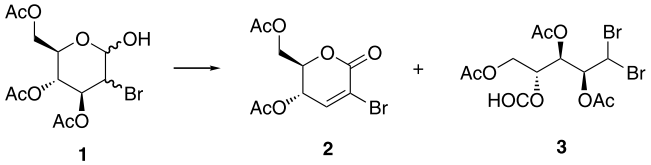
Received 20 February 2003; revised 3 June 2003; accepted 5 June 2003

Abstract—The reaction of 1,2-halohydrins derived from easily available carbohydrates with (diacetoxyiodo)benzene (DIB) in the presence of bromine is a mild procedure for the synthesis of 1-deoxy-1-halo-1-bromo-alditols with one carbon less than the original carbohydrate. The reaction goes through β-fragmentation of the intermediate anomeric alkoxyl radicals. These 1-halo-1-bromo polyhydroxy compounds may be valuable synthetic intermediates in organic synthesis.

1,1-Dihaloalkanes are valuable intermediates in organic synthesis for a variety of processes, including carbon–carbon bond formation and synthesis of carbocycles.[1] Notwithstanding, the synthetic applicability of these dihalides is severely restricted in natural products synthesis because their preparation requires reagents and/or conditions that are generally not compatible with complex or sensitive molecules. Thus, for instance, several procedures for the synthesis of 1,1-dibromo compounds have been developed: the reaction of aldehydes with boron tribromide,[2a] phosphorus pentabromide,[2b] and triphenyl phosphite/bromine,[2c] the treatment of hydrazones with copper(II) bromide,[2d] and the addition of hydrogen bromide to alkynes or vinyl halides.[2e] Other interesting methods are the alkylation of dibromomethyllithium[2f] and the reaction of 1,1-bis(trifluoromethyl)sulfonyloxy-alkanes with magnesium bromide.[2g] Moreover, several products possessing this 1,1-dibromo grouping have been isolated from marine natural sources.[3] Hence, there is still a need to develop general routes to this functionality under milder conditions.

In a previous paper from this laboratory we described the easy β-fragmentation of glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals, generated by reaction of carbohydrate anomeric alcohols with the (diacetoxyiodo)benzene (DIB) /iodine system, under

Table 1. Synthesis of 2,3,5-tri-*O*-acetyl-1-deoxy-4-*O*-formyl-1,1-dibromo-D-arabinitol (**3**)[a]



Entry	DIB (mmol)	Br_2 (mmol)	*T* (°C)	Time (h)	**1** (%)	**2** (%)	**3** (%)
1	1.1	3	40	24	6	40	18
2	3.3	4.5	0–5	14	5	21	56
3[b]	2.2	3	0–5	5	–	8	70

[a] All reactions were performed in dry CH_2Cl_2 (50 mL/mmol) under irradiation with two 80W tungsten-filament lamps.
[b] Powdered molecular sieves 4 Å (4 w/w) were added.

* Corresponding author. Tel.: 34 922 251004; fax: 34 922 260135; e-mail: esuarez@ipna.csic.es

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01399-6

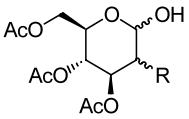
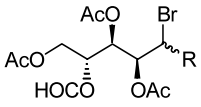
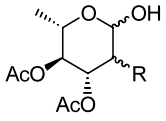
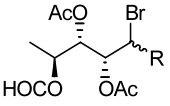
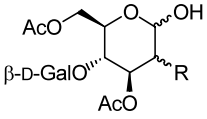
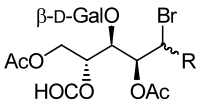
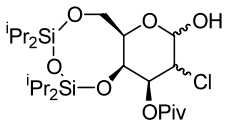
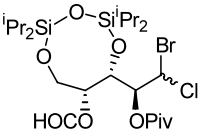
mild neutral conditions.[4] The presence of an electron-withdrawing group at C2 inhibits the oxidation of the intermediate C-radical and allows the possibility of radical-trapping by iodine atoms from the reaction medium.[5] The application of this methodology to 1,2-halohydrin derivatives from carbohydrates gave a simple method to prepare chiral 1-halo-1-iodo-compounds.[6]

The success of this strategy led us to consider whether it might be possible to generate 1-halo-1-bromo compounds using bromine instead of iodine to trap the C2-radical. This may be not a simple task, considering that the role of the halogen is not only to be the final radical trap but also to form the hypohalogenite intermediate.[7] Nevertheless, the major drawback could come from the differences of oxidation potential between both halogens. Indeed, it has long been known that under neutral conditions, bromine oxidizes an aldose almost quantitatively into the lactone of the aldonic acid.[8]

Unfortunately, as outlined in Table 1 (entry 1) this seemed to be the case for bromohydrin **1**, which under the normal conditions for the fragmentation reaction gave the dihydro-2*H*-pyran-2-one derivative **2**,[9] as the major product; the intended 1,1-dibromo compound **3**[10] was isolated in only 18% yield. Despite this discouraging initial observation, we chose to pursue the discovery of conditions to diminish this competitive oxidation process, and in this communication we describe the results obtained. After a variety of reaction conditions were attempted, we found that it was possible to diminish byproduct **2** by lowering the reaction temperature (entry 2). Eventually, the amount of the dibromo compound **3** could be further increased to 70% by adding powdered molecular sieves 4 Å to the reaction mixture (entry 3). Water is necessary for the oxidation to take place and consequently, the radical fragmentation reaction is substantially favored under strictly anhydrous conditions. Under these last conditions all the starting material was consumed and the yield of the undesired pyrone **2** could be kept at an acceptable level (8%).

We next sought to explore the generality of this reaction with other halohydrins (Table 2). The 1,2-halohydrins[11] of carbohydrates were prepared from the corresponding 2-deoxy-hex-1-enitol by reaction with Selectfluor™,[12] *N*-chlorosuccinimide,[13] *N*-bromoacetamide,[14] *N*-iodosuccinimide,[15] respectively, in the presence of water. The alkoxy radical fragmentation (ARF) reactions were performed under the conditions shown in Table 2.[16] In entries 1–4 we describe the reaction of several halohydrins **1** and **4**–**6** prepared from 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (3,4,6-tri-*O*-acetyl-D-glucal).[17] The reaction occurred with little, if any, diastereoselectivity to give 2,3,5-tri-*O*-acetyl-1-deoxy-4-*O*-formyl-1-halo-1-bromo-D-arabinitol derivatives **3** and **7**–**9** in moderate to good yields. In entry 5 we describe another synthesis of 1-bromo-1-iodo compound **9** by reaction of bromohydrin **1** with the DIB/iodine system.[6] This alternative procedure provides a better yield (compare entries 4 and 5) and therefore this method seems to be the best choice for the synthesis of 1-bromo-1-iodo compounds.

Table 2. Synthesis of 1-halo-1-bromo compounds[a]

Entry	Substrate	Time h	Product	Yield % (dr)
				
1	**4** R = F	4	**7** R = F	74 (1:1)
2	**5** R = Cl	5	**8** R = Cl	68 (1:1)
3	**1** R = Br	5	**3** R = Br	70
4[b]	**6** R = I	2.5	**9** R = I	53 (3:2)
5[c]	**1** R = Br	1.5	**9** R = I	99 (1:1)
				
6[b]	**10** R = F	3.5	**13** R = F	65 (3:2)
7	**11** R = Cl	4.5	**14** R = Cl	54 (2:1)
8	**12** R = Br	5	**15** R = Br	59
9[c]	**12** R = Br	2	**16** R = I	84 (1:1)
				
10	**17** R = F	4	**20** R = F	70 (4:3)
11	**18** R = Cl	3	**21** R = Cl	65 (1:1)
12	**19** R = Br	3.5	**22** R = Br	64
13[c]	**19** R = Br	2	**23** R = I	82 (1:1)
				
14[d]	**24**	12	**25**	59 (1:1)

[a] All reactions were performed in dry CH_2Cl_2 (50 mL/mmol) under irradiation with two 80W tungsten-filament lamps at 0–5 °C containing (diacetoxyiodo)benzene (DIB) (2.2 mmol), bromine (3 mmol) per mmol of substrate, and powdered molecular sieves 4 Å (4 w/w).

[b] DIB (1.1 mmol) and bromine (1.5 mmol) were used.

[c] The bromohydrin was treated with DIB and iodine as described in ref. 6.

[d] The reaction containing DIB (3.3 mmol) and bromine (4.5 mmol) at 0 °C was allowed to heat to rt for 12 h.

The 2,3-di-*O*-acetyl-1,5-dideoxy-4-*O*-formyl-1-halo-1-bromo-L-arabinitol derivatives **13**–**15**[18] were efficiently originated from the L-*rhamno* halohydrins **10**–**12** (entries 6–8). The disaccharide halohydrins **17**–**19** were obtained from lactosan, in order to study the compatibility of our method with the glycosidic linkage (entries 10–12). The ARF reaction cleanly proceeded to furnish 1-halo-1-bromo compounds **20**–**22**[19] in yields that are comparable to those observed in the monosaccharide runs. As previously commented, 1-bromo-1-iodo-com-

pounds **16** and **23** were obtained more efficiently using the DIB/iodine methodology (entries 9 and 13).

It was also observed that the reaction worked equally well for the D-*galacto* chlorohydrin **24** that has a sensitive 3,5-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl) as protecting group (entry 12). The 5-bromo-5-choro-D-arabinitol derivative **25** was obtained in comparable yield to the other bromo-chloro derivatives **8**, **14** and **21** (compare entry 14 with 2, 7, and 11).

Using this ARF methodology, with bromine or iodine as radical trap, we are able to prepare seven out of ten possible 1,1-dihaloalkanes, with the exceptions of 1,1-difluoro, 1,1-dichloro, and 1-fluoro-1-chloroalkanes. These dihalo-alditols can be useful multifunctional chiral synthons for the preparation of more complex molecules.

Acknowledgements

This work was supported by the Investigation Programmes no. BQU2000-0650 and BQU2001-1665 of the Dirección General de Investigación Científica y Técnica, Spain. C.R.-F. thanks the Dirección General de Universidades e Investigación del Gobierno de Canarias for a fellowship.

References

1. (a) Helquist, P. In *Comprehensive Organic Synthesis*; Trost, B.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp. 961–976; (b) Oshima, K. *J. Organomet. Chem.* **1999**, *575*, 1–20; (c) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429–1430; (d) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194–7208; (e) Smith, A. B.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423–7424; (f) Fujiwara, T.; Odaira, M.; Takeda, T. *Tetrahedron Lett.* **2001**, *42*, 3369–3372; (g) Hudlicky, T.; Ranu, B. C.; Naqui, S. M.; Srnak, A. *J. Org. Chem.* **1985**, *50*, 123–127; (h) Gaudino, J. J.; Wilcox, C. S. *Carbohydr. Res.* **1990**, *206*, 233–250.
2. For recent illustrative examples, see: (a) Xi, H.; Gibb, C. L. D.; Gibb, B. C. *J. Org. Chem.* **1999**, *64*, 9286–9288; (b) Cambie, R. C.; Rickard, C. E. F.; Starnge, G. A. *Aust. J. Chem.* **1997**, *50*, 841–848; (c) Hoffmann, R. W.; Bovicelli, P. *Synthesis* **1990**, 657–659; (d) Takeda, T.; Sasaki, R.; Nakamura, A.; Yamauchi, S.; Fujiwara, T. *Synlett* **1996**, 273–274; Takeda, T.; Sasaki, R.; Yamauchi, S.; Fujiwara, T. *Tetrahedron* **1997**, *53*, 557–566; (e) Larock, R. C.; Leong, W. W. In *Comprehensive Organic Synthesis*; Trost, B.; Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp. 279–287; (f) Onishi, T.; Otake, Y.; Hirose, N.; Nakano, T.; Torii, T.; Nakazawa, M.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 6337–6340; (g) Martínez, A. G.; Fernández, A. H.; Alvarez, R. M.; Fraile, A. G.; Calderón, J. B.; Barcina, J. O. *Synthesis* **1986**, 1076–1078.
3. (a) Cueto, M.; Darias, J.; Rovirosa, J.; San-Martín, A. *J. Nat. Prod.* **1998**, *61*, 1466–1468; (b) Francisco, M. E. Y.; Erickson, K. L. *J. Nat. Prod.* **2001**, *64*, 790–791; (c) Nicod, F.; Tillequin, F.; Vaquette, J. *J. Nat. Prod.* **1987**, *50*, 259–260.
4. (a) Francisco, C. G.; Freire, R.; González, C.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 1861–1866; (b) Francisco, C. G.; Martín, C. G.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099–2109; (c) Armas, P.; Francisco, C. G.; Suárez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865–8866.
5. Francisco, C. G.; Martín, C. G.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 8092–8093.
6. González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326–2328.
7. Courtneidge, J. L.; Lusztyk, J.; Pagé, D. *Tetrahedron Lett.* **1994**, *35*, 1003–1006.
8. (a) Theander, O. In *The Carbohydrates, Chemistry and Biochemistry*; Pigman, W.; Horton, D.; Wander, J. D., Eds.; Academic Press: London, 1980; Vol. 1B, pp. 1013–1099; (b) Isbell, H. S. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; Wolfrom, M. L.; BeMiller, J. N., Eds.; Academic Press: New York, 1963; Vol. II, pp. 13–14.
9. For the synthesis of the analogous (5*S*,6*R*)-5-acetoxy-6-(acetoxymethyl)-3-iodo-5,6-dihydro-2*H*-pyran-2-one using other methodology, see: Evans, R. D.; Schauble, J. H. *Synthesis* **1986**, 727–730.
10. 2,3,5-tri-*O*-Acetyl-1-deoxy-4-*O*-formyl-1,1-dibromo-D-arabinitol (**3**). Crystalline solid: mp 121–121.6°C (from *n*-hexane–EtOAc); $[\alpha]_D = +40$ ($CHCl_3$, $c = 1.03$); IR 1757, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 2.07 (3H, s), 2.15 (6H, s), 4.11 (1H, dd, $J = 12.5$, 5.6 Hz), 4.30 (1H, dd, $J = 12.5$, 3.1 Hz), 5.24 (1H, ddd, $J = 7.9$, 5.6, 3.1 Hz), 5.56 (1H, dd, $J = 7.6$, 2.4 Hz), 5.60 (1H, d, $J = 7.5$ Hz), 5.79 (1H, dd, $J = 7.9$, 2.4 Hz), 8.01 (1H, s); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 20.6 ($3\times CH_3$), 40.4 (CH), 61.5 (CH_2), 68.2 (CH), 68.4 (CH), 73.0 (CH), 159.4 (CH), 169.2 (C), 169.4 (C), 170.4 (C); MS (rel. intensity) 449 (M^+–H, <1), 434 (<1), 367 (4), 317 (12), 281 (6), 219 (17), 203 (100), 173 (44), 115 (72); HRMS calcd for $C_{12}H_{15}{}^{81}Br_2O_8$ 448.9093, found 448.9116. Anal. calcd for $C_{12}H_{16}Br_2O_8$: C, 32.17; H, 3.60. Found: C, 32.51; H, 3.31.
11. As determined by NMR spectroscopy the halohydrins were diastereoisomeric mixtures in most cases (see: Ref. 14). Chromatographically homogeneous products with correct elemental analyses were used in the fragmentation reactions.
12. (a) Albert, M.; Dax, K.; Ortner, J. *Tetrahedron* **1998**, *54*, 4839–4848; (b) Burkart, M. D.; Zhang, Z.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 11743–11746.
13. Rodriguez, J.; Dulcère, J.-P. *Synthesis* **1993**, 1177–1205.
14. Marzabadi, C. H.; Spilling, D. C. *J. Org. Chem.* **1993**, *58*, 3761–3766.
15. Smietana, M.; Gourverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 193–195.
16. Typical procedure: A mixture of the halohydrin (1 mmol) in CH_2Cl_2 (50 mL) containing (diacetoxyiodo)benzene (2.2 mmol) and powdered molecular sieves 4 Å (4 *w*/*w*) in a 100 mL round-bottom flask was immersed in a water bath at 0–5°C, cooled externally by a water-circulated double wall jacketed beaker (convenient refrigeration system in order to prevent local heating from the lamps over the long reaction times). To this solution was added bromine in CH_2Cl_2 (0.5 M, 3 mmol) and the mixture

irradiated, under nitrogen, with two 80 W tungsten-filament lamps at this temperature for the specified period of time (see Tables). The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with 10% aqueous sodium thiosulfate, dried and concentrated in vacuo. Chromatotron chromatography of the residue (*n*-hexane–EtOAc mixtures) afforded the required halo-bromine compound. Under these conditions formation of the pyranone byproducts apparently does not appear to occur to an appreciable extent. The reaction was performed under dilute conditions to avoid a high concentration of bromine but this aspect has not been optimized.

17. For the synthesis of 2-deoxy-hex-1-enitols (glycals), see: Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955–964.
18. 2,3-Di-*O*-acetyl-1,5-dideoxy-4-*O*-formyl-1,1-dibromo-L-arabinitol (**15**). Oil: $[\alpha]_D=-65$ ($CHCl_3$, $c=0.6$); IR 1757, 1032 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) 0.97 (3H, d, $J=6.3$ Hz), 1.59 (3H, s), 1.71 (3H, s), 5.07 (1H, dddd, $J=7.5$, 6.3, 6.3, 6.3 Hz), 5.36 (1H, d, $J=7.4$ Hz), 5.67 (1H, dd, $J=7.0$, 2.7 Hz), 5.70 (1H, dd, $J=7.4$, 2.7 Hz), 7.43 (1H, s); ^{13}C NMR (C_6D_6, 125.7 MHz), 16.0 (CH_3), 20.1 ($2\times CH_3$), 41.8 (CH), 67.5 (CH), 71.9 (CH), 73.3 (CH), 159.5 (CH), 168.9 (C), 169.0 (C); MS (rel. intensity) 345 (M^+-HCO_2, 1), 330 (1), 317 (14), 275 (14), 258 (11), 145 (100); HRMS calcd for $C_9H_{13}{}^{79}Br^{81}BrO_4$ 344.9160, found 344.9201. Anal. calcd for $C_{10}H_{14}Br_2O_6$: C, 30.80; H, 3.62. Found: C, 30.94; H, 3.66.
19. 2,5-Di-*O*-acetyl-1-deoxy-4-*O*-formyl-1,1-dibromo-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-D-arabinitol (**22**). Oil: $[\alpha]_D=-26$ ($CHCl_3$, $c=0.96$); IR 1754, 1371 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) 1.97 (3H, s), 2.07 (6H, s), 2.09 (3H, s), 2.15 (3H, s), 2.18 (3H, s), 3.97 (1H, ddd, $J=6.6$, 6.6, 0 Hz), 4.04 (1H, dd, $J=12.5$, 5.4 Hz), 4.20 (1H, dd, $J=11.4$, 6.7 Hz), 4.24 (1H, dd, $J=11.3$, 6.6 Hz), 4.52 (1H, dd, $J=8.0$, 1.4 Hz), 4.54 (1H, dd, $J=12.1$, 2.5 Hz), 4.54 (1H, d, $J=8.2$ Hz), 4.99 (1H, dd, $J=10.4$, 3.5 Hz), 5.07 (1H, ddd, $J=7.6$, 5.7, 2.5 Hz), 5.22 (1H, dd, $J=10.4$, 8.0 Hz), 5.38 (1H, dd, $J=3.5$, 0 Hz), 5.50 (1H, dd, $J=9.6$, 1.4 Hz), 5.99 (1H, d, $J=9.6$ Hz), 7.99 (1H, s); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 20.5 (CH_3), 20.7 ($5\times CH_3$), 43.5 (CH), 61.1 (CH_2), 61.3 (CH_2), 66.8 (CH), 68.8 (CH), 69.4 (CH), 70.9 (CH), 71.3 (CH), 73.5 (CH), 76.2 (CH), 101.8 (CH), 159.3 (CH), 169.2 (C), 169.6 (C), 170.0 (C), 170.1 (C), 170.2 (C), 170.4 (C); MS (rel. intensity) 676 (M^+-AcOH, <1), 617 (<1), 572 (<1), 307 (78), 247 (80), 145 (100); HRMS calcd for $C_{22}H_{28}{}^{79}Br^{81}BrO_{14}$ 675.9817, found 675.9821. Anal. calcd for $C_{24}H_{32}Br_2O_{16}$: C, 39.15; H, 4.38. Found: C, 39.14; H, 4.10.