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Alkoxyl radical fragmentation of 3-azido-2,3-dideoxy-2-halo-hexopyranoses: a new entry to chiral polyhydroxylated 2-azido-1-halo-1-alkenes

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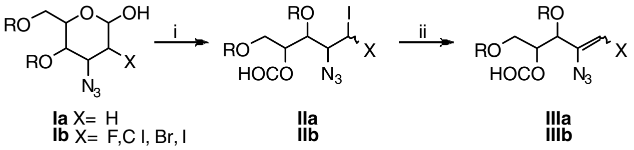
Abstract—A new general two-step methodology for the synthesis of chiral fluoro, chloro, bromo and iodo vinyl azides from carbohydrate-derived halohydrins has been developed. The anomeric alkoxyl radical fragmentation of 3-azido-2,3-dideoxy-2-halo-pyranoses under oxidative conditions with (diacetoxyiodo)benzene and iodine gave 2-azido-1,2-dideoxy-1-halo-1-iodo-alditols, which by chemoselective dehydroiodination afforded (*Z*,*E*)-2-azido-1,2-dideoxy-1-halo-4-*O*-formyl-pent-1-enitols in good overall yields. Preliminary thermolysis and photochemical studies of these compounds for the synthesis of hitherto unknown disubstituted 2-halo-3-alkyl-2*H*-azirines have also been accomplished.

Vinyl azides are useful intermediates in the synthesis of heterocycles, with versatility endowed by being precursors of vinyl nitrenes.[1] Since the pioneering work on the addition of iodine azide to olefins and the subsequent elimination of hydrogen iodide by Hassner and co-workers,[2] several methods for the synthesis of these compounds have been developed.[1,3] On the other hand, the synthesis of halo vinyl azides whose halogen atom offers another reaction site, has received much less attention. Although they can also be prepared by addition of halogen azides to vinyl halides,[4] other syntheses have been developed in order to avoid the use of these highly reactive and dangerous reagents: (a) the reaction of α-oxophosphonium ylides with *N*-halosuccinimides in the presence of azidotrimethylsilane[5] and (b) the addition of hydrazoic acid to some allenyl halides.[6] However, access to halo vinyl azides by these methods is limited to specific structures, for example, none of them could apparently be used for the synthesis of fluoro vinyl azides or for substances with a terminal 2-azido-1-halo-1-alkene arrangement. Indeed, there exists no general method to prepare 2-azido-1-halo-1-alkenes, as far as we know, the only report being on the isolation of the α-azido-β-chloro- and α-azido-β-bromo-styrene from the reaction of (haloethynyl)benzene with sodium azide in low yield.[7]

Recently, we have described a new synthetic entry to chiral vinyl azides making use of the anomeric alkoxyl radical β-fragmentation reaction (ARF) applied to 3-azido-2,3-dideoxy-hexopyranoses (**Ia**), as shown in Scheme 1 (X = H).[8] This methodology requires two steps, the radical fragmentation itself, which initially results in a β-iodo azide (**IIa**) and a dehydroiodination with DBU to 1,2-dideoxy-2-azido-pent-1-enitol (**IIIa**). The reaction proceeds under very mild conditions, avoids the use of halogen azides, and has been applied to a number of sensitive carbohydrate derivatives in high yields.



Scheme 1. Reagents: (i) $PhI(OAc)_2/I_2$; (ii) DBU.

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On the basis of these studies, we envisioned a general route to chiral 2-azido-1-halo-1-alkenes of the type **IIIb** (X = F, Cl, Br and I) utilising a similar methodology with the ARF reaction as the key step. The β-fragmentation of azido halohydrins **Ib** should give β-iodohalo azide **IIb** and the required vinyl halo azides **IIIb** should therefore be obtained by chemoselective elimination of the iodine atom (Scheme 1).[9]

To achieve this goal, we decided to prepare 3-azido-2,3-dideoxy-hex-1-enitols **1**[10] and **5**[11] utilizing previously reported procedures (Table 1). As in the case of azide **1**, the synthesis of **5** led to a diastereomeric mixture of azides. Although the separation is not strictly necessary, since C-3 is not a stereogenic center in the final product, it is convenient from the practical point of view and this study has been carried out with the major isomer, which corresponds to a D-*arabino*-hex-1-enitol stereochemistry.

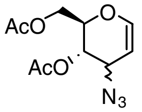
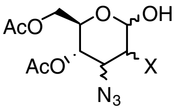
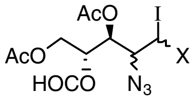
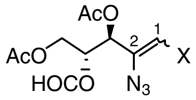
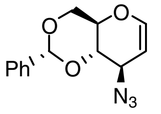
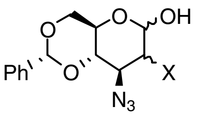
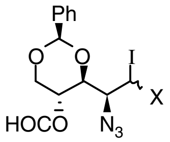
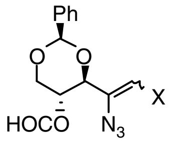
We have synthesised 1,2-halohydrins as outlined in Table 1. 1,2-Fluorohydrins (**2a**, **6a**), 1,2-chlorohydrins (**2b**, **6b**), 1,2-bromohydrins (**2c**, **6c**) and 1,2-iodohydrins (**2d**, **6d**) were prepared from the corresponding 2-deoxy-hex-1-enitol by reaction with Selectfluor™,[12] *N*-chlorosuccinimide,[13] *N*-bromoacetamide[14] and *N*-iodosuccinimide,[15] respectively.

The ARF reactions were performed under the conditions stated in Table 1, with (diacetoxyiodo)benzene (DIB) and iodine in CH_2Cl_2 at reflux temperature and irradiation with two 80-W tungsten filament lamps. The ARF reactions proceeded smoothly and 1-iodo-1-halo azides **3** and **7** were obtained in high yields. The reaction yields were determined using chromatographically homogeneous halohydrin mixtures giving correct elemental analyses and in all cases complete consumption of the starting material was observed. The dehydroiodination of the dihalo azides with DBU in benzene at room temperature afforded halo vinyl azides **4** and **8** in good yields. As expected, the reaction occurred with high chemoselectivity except for 1-bromo-1-iodo azides **3c** and **7c**, which gave significant amounts of vinyl iodides, 25% and 40%, respectively, by competitive dehydrobromination.

The stereochemistry of the double bond was assigned on the basis of 2D NOESY experiments. A NOE interaction was observed between H–C-1 and H–C-3 in the **4-*Z*** and **8-*Z*** isomers, such an interaction was not observed for the *E*-isomers.[16] Product structures were also established by spectroscopic (^{1}H, ^{13}C and ^{19}F NMR) correlation amongst *Z*- and *E*-isomers, for example, in the ^{19}F NMR spectra a difference of 8–10 ppm can be observed in the chemical shift of fluorine atoms between the *Z* and *E*-isomers of fluoro vinyl azides **4a** and **8a**. Furthermore, the structure and stereochemistry of **8d-*Z*** were determined unambiguously by single-crystal X-ray crystallography.[17]

The synthesis of halo vinyl azides **4** and **8** proceeded efficiently through the three steps, but in general with poor

Table 1. Synthesis of 2-azido-1,2-dideoxy-1-halo-pent-1-enitol compounds

Entry	Glycal	Time (h)	Halohydrin[a] yield (%)	Time (h)	β,β-Dihalo azide[b] yield (%)	Time (h)	Halo vinyl azide[c] yield (%, *E*:*Z*)
	 **1**						
1		5	**2a** X = F (66)	0.75	**3a** X = F (85)	0.75	**4a** X = F (82, 1:3)
2		5.75	**2b** X = Cl (90)	1.25	**3b** X = Cl (85)	0.75	**4b** X = Cl (86, 1:1)
3		2	**2c** X = Br (94)	1	**3c** X = Br (81)	0.75	**4c** X = Br (75, 1:1)[d]
4		1	**2d** X = I (94)	1	**3d** X = I (91)	0.5	**4d** X = I (100, 1:2)[e]
	 **5**						
5		17	**6a** X = F (65)	0.5	**7a** X = F (60)	1	**8a** X = F (60, 1:1)
6		11	**6b** X = Cl (89)	2.5	**7b** X = Cl (100)	1.75	**8b** X = Cl (92, 1:1)
7		8	**6c** X = Br (100)	1	**7c** X = Br (80)	1	**8c** X = Br (60, 1:2)[f]
8		1	**6d** X = I (100)	1.5	**7d** X = I (87)	1	**8d** X = I (91, 1:17)

[a] Reagents and conditions per mmol of substrate. Fluorohydrins: Selectfluor™ (1.5 mmol), nitromethane, H_2O, rt then reflux. Chlorohydrins: *N*-Chlorosuccinimide (2 mmol), THF, H_2O, 50 °C. Bromohydrins: *N*-Bromoacetamide (1.5 mmol), THF, H_2O, rt. Iodohydrins: *N*-Iodosuccinimide (1.2 mmol), THF, H_2O, rt.

[b] (Diacetoxyiodo)benzene (1.5 mmol), I_2 (1.5 mmol), CH_2Cl_2, *hν*, reflux.

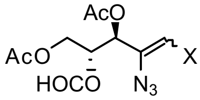
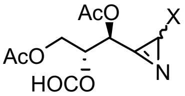
[c] DBU (2.5 mmol), PhH, rt.

[d] 25% of a mixture of *E*- and *Z*-vinyl iodides is also obtained.

[e] Inseparable mixture of isomers.

[f] 40% of a mixture of *E*- and *Z*-vinyl iodides is also obtained.

Table 2. Thermolysis and photolysis of 2-azido-1,2-dideoxy-1-halo-pent-1-enitol compounds

Entry	Substrate	Method[a]	Temp (°C)	Time (h)	Product yield[b] (%, dr)	
						
1[c]	**4a-*E*** X = F	A	80	1.25	**9** X = F	(71, 7:3)
2[c]	**4a-*Z*** X = F	A	120	2	**9** X = F	(78, 7:3)
3[c]	**4b-*E*** X = Cl	A	80	1.25	**10** X = Cl	(94, 6:4)
4[c]	**4b-*Z*** X = Cl	A	90	4.75	**10** X = Cl	(90, 6:4)
5	**4c-*E*** X = Br	A	80	1.5	—[d]	
6	**4c-*E*** X = Br	B	rt	0.5	**11** X = Br	(83, 6:4)
7	**4c-*Z*** X = Br	A	80	2	—[d]	
8	**4c-*Z*** X = Br	B	rt	0.5	**11** X = Br	(95, 6:4)
9	**4d-*EZ*** X = I	A	80	3	—[d]	
10	**4d-*EZ*** X = I	B	rt	0.5	**12** X = I	(87, 6:4)

[a] Method A: thermal conditions. All reactions were carried out in benzene (0.1 mM), the thermolysis of the *Z*-isomers in a heavy-walled Pyrex tube, sealed with a screw cap fitted with a Teflon gasket. Method B: photochemical conditions. All reactions in C_6D_6 (0.03 mM) under irradiation with the unfiltered light of a 450 W ACE-Hanovia medium-pressure mercury lamp.

[b] Crude yield.

[c] Similar results were obtained using method B, rt, 0.5 h.

[d] Under these conditions a mainly insoluble brown tar material was obtained.

diastereoselectivity. Only when the steric volume of the alkyl group and the halogen increased the diastereoselectivity improved significantly (compare Table 1 **4d** with **8d** or **8c** with **8d**).

The synthetic usefulness of these compounds for the synthesis of heterocycles has been preliminarily assessed through thermolysis (method A) and photolysis (method B) experiments, and the results are summarized in Table 2. According to the rules defined by Hassner, thermolysis of these vinyl halo azides with this 3-monoalkyl substitution pattern should give 3-alkyl-2-halo-2*H*-azirines.[18] On the other hand, due to the thermal instability of 2*H*-azirines the reaction was also carried out photochemically at a lower temperature. As far as we know, no examples of these disubstituted 3-alkyl-2-halo-2*H*-azirines have been reported to date and they are expected to be highly reactive and unstable on the basis of previous studies of related azirines.[19]

As can be observed in Table 2, thermolyses of the *E*-isomers of **4a**,**b** occur faster and at a lower temperature than those of *Z*-isomers (e.g., compare entries 1 and 2 or 3 and 4), a fact that has already been reported for the thermolysis of dehalogenated vinyl azides.[20] The stereochemistry of the double bond appears not to greatly influence the diastereoisomeric ratio of the final products (compare entries 1 with 2 and 3 with 4). Unfortunately, we were unable to obtain 2*H*-azirines **11** (X = Br) and **12** (X = I) from the thermolysis of **4c** and **4d**, respectively (entries 5, 7 and 9). On heating in benzene, increasing amounts of polymeric substances were observed and the substrate completely decomposed at reflux temperature. The preparation of the 2*H*-azirines was most conveniently achieved by irradiation with a medium-pressure mercury lamp (450 W) through a Pyrex filter at room temperature (entries 6, 8 and 10).

All the halo 2*H*-azirines synthesised in this Letter (**9**–**12**) proved to be unstable, could not withstand chromatographic purification and decomposed gradually, as diluted benzene solutions, within a few days in a freezer (−25 °C) under nitrogen. Notwithstanding, the instability increases from 2*H*-azirines **9** (X = F) to **12** (X = I) and we managed to fully characterize 2*H*-azirines **9** (X = F) and **10** (X = Cl) since crude reaction products were sufficiently pure to give clean ^{1}H and ^{13}C NMR spectra, HRMS and correct elemental analyses. From the most unstable 2*H*-azirines **11** (X = Br) and **12** (X = I) only ^{1}H NMR spectra could be obtained.[21]

In summary, we have developed a new two-step general methodology for the synthesis of polyhydroxylated 1-fluoro, 1-chloro, 1-bromo and 1-iodo-2-azido-1-alkenes making use of the ARF reaction. These carbohydrate-derived 2-azido-1,2-dideoxy-1-halo-pent-1-enitols may be of interest as chiral synthons for the preparation of polyhydroxylated heterocyclic systems.

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Supplementary data

Experimental procedures and analytical data for all new compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.190.

References and notes

1. For reviews, see: (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240; (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368; (c) Hassner, A. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, 1984; pp 35–94; (d) L'abbé, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 775–782; (e) L'abbé, G.; Hassner, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 98–104; (f) Smolinsky, G.; Pryde, C. A. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 555–585; For recent references, see: (g) Singh, P. N. D.; Carter, C. L.; Gudmundsdottir, A. D. *Tetrahedron Lett.* **2003**, *44*, 6763–6765; (h) Timen, A. S.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339–5341; (i) Mazal, C.; Jonas, J.; Zák, Z. *Tetrahedron* **2002**, *58*, 2729–2733.
2. (a) Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1965**, *87*, 4203–4204; (b) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077–2082; (c) Hassner, A.; Fowler, F. W. *J. Org. Chem.* **1968**, *33*, 2686–2691; (d) Hassner, A.; Boerwinkle, F. P.; Levy, A. B. *J. Am. Chem. Soc.* **1970**, *92*, 4879–4883.
3. For recent syntheses of vinyl azides, see: (a) Huang, X.; Shen, R.; Zhang, T. *J. Org. Chem.* **2007**, *72*, 1534–1537; (b) Zhu, W.; Ma, D. W. *Chem. Commun.* **2004**, 888–889.
4. (a) Ciabattoni, J.; Cabell, M. *J. Am. Chem. Soc.* **1971**, *93*, 1482–1483; (b) Padwa, A.; Blacklock, T. J.; Carlsen, P. H. J.; Pulwer, M. *J. Org. Chem.* **1979**, *44*, 3281–3287; (c) Gallagher, T. C.; Sasse, M. J.; Storr, R. C. *J. Chem. Soc., Chem. Commun* **1979**, 419–420.
5. d'A Rocha Gonsalves, A. M.; Cabral, A. M. T. D. P. V.; Pinho e Melo, T. M. V. D.; Gilchrist, T. L. *Synthesis* **1997**, 673–676.
6. Fotsing, J. R.; Banert, K. *Synthesis* **2006**, 261–272.
7. Tanaka, R.; Yamabe, K. *J. Chem. Soc., Chem. Commun.* **1983**, 329–330.
8. Alonso-Cruz, C. R.; Kennedy, A. R.; Rodríguez, M. S.; Suárez, E. *Org. Lett.* **2003**, *5*, 3729–3732.
9. (a) González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326–2328; (b) González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Chem. Eur. J.* **2003**, *9*, 5800–5809; (c) Francisco, C. G.; González, C. C.; Paz, N. R.; Suárez, E. *Org. Lett.* **2003**, *5*, 4171–4173; (d) Francisco, C. G.; González, C. C.; Kennedy, A. R.; Paz, N. R.; Suárez, E. *Tetrahedron: Asymmetry* **2004**, *15*, 11–14; (e) Francisco, C. G.; González, C. C.; Kennedy, A. R.; Paz, N. R.; Suárez, E. *Tetrahedron Lett.* **2006**, *47*, 35–38.
10. Glycal **1** was prepared from the isomeric mixture 4,6-di-*O*-acetyl-1,5-anhydro-3-azido-2,3-dideoxy-hex-1-enitol (Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1980**, *82*, 207–224. Dabrowska, A.; Dokurno, P.; Konitz, A.; Smiatacz, Z. *Carbohydr. Res.* **2000**, *323*, 230–234) by dehydration of the anomeric alcohol with Tf_2O and *s*-collidine (Charette, A. B.; Côté, B. *J. Org. Chem.* **1993**, *58*, 933–936).
11. Glycal **5** was prepared starting from 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-D-arabino-hex-1-enitol (Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2003**, *14*, 1767–1769) that was transformed into 1-*O*-benzoyl-4,6-*O*-benzylidene-2,3-dideoxy-D-erythro-hex-2-enopyranose by a Ferrier rearrangement under Mitsunobu conditions (Guthrie, R. D.; Irvine, R. W.; Davison, E. B.; Henrick, K.; Trotter J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 468–472) and finally to the required **5** by treatment with NaN_3 in HMPA (Guthrie, R. D.; Irvine, R. W.; Jenkins, I. D. *Aust. J. Chem.* **1980**, *33*, 2499–2508).
12. (a) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264–5279; (b) Albert, M.; Dax, K.; Ortner, J. *Tetrahedron* **1998**, *54*, 4839–4848; (c) 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, C. D. *J. Org. Chem.* **1993**, *58*, 3761–3766.
15. Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 193–195.
16. For NOE based stereochemistry of related trisubstituted vinyl halides, see: (a) Kim, J.; Zhang, Y.; Ran, C.; Sayre, L. M. *Bioorg. Med. Chem.* **2006**, *14*, 1444–1453; (b) Kattuboina, A.; Kaur, P.; Timmons, C.; Li, G. *Org. Lett.* **2006**, *8*, 2771–2774; (c) Cheng, C.; Shimo, T.; Somekawa, K.; Baba, M. *Tetrahedron* **1998**, *54*, 2031–2040; (d) Manfre, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060–2065; (e) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkarall, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439–7440.
17. Crystallographic data (excluding structure factors) for compound **8d-*Z*** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 648303. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
18. Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176–3180.
19. For a review on 2-halo-2*H*-azirine chemistry, see: (a) Pinho e Melo, T. M. V. D.; d'A Rocha Gonsalves, A. M. *Curr. Org. Synth.* **2004**, *1*, 275–292; For general reviews on 2*H*-azirines, see: (b) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219–269; (c) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401–2414; (d) Gilchrist, T. L. *Aldrichim. Acta* **2001**, *34*, 51–55; (e) Padwa, A.; Woolhouse, A. D. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 7, pp 47–93; (f) Anderson, D. J.; Hassner, A. *Synthesis* **1975**, 483–495.
20. (a) Yamabe, T.; Kaminoyama, M.; Minato, T.; Hori, K.; Isomura, K.; Taniguchi, H. *Tetrahedron* **1984**, *40*, 2095–2099; (b) Isomura, K.; Taniguchi, H.; Mishima, M.; Fujio, M.; Tsuno, Y. *Org. Magn. Reson.* **1977**, *9*, 559–562.
21. ^{1}H NMR (400 MHz, C_6D_6) chemical shifts for H–C1 of 2*H*-azirines **9**–**12**, major and minor isomer; **9**: 4.85 ($J_{FH} = 99.6$ Hz), 4.98 ($J_{FH} = 99.1$ Hz) ppm; **10**: 3.96, 4.08 ppm; **11**: 3.95, 4.05 ppm; **12**: 3.34, 3.41 ppm.