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Chemoselective 1-ethylpiperidine hypophosphite (EPHP)-mediated intermolecular radical additions of 1-deoxy-1-halo-1-iodo-alditols to electron-deficient olefins

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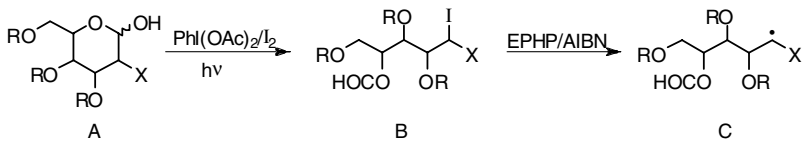
Abstract—The chemoselective radical reduction of the iodine atom in a series of 1-deoxy-1-halo-1-iodo-alditols with the 1-ethylpiperidine hypophosphite (EPHP)/AIBN system is described. EPHP is also a good chain carrier for the radical addition of *gem*-dihalocompounds to electron-deficient olefins. Thus, the synthesis of 4-halo-glycooctononitriles and 4-halo-glycoheptononitriles can be achieved by an intermolecular addition of the 1-deoxy-1-halo-alditol-1-yl radical intermediate to acrylonitrile.

Since Barton and Jang published their seminal work in 1992,[1] hypophosphorous acid and its salts have been transformed in a very useful and mild alternative to tin reagents in radical chemistry. 1-Ethylpiperidinium hypophosphite (EPHP) is one of the most effective substitutes,[2] not only for the dehalogenation of organic halides[3] and deoxygenation of alcohols,[4] but also as a radical chain carrier for C–C bond formation in intra and intermolecular radical additions.[5,6]

On the other hand, the reactivity of the tin and phosphorous reagents seems to be very different. Thus, under normal conditions chlorides, bromides, and iodides tend to react with tri-*n*-butyltin hydride (TBTH) at comparable rates, while fluorides are generally considered to be inert.[7] Based on a number of experiments already described in the literature a better chemoselectivity could be expected for the reaction of EPHP.

Although most of the EPHP studies have been made with alkyl iodides, bromides can also be used as radical precursors in addition reactions, although more forcing conditions are required.[6b] Furthermore, Barton and Jang in their early work pointed out the complete stability of 1-chloroadamantane under the hypophosphorous acid conditions.[1] Along this line, Murphy and co-workers[5e] recently described the completely chemoselective cyclization of *N*-(3-chloro-2-cyclohexen-1-yl)-2-iodoaniline in an interesting synthesis of *cis*-fused hexahydrocarbazols.

During the last years, we have developed the synthesis of 1-deoxy-1-halo-1-iodo-alditols (B) based on the anomeric alkoxyl radical β-fragmentation (ARF) of 2-deoxy-2-halo-glycofuranoses and glycopyranoses (A) (Scheme 1).[8] 1,1-Dihaloalkanes are versatile compounds in organic synthesis and have attracted much interest as



Scheme 1. Synthesis and chemoselective reduction of 1-deoxy-1-halo-1-iodo-alditols. R = protective group, X = F, Cl, Br.

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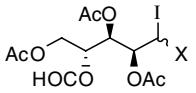
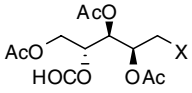
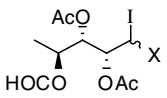
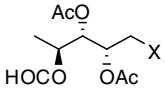
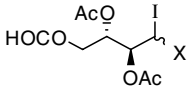
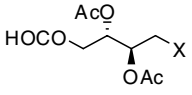
intermediates in C–C bond-forming reactions of which the Takai olefination constitutes a good example.[9]

With a view to studying the reactivity of these 1-deoxy-1,1-dihalo-alditols, the possibility of carrying out the selective reduction of one of the two halogens was examined by employing radical reactions promoted by EPHP. Clearly the radical intermediate C offers other synthetic opportunities such as an intermolecular addition to electron-deficient olefins, which is also explored in this letter. At the same time, this work also provided an excellent opportunity for a detailed study of the chemoselectivity of the EPHP dehalogenation reaction. The 1-deoxy-1-halo-1-iodo-alditols used in this letter were synthesized by visible light irradiation with two 80 W tungsten-filament lamps of the corresponding 2-deoxy-2-halo-carbohydrate using (diacetoxyiodo)benzene and iodine as radical promoters (Scheme 1).

Firstly, the possibility of reducing the iodine atom selectively in the presence of another halogen atom was examined. EPHP addition to a refluxed solution of 1-deoxy-1-halo-1-iodo-alditols in benzene using AIBN as initiator gave the results shown in Table 1. Dihalocompounds were obtained from D-glucal (**1**–**3**), L-rhamnal (**8**–**10**), and L-arabinal (**14**–**16**) as described previously.[8c] The reactions proceeded smoothly, affording the corresponding 1-deoxy-1-halo-alditols in good to excellent yields. In all cases, the iodine atom was reduced selectively, and no detectable amounts of didehalogenation products were observed. It is worth noting that even 1-bromo-1-iodo-alditols **3**, **10**, and **16** could be selectively reduced in a high yield (entries 6, 9, and 12).

Table 1. Chemoselective reduction of 1-deoxy-1-halo-1-iodo-alditols

Entry	Substrate[a]	Product	(%)[b]
			
1	**1** X = F[c]	**4** X = F	81
2	**1** X = F	**4** X = F	86
3	**2** X = Cl[c]	**5** X = H	96
4	**2** X = Cl	**6** X = Cl	85
5	**3** X = Br[c]	**5** X = H	96
6	**3** X = Br	**7** X = Br	76
			
7	**8** X = F	**11** X = F	86
8	**9** X = Cl	**12** X = Cl	95
9	**10** X = Br	**13** X = Br	73
			
10	**14** X = F	**17** X = F	65
11	**15** X = Cl	**18** X = Cl	85
12	**16** X = Br	**19** X = Br	85

[a] The solution of 1-deoxy-1-halo-1-iodo-alditol (1 mmol) in dry benzene (20 mL) containing EPHP (3 mmol) and AIBN (0.4 mmol) was refluxed for 1 h.

[b] Yields refer to chromatographically purified product.

[c] The solution of 1-deoxy-1-halo-1-iodo-alditol (1 mmol) in dry benzene (20 mL) containing TBTH (3 mmol) and AIBN (0.4 mmol) was refluxed for 1 h.

For comparison purposes, the reductions of dihalo-alditols **1**–**3** with TBTH have been included (Table 1, entries 1, 3, and 5). As expected, except for the fluoro-iodo compound **1**, complete didehalogenation was observed.

The remarkable chemoselectivity observed under the EPHP conditions could be exploited for synthetic purposes. Thus, the next process to be explored was the radical intermolecular addition to electron-deficient olefins, which is an important methodology for the radical-mediated construction of carbon–carbon bonds. No precedent has been found for the successful addition of 1,1-dihaloalkanes to olefins, the only related work being the iron- or nickel-catalyzed reaction of iodofluoro-acetates with alkenes as a route to α-fluoroesters.[10]

When EPHP was added to a mixture of dihaloalditol, acrylonitrile, and AIBN as the initiator in boiling benzene, two products were formed as outlined in Table 2. The radical addition halo-nitriles **20**–**28** were formed in competition with products of H-trapping that have been described above (Table 1).

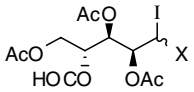
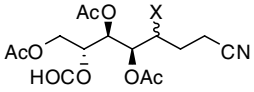
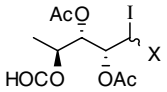
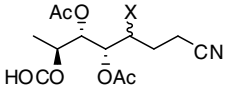
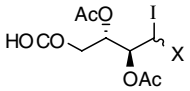
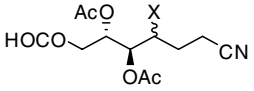
The ratio of addition to H-trapping products is markedly dependent on the attached halogen. As shown in Table 2, the addition yield decreases on going from fluorine (73–80%, entries 1, 4, and 7) to chlorine (53–54%, entries 2, 5, and 8) to bromine (40–45%, entries 3, 6, and 9) with a concomitant increase in the H-trapping yield (15–44%).

As might be expected, the diastereoselectivity was low and the nitriles were always obtained as a chromatographically inseparable mixture of isomers. Notwithstanding, significant levels of diastereoselectivity were achieved with bromine compounds as the steric demand of the sugar increased (compare entries 3, 6, and 9).

When the reaction was carried out with electron-donating olefins, the H-trapping products were the principal components observed. For example, the reaction of EPHP with dihalocompound **2** in the presence of allylbenzene afforded exclusively reduced chlorocompound **6** in an 85% yield. It is worth mentioning that the reaction of 1-iodo-1-fluor-alditol **1** when treated with allylbenzene gave a small amount of the addition product (15%), probably due to the known ambiphilic nature of the fluorinated alkyl radicals.[11]

In this letter, we have shown that EPHP is not only a convenient chemoselective reducing agent of iodine in the presence of other geminal-halogen atoms, but also a good radical chain carrier for C–C bond-forming processes in the preparation of polyhydroxylated γ-halo-nitriles.

Table 2. Chemoselective addition of 1-deoxy-1-halo-alditol-1-yl radicals to acrylonitrile

Entry	Substrate[a]	Products[b]	
		Addition (%) (dr)	Reduction (%)
			
1	**1** X = F	**20** X = F (75) (1:1)	**4** (22)
2	**2** X = Cl	**21** X = Cl (53) (1:1.7)	**6** (33)
3	**3** X = Br	**22** X = Br (40) (1:2.5)	**7** (40)
			
4	**8** X = F	**23** X = F (73) (1:1)	**11** (20)
5	**9** X = Cl	**24** X = Cl (54) (1:1.5)	**12** (40)
6	**10** X = Br	**25** X = Br (41) (1:1.7)	**13** (44)
			
7	**14** X = F	**26** X = F (80) (1:1)	**17** (15)
8	**15** X = Cl	**27** X = Cl (53) (1:1)	**18** (38)
9	**16** X = Br	**28** X = Br (45) (1:1)	**19** (41)

[a] The solution of 1-deoxy-1-halo-1-iodo-alditol (1 mmol) in dry benzene (20 mL) containing EPHP (3 mmol), acrylonitrile (5 mmol), and AIBN (0.4 mmol) was refluxed for 1 h.

[b] Yields refer to chromatographically purified product.

Acknowledgements

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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.2006.10.086.

References and notes

1. (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709–5712; (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838–6842; (c) Jang, D. O. *Tetrahedron Lett.* **1996**, *37*, 5367–5368.
2. EPHP is considerably less toxic and costly than tri-*n*-butyltin hydride, other advantages including an easy work-up process and no environmental pollution from waste. For additional details, see: (a) Leca, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858–865; (b) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603–10642; (c) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377–10441; (d) Studer, A.; Amrein, S. *Synthesis* **2002**, 835–849; (e) Murphy, J. A. *Pure Appl. Chem.* **2000**, *72*, 1327–1334.
3. (a) Marotta, E.; Righi, P.; Rosini, G. *Org. Lett.* **2000**, *2*, 4145–4148; (b) Takamatsu, S.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. *Tetrahedron Lett.* **2001**, *42*, 7605–7608.
4. (a) Graham, A. E.; Thomas, A. V.; Yang, R. *J. Org. Chem.* **2000**, *657*, 2583–2585; (b) Jang, D. O.; Cho, D. H. *Tetrahedron Lett.* **2002**, *43*, 5921–5924.
5. For intramolecular processes, see: (a) McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *Chem. Commun.* **1998**, 2691–2692; (b) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415–2416; (c) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071–3073; (d) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791–3792; (e) Martin, C. G.; Murphy, J. A.; Smith, C. R. *Tetrahedron Lett.* **2000**, *41*, 1833–1836; (f) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104–105; (g) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anilkumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157–1160; (h) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 225–235; (i) Lee, E.; Han, H. O. *Tetrahedron Lett.* **2002**, *43*, 7295–7296; (j) Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron* **2002**, *58*, 2435–2439; (k) Dubert, O.; Gautier, A.; Condamine, E.; Piettre, S. R. *Org. Lett.* **2002**, *4*, 359–362; (l) Reding, M. T.; Kaburagi, Y.; Tokuyama, H.; Fukuyama, T. *Heterocycles* **2002**, *56*, 313–330; (m) Cho, D. H.; Jang, D. O. *Bull. Korean Chem. Soc.* **2003**, *24*, 15–16; (n) Nambu, H.; Anilkumar, G.; Matsugi, M.; Kita, Y. *Tetrahedron* **2003**, *59*, 77–85; (o) Khan, T.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971–2974; (p) Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mali, U. W. *Org. Lett.* **2005**, *7*, 3287–3289; (q) Chevet, C.; Jackson, T.; Santry, B.; Routledge, A. *Synlett* **2005**, 477–480; (r) Lang, S.; Corr, M.; Muir, N.;

Khan, T. A.; Schönebeck, F.; Murphy, J. A.; Payneb, A. H.; Williams, A. C. *Tetrahedron Lett.* **2005**, *46*, 4027–4030.
6. For intermolecular processes, see: (a) Deprele, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66*, 6745–6755; (b) Jang, D. O.; Cho, D. H.; Chung, C.-M. *Synlett* **2001**, 1923–1924; (c) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631–633; (d) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674–686; (e) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 1523–1525; (f) Caddick, S.; Hamza, D.; Judd, D. B.; Reich, M. T.; Wadman, S. N.; Wilden, J. D. *Tetrahedron Lett.* **2004**, *45*, 2363–2366.
7. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1991; pp 29–37.
8. (a) González, C. G.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326–2328; (b) González, C. G.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Tetrahedron Lett.* **2003**, *44*, 6347–6350; (c) González, C. G.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Chem. Eur. J.* **2003**, *9*, 5800–5809.
9. Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953.
10. Wang, Y.; Yang, Z.-Y.; Burton, D. J. *Tetrahedron Lett.* **1992**, *33*, 2137–2140.
11. Dolbier, W. R., Jr. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer: Berlin, 1997; Vol. 192, pp 97–163.