Al–Hg promoted chemoselective dehalogenation of halohydrin aldol adducts

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Al–Hg mediated chemoselective cleavage of the carbon–halogen bond of α-halocarboxylates allows for a facile and clean transformation of halohydrin aldol adducts into β-hydroxy acid derivatives with no evidence of dehydroxyhalogenation.

Chemoselective transformations of halohydrin aldol adducts into β-hydroxy acid derivatives are very important owing to the ready availability of the chiral starting materials[1] and the significance of the products as building blocks in the synthesis of drugs and natural products.[2] The recently reported catalytic hydrogenolysis (H_2/Pd–C) of α-bromo-β-hydroxy esters and tri-*n*-butyltin hydride mediated radical cleavage of carbon–bromo bonds provided β-hydroxy acid derivatives with the added benefit of good to excellent yields.[3]

However, their utilization is not unproblematic. Chemoselective hydrogenolysis of the C–Br bond in the presence of C=C double bonds is not possible while tributyltin hydride is relatively unstable, toxic and expensive. Furthermore, the tin byproducts are not always easy to separate. The invention and development of a new chemoselective procedure for removing the halogen from halohydrin aldol adducts would be of great synthetic value. A promising solution to this problem appeared to be metal-promoted reductive cleavage of carbon–halogen bonds. Although this process has been used in reductive elimination reactions such as zinc-mediated dehydroxybromination[4] and aluminium amalgam-mediated deacetoxybromination,[5] they leave open the question of whether these methodologies can be applied to the chemoselective cleavage of carbon–halogen bonds of halohydrin aldol adducts without concurrent elimination of the β-hydroxy group. We were attracted to the Al–Hg mediated process because of the mild neutral conditions.

Initial work centered on the debromination of various α-bromo-β-hydroxy esters **1** derived from aldolizations of bromoacetate enolates with isobutyraldehyde.[1] Treatment of *tert*-butyl ester **1a** with 3–5 equiv. of Al–Hg (mercury content *ca.* 2.5%) in aqueous acetonitrile (1:10) at 0 °C led to clean debromination within 30 min to give **2a** in 86% isolated yield [eqn. (1)]. Dehydroxybromination does not appear to compete with carbon–hydrogen bond formation, although products arising from elimination of hydroxy groups would not be isolable owing to their volatility. To quantify the potentially small degree of elimination that may be occurring, we chose to explore the related reductive cleavage of the C–Br bond using *p*-methoxybenzyl α-bromo-β-hydroxy ester **1b** derived from the transesterification of thioimide aldol.[6] The chemoselective debromination proceeded efficiently yielding the corresponding β-hydroxy ester **2b**† in excellent yield (96%) [eqn. (2)]. We were unable to detect any 4-methyl-2-pentenoate, a product of elimination, under careful analysis of the crude reaction mixture. In addition, allyl ester **1c**, which is particularly prone to hydrogenolysis, can also be cleanly converted to the correspopnding β-hydroxy ester **2c** under our standard conditions [eqn. (3)]. Switching the bromo ester from allyl to methyl had little effect. The debromination product **2d** was obtained in 80% isolated yield [eqn. (4)].


$$(1)$$
$$(2)$$
$$(3)$$
$$(4)$$
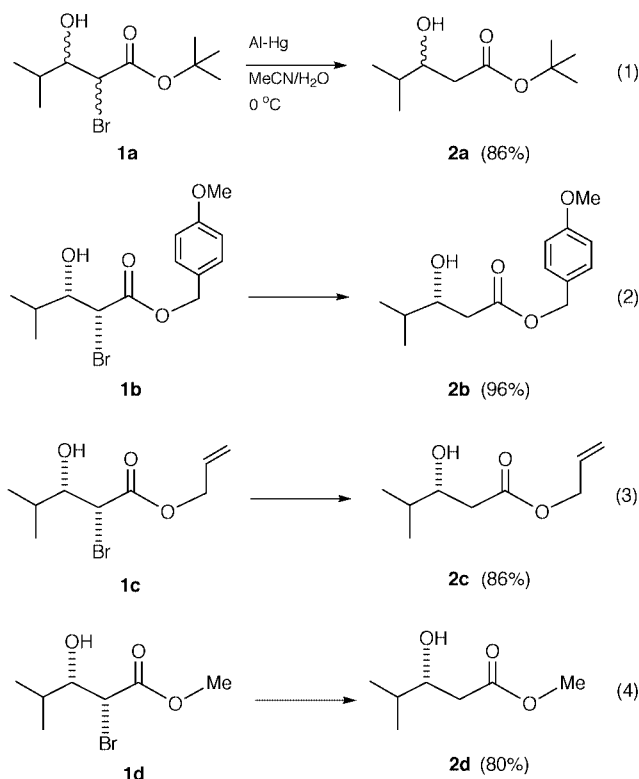
Variation of the halogen was briefly explored. Halohydrin aldols such as iodohydrin **3a**, bromohydrin **3b** and chlorohydrin **3c** were utilized to test the feasibility of Al–Hg promoted reductive cleavage. On exposure to an excess of Al–Hg in aqueous CH_2Cl_2 (1:10) at 0 °C for 2 min, the C–I bond in **3a** was completely cleaved (Scheme 1) while the same conditions effected complete debromination of **3b** within 30 min to afford β-hydroxy ester **4** in 94% isolated yield. Switching the halohydrin from bromo to chloro had a rate retardation effect while maintaining excellent yield. Thus, after 1 h at 0–25 °C, **3c** was cleanly converted to the ester **4** in 90% isolated yield with no evidence of dehydroxychlorination to the α,β-unsaturated ester.

Extension of these observations to other carboxylic acid derivatives confirms the generality of this procedure. We were


3b: X = I	X = I (93%)	**4**
3b: X = Br	X = Br (94%)	
3c: X = Cl	X = Cl (90%)	
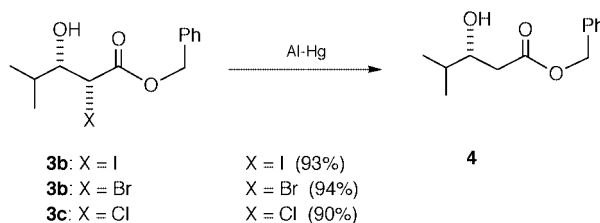
Scheme 1

pleased to find that switching the α-bromo-β-hydroxy acid derivative from ester **3** to amide **5** had little effect. The debromination product **6** was obtained in 91% yield under the usual conditions in 30 min [eqn. (5)].

(5)
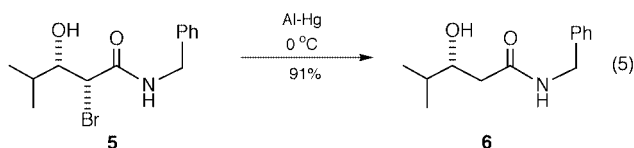
The broad scope of the reaction is illustrated by the additional examples provided below. A particularly interesting example illustrating the chemoselectivity of this process is the debromination of chiral bromohydrin aldol adduct **7**, which by virtue of the sensitivity of allyl-type alcohol requires very mild methods. Using these standard reduction conditions, only reductive cleavage of the C–Br bond to give β-hydroxy ester **8** is observed, without concurrent reductive cleavage of the C–OH bond or dehydroxybromination [eqn. (6)]. Using an α-bromo ester bearing a benzyl-type alcohol **9**, the identical reaction gave the corresponding methyl β-hydroxy ester **10** in 90% isolated yield [eqn. (7)].[7]

(6)

(7)
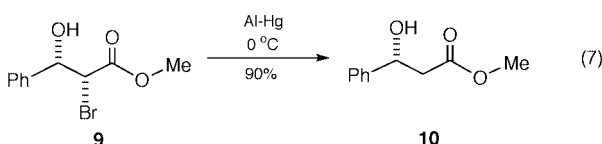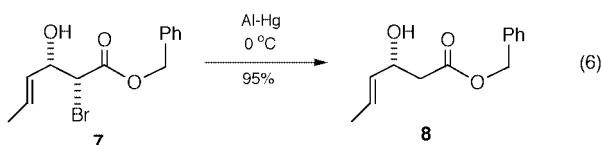
This Al–Hg mediated reductive cleavage of carbon–halogen bonds represents an extremely simple, practical and efficient elaboration of various halohydrin compounds into α-unsubstituted β-hydroxy acid derivatives. Its use in the reduction of halohydrin aldols to β-hydroxy acid derivatives compares very favorably with other methods such as catalytic hydrogenolysis or reduction with tri-*n*-butyltin hydride. Further studies on the reductive cleavage of isolated halohydrins and other α,β-difunctional aldol adducts such as α,β-epoxy esters and amides are currently underway and will be reported in due course.

Notes and references

† *Selected data* for **2b**: δ_H(300 MHz, CDCl$_3$) 7.26–7.32 and 6.87–6.92 (m, 4 H, C$_6$H$_4$), 5.09 (s, 2 H, OCH$_2$C$_6$H$_4$), 3.74–3.82 (m, 4 H, OCH$_3$, CHOH), 2.53 (dd, *J* 16.5, 3.0 Hz, 1 H, HCHC=O), 2.43 (dd, *J* 16.5, 9.3 Hz, 1 H, HCHC=O), 1.70 [octet, *J* 6.3 Hz, HC(CH$_3$)$_2$], 0.94 and 0.91 [2 d, *J* 6.9 Hz, HC(CH$_3$)$_2$]; δ_C(75 MHz, CDCl$_3$) 173.34, 159.66, 130.14, 127.64, 113.94, 72.64, 66.33, 55.25, 38.47, 33.10, 18.28, 17.70; high-resolution MS (EI+) *m/z* calcd for C$_{14}$H$_{20}$O$_4$ 252.1362, found 252.1359; $[\alpha]_D^{25}$ +23.6° (*c* 0.6, CH$_2$Cl$_2$). For **6**: δ_H(300 MHz, CDCl$_3$) 7.24–7.36 (m, 5 H, C$_6$H$_5$), 6.48 (br s, 1 H, HNC=O), 4.42 (d, *J* 5.7 Hz, 2 H, HNCH$_2$Ph), 3.74–3.80 (m, 1 H, CHOH), 2.95 (br s, 1 H, OH), 2.38 (dd, *J* 15.0, 3.0 Hz, 1 H, HCHC=O), 2.29 (dd, *J* 15.0, 9.0 Hz, 1 H, HCHC=O), 1.69 [octet, *J* 6.6 Hz, HC(CH$_3$)$_2$], 0.93 and 0.91 [2 d, *J* 6.9 Hz, HC(CH$_3$)$_2$]; δ_C(75 MHz, CDCl$_3$) 172.76, 137.93, 128.69, 127.68, 127.51, 73.41, 43.44, 39.51, 33.44, 18.28, 17.72; high-resolution MS (EI+) Calc. for C$_{13}$H$_{19}$NO$_2$ *m/z* 221.1415, found 221.1412; $[\alpha]_D^{25}$ +38.7°° (*c* 0.5, CH$_2$Cl$_2$). For **10**: δ_H(400 MHz, CDCl$_3$) 7.18–7.31 (m, 5 H, C$_6$H$_5$), 5.05 (dd, *J* 8.8, 4.0 Hz, 2 H, HOCHCH$_2$), 3.64 (s, 3 H, H$_3$C–O), 2.70 (dd, *J* 16.4, 8.8 Hz, 1 H, HCHC=O), 2.63 (dd, *J* 16.4, 4.0 Hz, 1 H, HCHC=O); δ_C(100 MHz, CDCl$_3$) 172.46, 142.35, 128.40, 127.68, 125.50, 70.32, 51.87, 43.24; high-resolution MS (EI+) Calc. for C$_{10}$H$_{12}$O$_3$ *m/z* 180.0787, found 180.0788; $[\alpha]_D^{25}$ +36.1° (*c* 0.5, CH$_2$Cl$_2$).

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7 New compounds have been satisfactorily characterized spectroscopically, and their elemental composition has been established by high-resolution mass spectrometry or combustion analysis.

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