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IBX/LiBr-promoted one-pot oxidative anti-Markownikov bromohydroxylation/bromoalkoxylation of Baylis–Hillman olefins

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ABSTRACT

The first example of one-pot oxidative anti-Markownikov bromohydroxylation and bromoalkoxylation of Baylis–Hillman (BH) adducts (olefins) is reported. The reaction is performed at rt using LiBr as the bromine source and 2-iodoxybenzoic acid (IBX) as the oxidant. The process involves oxidation of BH adducts with IBX to give β-ketomethylene compounds in situ, which undergo highly regioselective vicinal functionalization with LiBr/H_2O or LiBr/ROH in the same vessel to afford α-bromo-β-hydroxy or α-bromo-β-alkoxy compounds, respectively, in excellent yields. The α-bromo-β-hydroxy compounds are readily transformed into epoxides in aq NaOH.

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The development of new, one-pot and selective synthetic methodologies has been an important area of current research in organic chemistry. These sequential multistep reactions are of increasing academic, economic and ecological interests because they address fundamental principles of synthetic efficiency and reaction design. The vicinal functionalization of an olefin is a powerful synthetic tool for organic chemists, especially when the reaction is carried out in regioselective fashion. A great deal of attention has been paid to the selective introduction of two different functional groups such as hydroxy or alkoxy and halogen, in organic synthesis.[1] The resulting halohydrins and alkoxy halides are important building blocks in organic, medicinal as well as industrial chemistries.[2,3] α-Halo-β-hydroxy derivatives (halohydrins) are versatile precursors, which can be readily transformed into epoxides, ketones and unusual β-hydroxy-α-amino acids,[4] and thus enhance the versatility of molecules containing these structural fragments. Haloalkoxy compounds have been used as versatile intermediates in the synthesis of various natural products.[5,6] Hence, the development of a convenient and efficient methodology for the synthesis of α-halo-β-hydroxy and α-halo-β-alkoxy compounds (haloethers) is an interesting target of investigation. Herein, Baylis–Hillman (BH) chemistry has been applied for this purpose.

Baylis–Hillman adducts contain a minimum of three chemospecific functional groups, that is, hydroxy (or amino), alkene and electron-withdrawing groups, thereby providing handles for further manipulation in a multitude of synthetic organic transformations.[7] BH adducts have been employed as Michael acceptors to produce functionalized aldol products with oxygen, sulfur, nitrogen and carbon-centred nucleophiles.[8] However, there has been no report on vicinal functionalization of BH olefins **1** via oxidative bromohydroxylation and bromoalkoxylation (Scheme 1).

Usual methods available for the synthesis of halohydrins include ring opening of epoxides[9] or cyclic sulfates[10] by hydrogen halides or metal halides. The general approach for heterolytic additions of halogen and water to an olefinic bond involves the use of molecular halogen or *N*-halosuccinimide.[11] α,β-Unsaturated carbonyl compounds and carboxylic acids have also been reported to undergo halohydrin reactions with *N*-halosuccinimide.[12]

However, the halohydrin reactions suffer from several disadvantages such as the use of stoichiometric amounts of corrosive Br_2/*N*-halosuccinimide or the formation of large amounts of organic and inorganic wastes.[12] Recently, halohydrin reactions have been advantageously performed using LiBr as the halogen source in the presence of an oxidant $NaIO_4$[13] or ceric ammonium nitrate (CAN).[14]

Amongst various hypervalent iodine reagents,[15] 2-iodoxybenzoic acid (IBX) has become the reagent of choice due to its easy handling, ready availability, tolerance to moisture,[16] mild reaction conditions and zero toxic waste generation. IBX selectively oxidizes alcohols in the presence of olefins, thioethers and amino groups,[17] and is also useful for other elegant oxidative transformations.[18] It has been reported that IBX efficiently oxidizes BH alcohols to the corresponding ketones.[19] Because of IBX explosiveness and insolubility in most organic solvents, several research groups have synthesized IBX derivatives that are stable and

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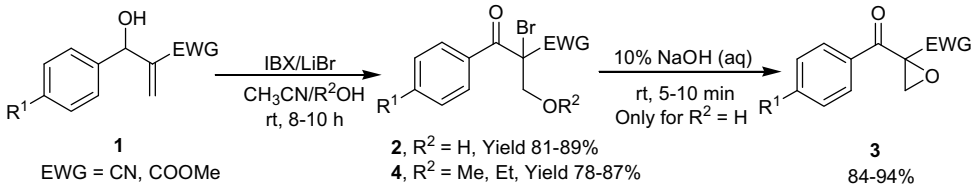
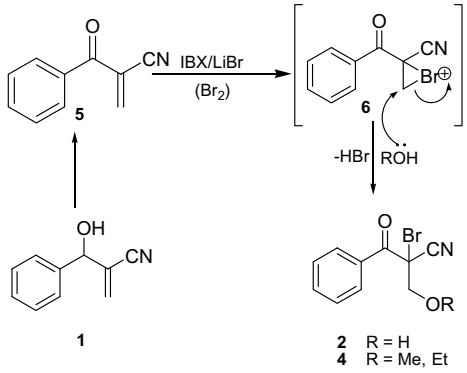


Scheme 1. IBX/LiBr-promoted oxidative bromohydroxylation and bromoalkoxylation of BH olefins **1**.



Scheme 2. Plausible mechanism for the oxidative bromohydroxylation and bromoalkoxylation of BH olefins **1**.

soluble.[20] Furthermore, some preparations of IBX scaled up to its one mole have also been reported.[21] During experimentation with IBX, we have found that it smoothly liberates Br_2 from LiBr under ambient conditions.

Considering the above points and our ongoing efforts to develop new one-pot synthetic processes,[22] we report herein, the first example of IBX/LiBr-promoted one-pot oxidative bromohydroxylation and bromoalkoxylation of BH adducts **1** (Scheme 1), which opens up a new aspect of the synthetic utility of BH adducts. In order to optimize reaction conditions, we carried out bromohydroxylation[23] of the representative BH adduct **1** (Scheme 1) using KBr, NaBr, or LiBr as the bromine source and $NaIO_4$, CAN, or IBX as the oxidant. Among these, LiBr and IBX gave the best results in terms of the yield of bromohydrin **2** (86%) under the reaction conditions.[23] Herein, Li^+ ions appear to play a more efficient catalytic role than K^+ or Na^+ ions in the addition of Br_2 to the olefinic bond, which leads to the formation of **2** or **4** (Scheme 2). This is in conformity with earlier observations that LiBr is useful as an efficient Lewis acid in a variety of organic transformations including Biginelli, Knoevenagel, Wadsworth–Emmons reactions, dithioacetalizations and dihydrohalogenations.[24] Similarly, the use of LiBr with the oxidant $NaIO_4$ or CAN under the same reaction conditions afforded **2** in 51% or 42% yields, respectively. This is presumably because IBX oxidizes BH alcohols into the corresponding ketones more efficiently as compared to $NaIO_4$ or CAN under the same reaction conditions.[23] Thus, the overall yield of **2** (86%) is significantly higher in the case of IBX than in the case of $NaIO_4$ (51%) or CAN (42%).

Next, optimization of the solvent for the synthesis of **2** (Scheme 1) was investigated and it was found that, in general, a CH_3CN–H_2O mixture was a better solvent system than the corresponding THF–H_2O mixture in terms of reaction time and the yield of **2** (Table 3). This is because of a lower solubility of substrates in the THF–H_2O system than in the CH_3CN–H_2O mixture. Among the proportions of CH_3CN–H_2O, (2:1) was found to be the best solvent system affording the highest yield (86%) of **2** in the shortest (9 h) reaction time (Table 3, entry 5). The present optimized synthesis of **2**[23] involves stirring a mixture of adduct **1** and IBX at rt for 2 h in CH_3CN followed by the addition of an aq LiBr solution and stirring for a further 6–8 h at rt to afford bromohydrin **2** in consistently good yields (81–89%) (Table 1). Bromohydrins **2** were transformed into the corresponding epoxides **3**[25] in (84–94%) yields on treatment with 10% aq NaOH at rt for 5–10 min (Table 1). The requisite BH adducts **1** and IBX were prepared employing the known method.[21a,26]

Table 1
One-pot oxidative synthesis of bromohydrins **2** and epoxides **3** (Scheme 1)

Compound **2**, **3**	R^1	EWG	Reaction time (h)		Yield[a,b] (%)	
			2	**3**	**2**	**3**
a	H	CN	9	7	86	89
b	H	COOMe	9	7	85	87
c	OMe	CN	10	8	83	85
d	OMe	COOMe	10	8	81	84
e	Cl	CN	8	5	89	94
f	Cl	COOMe	9	8	87	91

[a] Yield of pure products **2** and **3** after column chromatography.
[b] All compounds gave C, H and N (if present) analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

Table 2
One-pot oxidative synthesis of bromoethers **4** (Scheme 1)

Compound **4**	R^1	EWG	R^2	Reaction time (h)	Yield[a,b] (%)
a	H	CN	Me	9	84
b	H	COOMe	Me	9	82
c	OMe	CN	Me	10	83
d	OMe	COOMe	Me	10	80
e	Cl	CN	Me	8	87
f	Cl	COOMe	Me	8	85
g	H	CN	Et	9	81
h	H	COOMe	Et	9	80
i	OMe	CN	Et	10	81
j	OMe	COOMe	Et	10	78
k	Cl	CN	Et	9	84
l	Cl	COOMe	Et	9	82

[a] Yield of pure products **4** after column chromatography.
[b] All compounds gave C, H and N (if present) analyses within ±0.38% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

Table 3
Optimization of the solvent for the synthesis of **2**[21] (Scheme 1)

Entry	Solvent-system	Reaction time (h)	Yield[a] (%)
1	THF/H_2O (1:1)	18	39
2	THF/H_2O (2:1)	16	44
3	THF/H_2O (3:1)	13	48
4	CH_3CN/H_2O (1:1)	12	67
5	CH_3CN/H_2O (2:1)	9	86
6	CH_3CN/H_2O (3:1)	10	79

[a] Isolated yields.

After a successful attempt at the synthesis of bromohydrins **2**, we applied the same procedure for the synthesis of bromoethers **4** from BH adducts **1** using MeOH or EtOH instead of H_2O to afford **4** in 78–87% yields[27] (Table 2).

A plausible mechanistic pathway for the regioselective formation of bromohydrins **2** and bromoethers **4** is depicted in Scheme 2. Possibly a three-membered cyclic bromonium ion intermediate **6** is formed by the electrophilic addition of Br_2 (generated in situ from LiBr/IBX) to the double bond of the olefin **5**, which is then attacked by H_2O, MeOH, or EtOH to form the product **2** or **4**. With all the substrates studied, the reaction proceeded with complete regioselectivity in favour of the anti-Markownikov product, that is, the hydroxy or alkoxy group is added to the β-position, exclusively (Scheme 2). No traces of dibromides were observed in the case of any of the substrates **1** used in the present study.

In summary, we have presented the first example of one-pot oxidative bromohydroxylation and bromoalkoxylation of BH adducts to afford the corresponding α-bromo-β-hydroxy and α-bromo-β-alkoxy compounds by using LiBr as the bromine source and IBX as the oxidant. The methodology avoids the use of heavy metal halides or *N*-halosuccinimides as the halogen source, and opens up a new aspect of the synthetic utility of BH adducts.

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23. *General procedure for the synthesis of bromohydrins* **2**: A mixture of BH adduct **1** (1 mmol) and IBX (2.4 mmol) in acetonitrile (10 mL) was stirred at rt for 2 h followed by the addition of a solution of LiBr (2 mmol) in H_2O (5 mL) and stirring for a further 6–8 h at rt (Table 1). After completion of the reaction (monitored by TLC), the mixture was diluted with water and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with sodium thiosulfate followed by brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was purified by silica gel column chromatography using hexane/ethyl acetate (9.4:0.6) as eluent to afford an analytically pure sample of **2**. Physical data of representative compounds. *Compound* **2a**: Yellowish solid, yield 86%, mp 156 °C. IR (KBr) ν_{max} 3490, 3068, 2870, 2241, 1666, 1602, 1584, 1455, 760, 695, 534 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.30 (br s, 1H, OH), 4.61 (d, 1H, J = 12.2 Hz, β-H_a), 4.30 (d, 1H, J = 12.2 Hz, β-H_b), 7.34–7.95 (m, 5H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 58.1, 63.3, 116.8, 127.0, 127.9, 133.5, 136.7, 198.3. EIMS (m/z): 253 (M^+). Anal. Calcd for $C_{10}H_8BrNO_2$: C, 47.43; H, 3.16; N, 5.53. Found: C, 47.07; H, 3.48; N, 5.19. *Compound* **2d**: Yellowish solid, yield 81%, mp 193 °C. IR (KBr) ν_{max} 3470, 2993, 1741, 1665, 1605, 1543, 1340, 855, 565 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.10 (br s, 1H, OH), 3.60 (s, 3H, COOMe), 3.80 (s, 3H, OMe), 4.56 (d, 1H, J = 12.2 Hz, β-H_a), 4.25 (d, 1H, J = 12.2 Hz, β-H_b), 7.11 (d, 2H, J = 7.9 Hz, H_{arom}), 7.69 (d, 2H, J = 7.9 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 50.2, 55.0, 65.4, 71.6, 112.1, 130.1, 131.2, 167.7, 173.0, 196.8. EIMS (m/z): 316 (M^+). Anal. Calcd for $C_{12}H_{13}BrO_5$: C, 45.57; H, 4.11. Found: C, 45.23; H, 4.43.
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25. *General procedure for the synthesis of epoxides* **3**: Bromohydrin **2** (1 mmol) was stirred in a 10% aq NaOH solution (5 mL) for 5–10 min (Table 1). Then, water (5 mL) was added to the reaction mixture and it was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. The extract was filtered and the filtrate was evaporated under reduced pressure to leave a residue, which was purified by silica gel column chromatography (hexane/EtOAc 9.3:0.7) to afford the pure product **3**. *Compound* **3a**: White solid, yield 89%, mp 110–111 °C. IR (KBr) ν_{max} 3054, 2235, 1695, 1260, 870, 765, 698, cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.91 (d, 1H, J = 6.0 Hz, β-H_a), 3.20 (d, 1H, J = 6.0 Hz, β-H_b), 7.34–7.95 (m, 5H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 40.7, 63.4, 117.1, 127.8, 128.8, 131.2, 136.7, 198.2. EIMS (m/z): 173 (M^+). Anal. Calcd for $C_{10}H_7NO_2$: C, 69.34; H, 4.04; N, 8.09. Found: C, 69.69; H, 4.40; N, 7.76. *Compound* **3d**: White solid, yield 84%, mp 147–149 °C. IR (KBr) ν_{max} 2995, 2854, 1746, 1693, 1605, 1543, 1340, 1265, 875, 853 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 2.81 (d, 1H, J = 6.0 Hz, β-H_a), 3.20 (d, 1H, J = 6.0 Hz, β-H_b) 3.53 (s, 3H, COOMe), 3.64 (s, 3H, OMe), 7.11 (d, 2H, J = 7.9 Hz, H_{arom}), 7.69 (d, 2H, J = 7.9 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 40.7, 55.8, 61.5, 76.8, 113.6, 128.0, 128.9, 130.3, 173.6, 196.8. EIMS (m/z): 236 (M^+). Anal. Calcd for $C_{12}H_{12}O_5$: C, 60.99; H, 5.08. Found: C, 61.34; H, 5.36.
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27. *General procedure for the synthesis of bromoethers* **4**: The procedure followed was the same as described above for the synthesis of **2**[21] except that MeOH or EtOH (5 mL) was used instead of H_2O (5 mL). The crude product was purified by column chromatography on silica gel with hexane/EtOAc (9.5:0.5) as eluent to afford the pure product **4**. *Compound* **4a**: Yellowish solid, yield 84%, mp 125 °C. IR (KBr) ν_{max} 3052, 2996, 2856, 2239, 1697, 760, 697, 557 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 3.31 (s, 3H, OMe), 4.25 (d, 1H, J = 12.2 Hz, β-H_a), 4.56 (d, 1H, J = 12.2 Hz, β-H_b), 7.34–7.95 (m, 5H_{arom}). ^{13}C NMR (100 MHz;

$CDCl_3$/TMS): δ 51.0, 55.1, 72.8, 116.4, 117.1, 127.8, 128.9, 131.2, 198.2. EIMS (m/z): 267 (M^+). Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.44; H, 3.74; N, 5.24. Found: C, 49.78; H, 3.38; N, 4.91. *Compound* **4j**: Yellowish solid, yield 78%, mp 160 °C. IR (KBr) ν_{max} 2995, 2854, 1742, 1695, 1605, 1543, 1340, 853, 560 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ 1.23 (t, 3H, CH_2CH_3), 3.56 (q, 2H, CH_2CH_3), 3.53 (s, 3H, COOMe), 3.64 (s, 3H, OMe), 4.21 (d, 1H, J = 12.2 Hz, β-H_a), 4.52 (d, 1H, J = 12.2 Hz, β-H_b), 7.11 (d, 2H, J = 7.9 Hz, H_{arom}), 7.69 (d, 2H, J = 7.9 Hz, H_{arom}). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ 15.5, 47.9, 56.9, 64.4, 69.2, 72.6, 113.7, 128.1, 128.9, 167.2, 171.1, 198.3. EIMS (m/z): 344 (M^+). Anal. Calcd for $C_{14}H_{17}BrO_5$: C, 48.83; H, 4.94. Found: C, 48.45; H, 4.67.