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CF_3CO_2ZnEt-mediated highly regioselective rearrangement of bromohydrins to aldehydes

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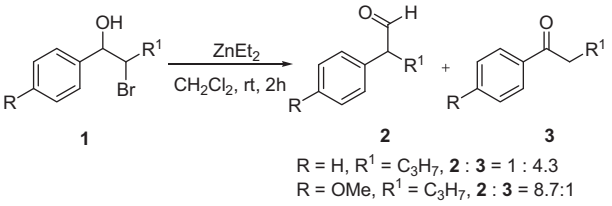
ABSTRACT

A highly efficient and selective rearrangement reaction of bromohydrins to aldehydes mediated by CF_3CO_2ZnEt was described. The secondary and tertiary aldehydes were prepared under mild conditions in good to excellent yields (85–99%). The scope and limitations of this rearrangement process were also investigated.

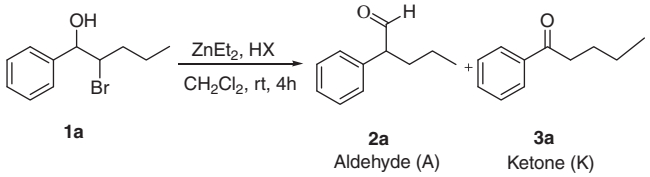
Halohydrins have attracted considerable attention and emerged as powerful substrates in modern organic synthesis due to their high reactivity[1,2] and easy availability through a variety of methods.[3,4] Rearrangement of halohydrins to corresponding carbonyl compounds is one of the useful synthetic methods.[5,6] An efficient ring-expansive rearrangement of bromohydrins mediated by Grignard reagent was reported by Sisti.[7] Reactions of 1-(α-bromobenzyl)-1-cycloalkanols with isopropyl magnesium bromide in benzene under reflux conditions gave rise to the corresponding ring-expansive α-phenyl ketones in good yields.[7b] Recently, Pushpito found that iodohydrins could be converted into ketones or aldehydes through acid activation of bromate/bromide couple.[8]

In our previous work, we reported an efficient procedure to synthesize ketone carbonyl compounds from bromohydrins using $ZnEt_2$ under mild conditions.[9] The tertiary β-bromo alcohols, which the hydroxyl group was attached on the tertiary carbon atom, were treated with 0.6 equiv of Et_2Zn at room temperature to give the regioselective α-aryl ketones with high yields. As for secondary β-bromo alcohols **1**, a mixture of aldehydes and ketones were obtained and the ratio of **2** and **3** was dependent on the substitute on benzene ring (Scheme 1). The aldehyde group is one of the most versatile functional groups, which can be converted to a variety of valuable chemicals, such as amines, imines, alcohols, and acids. However, development of simple, highly selective and efficient synthetic approaches for aldehyde remains a challenging work. Our interest in the reactivity of organozinc reagents (XZnEt) enhanced by X group prompted us to verify the possibility of regioselective preparation of aldehydes from secondary β-bromo alcohols.

Initially, 2-bromo-1-phenylpentan-1-ol **1a** was used as a model substrate to develop appropriate reaction conditions (Scheme 2, Table 1). The organozinc reagents (XZnEt) were formed from the reaction of diethylzinc with alcohols or acids (HX). Reaction of **1a** with 0.6 equiv of i-C_3H_7OZnEt at room temperature for 4 h provided a mixture of 2-phenylbutanal **2a** and 1-phenyl-1-pentanone **3a** in 88% yield. Gratifyingly, **2a** as the major isomer was formed and the ratio of the two isomers **2a** and **3a** was 10:1 which was determined by ^1H NMR spectroscopic analysis. When alcohols were replaced by acetic acid and methanesulfonic acid, the ratios of **2a** and **3a** increased to 42:1 and 40:1, respectively. But their yields became a little lower. It was found that the rearrangement mediated by 0.6 equiv of CF_3CO_2ZnEt gave aldehyde **2a** with excellent regioselectivity (>99:1) in 94% yield. Further increasing the amount of CF_3CO_2ZnEt did not increase the yield, whereas reducing the amount of CF_3CO_2ZnEt to 0.3 equiv led to a lower yield and a



Scheme 1. Rearrangement of β-bromo alcohols mediated by Et_2Zn.



Scheme 2. Rearrangement of bromohydrin **1a** mediated by organozinc species.

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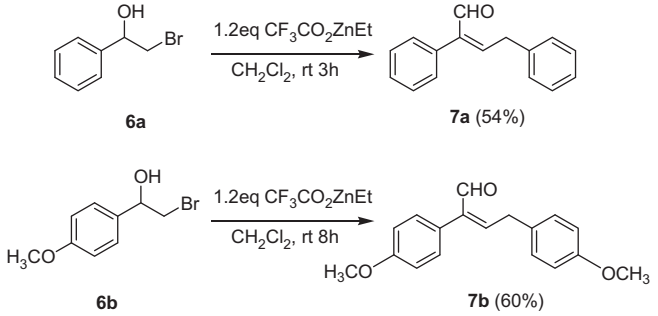
Table 1
Reaction of 2-bromo-1-phenylpentan-1-ol **1a** with organozinc species

Entry	Organozinc species	Yield (%)[a]	A:K[b]
1	*i*-C_3H_7OZnEt (0.6 equiv)	88	10:1
2	*t*-C_4H_9OZnEt (0.6 equiv)	92	6:1
3	C_2H_5OZnEt (0.6 equiv)	92	9:1
4	CH_3CO_2ZnEt (0.6 equiv)	76	42:1
5	CH_3SO_3ZnEt (0.6 equiv)	59	40:1
6	CF_3CO_2ZnEt (0.6 equiv)	94	>99:1
7[c]	CF_3CO_2ZnEt (0.6 equiv)	75	73:1
8	CF_3CO_2ZnEt (0.3 equiv)	75	44:1
9	CF_3CO_2ZnEt (0.8 equiv)	90	>99:1

[a] Isolated yield after flash chromatography.
[b] Ratio of aldehyde and ketone was determined by ^1H NMR spectra, the two isomers were not separated.
[c] Reaction was performed at 0 °C.



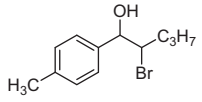
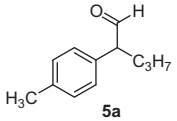
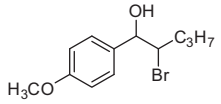
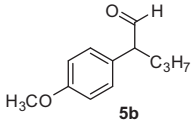
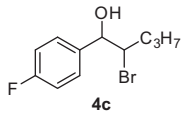
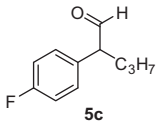
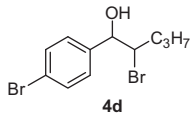
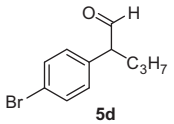
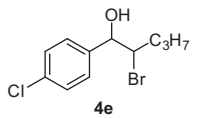
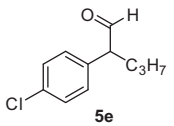
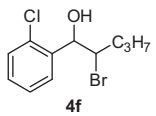
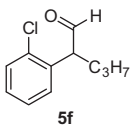
Scheme 3. CF_3CO_2ZnEt-promoted rearrangement of bromohydrins to form α,β-unsaturated aldehydes.

lower regioselectivity of the desired product **2a**. The yield and selectivity decreased as well when the reaction was stirred at 0 °C.

Under the optimized reaction conditions, we explored the feasibility of the reaction with a variety of secondary bromohydrins.[13] The results are summarized in Table 2. The rearrangement reaction could afford the corresponding aldehydes in high yields and excellent selectivity regardless of the different substitutions on the aromatic ring. For example, when substrates contained an electron-withdrawing group, such as fluoro, bromo, and chloro on *para* position of the phenyl ring, the desired aldehydes **5c–e** were obtained with excellent selectivity. The chloro and bromo group on *ortho* position of its phenyl ring has no effect on the selectivity. The substrate with an electron-donating group, such as methyl and methoxy, on the aromatic ring gave a better selectivity than that of an electron-withdrawing group on the aromatic ring. The naphthyl substrate **4i** also reacted smoothly with CF_3CO_2ZnEt to give the desired product **5i** in 98% yield. However, treatment of 2-bromo-1,2-diphenylethanol **4k** under the same condition afforded many byproducts. When the amount of CF_3CO_2ZnEt increased to 1.2 equiv, a yield of 99% was obtained at 0 °C for 10 min, but with a little low regioselectivity (24:1).

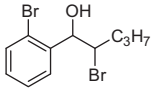
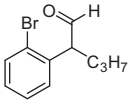
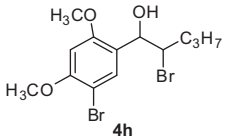
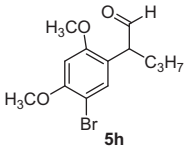
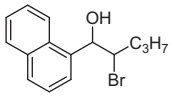
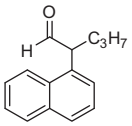
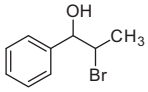
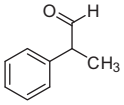
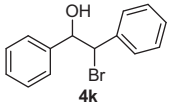
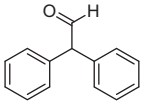
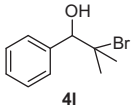
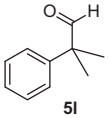
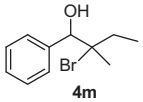
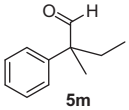
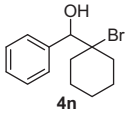
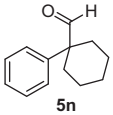
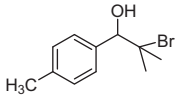
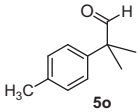
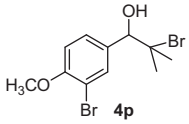
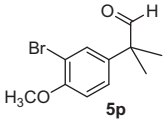
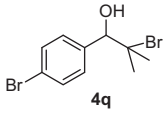
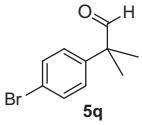
To further evaluate the scope of this reaction, several tertiary halides **4l–q** that bromo atom was attached to the tertiary carbon position were employed to the rearrangement reaction. The steric hindrance had obvious effect on the regioselectivity of products. The selectivity to aldehyde decreased with the increasing hindrance of groups. For example, treatment of 2-bromo-2-methyl-1-phenylpropan-1-ol **4l** with 0.6 equiv of CF_3CO_2ZnEt at room temperature for 1 h gave the desired tertiary aldehyde **5l** and ketone in a ratio of 19:1 with a combined yield of 92%. The ratio of aldehyde to ketone decreased to 5:1 when a more bulky substrate **4n** was applied

Table 2
CF_3CO_2ZnEt-promoted rearrangement of bromohydrins to form aldehydes

Entry	Substrate	Time (h)	Product	Yield (%)[a] (A:K)[b]
1	 **4a**	2	 **5a**	96 (>99:1)
2	 **4b**	5	 **5b**	91 (>99:1)
3	 **4c**	4	 **5c**	94 (99:1)
4	 **4d**	5	 **5d**	95 (99:1)
5	 **4e**	4	 **5e**	91 (99:1)
6	 **4f**	16	 **5f**	88 (100)

(*continued on next page*)

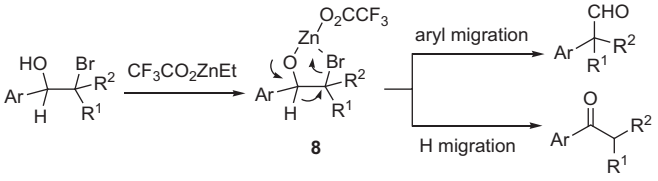
Table 2 (*continued*)

Entry	Substrate	Time (h)	Product	Yield (%)[a] (A:K)[b]
7	 **4g**	16	 **5g**	85 (100)
8	 **4h**	0.5	 **5h**	99 (100)
9	 **4i**	4	 **5i**	98 (100)
10	 **4j**	4	 **5j**	89 (99:1)
11[c]	 **4k**	10 min	 **5k**	99 (24:1)
12	 **4l**	1	 **5l**	92 (19:1)
13	 **4m**	0.5	 **5m**	94 (12:1)
14	 **4n**	1	 **5n**	99 (5:1)
15	 **4o**	1	 **5o**	99 (>99:1)
16	 **4p**	2	 **5p**	99 (100)
17	 **4q**	2	 **5q**	95 (7:1)

[a] Isolated yield after flash chromatography.
[b] Determined by ^{1}H NMR spectra.
[c] Reaction was performed with 1.2 equiv of CF_3CO_2ZnEt at 0 °C.

to the reaction. The substrates **4o** and **4p** with electron-donating group, such as methyl and methoxy, on the aromatic ring gave high yields and excellent selectivity of the corresponding aldehydes. However, the substrate **4q** with a bromo group on *ortho* position of its phenyl ring afforded a mixture of aldehyde and ketone with a ratio of 7:1.

It is noted that the rearrangement of primary halide **6a** mediated by CF_3CO_2ZnEt occurred and gave a product of α,β-unsaturated aldehyde **7a** in 54% yield (Scheme 3). The primary halide does not rearrange unless a good migrating group is involved.[10,6b] The rearrangement reaction of **6a** in the presence of 0.6 equiv of Et_2Zn or $EtZnCH_2I$ did not work in our previous



Scheme 4. A possible mechanism for the rearrangement reaction.

report.[9] When 2-bromo-1-(4-methoxyphenyl)ethanol **6b** was submitted to the reaction, 60% yield of **7b** was obtained under similar conditions. The reaction process involves an initial rearrangement of bromohydrin to arylacetaldehyde, followed by self aldol condensation to form α,β-unsaturated aldehyde.[11]

A possible mechanism for this pinacol-type rearrangement mediated by CF_3CO_2ZnEt is shown in Scheme 4. CF_3CO_2ZnEt reacts with bromohydrin to afford zinc complex **8**, followed by the migration of aryl group to form the desired aldehyde and an elimination of CF_3CO_2ZnBr. Hydrogen migration in intermediate **8** will give ketone isomer.[9,12] The aryl group containing electron-donating substitutions on the aromatic ring is beneficial to generate aldehyde. On the other hand, the steric feature of groups R^1 and R^2 has effect on the regioselectivity. Bulky R^1 and R^2 obstruct the aryl migration and prefer the formation of ketone.

In summary, we have described a highly efficient and selective rearrangement reaction of bromohydrins to aldehydes. The reaction mediated by 0.6 equiv of CF_3CO_2ZnEt under mild conditions gave the secondary and tertiary aldehydes in high yields (85–99%) and with good to excellent regioselectivity. The electron-donating substitutions on the aromatic ring are beneficial to generate aldehyde. The presented procedure leads to building of useful aldehydes for organic chemicals.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.134.

References and notes

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13. *General reaction procedure*: A 25 mL round-bottom flask was charged with dry methylene chloride (2 mL), and diethylzinc (0.3 ml, 0.3 mmol) was added via syringe under an atmosphere of nitrogen at 0 °C. Then trifluoroacetic acid (22.5 μL, 0.3 mmol) was added dropwise via syringe under nitrogen and the resulting mixture was stirred for additional 30 min. Bromohydrin (0.5 mmol) was added to the reaction mixture and then the ice bath was removed. The solution was allowed to stir at room temperature until TLC indicated complete consumption of the starting bromohydrin. The reaction mixture was concentrated in vacuo, and purified by column chromatograph packed with silica gel using petroleum ether/ethyl acetate (10:1) as eluent to afford the pure product. Compound **5h**: ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 9.60 (s, 1H), 7.22 (s, 1H), 6.50 (s, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 1H), 2.06–1.97 (m, 1H), 1.68–1.59 (m, 1H), 1.33–1.23 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 201.3, 157.8, 156.0, 133.5, 119.2, 102.1, 96.7, 56.4, 55.8, 52.0, 30.5, 20.4, 14.0; IR (neat; cm^{-1}): 2959, 1723, 1600, 1499, 1460, 1296, 1207, 1029, 819; HRMS (EI): calcd for $C_{13}H_{17}BrO_3$ $(M+H)^+$, 301.0434; found, 301.0426. Compound **5p**[14]: ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm): 9.44 (s, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.16 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.9 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm): 201.6, 155.1, 134.7, 131.7, 127.0, 112.1, 112.0, 56.3, 49.6, 22.5; IR (neat; cm^{-1}): 3428, 2970, 1727, 1600, 1262, 1055, 810.
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