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$CuBr_2$ catalyzed bromination/oxidation of isochromans to benzaldehyde derivatives

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ABSTRACT

A series of isochromans were oxidized and brominated by using 1.2 equiv of $CuBr_2$ in CH_3CN at reflux to give the corresponding bromo benzaldehydes in moderate yields. A plausible mechanism for this transformation has been suggested.

The oxidation of benzylic alcohols and ethers to the corresponding carbonyl compounds represents a widely used transformation in organic synthesis.[1] The cleavage of benzylic ethers via their reaction with an oxidizing agent, such as HBr, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), NO_2, or *N*-bromosuccinimide (NBS) is a particularly effective method for the synthesis of benzaldehydes.[2] For example, the oxidation of benzyl acyclic methyl ethers with NBS under visible light irradiation conditions provided the corresponding benzaldehydes in good yields.[2c] It is noteworthy that although CH_3Br could also be generated during the course of this reaction, which was not detected in the reaction mixtures. If the benzyl cyclic ethers were subjected to these conditions to be cleaved by a halogen-based species, then a halogenated benzaldehyde should be produced. In fact, isochroman[3] (**1**) can be converted into the halogenated benzaldehyde **2** via a two-step procedure using Br_2 or DDQ in MeOH followed by treatment with HBr or a mixture of trimethylsilyl bromide (TMSBr) and tetrabutylammonium bromide (Bu_4NBr) (Scheme 1).[4]

For both of these methods, the first step involves the transformation of the benzylic ether to acetal **3**, which was subsequently cleaved under high temperature and acidic conditions to give 2-(2-bromoethyl)benzaldehyde (**2**) via the nucleophilic attack of a bromide anion on the C–O ether bond. It has been reported that the use of a strong Lewis acid, such as a metal bromide, can lead to the generation of Br_2 under high temperature conditions.[5] With this in mind, it was envisaged that the reaction of a metal bromide with isochroman under high temperature conditions would afford the 2-(2-bromoethyl)benzaldehyde (**2**) in one step. Herein, we report the use of stoichiometric $CuBr_2$ as a mild reagent not only for the oxidation of benzylic ethers but also for their bromination to afford the corresponding 2-(2-bromoethyl) benzaldehydes in good yields in one step (Scheme 1). The products themselves are good building blocks for the synthesis of other complex intermediates.

A variety of different bromide-based oxidation systems have recently been developed for the oxidation of the benzylic group, including $CuBr_2$/(2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), $CuBr_2$/*tert*-butyl hydroperoxide (TBHP), KBr/oxone, and NBS.[6] For our initial attempt at the proposed transformation, 1.2 equiv $FeBr_2$ was selected as the metal bromide and reacted with isochroman in CH_3CN at reflux under an atmosphere of N_2 (Table 1, entry 1). Unfortunately, however, none of the desired product was formed. We then proceeded to evaluate a variety of different metal bromides, including $FeBr_3$, $ZnBr_2$, $MnBr_2$, $CoBr_2$, and $CuBr_2$ under the same reaction conditions. Unfortunately, none of the desired product was formed in any of these reactions (Table 1, entries 2–6). Pleasingly, when $CuBr_2$ was used as the metal bromide, the desired product was formed in 68% yield (Table 1, entry 7). When the reaction was conducted in the presence of NBS with the absence of a metal bromide at reflux or under UV irradiation, the product was formed in 40% yield, respectively (Table 1, entry 8). Based on these

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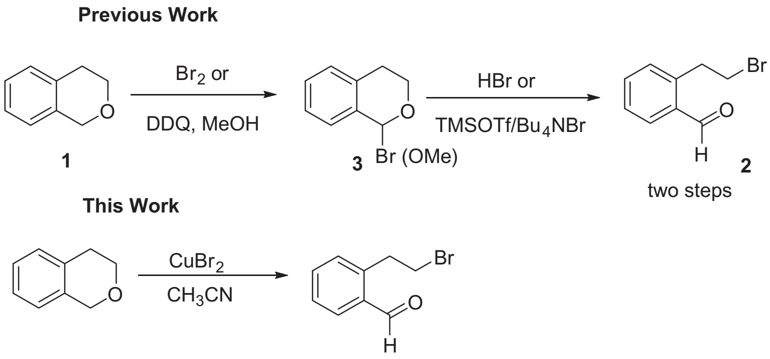
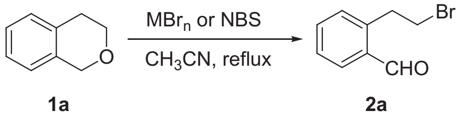


Scheme 1. Strategies for the oxidation isochroman to 2-(2-bromoethyl)benzaldehyde.

Table 1
Optimization of catalytic system[a]



Entry	Catalytic system	Time (h)	Yield[b] (%)
1	$FeBr_2$	24	0
2	$FeBr_3$	24	0
3	$ZnBr_2$	12	0
4	$MnBr_2$	12	0
5	$CoBr_2$	12	8
6	CuBr	24	0
7	$CuBr_2$	1	68
8	NBS	1	40[c]
9	$CuBr_2/Bu_4NBr$/TBHP (0.2:1.2:1.2)	6	30
10	$CuBr_2/Bu_4NBr/O_2$ (0.2:1.2)	24	36
11	$CuBr_2/FeBr_3$ (0.2:1.2)	24	20

[a] Reaction conditions: isochroman (0.5 mmol) in CH_3CN (1 mL) with 1.2 equiv of catalyst at reflux under an atmosphere of N_2.
[b] Isolated yields.
[c] 2.0 equiv NBS was used under UV irradiation at room temperature.

results, $CuBr_2$ was selected for further studies with a variety of different co-oxidants. Unfortunately, however, the use of $CuBr_2/Bu_4NBr$/TBHP, $CuBr_2/Bu_4NBr/O_2$, and $CuBr_2/FeBr_3$ systems did not provide any improvement in the yield. In addition, the choice of solvent was found to have a significant impact on the yield of the transformation (Table 2). The use of DMSO or THF as the solvent provided only a trace of the desired product. In contrast, toluene, EtOAc, and benzene provided improved yields of the product, although they were lower than that achieved with CH_3CN. CH_3CN was therefore confirmed to be the best solvent for the transformation and afforded the highest yield for the reaction. The common CH_3CN was used for this reaction as opposed to anhydrous solvent and gave the desired product in 60% yield (Table 2, entry 4). Having determined the best metal bromide and solvent for the transformation, we proceeded to investigate the effect of the amount of oxidant. When 1.0 equiv of $CuBr_2$ was used, a 62% yield of product was achieved (Table 2, entry 5). Increases in the amount of $CuBr_2$ added to the reaction did not provide an increase in the yield. The effects of different additives were also examined, although the addition of a hydrogen acceptor or a base did not have any discernible impact on the results (Table 2, entries 8 and 9, respectively). A reduction in the temperature of the reaction led to a lower yield of the product, even after the extension of reaction time (Table 2, entry 10).

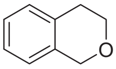
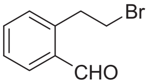
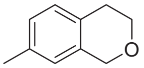
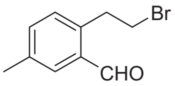
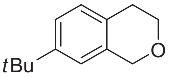
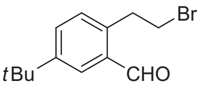
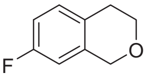
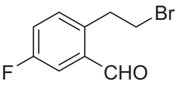
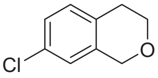
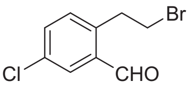
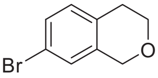
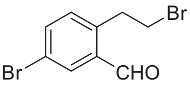
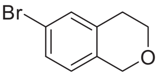
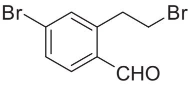
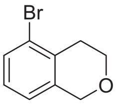
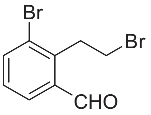
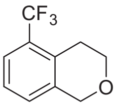
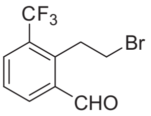
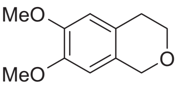
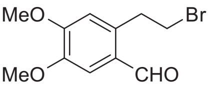
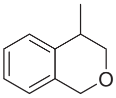
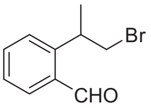
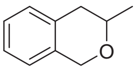
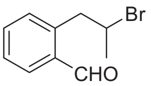
Table 2
Optimization of reaction conditions[a]

Entry	Solvent	T (°C)	Additive	Yield[b] %
1	EtOAc	77	None	28
2	PhMe	110	None	42
3	PhH	80	None	25
4	CH_3CN	82	None	60[c]
5	CH_3CN	82	None	62[d]
6	CH_3CN	82	None	67[e]
7	CH_3CN	82	Ac_2O	45
8	CH_3CN	82	BQ[f]	55
9	CH_3CN	82	$NaHCO_3$	0
10	CH_3CN	40	None	42

[a] Reaction conditions: isochroman (0.5 mmol) in solvent (1 mL) with 1.2 equiv of $CuBr_2$ at reflux under an atmosphere of N_2.
[b] Isolated yields.
[c] CH_3CN was used without being dried.
[d] 1.0 equiv $CuBr_2$ was used.
[e] 2.0 equiv $CuBr_2$ was used.
[f] BQ: benzoquinone.

With the optimized conditions in hand, we proceeded to investigate the substrate scope of the transformation with a variety of substituted isochromans (Table 3). Isochromans bearing substituents at the 7-position of the benzene ring gave the desired aldehydes with good yields (Table 3, entries 2–6). For examples, isochromans **1d**–**f** bearing different halogens at the 7-position gave the similar yields of the desired products (61–63%). In contrast, the isochroman bearing a NO_2 group at the 7-position did not provide any of the desired product. The application of an isochroman bearing a bromide at the 6-position (Table 3, entry 7) provided a lower yield, comparing with the isochroman bearing a bromine at the 7-position. In contrast, the isochroman bearing a bromide at the 5-position **1h** gave a similar yield (Table 3, entry 8) to **1f**. In addition, when the isochroman bearing a CF_3 group at the 5-position was subjected to the optimized reaction conditions, the desired product was isolated in a low yield, even with an extended reaction time (Table 3, entry 9). When an isochroman bearing two OMe groups was subjected to the optimized reaction conditions (Table 3, entry 10), the desired product **2j** was obtained in a low yield. Taken together, these results indicated that the nature of the substituent on the benzene ring had a significant influence of this oxidative reaction, because strong electron withdrawing group would make the bromination not easy to occur and strong electron donating group would make the bromination reaction on the phenyl group. To further expand the substrate scope, we also examined the impact of introducing a methyl group at different positions on the ether ring (Table 3, entries 11–12). The first of these two reactions proceeded smoothly to afford the desired product **2k** in 51% yield,

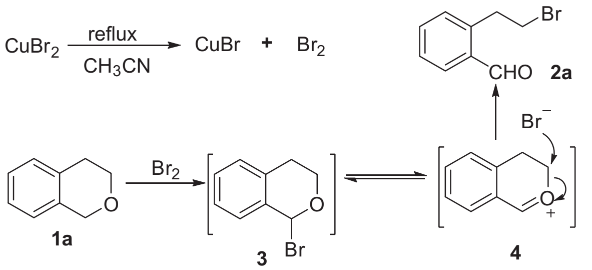
Table 3
$CuBr_2$ catalyzed oxidation of isochromans[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **1a**	 **2a**	68 (67)[c]
2	 **1b**	 **2b**	57
3	 **1c**	 **2c**	57
4	 **1d**	 **2d**	62
5	 **1e**	 **2e**	61
6	 **1f**	 **2f**	63
7	 **1g**	 **2g**	35
8	 **1h**	 **2h**	62
9	 **1i**	 **2i**	33
10	 **1j**	 **2j**	33
11	 **1k**	 **2k**	51
12	 **1l**	 **2l**	35

[a] All products were characterized by ^1H NMR and ^{13}C NMR spectroscopy.
[b] Isolated yields.
[c] 10 mmol of the substrate was used.

whereas the second reaction provided the product **2l** in a lower yield of 35%.

Based on our results, we have proposed a mechanism for the current oxidation process, as shown in Scheme 2. Initially, bromine could be produced by heating $CuBr_2$ in CH_3CN under reflux conditions.[5] The isochroman could then react with bromine to give the monobrominated intermediate **3**,[7] which would probably be unstable under the high temperature with Lewis acid conditions of the reaction and be converted into the corresponding oxocarbenium ion **4**. This intermediate could then be further bromated to give the bromo benzaldehyde products.



Scheme 2. Proposed mechanism for the $CuBr_2$ catalyzed oxidation/bromination of isochromans.

In summary, we have developed a new efficient method for the oxidation/bromination of isochromans to afford the corresponding 2-(2-bromoethyl)benzaldehydes in moderate yields using only $CuBr_2$, which only occurred for isochromans bearing no strong electron withdrawing or electron donating groups. Further investigations toward exploring the tandem reactions of isochroman and other substrates are currently underway in our group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.078.

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