Organometallic Chemistry

Stereoselective Transformations of Trihalomethylcarbinols Induced by Chromous Chloride**

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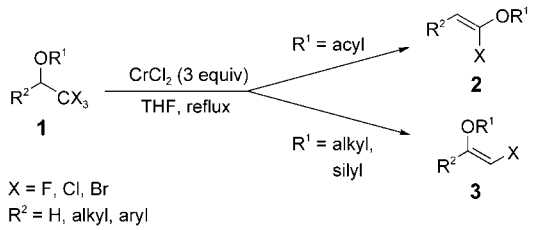
Organochromium reagents are gaining greater prominence in organic synthesis owing to their unique reactivities, high stereoselectivities, compatibility with numerous functional groups, and the recent introduction of regeneration systems that only require catalytic chromium.[1–3] As part of our continuing investigations into novel organochromium methodology, we discovered that trihalomethylcarbinol esters and ethers **1** undergo efficient, stereoselective intramolecular rearrangements induced by chromous chloride in THF. The resultant products, (*Z*)-α-haloenol esters **2** and (*Z*)-β-haloenol ethers **3**, respectively, are potentially useful, yet highly elusive synthetic intermediates (Scheme 1).[4] Esters **2** are new, stable acyl halide enolate equivalents. They have only been mentioned briefly in the literature as minor by-products and their synthetic utility remains to be explored.[5] To help



Scheme 1. Reactivity of trihalomethylcarbinols esters and ethers with $CrCl_2$.

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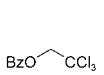
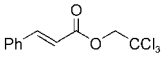
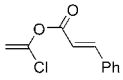
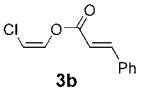
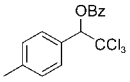
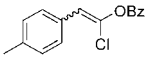
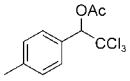
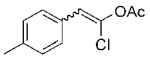
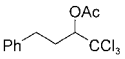
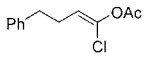
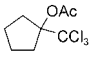
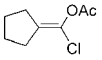
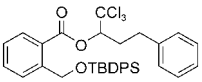
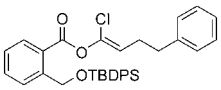
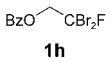
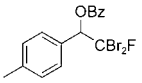
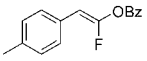
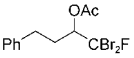
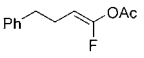
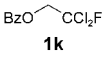
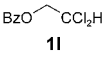
expedite access to these highly functionalized olefins and to better understand their formation, we report herein the results of treating a series of representative trihalomethylcarbinol esters and ethers with $CrCl_2$ as well as insights from mechanistic studies.

When trihalomethylcarbinol ester **1a** was stirred with commercial $CrCl_2$ (3 equiv) for 3 h with heating at reflux in THF under an argon atmosphere, α-haloenol ester **2a** was obtained as the principal product in 76% yield (Table 1, entry 1). Applying Fürstner's catalytic system, which utilizes Mn^0 powder to recycle chromium(III) to chromium(II), also gave rise to **2a**, though in lower but acceptable yield (entry 2).[6] The scope of the reaction was explored by using various esters: cinnamate (entry 3), benzoate (entry 4), and acetate (entry 5); all of these primarily undergo 1,2-migration of the acyloxy group. Likewise, trichloromethylcarbinol and dibromofluoromethylcarbinol esters derived from aliphatic aldehydes (entries 6, 8, and 11), aryl aldehydes (entries 5 and 10), a cyclic ketone (entry 7), and (formally) formaldehyde (entry 9) behaved analogously to furnish good to excellent yields of (*Z*)-α-haloenol esters. In contrast, dichloromethyl- and dichlorofluoromethylcarbinols are refractory under the standard conditions (entries 12 and 14). Addition of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) as donor ligand, which enhances the reduction power of chromium(II), did not improve this result (entry 13). On the other hand, tribromomethylcarbinols, which are more reactive toward chromous chloride, only furnished complex mixtures of products; for example, 2,2,2-tribromoethyl benzoate gave a mixture of 1-bromoethyl benzoate, 1-chloroethyl benzoate, 2,2-dibromoethyl benzoate, and several unidentified compounds.[7]

The data in Table 1 also indicate that the carbinol substitution pattern influences the stereoselectivity of the rearrangement. For instance, the hydrocinnamyl adducts **1e**,**g**, and **j**, and dibromofluoromethylcarbinol derivative **1i** afforded exclusively the *Z* isomers **2e**,**g**, and **j**, and **2i**, respectively, whereas the *p*-tolyl-trichloromethylcarbinols **1c** and **d** yielded **2c** and **d** as mixtures of *Z* and *E* isomers.[8]

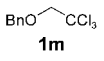
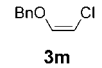
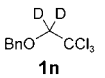
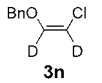
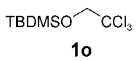
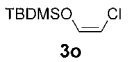
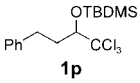
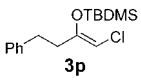
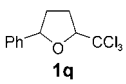
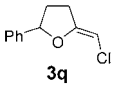
Table 1: Conversion of trihalomethylcarbinol esters into *(Z)*-α-haloenol esters.

Entry	Trihalomethyl carbinol ester **1**	Product(s)	Yield [%][a]
1	 **1a**	 **2a**	76
		 **3a**	7[b]
2[c]	**1a**	**2a**	53
		3a	5
		1k	2[b]
3	 **1b**	 **2b**	85
		 **3b**	4[b]
4	 **1c**	 **2c**	84 (Z/E = 78:22)
5	 **1d**	 **2d**	75 (Z/E = 87:13)
6	 **1e**	 **2e**	80 (Z/E > 99:1)[d]
7	 **1f**	 **2f**	82
8	 **1g**	 **2g**	84 (Z/E > 99:1)[d]
9	 **1h**	 **2h**	80[e]
10	 **1i**	 **2i**	98 (Z/E > 99:1)[d]
11	 **1j**	 **2j**	98 (Z/E > 99:1)[d]
12	 **1k**	[f]	0
13[g]	**1k**	[f]	0
14	 **1l**	[f]	0

[a] Yields for isolated materials after purification by column chromatography, unless otherwise stated. [b] Yields calculated from ^{1}H NMR spectrum of isolated mixture of **2** and **3**. [c] Reaction was conducted using catalytic chromium and excess Mn^0 powder. [d] Only one isomer was detected by ^{1}H NMR and/or GC analysis of crude material. [e] Crude purity greater than 97%; volatile compound not purified by column chromatography. [f] Starting material was recovered in 100% yield. [g] Two equivalents of TMEDA added. Bz = benzoyl, Ac = acetyl, TBDPS = *tert*-butyldiphenylsilyl.

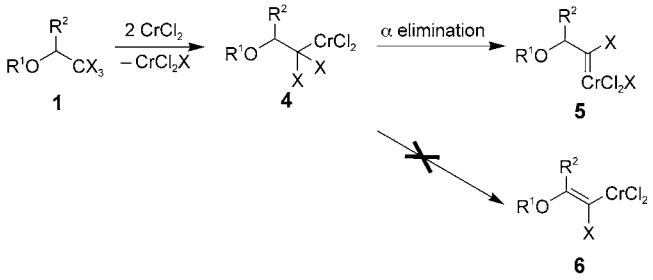
The isolation in some cases of minor amounts of (*Z*)-β-haloenol ester, such as **3a**,**b**, is consistent with the expectation that acyloxy groups have a significantly better migratory aptitude relative to hydrogen. This also prompted an examination of the reactivity of trichloromethylcarbinol ethers.[9] As anticipated, when treated with commercial $CrCl_2$ under the standard conditions these ethers exclusively formed *(Z)*-β-chlorovinyl ethers **3** in good yields and with good stereoselectivities (Table 2, entries 1–5).[10]

Table 2: Conversion of trichloromethylcarbinol ethers into (*Z*)-β-chloroenol ethers.

Entry	Trichloromethyl ether **1**	Product	Yield [%][a]
1	 **1m**	 **3m**	89
2	 **1n**	 **3n**	77
3	 **1o**	 **3o**	76
4	 **1p**	 **3p**	75
5	 **1q**	 **3q**	75

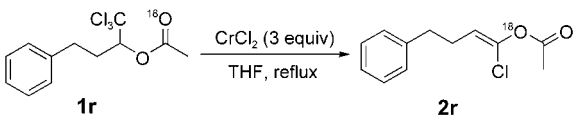
[a] Yields for isolated materials after purification by column chromatography. Bn = benzyl, TBDMS = *tert*-butyldimethylsilyl.

Mechanistically, the formation of **2** from **1** probably proceeds initially through oxidative addition of chromium into a C–X (X = Cl, Br) bond through two consecutive single-electron transfers (Scheme 2).[11] Next, the dichlorocarbenoid



Scheme 2. Proposed mechanism for the rearrangement of trichloromethylcarbinol esters and ethers.

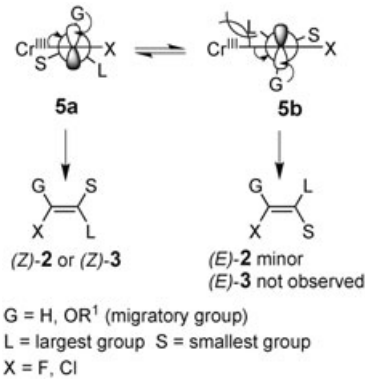
4 species undergoes an α elimination of $CrCl_2X$ through metal-assisted ionization[12] to give the proposed carbene **5**. Then, intramolecular nucleophilic rearrangement involving the nonbonded (n) electrons of the carbonyl group converts this highly reactive intermediate into ester **2**. This suprafacial rearrangement is most likely a concerted 2,3-shift mechanism through a five-center cyclic transition state: $CrCl_2$ reduction of ^{18}O-labeled substrate **1r** indicates a complete exchange of the carbonyl and carboxyl oxygens [Eq. (1)]. This trans-



(1)

formation is comparable to the Surzur–Tanner rearrangement, which involves intramolecular 1,2-suprafacial migration of the acyloxy group of β-acyloxyalkyl halides under radical conditions.[4,13] We postulate that this particular reactivity of trihalomethylcarbinol esters with chromium(II) is a result of coordination of the β oxygen atom to the metal which induces rehybridization of the organochromium species **4**, thus precluding oxidative addition of $CrCl_2$ into a second C–X bond.[14]

The observed *Z* stereochemistry of products **2c–e**, **g**, **i**, and **j** may be rationalized if one takes into account the possible conformations of the postulated Fischer carbene **5** (Scheme 3).[15] Of both possible conformations of the



Scheme 3. Stereochemical model for the migration.

chromium(III) carbene complex, conformer **5a** is much more favored than **5b** because of steric interactions between hexacoordinated chromium and the large group L (R^2). Secondary steric repulsion between L and the halogen atom in **5a** might be responsible for the formation of minor amounts of the *E* stereoisomer. Interestingly, when the latter steric interaction is decreased by using less-bulky substituents such as cinnamyl (versus *p*-tolyl) or fluoride (versus chloride), the reaction provides exclusively and stereospecifically the *Z* isomers in good isolated yields (Table 1, entries 6, 8, 10, and 11).

The 1,2-migration of hydride in chlorocarbene **5** (Scheme 2) rationalizes the origin of the ethers in Table 2. A pathway proceeding through the β-oxy-vinylidene carbenoid **6** is disproved.[16] Quenching with D_2O the reduction of **1m** by $CrCl_2$ did not lead to 2-chloro-2-*d*-vinyloxybenzyl: **3m** was obtained instead.[16,17] Moreover, the deuterated compound 2,2,2-trichloro-1,1-d_2-ethoxybenzyl **1n** gives exclusively *(Z)*-2-chloro-1,2-d_2-vinyloxybenzyl **3n**, consistent with a 1,2-migration of a deuterium atom (Table 2, entry 2). As above, the *Z* stereochemistry of ethers **3** can be rationalized if the possible conformations of the proposed Fischer carbene are taken into account (Scheme 3).

This intriguing new reactivity, observed for carboxylic esters and ethers of trihalomethylcarbinols, led us finally to study sulfonic and phosphoric esters. Unfortunately, no rearrangement was observed. Fragmentation occured preferentially to lead to 1,1-dichloroalkenes.[18]

In conclusion, we have demonstrated that (*Z*)-α-haloenol esters **2** and (*Z*)-β-haloenol ethers **3** can be efficiently obtained from trihalomethylcarbinol esters and ethers, respectively, with chromous chloride in THF. A mechanism has been proposed which accounts for both the nature of the

observed products and their preferred *Z* stereochemistry. This contribution to organochromium chemistry affords new insight into β-oxy-alkylidene carbenoids and chlorochromium(III)–carbene complexes as proposed key intermediates. Finally, we also established a reactivity scale of *gem*-polyhalide compounds with chromous chloride: $CBr_3 > CCl_3$ and $CBr_2F \gg CCl_2F$ and CCl_2H (not reactive). Further extensions are underway in our laboratory, including the use of (*Z*)-α-haloenol esters **2** as unique ketene precursors.

Experimental Section

$CrCl_2$ was purchased from Strem. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl before use.

General Procedure: Compound **1** (0.39 mmol)[19] in THF (2 mL) was added to a stirring suspension of chromium(II) chloride (145 mg, 1.17 mmol) in anhydrous THF (3 mL) at RT under argon. The mixture was heated at reflux for 3 h, cooled to RT, quenched with 5% HCl, and diluted with Et_2O. The layers were separated, and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed twice with brine, dried over $MgSO_4$, and filtered over Florisil. Alternatively, the reaction mixture can be diluted with Et_2O and filtered through a small pad of SiO_2. After concentration of the organic extract under vacuum, the crude product was purified by chromatography on silica gel to give **2** and/or **3**.

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