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(*Z*)-α-Haloacrylates: An Exceptionally Stereoselective Preparation via Cr(II)-Mediated Olefination of Aldehydes with Trihaloacetates

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α-Halo-α,*β*-unsaturated esters, also known as α-haloacrylates, are broadly useful intermediates. Applications range from the preparation of α-amino acids, heterocycles, polymers, and aziridines to natural products and pharmaceuticals.[1] With the advent in recent years of efficient transition metal catalyzed cross-couplings, α-haloacrylates have also been widely exploited for the stereospecific synthesis of trisubstituted olefins.[2] However, procedures for the preparation of α-haloacrylates, inter alia, dehydrohalogenation,[3] rearrangements,[4] alkoxycarbonylation,[5] deoxygenation of glycidic esters,[6] thermal eliminations,[7] and Wittig/Horner−Emmons/Peterson-type condensations,[8] often suffer from poor stereoselectivities, unsatisfactory yields, costly reagents, and/or lengthy procedures. As part of our continuing investigations into the utility of organochromium reagents in synthesis,[9] we report herein the preparation of (*Z*)-α-fluoro-, (*Z*)-α-chloro-, and (*Z*)-α-bromoacrylates **3** in excellent yields[10] with unprecedented stereocontrol (>99%) via room-temperature olefination of aldehydes with commercial trihaloacetates **1** mediated by stoichiometric Cr(II) salts or by catalytic Cr(II) with a regeneration system[11] (eq 1). While the intermediate Reformatsky-type adduct[12] **2** can be isolated in good yield, the overall transformation follows a dramatically different course than magnesium- and zinc-induced additions and does not require strong Lewis acids.[13]

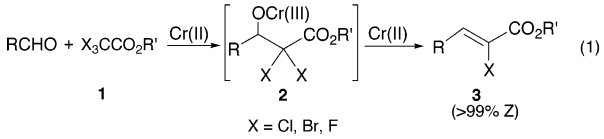
The results from the *Z*-olefination of a panel of typical aldehydes are summarized in Table 1. For simple, aliphatic aldehyde **4** or branched aldehyde **7**, stirring with 4 equiv of commercial $CrCl_2$ and methyl trichloroacetate[14] at room temperature for 0.5 h generated methyl (*Z*)-α-chloroacrylates **5** (entry 1) and **8** (entry 2), respectively, in excellent yields. None of the (*E*)-isomers could be detected by NMR analysis of the crude reaction mixtures, indicating >99% stereochemical purity. Notably, catalytic Cr(II), coupled to a Mn/TMSCl regeneration system,[11] gave comparable results. Condensation of chiral glyceraldehyde **9** likewise proceeded without incident and gave rise to ester **10**[15] (entry 3) exclusively in nearly quantitative yield.

Aryl and conjugated aldehydes, represented by benzaldehyde (**11**) and cinnamaldehyde (**13**), behaved analogously and evolved methyl (*Z*)-α-chlorocinnamate[4] **12** (entry 4) and *Z*,*E*-diene **14** (entry 5), respectively, as the sole products. Neither electron-withdrawing (entry 6) nor electron-donating (entry 7) substituents significantly influenced the reaction rate or yields as illustrated in the conversion of *p*-trifluoromethylbenzaldehyde (**15**) to **16** and *p*-methoxybenzaldehyde (**17**) to **18**.[4] The latter reaction was equally facile using methyl tribromoacetate and supplied (*Z*)-α-bromo analogue **19**. The compatibility of the reaction conditions, both stoichiometric and catalytic, with a variety of functional groups was demonstrated by the smooth condensations of benzyloxy **21** (entry 8), bromide **23** (entry 9), methylenedioxy **25** (entry 10), dimethylaniline **28** (entry 11), and indole **30** (entry 12) to give (*Z*)-α-haloacrylates **22**, **24**, **26**,[16,17] **27**,[17,18] **29**, and **31**, respectively.

Table 1. Synthesis of (*Z*)-α-Haloacrylates **3**

entry	aldehyde	acrylate	yield (%)
1	**4** R = $PhCH_2CH_2$	**5** X = Cl, R′ = Me	99
		6 X = F, R′ = Et	98
2	**7** R = $PhCH(CH_3)$	**8** X = Cl, R′ = Me	99
3	**9** R = 	**10** X = Cl, R′ = Me	99
4	**11** R = Ph	**12** X = Cl, R′ = Me	100
5	**13** R = cinnamyl	**14** X = Cl, R′ = Me	99
6	**15** R = 4-$CF_3C_6H_4$	**16** X = Cl, R′ = Me	98
7	**17** R = 4-$MeOC_6H_4$	**18** X = Cl, R′ = Me	98
		19 X = Br, R′ = Me	98
		20 X = F, R′ = Et	98
8	**21** R = 3-(MeO)-4-Bn-C_6H_3	**22** X = Cl, R′ = Me	99
9	**23** R = 3-BrC_6H_4	**24** X = Cl, R′ = Me	99
10	**25** R = piperonyl	**26** X = Cl, R′ = Me	99
		27 X = Br, R′ = Me	98
11	**28** R = 4-$Me_2NC_6H_4$	**29** X = Cl, R′ = Me	98
12	**30** R = 3-indolyl	**31** X = Cl, R′ = Me	91[a]

[a] Required 8 equiv of $CrCl_2$.



Access to (*Z*)-α-fluoroacrylates, in contrast, proved initially elusive. Methyl trifluoroacetate was refractory under all conditions and could be recovered unchanged. However, commercial methyl dibromofluoroacetate readily condensed with aliphatic and aromatic aldehydes under the standard conditions to give (*Z*)-α-fluoroacrylates, for example, **6**[8h] and **20**,[7b] respectively.

While the details have yet to be elucidated, we favor a reaction mechanism involving the oxidative addition of Cr(II) into a C−Cl bond via two consecutive single electron transfers,[19] and subsequent addition to the aldehyde carbonyl. Subsequent E2-elimination of the resultant Reformatsky-type adduct **2** (eq 1) affords α-haloacrylate **3**. Of the possible antiperiplanar conformations, conformer A (Scheme 1) is favored because it minimizes the steric interactions between the ester and R group. Selective metalation of the chloride furthest from the chromate ester ensures the observed *Z*-stereochemistry.

Consistent with this proposal, the corresponding dihalohydrins **32**[12a]−**37** could be isolated in good yield under conditions of

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Scheme 1

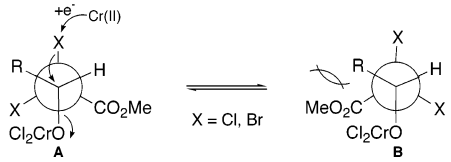
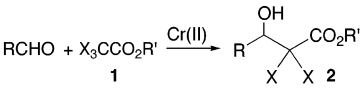


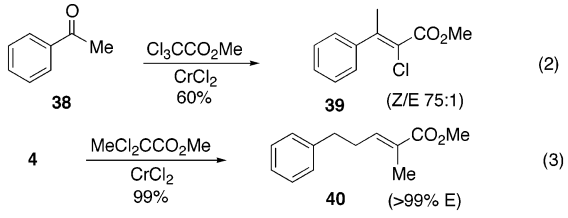
Table 2. Synthesis of Dihalohydrin **2**



entry	aldehyde		dihalohydrin	yield (%)
1	**11**	**32**	X = Cl, R′ = Me	82
2	**11**	**33**	X = Br, R′ = Me	65
3	**4**	**34**	X = Cl, R′ = Me	84
4	**13**	**35**	X = Cl, R′ = Me	78
5	**9**	**36**	X = Cl, R′ = Me (de 1:1.4)	75
6	**4**	**37**	X = F, R′ = Et	76

limiting chromium and low temperature (Table 2).[12c] Adduct **37**[12b] was prepared using commercial ethyl bromodifluoroacetate, whereas the others were derived from the corresponding trichloro- or tribromoacetates. Exposure of **32**−**36** to the original reaction conditions gave rise, as expected, to only (*Z*)-α-haloacrylates in yields comparable to those in Table 1.

In conclusion, we have validated a highly stereoselective synthesis of (*Z*)-α-haloacrylates **3** via $CrCl_2$-mediated olefinations of aldehydes with commercial trihaloacetates and also described the isolation of the dihalohydrin intermediate **2**. Initial experiments indicate this methodology has a wide scope. In contrast with most organochromium reagents, ketones are suitable substrates for the combination of trihaloacetate and $CrCl_2$. In some instances, remarkably high stereoselectivities are observed as in the case of acetophenone (**38**), which furnished the tetrasubstituted olefin **39**[13] in a 75:1 *Z*/*E* ratio[20] (eq 2), but modest yield. In yet another



variation, the efficient transformation of aldehyde **4** to (*E*)-methacrylate **40**[21] using methyl 2,2-dichloropropionate is unrivaled by conventional reagents for its stereoselectivity and yield (eq 3).[22] We anticipate Cr-mediated olefinations will find broad applicability and plan to publish additional findings soon.

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Supporting Information Available: Physical and spectroscopic data for all new compounds (PDF); X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) General Procedure for the Synthesis of (*Z*)-α-Haloacrylates (**3**)/Using Stoichiometric Chromium: Methyl trihaloacetate[16] (**1**) (1 mmol) and aldehyde (1 mmol) in THF (2 mL) were added to a stirring suspension of anhydrous $CrCl_2$[23] (4.5 mmol) in THF (8 mL) at ambient temperature. After 0.5 h, the resultant reddish reaction mixture was quenched with water, extracted thrice with ether, and the combined ethereal extracts were evaporated. Chromatographic purification of the residue on SiO_2 furnished methyl (*Z*)-α-haloacrylate (**3**) in the indicated yields (Table 1). Using Catalytic Chromium: Methyl trihaloacetate[16] (**1**) (1 mmol) and aldehyde (1 mmol) in THF (2 mL) were added to a stirring suspension of anhydrous $CrCl_2$[23] (50 mol %), Mn powder (4 mmol), and freshly distilled TMSCl (6 mmol) in THF (8 mL) at ambient temperature. After 12 h, the resultant reddish reaction mixture was quenched with water, extracted thrice with ether, and the combined ethereal extracts were evaporated. Chromatographic purification of the residue on SiO_2 gave (*Z*)-α-haloacrylate (**3**) in the indicated yields (Table 1). Preparation of Dihalohydrins (**2**): Methyl trihaloacetate[16] (**1**) (1 mmol) and aldehyde (1 mmol) in THF (2 mL) were added to a stirring suspension of anhydrous $CrCl_2$[23] (2.5 mmol) in THF (8 mL) at 0 °C. After 12 h at 0 °C, the resultant reddish reaction mixture was quenched with water, extracted thrice with ether, and the combined ethereal extracts were evaporated. Chromatographic purification of the residue on SiO_2 gave dihalohydrin **3** in the indicated yields (Table 2).

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(20) The *Z*/*E*-ratio was highly dependent upon the solvent composition, ranging from 5:1 in THF alone to 75:1 in DMF/THF (1:1) at 0 °C.

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(23) While the physical appearance and color varied, equivalent results were obtained using $CrCl_2$ from different commercial sources, inter alia, Strem and Aldrich Chem. Co.

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