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A highly stereospecific synthesis of (*E*)-α,β-unsaturated esters

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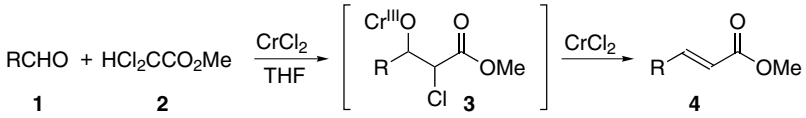
Abstract—$CrCl_2$-induced olefination of aldehydes using methyl dichloroacetate exclusively generates (*E*)-α,β-unsaturated esters in excellent yields. The intermediate α-chloro-β-hydroxy adducts could also be isolated in good yields under conditions of limited reagent.

1. Introduction

α,β-Unsaturated esters, also known as acrylates, are common structural elements in numerous compounds of interest[1] as well as key intermediates in the preparation of other functionality.[2] Despite their prominence, however, procedures for the preparation of α,β-unsaturated esters often suffer from poor stereoselectivities, unsatisfactory yields, harsh reaction conditions, costly reagents, and/or lengthy protocols.[3–10] As part of our continuing investigations into the utility of organochromium reagents, [11] we report herein a convenient, high yield synthesis of α,β-unsaturated esters **4** with exceptional (*E*)-stereoselectivity (>99%) via $CrCl_2$-mediated olefination of aldehydes **2** using commercial methyl dichloroacetate **1** (Eq. 1).[12]

The results from the (*E*)-olefination of a panel of representative aldehydes are summarized in Table 1. For aliphatic aldehyde **5** or branched aldehyde **7**, stirring with a heterogeneous mixture of commercial[13] anhydrous $CrCl_2$, and methyl dichloroacetate at either room temperature for 12 h or under reflux for 2 h, gave rise to (*E*)-α,β-unsaturated ester **6**[14] (entry 1) and **8**[15] (entry 2), respectively, in excellent yields. None of the (*Z*)-isomers could be detected by NMR analysis of the crude reaction mixtures, indicating >99% stereochemical purity.[16] Aryl and conjugated aldehydes, represented by benzaldehyde (**9**) and cinnamaldehyde (**11**), behaved analogously and evolved methyl (*E*)-cinnamate **10**[17] (entry 3) and *E*,*E*-diene **12**[18] (entry 4) as the sole products. Neither electron-withdrawing (entry 5) nor electron-donating (entry 6) substituents significantly influenced the reaction rate or yields as illustrated in the conversion of *p*-trifluoromethylbenzaldehyde (**13**) to **14**[19] and *p*-methoxybenzaldehyde (**15**) to **16**.[20] The compatibility of the reaction conditions with a variety of functional groups was demonstrated by the smooth condensations of benzyloxy/methoxy **17** (entry 7), bromide **19** (entry 8), methylenedioxy **21** (entry 9), dimethylaniline **23** (entry 10), and indole **25** (entry 11) furnishing (*E*)-α,β-unsaturated esters **18**,[21] **20**,[22] **22**,[23] **24**,[24] and **26**,[25] accordingly.



1 2 3 4 (1)

Keywords: Chromium; Olefination; Stereoselective; Condensations; Halo esters.
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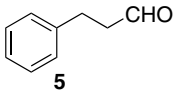
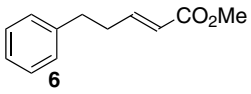
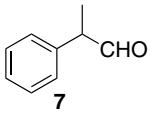
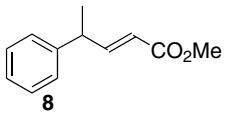
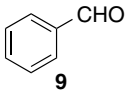
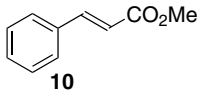
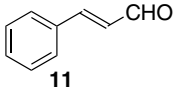
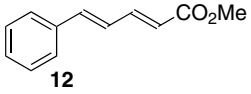
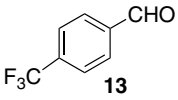
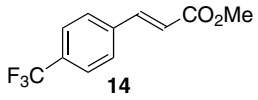
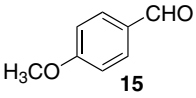
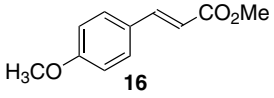
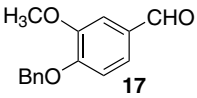
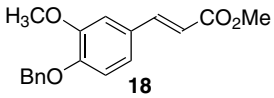
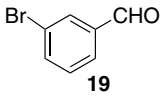
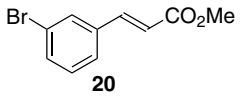
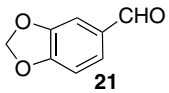
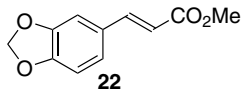
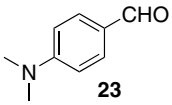
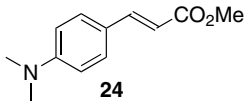
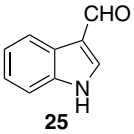
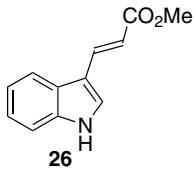
Table 1. Synthesis of (*E*)-α,β-unsaturated esters

Entry	Aldehyde	Acrylate	Yield (%)
1	 **5**	 **6**	98
2	 **7**	 **8**	98
3	 **9**	 **10**	97
4	 **11**	 **12**	99
5	 **13**	 **14**	98
6	 **15**	 **16**	98
7	 **17**	 **18**	99
8	 **19**	 **20**	99
9	 **21**	 **22**	98
10	 **23**	 **24**	78
11	 **25**	 **26**	65

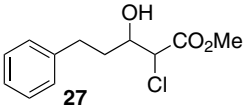
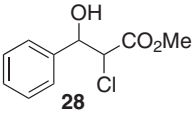
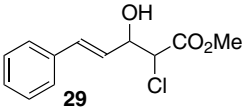
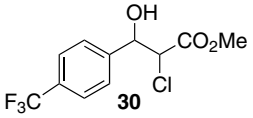
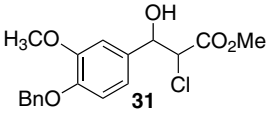
In analogy with our earlier studies,[12] the olefinations most likely involve initial metalation of **2** and addition of the nascent chromate anion to the aldehyde carbonyl. Subsequent β-elimination of the resultant Reformatsky-type adduct **3** (Eq. 1) affords α,β-unsaturated ester **4**. Consistent with this proposal, the anticipated chlorohydrins **27**,[26] **28**,[27] and **29**–**31**[26] could be isolated in good yield using limited $CrCl_2$ (Table 2). In contrast with most Reformatsky protocols,[28] the *anti*-isomer predominated (~2.5–3:1) in all cases.[29] Exposure of **27**–**31** to the original reaction conditions led to only (*E*)-α,β-unsaturated esters in yields comparable to those in Table 1.[10]

2. General procedure

2.1. Preparation of (*E*)-α,β-unsaturated ester 4

Aldehyde **1** (1 mmol) and methyl dichloroacetate (**2**) (1.2 mmol) in THF (2 mL) were added to a stirring suspension of anhydrous[13] $CrCl_2$ (7.0 mmol) in THF (8 mL) at ambient temperature under an argon atmosphere. After 12 h at ambient temperature or 2 h under reflux, 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 fur-

Table 2. Synthesis of chlorohydrin adducts

Entry	Aldehyde	Chlorohydrin	Yield (%)
1	**5**	 **27**	85
2	**9**	 **28**	89
3	**11**	 **29**	86
4	**13**	 **30**	83
5	**17**	 **31**	88

nished methyl (*E*)-α,β-unsaturated ester **4** in the indicated yields (Table 1).

2.2. Preparation of chlorohydrin 3

Aldehyde **1** (1 mmol) and methyl dichloroacetate (**2**) (1 mmol) in THF (2 mL) were added to a stirring, room temperature suspension of anhydrous[13] $CrCl_2$ (2.5 mmol) in THF (8 mL) under an argon atmosphere. After 12 h, the reaction was quenched and the products isolated as described above to give chlorohydrins **3** in the indicated yields (Table 2).

Acknowledgements

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26. Compound **27** (*anti*-isomer, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 5H), 4.21 (d, $J = 6.8$ Hz, 1H), 4.04–3.98 (m, 1H), 3.80 (s, 3H), 2.92–2.82 (m, 1H), 2.76–2.68 (m, 1H), 2.48 (d, $J = 6.0$ Hz, 1H), 2.10–2.02 (m, 1H), 1.88–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.36, 141.36, 128.65, 128.61, 126.28, 126.23, 71.18, 59.60, 53.26, 34.71, 34.71, 31.60. Compound **27** (*syn*-isomer, 25%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.18 (m, 5H), 4.32 (d, $J = 4.0$ Hz, 1H), 4.12–4.05 (m, 1H), 3.80 (s, 3H), 2.92–2.82 (m, 1H), 2.76–2.68 (m, 1H), 2.48 (d, $J = 6.0$ Hz, 1H), 2.10–2.02 (m, 1H), 1.88–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.19, 141.20, 128.65, 128.61, 126.28, 126.23, 71.29, 62.06, 53.39, 35.48, 34.71, 31.80. Compound **29** (*anti*-isomer, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.25 (m, 5H), 6.76 (d, $J = 15.0$ Hz, 1H), 6.28 (dd, $J = 15.0$, 6.6 Hz, 1H), 4.80–4.70 (m, 1 H), 4.34 (d, $J = 6.6$ Hz, 1H), 3.83 (s, 3H), 2.67 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.05, 136.07, 134.06, 134.06, 128.75, 128.35, 126.88, 125.94, 73.69, 59.49, 53.30. Compound **29** (*syn*-isomer, 29%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.25 (m, 5H), 6.74 (d, $J = 15.0$ Hz, 1H), 6.20 (dd, $J = 15.0$, 6.6 Hz, 1H), 4.80–4.70 (m, 1H), 4.43 (d, $J = 5.4$ Hz, 1H), 3.81 (s, 3H), 2.67 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.61, 136.00, 133.94, 133.94, 128.75, 128.41, 126.88, 125.89, 73.40, 61.77, 53.36. Compound **30** (*anti*-isomer, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 2H), 7.54–7.51(m, 2H), 5.12 (dd, $J = 7.6$, 4.8 Hz, 1H), 4.36 (d, $J = 7.6$ Hz, 1H), 3.81 (s, 3H), 3.13 (d, $J = 4.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.36, 142.79, 127.62, 127.62, 125.61, 74.81, 58.92, 53.44. Compound **30** (*syn*-isomer, 25%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 2H), 7.54–7.51(m, 2H), 5.26 (dd, $J = 5.6$, 4.4 Hz, 1H), 4.46 (d, $J = 5.6$ Hz, 1H), 3.74 (s, 3H), 3.11 (d, $J = 4.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.64, 142.43, 127.15, 127.15, 125.92, 73.77, 62.41, 53.44. Compound **31** (*syn*-isomer, 34%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5H), 6.96 (s, 1H), 6.88–6.82 (m, 2H), 5.16 (s, 2H), 5.07 (d, $J = 6.4$ Hz, 1H), 4.43 (d, $J = 6.4$ Hz, 1H), 3.91 (s, 3H), 3.67 (s, 3H), 2.88 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.60, 149.82, 148.53, 137.04, 131.24, 128.70, 128.70, 128.04, 127.41, 127.41, 119.18, 113.78, 110.26, 75.00, 71.06, 62.89, 56.17, 53.13. Compound **31** (*anti*-isomer, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5H), 6.96 (s, 1H), 6.88–6.82 (m, 2H), 5.17 (s, 2H), 5.00 (d, $J = 8.0$ Hz, 1H), 4.37 (d, $J = 8.0$ Hz, 1H), 3.91 (s, 3H), 3.67 (s, 3H), 2.88 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.57, 149.79, 148.62, 137.08, 131.94, 128.70, 128.70, 128.04, 127.41, 127.41, 119.64, 113.64, 110.37, 75.32, 71.06, 59.26, 56.17, 53.26.
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