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# Synthesis of (*E*)-α,β-unsaturated esters with total diastereoselectivity by using chromium dichloride

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**Abstract**—Synthesis of di- and trisubstituted (*E*)-α,β-unsaturated esters is easily achieved by using chromium dichloride through an elimination reaction of a diastereoisomeric mixture of α-halo-β-hydroxy esters. The starting materials were easily prepared by the aldol reaction of lithium enolates of α-chloroesters with aldehydes. A mechanism to explain this elimination process is proposed.

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The continuing demand for ever more efficacious and stereoselective synthetic methodology has stimulated broad interest in the formation of carbon–carbon double bonds.[1] Consequently, the diastereoselective synthesis of α,β-unsaturated esters has been extensively developed due to the synthetic applications of these compounds.[2]

Synthesis of α,β-unsaturated esters is generally achieved by C=C bond formation by Wittig,[3] Horner–Emmons,[4] Heck[5] or Peterson[6] reactions. Other useful approaches employ the Cope rearrangement,[7] utilise acetylenic compounds[8] or using α-mercaptoester derivatives.[9] However, most of these methodologies, give a mixture of diastereoisomers and poor yields can be obtained. In other cases, poor generality is a major limitation. In addition, preparations of α,β-unsaturated esters in which the C=C bond is trisubstituted are scarce.[10]

The aforementioned limitations have led to the use of chromium dichloride to promote β-elimination reactions. So, the synthesis of unsaturated compounds such as alkenes,[11] vinyl chlorides[12] or iodides,[13] 1,1-bis(trimethylsilyl)alkenes,[14] trialkylvinylstannanes or silanes,[15] 1-alkenyl sulfides,[16] alkenylboronic esters[17] and 2-haloalk-2-en-1-ols[18] have been described by using $CrCl_2$. To the best of our knowledge, chromium dichloride has not been applied to obtain α,β-unsaturated esters.[19]

Recently, we described a diastereoselective synthesis of (*E*)-α,β-unsaturated esters by the reaction of α-halo-β-hydroxy esters with samarium diiodide.[20] In this case, when attempts were carried out in order to obtain γ-amino-α,β-unsaturated esters (from γ-amino-α-halo-β-hydroxy esters), the methodology was unsuccessful. For this reason, we continued our investigations into diastereoselective β-elimination reactions as a means to find alternatives to $SmI_2$ to promote 1,2 elimination reactions. Herein, we report preliminary results of a new methodology to obtain α,β-unsaturated esters **2** with total diastereoselectivity by treatment of easily available α-halo-β-hydroxy esters **1** with chromium dichloride. A mechanism to explain this β-elimination process is also proposed.

Our first attempts were carried out using α-chloro-β-hydroxy esters and α,β-epoxy esters in order to determine suitable starting materials. Thus, treatment of a solution of ethyl 2-chloro-3-hydroxy-2-methyldecanoate **1d** in THF with $CrCl_2$ at reflux over 4 h afforded ethyl 2-methyldecan-2-enoate **2d**, after hydrolysis, with total diastereoselectivity (de >98%) and 64% yield. The same treatment of 2,3-epoxy-2-methyldecanoate **3d**, gave **2d** with slightly lower diastereoselection (de 95%) and yield (51%). Based on these results, the preparation of α,β-unsaturated esters was performed from compounds **1**. The treatment of different α-halo-β-hydroxy esters **1** with $CrCl_2$ (3 equiv) at room temperature afforded (*E*)-α,β-unsaturated esters with total diastereoselectivity (Scheme 1).[21] Table 1 summarises the results obtained.

The starting materials **1** were easily prepared by reaction of the corresponding lithium enolates of α-halo esters **4**

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*Keywords*: Chromium; Eliminations; Esters.

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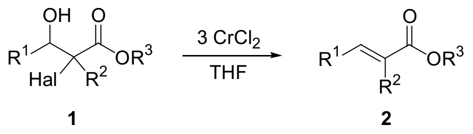
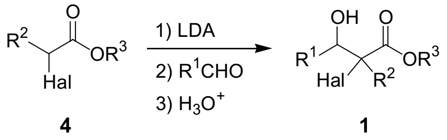


**Scheme 1.** Synthesis of (*E*)-α,β-unsaturated esters **2**.



**Scheme 2.** Preparation of starting compound **1**.

(generated by treatment of α-halo esters with LDA at −78 °C) with aldehydes at −78 °C (Scheme 2 and Table 1).[22]

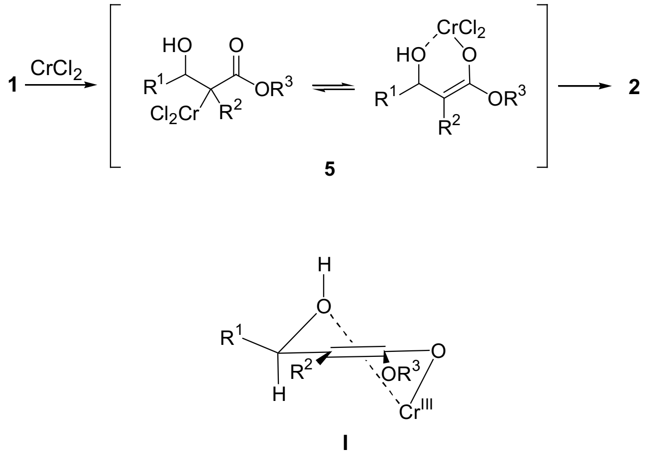
It is noteworthy that although 1:1 mixtures of diastereoisomers of **1** were used, the corresponding α,β-unsaturated esters **2** were obtained with total diastereoselectivity.

The diastereoisomeric excess was determined by $^1$H NMR spectroscopy (300 MHz) and GC–MS of the crude mixtures of products **2**, showing the presence of a single diastereoisomer. The *E* stereochemistry in the C=C double bond of α,β-unsaturated esters **2** was assigned on the basis of the values of $^1$H NMR coupling constants between the olefinic protons of compounds **2a–c** (Table 1, entries 1–3),[23] and by NOE experiments in the case of the trisubstituted compounds **2g** and **2i** or by comparison with the $^1$H and $^{13}$C NMR spectra of authentic samples described in the literature (**2d–e**).[20]

This methodology for obtaining α,β-unsaturated esters is general: R$^1$, R$^2$ and R$^3$ can be widely varied. R$^1$ can be aliphatic (linear, branched or cyclic) or aromatic and substitution at the C2 position could also be changed using different esters to prepare the starting compounds **1** (Scheme 2). Interestingly, the diastereoselectivity was unaffected by changing the carboxylic ester (compounds **2a**, **2d** and **2j**) in contrast to the Wittig olefination reaction.[24] Although chloro and bromo hydroxy esters (compounds **1h** and **1i**) can be used as the starting material, the elimination reaction has mainly been carried out with chloro esters rather than with bromo derivatives because in this case, the starting compounds **1** were obtained in lower yields.[25]

The observed C=C double bond configuration of products **2** may be explained by assuming a chelation-control model (Scheme 3). Thus, metallation of the C-Hal bond (via two consecutive single electron transfers) generates the enolate intermediate **5**.[26] Chelation of the Cr$^{III}$ center with the oxygen atom of the alcohol group produces a six-membered ring.[27] Indirect proof of this fact is the lower yield (45%) and diastereoselection (72%) obtained when elimination was performed on the O-acetylated form of starting compound **1a**. Tentatively, we surmise that the chair-like transition state model **I** might be involved, with the R$^1$ group in the equatorial orientation. Elimination from **I** affords (*E*)-α,β-unsaturated esters.

The synthesis of **2** with total diastereoselection from a mixture of diastereoisomers of **1** can also be explained by this mechanism. After reaction of **1** with CrCl$_2$, the two starting diastereoisomers **1** are transformed into



**Scheme 3.** Proposed mechanism.

**Table 1.** Synthesis of α-halo-β-hydroxy esters **1** and (*E*)-α,β-unsaturated esters **2**

| **1** or **2** | R$^1$ | R$^2$ | R$^3$ | Hal | Yield **1** (%)[a] | Yield **2** (%)[b] | De (%)[c] |
|---|---|---|---|---|---|---|---|
| **a** | *n*-C$_7$H$_{15}$ | H | Me | Cl | 86 | 65 | >98 |
| **b** | *p*-Cl–C$_6$H$_4$ | H | Me | Cl | 85 | 68 | >98 |
| **c** | MeCH(Ph) | H | Me | Cl | 80 | 52 | >98 |
| **d** | *n*-C$_7$H$_{15}$ | Me | Et | Cl | 78 | 64 | >98 |
| **e** | Cyclohexyl | Me | Et | Cl | 75 | 65 | >98 |
| **f** | Ph | Me | Et | Cl | 85 | 60 | >98 |
| **g** | *p*-MeO–C$_6$H$_4$ | Me | Et | Cl | 90 | 70 | >98 |
| **h** | Ph | *n*-C$_6$H$_{13}$ | Et | Br | 55 | 65 | >98 |
| **i** | Ph | *n*-C$_5$H$_{11}$ | Et | Br | 60 | 90 | >98 |
| **j** | Cyclohexyl | Me | $^i$Pr | Cl | 76 | 70 | >98 |

[a] Isolated yields after column chromatography based on the starting aldehyde.

[b] Isolated yield after column chromatography based on compound **1**.

[c] Determined by $^1$H NMR spectroscopy and GC–MS of the crude reaction products.

two enolate enantiomers, which afford a single *E*-diastereoisomer through a β-elimination reaction.

In conclusion, an easy and general methodology has been developed to synthesise α,β-unsaturated esters with total *E*-diastereoselectivity from easily available α-halo-β-hydroxy esters, being promoted by chromium dichloride. Attempts to carry out diastereoselective 1,2 elimination of γ-amino-α-halo-β-hydroxy esters are currently under investigation within our laboratory.

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## References and notes

1. (a) *The Chemistry of Alkenes*; Patai, S., Ed.; Interscience: New York, 1968; 2; (b) Shen, Y. *Acc. Chem. Res.* **1998**, *31*, 584–592.
2. Sánchez-Sancho, F.; Mann, E.; Herradon, B. *Adv. Synth. Catal.* **2001**, *343*, 360–368.
3. For recent reviews on the synthesis of α,β-unsaturated esters, see: (a) Franklin, A. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2451–2465; (b) Shen, Y. *Acc. Chem. Res.* **1998**, *31*, 584–592.
4. For recent examples of the preparation of α,β-unsaturated esters by Wittig reaction, see: (a) Patil, V. J.; Mävers, U. *Tetrahedron Lett.* **1996**, *37*, 1281–1284; (b) Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8653–8655; (c) Beji, F.; Lebreton, J.; Villieras, J.; Amri, H. *Synth. Commun.* **2002**, *32*, 3273–3278; (d) Huang, Z.; Sun, R. J. *Chin. J. Org. Chem.* **2002**, *20*, 1460–1462.
5. (a) Moreno-Mañas, M.; Pérez, M.; Pleixants, R. *Tetrahedron Lett.* **1996**, *37*, 7449–7452; (b) Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939; (c) Jin, Y. Z.; Yasuda, N.; Inanaga, J. *Green Chem.* **2002**, *4*, 498–500.
6. (a) Zou, G.; Wang, Z.; Zhu, J.; Tang *J. Chem. Commun.* **2003**, *6*, 2438–2439; (b) Salgado, A.; Manmn, E.; Sánchez-Sancho, F.; Herradon, B. *Heterocycles* **2003**, *60*, 57–71.
7. (a) Palomo, C.; Aizpurua, J. M. *J. Org. Chem.* **1990**, *55*, 2498–2503; (b) Hayes, B. L.; Adams, T. A.; Pickin, K. A.; Day, C. S.; Welker, M. E. *Organometallics* **2000**, *19*, 2730–2740.
8. (a) Lambert, T. H.; MacMillan, D. W. *J. Am. Chem. Soc.* **2002**, *124*, 13646–13647; (b) Liao, B.; Negishi, E. *Heterocycles* **2000**, *52*, 1241–1249.
9. (a) Trost, B. M.; Parquette, J. R. *J. Org. Chem.* **1993**, *58*, 1579–1681; (b) Tanikaga, R.; Miyashita, K.; Ono, N.; Kaji, A. *Synthesis* **1982**, 131–132.
10. (a) Castells, J.; López-Calahorra, F.; Yu, Z. *Tetrahedron* **1994**, *50*, 13765–13774; (b) Maercker, A.; Van de Flierdt, J.; Giresser, U. *Tetrahedron* **2000**, *56*, 3373–3383.
11. (a) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582–1589; (b) Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951–953; (c) Knecht, M.; Boland, W. *Synlett* **1993**, 834–837.
12. (a) Baati, R.; Barma, D. K.; Krishna, U. M.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 959–961; (b) Wolf, R.; Steckhan, E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 733–739.
13. (a) Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, 1268–1270; (b) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410; (c) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497–4513.
14. Hodgson, D. M.; Comina, P. *Tetrahedron Lett.* **1994**, *35*, 9469–9470.
15. (a) Cliff, M. D.; Pyne, S. G. *Tetrahedron Lett.* **1995**, *36*, 763–766; (b) Hodgson, D. M.; Boulton, L. T.; Maw, G. N. *Tetrahedron Lett.* **1994**, *35*, 2231–2234; (c) Hodgson, D. M. *Tetrahedron Lett.* **1992**, *33*, 5603–5604.
16. Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 1443–1446.
17. Takai, K.; Shinomiya, N.; Kaihara, H.; Yoshida, N.; Moriwake, T. *Synlett* **1995**, *3*, 963–964.
18. Baati, R.; Barma, D. K.; Falk, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2183–2185.
19. While this paper was being elaborated, a synthesis of α-chloro-α,β-unsaturated esters with total diastereoselectivity using $CrCl_2$was described Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218–3219.
20. Concellón, J. M.; Pérez-Andrés, J. A.; Rodríguez-Solla, H. *Angew. Chem.* **2000**, *112*, 2866–2868; *Angew. Chem., Int. Ed.* **2000**, *39*, 2773–2775.
21. General procedure for the synthesis of compound **2**: To a stirred solution of the corresponding α-halogenated-β-hydroxy ester **1** (0.4 mmol) in dry THF (5 mL) was added $CrCl_2$ (0.15 g, 1.2 mmol). After 4 h at reflux the reaction mixture was quenched with water. The usual work-up and filtration through a pad of Celite provided α,β-unsaturated esters **2**, which were purified by flash column chromatography on silica gel (hexane/AcOEt 15/1).
22. General procedure for the synthesis of compounds **1**: To a stirred solution of the α-halo ester (9.7 mmol) in dry THF (8 mL) at −78 °C was added dropwise lithium diisopropylamide [prepared from MeLi (6.5 mL of 1.5 M solution in ether) and diisopropylamine (1.4 mL, 10 mmol) in THF (50 mL) at 0 °C]. After stirring for 10 min, a solution of the aldehyde (5 mmol) in dry THF (4.5 mL) was added dropwise at −78 °C and the mixture was stirred for 2 h. Then the reaction mixture was quenched with a saturated aqueous solution of $NH_4Cl$ (20 mL). The usual work-up provided the corresponding α-halo-β-hydroxy ester **1**, which was purified by flash column chromatography on silica gel (hexane/AcOEt 10/1).
23. The coupling constant between the olefinic protons of compounds **2a**, **2b** and **2c** were $J = 15.4$, 16.1 and 15.6 Hz, respectively; this is in accordance with the average literature values.
24. One of the great challenges associated with the Wittig reaction in the preparation of α,β-unsaturated esters relates to stereocontrol: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863–927.
25. Condensation of the bromoenolate with aldehydes affords a mixture of compound **1** and the corresponding α,β-epoxyester **3** (Darzens' reaction) even at low temperature.
26. Chromium(III) enolates and related species have been proposed as intermediates in the chromium-Reformatsky reaction: Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36.
27. A similar chelated transition state model was proposed to explain the selectivity in other reactions of $CrCl_2$: Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037–1040.