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Stereoselective synthesis of methyl (*Z*)-α-methoxyacrylates via two-carbon homologation of aldehydes

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Dedicated to the memory of Dr. Charles Mioskowski

ABSTRACT

Methyl (*Z*)-α-methoxyacrylates are generated in good yields by a mild, stereospecific two-carbon homologation of a wide variety of aldehydes utilizing commercial methyl 2,2-dichloro-2-methoxyacetate and $CrCl_2$ under Barbier conditions at room temperature. A rational mechanism based upon a Reformatsky-type addition pathway or an in situ generated (*E*)-trioxo-chromium vinylidene carbenoid is proposed.

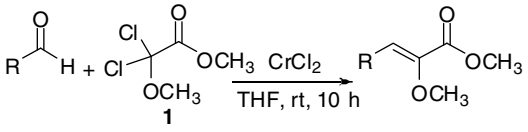
2-Alkoxyacrylic moieties are present in many natural and semi-synthetic products,[1] and have been used as key intermediates for the preparation of biologically active compounds.[2] The derivatives of arylalkadienes are useful in the treatment of osteoporosis and other diseases.[3] Moreover, the C–C double bond present in these compounds can be used for diverse transformations such as Claisen rearrangement,[4] Diels–Alder,[2a,5] and Heck reactions.[2b,6] Several methods are available in the literature for the preparation of 2-alkyloxy-α,β-unsaturated alkenoates, and most of them rely either on Horner–Emmons condensations using α-alkoxy phosphono acetates,[2e–g,3,7] or on reactions of aldehydes with alkyl esters under basic conditions.[1d,2j,8] Other methods used for this purpose are palladium cross-coupling with vinylic electrophiles[9] via alkenyl metallic species[10] and phosphine-catalyzed addition of arylpropiolates to oxygen nucleophiles.[11] However, some of these methods present quite often serious drawbacks such as multistep transformations, low yields, and more importantly low selectivity. Moreover, some reaction conditions are not compatible with common functional groups.

During the past few years we have been engaged with the studies of organochromium compounds for stereoselective C–C bond forming reactions.[12] In this connection, recently we reported the preparation of (*Z*)-methyl 2-methoxy-3-phenylacrylate by the reaction of benzaldehyde and 2,2-dichloro-2-methoxy acetate in presence of $CrCl_2$.[13] With this background and considering the importance of methoxyacrylates, we report herein, the generality of the reaction for the preparation of (*Z*)-α-methoxyacrylates via two-carbon homologation of a large panel of aldehydes utilizing commercial methyl 2,2-dichloro-2-methoxy acetate (**1**) and $CrCl_2$ at room temperature (Scheme 1).

The reaction parameters were optimized with equimolar **1** and *p*-tolualdehyde (**2**). Utilizing 4 equivalents of anhydrous $CrCl_2$ at rt in THF under Barbier conditions, (*Z*)-α-methoxyacrylate **3** ($Z/E > 97:3$)[14] was obtained in 54% yield. The yield of **3** increased proportionately to a maximum of 88% with the application of 6 equivalents of $CrCl_2$ (Table 1, entry 1).[15] No further improvements were realized if more equivalents of $CrCl_2$ were used.

Homologations were also observed in EtOAc, benzene, and dioxane, but yields were inferior.[16] Likewise, attempts to utilize catalytic amounts of $CrCl_2$ regenerated in situ by excess Fe(0) or Mn(0) proved unsatisfactory, even at elevated temperatures.

With suitable reaction conditions in hand, the scope of our methodology was then investigated using a panel of structurally representative aliphatic and aromatic aldehydes. Aromatic aldehydes bearing electron-donating substituents, for example, 4-methoxybenzaldehyde (**4**, entry 2) and piperonal (**6**, entry 3), as well as electron-withdrawing groups, for example, methyl 4-formylbenzoate (**8**, entry 4) and 4-trifluoromethyl benzaldehyde (**10**, entry 5) underwent smooth condensations to give stereoselectively *Z*-configured adducts **5**, **7**, **9**, and **11**, respectively, in good yields (70–80%). Significantly, our two-carbon homologation is also compatible with a variety of functional groups as demonstrated by



Scheme 1. Stereoselective synthesis of (*Z*)-α-methoxy-α,β-unsaturated alkenoic esters.

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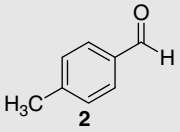
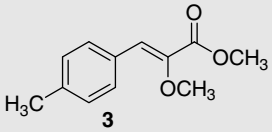
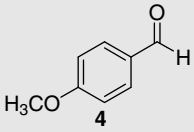
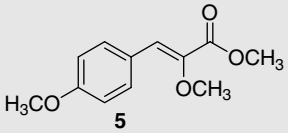
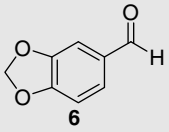
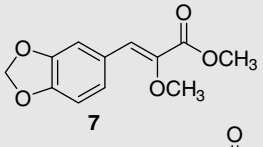
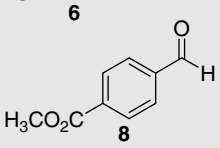
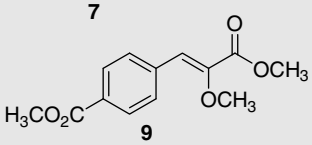
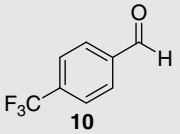
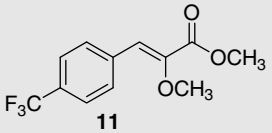
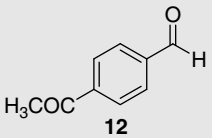
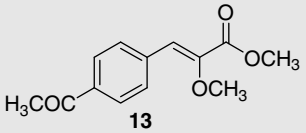
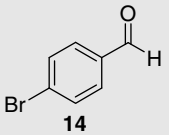
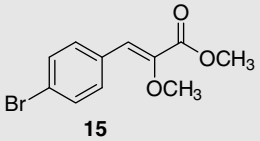
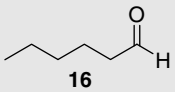
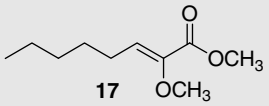
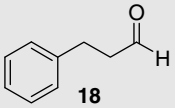
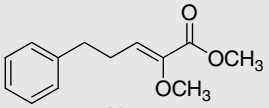
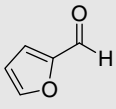
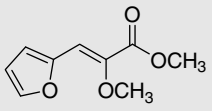
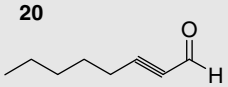
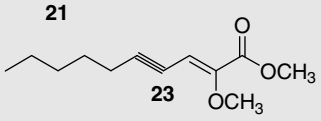
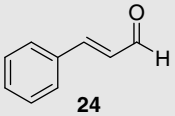
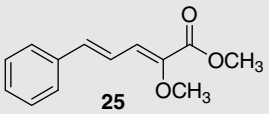
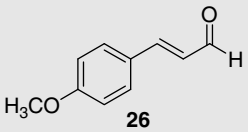
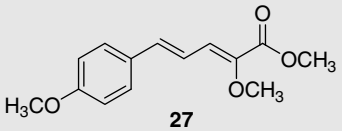
Table 1
Various functionalized alkenoic esters

Entry	Aldehyde	Alkenoate	Yield (%)
1	 **2**	 **3**	88
2	 **4**	 **5**	70
3	 **6**	 **7**	75
4	 **8**	 **9**	77
5	 **10**	 **11**	80
6	 **12**	 **13**	85
7	 **14**	 **15**	84
8	 **16**	 **17**	70
9	 **18**	 **19**	77
10	 **20**	 **21**	69
11	 **22**	 **23**	71
12	 **24**	 **25**	62
13	 **26**	 **27**	62

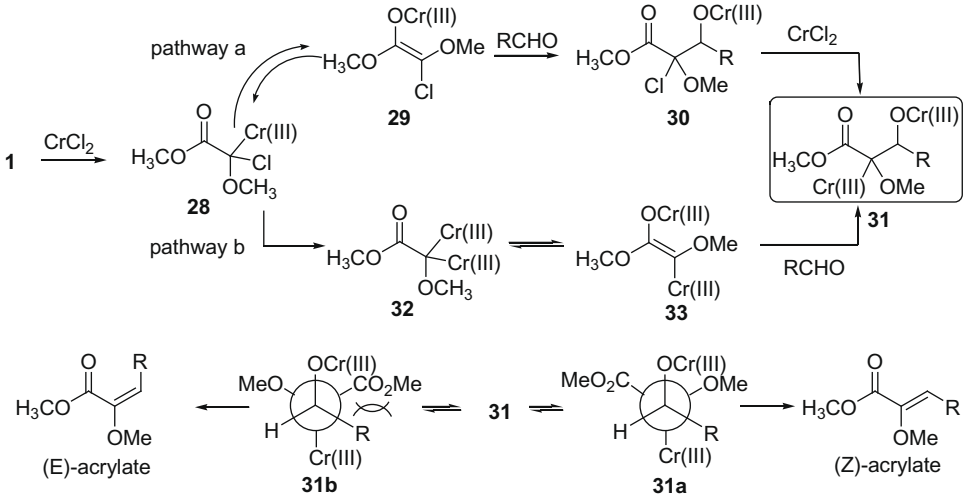


Figure 1. Mechanism for stereoselective *Z*-alkenoic ester formation.

the selective transformations of an aromatic ketoaldehyde (**12**→**13**, entry 6) and an aromatic bromide (**14**→**15**, entry 7).

It is noteworthy that aliphatic aldehydes like *n*-hexanal (**16**) and hydrocinnamaldehyde (**18**) were well tolerated and led to (*Z*)-acrylates **17** (entry 8) and **19** (entry 9), respectively, without complications. Heterocyclic aldehyde furfural (**20**, entry 10) was also a suitable substrate, and furnished the corresponding (*Z*)-acrylate **21** in modest yield (69%) along with recovered starting material (22%). Extension of the homologation procedure to α,β-unsaturated aldehydes (entries 11–13) was satisfactory in terms of reactivity and stereoselectivity ($Z/E \approx 97{:}3$), although slightly lower yields were obtained.

In concert with prior mechanistic studies,[12,13] we propose that reaction of **1** with $CrCl_2$ initially generates 2-chloro-2-methoxy-2-chromium carbenoid **28** (Fig. 1). Addition of this species to the aldehyde results in a Reformatsky-type adduct **30** (pathway a), which upon further reduction affords **31**. Alternatively, pathway **b** could also be invoked for the formation of the intermediate **31**, via the possible formation of a nucleophilic trioxo-vinylidene carbenoid **33**. Subsequent anti-periplanar E2 elimination through the less congested conformer **31a** preferentially delivers *Z*-olefin. The high selectivity observed for the α-methoxyacrylates might be ascribed to the high steric hindrance in conformer **31b,** which favors the elimination from the more stable conformer **31a** predominantly. At this stage of our investigations, the most probable pathway **a** or **b** is not settled, and attempts to trap the intermediates are underway in our laboratories.

In conclusion, we have demonstrated and established the scope and the functional group compatibility of the stereospecific synthesis of (*Z*)-α-methoxyacrylates via a $CrCl_2$-promoted condensation of methyl 2,2-dichloro-2-methoxy acetate with various aldehydes. We believe that the modular strategy outlined here will be a convenient general way to prepare this useful class of highly functionalized, trisubstituted alkenes.

Acknowledgments

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14. The *Z/E* ratio was determined by quantitative integration of the vinyl proton of both isomers in the ^{1}H NMR of the crude reaction mixture. The stereochemistry of the major *Z* acrylate was assigned by NOE experiments.
15. *Procedure for the preparation of alkenoic ester* **3**: To a solution of methyl 2,2-dichloro-2-methoxy acetate **1** (100 mg, 0.57 mmol) in dry THF (5 mL) was added 4-methyl benzaldehyde **2** (69 mg, 0.57 mmol)) followed by $CrCl_2$ (6 equiv). The mixture was allowed to stir at rt for 10 h. After completion of the reaction (TLC), it was quenched with water (10 mL) and extracted with ether (2 × 25 mL). Combined organic layers were washed with brine, water, and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography. Elution of the column with cyclohexane/EtOAc (98/2) mixture gave desired alkenoic ester **3** (104 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.92 (s, 3H), 4.00 (s, 3H), 7.14 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 52.5, 59.5, 124.3, 129.7, 130.1, 130.9, 139.7, 145.2, 165.4.; MS (EI) 206.1. *Spectral data for compound* **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 6.91 (d, J = 9.03 Hz, 2H), 6.98 (s, 1H), 7.72 (d, J = 8.43 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 55.6, 59.4, 114.4, 124.6, 132.2, 144.2, 160.6, 165.5. Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.84 (s, 3H), 5.99

(s, 2H), 6.80 (d, J = 8.1 Hz, 1H), 6.92 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 59.5, 101.7, 108.7, 109.9, 114.4, 124.5, 125.9, 127.9, 132.1, 144.4, 148.2, 148.6, 165.3. Compound **9**: ^{1}H NMR (200 MHz, $CDCl_3$,): δ 3.81 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 6.96 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 8.02–8 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2, 52.3, 59.4, 122.2, 129.7, 129.90, 129.97, 137.8, 147.0, 164.4, 166.6. ESI: $(M+H)^+$ = 251. Compound **13**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 6.95 (s, 1H), 7.80 (d, J = 6.4 Hz, 2H), 7.97 (d, J = 6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.2, 52.6, 59.6, 122.3, 128.7, 130.3, 138.2, 147.4, 164.6, 197.5. ES+: $(M+H)^+$ = 235. Compound **19**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.58–2.66 (t, J = 8.4 Hz, 2H), 2.75–2.82 (t, J = 8.2 Hz, 2H), 3.58 (s, 3H), 3.81 (s, 3H), 6.29–6.36 (t, J = 14.8 Hz, 1H), 7.20–7.24 (m, 2H), 7.30–7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.4, 34.9, 52.0, 60.1, 126.2, 128.0, 128.5, 141.2, 146.5, 164.3. ESI:$(M+H)^+$ = 221. Compound **21**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.83 (s, 3H), 6.50–6.47 (m, 1H), 6.90–6.92 (d, J = 3.4 Hz, 2H), 6.99 (s, 1H), 7.46–7.47 (d, J = 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2, 59.3, 112.4, 113.7, 114.1, 143.2, 143.4, 149.4, 164.5. GC–MS: $(M)^+$ = 182. Compound **27**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 6.76 (d, J = 15.4 Hz, 1H), 6.88 (d, J = 9.02 Hz, 2H), 7.00 (d, J = 10.54 Hz, 1H), 7.08 (d, J = 11 Hz, 1H), 7.43 (d, J = 8.8 Hz, 2H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ 53.3, 55.7, 61.1, 114.6, 119.7, 127.2, 128.9, 129.8, 137.8, 144.5, 160.5, 164.9.

16. The use of other solvents, under otherwise identical conditions, was not satisfactory: EtOAc, benzene, and dioxane afforded **3** in 18%, 5%, and 38% yield, respectively.