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Synthesis of Unsaturated Esters from Aldehydes: An Inexpensive, Practical Alternative to the Horner–Emmons Reaction under Neutral Conditions

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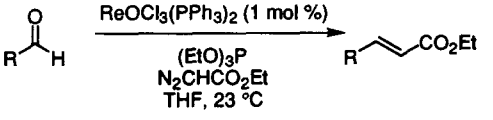
Abstract. A practical, efficient, and mild process is described for the synthesis of unsaturated esters from aldehydes in good yields and diastereoselectivities. All of the reagents used in the protocol are commercially available at a nominal price: N_2CHCO_2Et, catalytic (1 mol%) $ReOCl_3(PPh_3)_2$, and $(EtO)_3P$. Additionally, the reaction process can be carried out successfully in good yields (85%) and diastereoselectivities (>20:1) with reagent-grade solvent without prior purification of the reagents.

The olefination of aldehydes to give α,β–unsaturated esters is an important synthetic transformation which affords valuable and versatile synthetic intermediates. Partial reduction of such esters gives α,β–enals, which are amenable to subsequent synthetic elaboration. Complete reduction of the carbonyl functionality affords synthetically useful allylic alcohols, the requisite substrates for many directed asymmetric functionalization reactions such as epoxidation[1] and cyclopropanation.[2] Recursive strategies have been developed for the synthesis of 1,3-skipped polyols involving conversion of an aldehyde to the corresponding allylic alcohol followed by Sharpless asymmetric epoxidation and subsequent elaboration of the epoxy alcohol product to the protected β–hydroxy aldehyde.[3,4] A related iterative strategy has been reported for the preparation of polycyclopropane-derived natural products from allylic alcohols.[5]

In this letter, we report a practical and efficient process for the synthesis of unsaturated esters from aldehydes in good yields and diastereoselectivities. All of the reagents used in the protocol are commercially available at a nominal price: N_2CHCO_2Et, catalytic (1 mol%) $ReOCl_3(PPh_3)_2$, and $(EtO)_3P$ (Eq 1). In contrast to established methods, the procedure eliminates the deprotonation step typically required when using conventional protocols involving phosphonoacetates or phosphoranes. Additionally, we show that the reaction process can be carried out successfully (85% yield, >20:1 diastereoselectivity) with reagent-grade solvent without purification of the reagents.



(1)

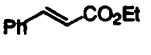
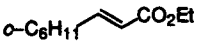
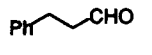
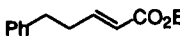
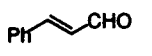
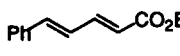
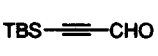
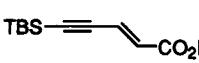
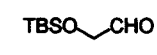
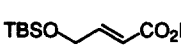
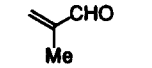
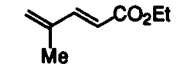
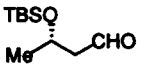
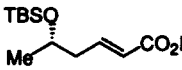
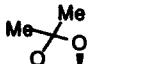
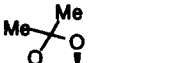
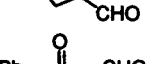
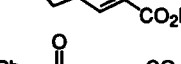
The method described herein is based on a report by Herrmann that $MeReO_3$ (5–10 mol%) catalyzed the olefination of a selection of aldehydes with N_2CHCO_2Et and a stoichiometric amount of PPh_3.[6] In the proposed mechanism, $MeReO_3$ is reduced by Ph_3P to give Ph_3PO and a Re(V) species which in turn reacts with the diazoacetate to give an intermediate metal alkylidene as the active olefination agent. Reaction of the Re–alkylidene with an aldehyde affords the unsaturated ester and regenerates $MeReO_3$. In subsequent work aimed at identifying the catalytically active species, Herrmann reported a single example in which $ReOCl_3(PPh_3)_2$ catalyzed the reaction of *p*-$NO_2C_6H_4CHO$ with N_2CHCO_2Et.

Three key issues make the method described in these preliminary reports unsuitable for use as a practical alternative to the Horner-Wadsworth-Emmons condensation: (1) the (*E*)/(*Z*) product ratios reported were not generally high; (2) the use of Ph_3P as the stoichiometric reagent gives Ph_3PO as a coproduct, which can often complicate product isolation and purification; and (3) optimal yields of the enoate required relatively high loads of the expensive $MeReO_3$ catalyst (5-10 mol%).

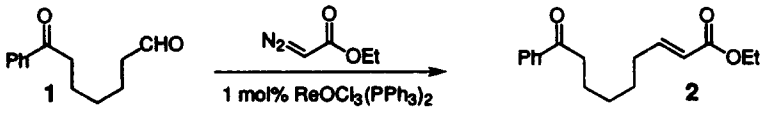
We set out to develop a more practical process based on Herrmann's work. In addition, $ReOCl_3(PPh_3)_2$ was chosen for study since it is considerably cheaper than $MeReO_3$ (1g/$21.75 and 500mg/$53, respectively, Aldrich). We sought an inexpensive, commercially available substitute for Ph_3P whose oxidized product would be easily separated from the desired enoates, thus facilitating purification. A variety of reductants were screened (sulfides, sulfites, hydrazine, disilanes, silanes) under a number of conditions, with little success. While some of these were capable of effecting the reduction of Re(VII) to Re(V), as demonstrated by a color change of the reaction mixture from pale yellow to orange-brown, they were not able to promote aldehyde olefination. However, trialkyl phosphites were found to function as effective stoichiometric reducing agents that led to aldehyde olefination. Using only 1 mol% $ReOCl_3(PPh_3)_2$, 1 equiv $(EtO)_3P$, and 1 equiv N_2CHCO_2Et, unsaturated esters were isolated in 65-95% yields and up to >20:1 diastereoselectivity (Table 1). The generality of the reaction is demonstrated by the selection of substrates that may be employed succesfully; aromatic, aliphatic, unsaturated, and functionalized aldehydes serve effectively as substrates. For each case, the diastereoselectivity of the reaction was assayed by ^1H NMR spectroscopy against known enoate products, or against authentic cis-enoates prepared according to the method of Still ($(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF).[7,8,9] It is interesting to note that the enoate formed from glyceraldehyde acetonide (Entry 9) did not undergo racemization, as determined by comparison with the known product. In addition, as illustrated by the keto aldehyde substrate of Entry 10, the reaction is highly chemoselective and gives the product of aldehyde olefination exclusively.

A unique property of the non-basic, mild process described herein is illustrated by Eq 2. Treatment of keto aldehyde **1** with N_2CHCO_2Et, $ReOCl_3(PPh_3)_2$, and $(EtO)_3P$ gave **2** in 85% yield and >20:1 diastereoselectivity as determined by ^1H NMR spectroscopy. By contrast, when keto aldehyde **1** was subjected to the standard conditions of the Horner–Wadsworth–Emmons reaction ($(EtO)_2P(O)CH_2CO_2Me$, NaH, THF) a mixture of cyclic aldol condensation products was obtained, with the desired product formed in <5% yield.

Table I. Aldehyde olefination with N_2CHCO_2Et, 1 mol% $ReOCl_3(PPh_3)_2$, and $(EtO)_3P$.[a]

Entry	Aldehyde	Enoate	Yield	E:Z[b]	^1H NMR data ($CDCl_3$)
1	PhCHO		90%	>20:1	E: H_α δ 6.45; H_β δ 7.66 Z: H_α δ 5.90; H_β δ 6.95
2	o-C_6H_{11}CHO		91%	9:1	E: H_α δ 5.78; H_β δ 6.95 Z: H_α δ 5.62; H_β δ 6.00
3			95%	11:1	E: H_α δ 5.90; H_β δ 7.06 Z: H_α δ 5.88; H_β δ 6.35
4			95%	11:1	E: H_α δ 6.03; H_β δ 6.76 Z: H_α δ 5.75; H_β δ 8.18
5			90%	7:1	E: H_α δ 6.28; H_β δ 6.78 Z: H_α δ 6.09; H_β δ 6.17
6			85%	5:1	E: H_α δ 6.07; H_β δ 6.97 Z: H_α δ 5.72; H_β δ 6.35
7			65%	5:1	E: H_α δ 5.80; H_β δ 7.30 Z: H_α δ 5.81; H_β δ 6.45
8			90%	14:1	E: H_α δ 5.84; H_β δ 6.96 Z: H_α δ 5.83; H_β δ 6.34
9			70%	3:1	E: H_α δ 6.05; H_β δ 6.88 Z: H_α δ 5.80; H_β δ 6.35
10			85%	20:1	E: H_γ δ 2.50 Z: H_γ δ 2.80

[a]For a general experimental procedure, see ref 10. [b]The diastereomeric ratio of enoates was determined by analysis of ^1H NMR spectra and comparison to published data for (*E*)- and (*Z*)- stereoisomers (see ref 8), or to spectra of authentic (*Z*)-enoates prepared by the method of Still (see refs 7 and 9).



(2)

In order to demonstrate the practicality of the process, we conducted the olefination reaction on hydrocinnamaldehyde with unpurified reagent-grade solvent and starting materials. Employing THF, $(EtO)_3P$, and N_2CHCO_2Et directly as purchased delivered ethyl 5-phenyl-2-pentenoate in 85% yield as a 11:1 trans/cis mixture. Because the co-product $(EtO)_3PO$ is water soluble, none is extracted into the organic layer, greatly simplifying purification of the enoate.[10]

In conclusion, we have developed a process that converts aldehydes to (*E*)–α,β–unsaturated esters under mild, neutral conditions. All of the reagents employed in the procedure, N_2CHCO_2Et, $(EtO)_3P$, and catalytic $ReOCl_3(PPh_3)_2$ are commercially available and may be used without purification in reagent-grade solvent. An additional advantage of this procedure over the well-established Horner-Wadsworth-Emmons or Horner–Wittig protocols is the fact that no phosphonate or phosphorane deprotonation step is required. Moreover, when compared to $MeReO_3$, a procedure which utilizes stoichiometric Ph_3P and consequently affords Ph_3PO, the olefination reaction using $ReOCl_3(PPh_3)_2$ gives $(EtO)_3PO$ which is easily removed upon aqueous work-up.

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References and Footnotes

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8. With the exception of enoates in Entries 5, 6, 8, 10 and that in Eq 2, the enoate products are known: (a) Entry 1, Nonnemacher, A.; Mayer, R.; Plienger, H. *Liebigs Ann. Chem.* **1983**, 2135. (b) Entries 2&3, Vedejs, E.; Fleck, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 5861. (c) Entry 4, Takahashi, H.; Fujiwara, K.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1498. (d) Entry 7, Sundberg, R. J.; Bukowick, P. A.; Holcombe, F. U. *J. Org. Chem.* **1967**, *32*, 2938. (e) Entry 9, Takano, S.; Kurotaki, A.; Takahashi, M.; Ogasawara, K. *Synthesis* **1986**, 403.
9. Authentic *cis*–enoate products of Entries 5, 6, 8, 10 and Eq 2 were prepared using $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ followed by transesterification with NaOEt/EtOH.
10. As a representative procedure: to a 25–mL round-bottom flask equipped with a stirbar was added 20 mg of $ReOCl_3(PPh_3)_2$ (0.024 mmol, 0.01 equiv). The yellow powder was suspended in 5 mL of THF and 400 μL of $(EtO)_3P$ was added (2.4 mmol, 1 equiv). To the mixture was added 320 mg (2.4 mmol) of hydrocinnamaldehyde followed by 275 μL (2.4 mmol) of N_2CHCO_2Et. Gas evolution was observed and the reaction turned brown. Following stirring at 23 °C for 2 hr, the reaction was quenched by pouring onto 50 mL of Et_2O and 50 mL of water. The layers were separated and the aqueous layer was extracted twice with 50 mL of Et_2O. The organic layers were combined and dried over anhydrous Na_2SO_4. The solution was concentrated *in vacuo* to a yellow oil which was purified by chromatography on silica gel (15 cm x 1 cm, R_f = 0.55, 6:1 hexanes/ethyl acetate) to give 470 mg of ethyl (*E*)-5-phenyl-2-pentenoate (95 % yield, 2.3 mmol).

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