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DIRECT SYNTHESIS OF Z-UNSATURATED ESTERS. A USEFUL MODIFICATION OF THE HORNER-EMMONS OLEFINATION.

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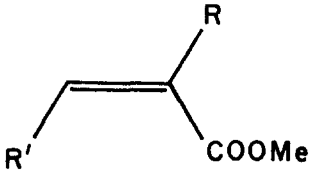
Summary: New phosphonoester reagents and reaction conditions are described which yield Z-alpha,beta-unsaturated esters stereoselectively and in high yield from aliphatic and aromatic aldehydes.

The Horner-Emmons reaction is a classical method for the preparation of unsaturated esters.[1] Like the related reaction of stabilized ylides with aldehydes, the Horner-Emmons olefination shows a preference for formation of the more stable E-olefins. It has been found however that Z selectivity may be obtained under certain conditions where elimination of the initial adduct is faster than adduct equilibration and several efforts have been made to raise the Z selectivity to synthetically useful levels.[2] Recent results with trimethylphosphonopropionate/KOtBu and saturated, alpha-branched aldehydes have shown that at least one class of trisubstituted unsaturated ester (**1**, R = Me, R' = 2^o) may be prepared with high Z selectivity by a Horner-Emmons reaction.[3] With other types of aldehydes the trisubstituted Horner-Emmons is less Z-selective and an effective procedure for the direct synthesis of Z-disubstituted olefinic esters (**1**, R = H) seems unknown for any class of aldehyde. In this Letter, we report a solution to these longstanding problems and show that unsaturated esters **1** (R = H, Me) may be prepared from a variety of aromatic, saturated and unsaturated aliphatic aldehydes with high Z stereoselectivity using electrophilic bis(trifluoroethyl) phosphonoesters (**2**, R = H, Me) and/or strongly dissociated base systems like $KN(TMS)_2$/18-crown-6.



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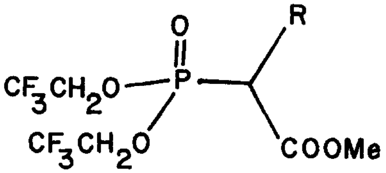
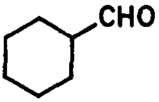
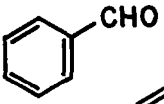
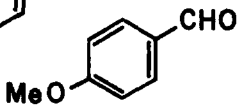
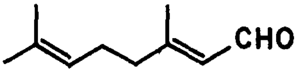


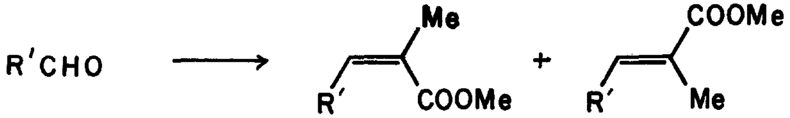
2 R = H, Me

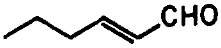
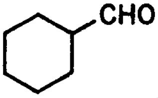
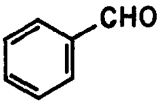
Aldehyde	Conditions	$(TFEO)_2POCH_2COOMe$(**2**) Z:E (Yield)	$(MeO)_2POCH_2COOMe$(**3**) Z:E (Yield)
	A	12:1 (90%)	8:1 (85%)
	B	7:1 (84%)	
	C	6:1 (71%)	
	D		2:5 (70%)
	A	>50:1 (87%)	2:7 (50%)
	C	17:1 (65%)	
	A	4:1 (74%)	12:1 (80%)
	B	4:1 (88%)	
	A	>50:1 (>95%)	1:>50 (>95%)
	B	5:1 (>95%)	
	A	>50:1 (>95%)	
	A	19:1 (76%)	
	A	22:1 (81%)	

Conditions: A - $KN(TMS)_2$/18-crown-6/THF; B - Triton B/THF;
C - K_2CO_3/18-crown-6/$PhCH_3$; D - KOtBu/THF

The trifluoroethylphosphonoester **2** (R=H) was readily prepared from commercially available trimethylphosphonoacetate (**3**) and trifluoroethanol[4], and the reactions summarized above were conducted at -78 deg except for the K_2CO_3 procedure (0 deg).[5] Isomer ratios were measured by integration of well-resolved signals in the 270 MHz ^1H NMR or by capillary VPC. It is clear that except for branched saturated aldehydes where **3** with $KN(TMS)_2$/18-crown-6 is most effective, the fluoro reagent **2** is significantly more selective than **3** for the formation of Z-unsaturated esters. The almost stereoexclusive conversions of benzaldehyde to cis-cinnamate with **2** and to trans-cinnamate with **3** are particularly dramatic and we believe that the former represents the only known direct route from aromatic aldehydes to pure Z disubstituted cinnamic esters. The transformations of unsaturated aldehyes to E,Z-dienoates and E,E,Z-trienoates are also noteworthy.

Among the bases examined, KN(TMS)$_2$/18-crown-6 was found to be particularly effective and allowed highly stereoselective formation of Z unsaturated esters with every aldehyde examined. The K_2CO_3 procedure is also effective in many instances and has the virtue of operating under mild, weakly basic conditions. As pointed out by Seyden-Penne[2] the use of base systems having minimally complexing counterions is important in facilitating elimination and thus maintaining high Z stereoselection. All of the effective bases found in our study seem to meet this requirement and we expect that other conditions[6] can be devised accordingly and used with reagents like **2** and **3** for efficient Z olefination.



Aldehyde	Conditions	(TFEO)$_2$POCHMeCOOMe(**2**) Z:E (Yield)	(MeO)$_2$POCHMeCOOMe Z:E (Yield)
	A	46:1 (88%)	10:1 (74%)
	A	>50:1 (79%)	3:2 (59%)
	A	>50:1 (80%)	12:1 (61%)
	A	30:1 (>95%)	1:22 (83%)

The substituted trifluoroethylphosphonoester **2** (R = Me) with the optimal base system KN(TMS)$_2$/18-crown-6 is also quite effective at producing Z trisubstituted unsaturated esters as summarized in the table above. The generally improved Z stereoselection with added substitution is typical of Horner-Emmons olefinations and may reflect the enhanced stability of the product and facilitation of the elimination or may simply result from the absence of an acidic proton in the intermediate adduct.

Finally we note that while our study has concentrated on methyl ester preparations, the Z Horner-Emmons is relatively insensitive to changes in carboxylate alkoxy substitution and only slightly diminished Z:E ratios were obtained with cyclohexyl esters of **3** and KN(TMS)$_2$/18-crown-6.

Notes and References:

1. Reviews: J. Boutagy and R. Thomas, Chem. Rev., **74**, 87 (1974); W.S. Wadsworth, Org. React., **25**, 73 (1977).

2. T.H. Kinstel and B.Y. Mandanas, Chem. Commun., 1699 (1968); G. Lefebvre and J. Seyden-Penne, ibid., 1308 (1970); B. Deschamps, G. Lefebvre and J. Seyden-Penne, Tetrahedron, **28**, 4209 (1972); A. Redjal and J. Seyden-Penne, Tetrahedron Lett., 1733 (1974); B. Deschamps, J.P. Lampin, F. Mathey and J. Seyden-Penne, ibid., 1137 (1977); E. Breuer and D.M. Bannet, ibid., 1141 (1977).

3. H. Nagaoka and Y. Kishi, Tetrahedron, **37**, 3873 (1981); G. Schmid, T. Fukuyama, K. Akasaka and Y. Kishi, J. Am. Chem. Soc., **101**, 259 (1979).

4. **Preparation of 2:** Trimethyl phosphonoacetate (18.2 gm, 0.1 mole) was cooled to 0 deg C and stirred while PCl_5 (52.7 gm, 0.25 mole) was added. An exothermic reaction took place and MeCl was evolved. The mixture was stirred at 25 deg for 1 hr and then at 75 deg for 3 hrs. Distillation removed the byproduct $POCl_3$ (bp 40 deg, 20 mm) and excess PCl_5 (0.1 mm), and yielded ca 16 gm Cl_2POCH_2COOMe (bp 78-80 deg, 0.1 mm). This procedure was taken from: N.D. Bodnarchuk, V.V. Malovik and G.I. Derkach, Zh. Obshch. Khim., **40**, 1210 (1970). $Cl_2POCHMeCOOMe$ (bp 71-73 deg, 0.05 mm) was prepared similarly.

The dichloride above was dissolved in 100 ml benzene and treated at 0 deg with a solution of trifluoroethanol (16.7 gm, 0.167 mole) and iPr_2NEt (21.7 gm, 0.167 mole) in 150 ml benzene. After stirring for 1 hr at 25 deg, the solvent was evaporated and the residue was filtered through a 4 inch plug of silica gel with 7:3 ethyl acetate:petroleum ether to remove contaminating $(MeO)(TFEO)POCH_2COOMe$ (ca 5%) and yielded **2** (R=H) (ca 13 gm, 40%). $(TFEO)_2POCHMeCOOMe$ was prepared similarly in 40% overall yield.

5. **Typical Z Horner-Emmons Procedure - $KN(TMS)_2$:** A solution of **2** (1 mmol), 18-crown-6 (5 mmol)(recrystallized CH_3CN complex - J. Org. Chem., **39**, 2445 (1974)) in 20 ml anhydrous THF was cooled to -78 deg under nitrogen and treated with 1 mmol of $KN(TMS)_2$ (0.6M in toluene, Callery Chemical Company). The aldehyde (1 mmol) was then added and the resulting mixture was stirred for 30 min at -78 deg. Saturated NH_4Cl was added and the product was extracted into ether (3X). The ether extracts were dried (Na_2SO_4) and evaporated, and the product was isolated by flash chromatography.

K_2CO_3: Finely ground K_2CO_3 (6 mmol) and 18-crown-6/CH_3CN (12 mmol) in 10 ml toluene were stirred for 1 hr at 25 deg and then cooled to -20 deg. The aldehyde (1 mmol) and **2** (1 mmol) were added and the mixture was stirred and allowed to warm to 0 deg. After stirring for 30 min at 0 deg, the reaction was worked up and the product isolated as above.

6. Other bases including NaH/DME, Cs_2CO_3/DMF and $KN(TMS)_2$ without added 18-crown-6 were significantly less effective. Other metal chelating agents dicyclohexyl-18-crown-6, HMPA and cryptand [2.2.2] were also briefly examined and found to be relatively ineffective at promoting Z olefination. Crown ethers have been used previously to catalyze Horner-Emmons-like olefinations: R. Baker and R.J. Sims, Synthesis, 117 (1981).

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