A new and convenient one-pot synthesis of α,β-unsaturated trifluoromethyl ketones

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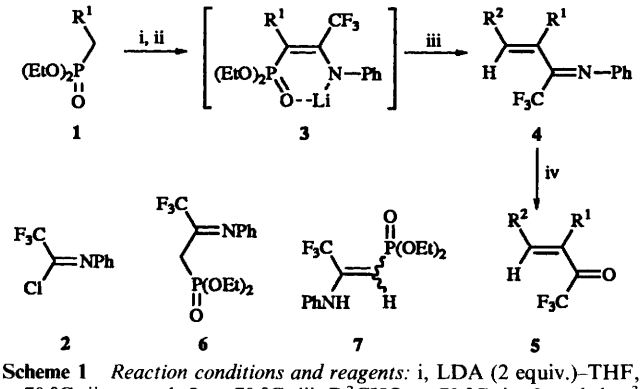
Alkylphosphonates react with *N*-phenyltrifluoroacetimidoyl chloride in the presence of lithium diisopropylamide to afford mixtures which when treated with aldehydes and subjected to acid hydrolysis afford α,β-unsaturated trifluoromethyl ketones.

α,β-Unsaturated trifluoromethyl ketones have potential as versatile synthetic precursors in the preparation of trifluoromethyl-containing compounds, themselves of interest in view of their unique biological properties.[1] However, their synthesis is not simple. Thus, before $CH_2{=}CHCH_3(CF_3)OH$ can be oxidized with Dess–Martin's reagent,[2] CF_3CHO and unstable fluorinated organometallic reagents[4] are involved in its preparation. Attempted aldol condensation of trifluoroacetone with aldehydes provides only modest yields of unsaturated trifluoromethyl ketones with aryl or unsaturated aldehydes,[5] and the addition of organocuprate reagents to alkynyl trifluoromethyl ketones affords both 1,2- and 1,4-addition adducts.[6] Linderman and co-workers have recently reported a three-step route to β-alkyl-α,β-unsaturated trifluoromethyl ketones,[7] but this has limitations because of its use of Dess–Martin's reagent, inaccessible starting materials and multistep manipulation. Herein we report a simple and general one-pot synthesis of α,β-unsaturated trifluoromethyl ketones from diethyl alkylphosphonates, *N*-phenyltrifluoroacetimidoyl chloride and aldehydes.



Scheme 1 *Reaction conditions and reagents:* i, LDA (2 equiv.)–THF, −70 °C; ii, compd. **2**, −70 °C; iii, R^2CHO, −70 °C; iv, 2 mol dm^{-3} HCl, room temp.

Trifluoroacetimidoyl chlorides have been reported to react with Grignard reagents to afford trifluoromethyl ketimines.[8] When we allowed *N*-phenyltrifluoroacetimidoyl chloride **2** to react at −70 °C with diethoxyphosphorylmethyllithium, generated *in situ* from equimolar proportions of diethyl methylphosphonate and butyllithium, quenching of the reaction mixture and work-up gave a mixture of the imino phosphonate **6** and enamine **7** (72:28 by ^1H NMR). When treated with butyllithium **6** and **7** gave rise to the same anion **3** (R^1 = H), which underwent Horner–Emmons olefination with propionaldehyde to afford the 1-aza-1,3-diene **4** (R^1 = H, R^2 = Et). This was assigned an *E*-configuration on the basis of the vinylic H,H coupling constant (*J* 17.4 Hz). This reaction constitutes a one-pot synthesis of an α,β-unsaturated trifluoromethyl ketone in which (see Scheme 1) the anion **3** is formed by initial treatment of the alkylphosphonate **1** at −70 °C with lithium diisopropylamide (2 equiv.) and then with *N*-phenyltrifluoroacetimidoyl chloride **2**. Subsequent reaction of the anion **3** with aldehydes followed by acid hydrolysis provided good yields of the expected products **5**. Butyllithium cannot be used as the base since, in excess, it reacts with the imidoyl chloride **2** more rapidly than diethoxyphosphorylmethyllithium.

As demonstrated in Table 1, a variety of aldehydes (aliphatic, aromatic and unsaturated) may be converted into α,β-unsaturated trifluoromethyl ketones. All the compounds showed a singlet in their ^{19}F NMR spectra and were identified as *E*-isomers from vinylic H,H or Me,H coupling constants. The stereochemistry is probably the result of the bulky *N*-phenyltrifluoroacetimidoyl group which favours the less hindered *threo* diastereoisomers of the oxyanion intermediates in the course of the Horner–Emmons reaction, yielding *E*-olefins upon *syn* elimination.

Although 2-trifluoromethyl-2-(methylimino)ethyl phosphonate, which is similar to the intermediate **6**, has been utilized by Ishihara to prepare α,β-unsaturated trifluoromethyl ketones,[9] the approach is inconvenient since it requires an earlier four-step preparation of the imino phosphonate from pentafluoropropionic acid. It is also uneconomical since not easily available sources of fluorine and phosphorus are wasted. Our methodology, which first described the reaction of alkylphosphonate with imidoyl chloride, is both simpler and more convenient because it is a one-pot operation starting from readily obtainable materials.[10] Since a variety of substituted methyl phosphonates (R^1 = functional group) are available by Arbuzov and Michaelis-Becker reactions,[11] the present method is a general one, providing α,β-disubstituted α,β-unsaturated trifluoromethyl ketones, not preparable by earlier methods. It is significant that our procedure is stereospecific providing *E*-isomers exclusively.

Experimental

Typical procedure. To a stirred solution of diisopropylamine (10 mmol, 1.54 cm^3) in dry THF (20 cm^3) was added dropwise butyllithium (1.6 mol dm^{-3} in hexane; 10 mmol, 6.25 cm^3) at 0 °C. After 10 min, the solution was cooled to −70 °C and diethyl methylphosphonate (5 mmol, 0.75 cm^3) was added to it. After the mixture had been stirred for 30 min at the same temperature, *N*-phenyltrifluoroacetimidoyl chloride (5 mmol, 0.80 cm^3) was gradually added to it and stirring was continued at −70 °C for 1 h; freshly distilled *p*-tolualdehyde (5 mmol, 0.59 cm^3) was then added dropwise. The resulting mixture was warmed to room temperature over 2 h and then stirred overnight. After addition of 2 mol dm^{-3} aq. HCl (10 cm^3) to the mixture it was stirred at room temperature for 4 h and then

Table 1 α,β-Unsaturated trifluoromethyl ketones

	R^1	R^2	Yield (%)		R^1	R^2	Yield (%)
5a	H	Bu	48	**5f**	H	*p*-$NO_2C_6H_4$	59
5b	H	Pentyl	52	**5g**	H	PhCH=CH	60
5c	H	Ph	59	**5h**	Me	*p*-MeC_6H_4	54
5d	H	*p*-MeC_6H_4	63	**5i**	Me	*p*-FC_6H_4	58
5e	H	*p*-FC_6H_4	72	**5j**	Me	PhCH=CH	60

extracted with diethyl ether (3 × 20 cm^3). The combined extracts were washed successively with 5% aq. $NaHCO_3$ and brine until pH 6 was reached, after which they were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel using light petroleum as eluent to give compound **5d** (0.67 g, 63%) as a pale yellow oil (Found: C, 61.6; H, 4.3. $C_{11}H_9F_3O$ requires C, 61.7; H, 4.2%); ν_{max}(neat)/cm^{-1} 1720 (C=O) and 1620 (C=C); δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.86 (1 H, d, *J* 15.8, =CHPh), 7.54 (2 H, d, *J* 8.2, Ph), 7.25 (2 H, d, *J* 8.0, Ph), 6.88 (1 H, d, *J* 15.8, =CHCOCF$_3$) and 2.41 (3 H, s, Me); δ_F(60 MHz; CCl_4; $CFCl_3$) −76.7 (s); *m/z* 214 (M^+, 30%), 199 (71), 149 (45), 145 (100), 117 (53), 115 (86), 91 (55) and 57 (35).

Acknowledgements

We gratefully acknowledge the financial support of the National Natural Science Foundation of China.

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Paper 5/00354G
Received 20*th January* 1995
Accepted 26*th January* 1995