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A Mild and Stereoselective Synthesis Of β-Phosphonylacrylates

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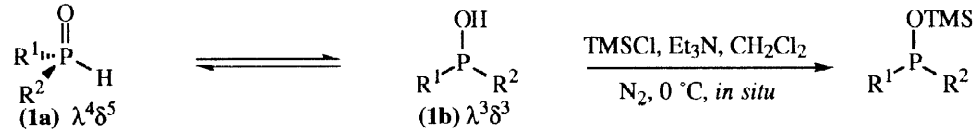
Abstract: The addition of trimethylsilyloxy phosphorus (III) derivatives, generated *in situ*, to α-haloacrylates and acrylonitriles at room temperature provides a mild, general and stereoselective route to β-phosphonoacrylates.

Although recognised as valuable synthetic building blocks, β-phosphonoacrylates have seen limited use due to the lack of easy and stereoselective synthetic access.[1,2] In particular, no stereoselective route to β-phosphonoacrylates is reported in the literature, except for ketovinylphosphonates.[3] We have recently initiated a programme of study into the use of vinylphosphonates and in particular β-phosphonoacrylates and here report a very convenient and stereoselective route to this useful class of compounds.

Silyl esters of phosphorous acids react with a range of functional groups under relatively mild conditions[4] and are now commonly accepted as useful reagent for the synthesis of organophosphorus compounds. Although these silylated phosphites are clearly chemically very useful, the difficulty in their preparation and their hydrolytic sensitivity, prompted us to introduce a method for their *in situ* formation prior to reaction with electrophilic species. Our subsequent investigations showed that the pattern of reactivity of silylated esters towards imines can be rationalised in terms of pre-bonding of the silyl group to the lone pair of imine nitrogen.[5] Here we report on the unusually mild reactions of these silylated phosphites and phosphonites with α-haloacrylates to afford good yields of *trans* β-phosphonylacrylate regioselectively.

Under forcing thermal conditions, trialkylphosphites undergo addition to α-haloacrylates to afford β-phosphonylacrylates.[6] The by-product of the reaction is the corresponding alkylhalide and therefore the mechanism of the reaction is thought to be similar to that of the Arbuzov reaction, initiated by Michael addition to the acrylate. Dialkyl phosphites do not undergo any addition. This is expected since the tautomeric equilibrium between the $\lambda^4\delta^5$ form **(1a)** and the nucleophilic $\lambda^3\delta^3$ form **(1b)** of the dialkyl phosphites lies strongly on the side of the former (Scheme 1).



Scheme 1

We reasoned that since the silylation locks the molecule in its $\lambda^3\delta^3$ tautomeric form, then addition to α,β-unsaturated systems would be encouraged. Indeed, when diethyl phosphite is transformed to diethyl trimethylsilyl phosphite (TMSCl 1.0 equivalent, Et_3N 1.0 equivalent, CH_2Cl_2, 0° C) and reacted under mild conditions with α-chloroacrylonitrile (1.0 equivalent, 5 hours, room temp), a 76% yield of addition product is obtained as a single regioisomer (δ_p = 10.2 ppm). Based on the size of the proton coupling (J_{HH} = 18 Hz) in the nmr, this was assigned the *trans*-isomer. Furthermore, nmr analysis on the crude reaction mixture, showed it to contain no other major products.[5] Our further investigation has demonstrated that the reaction is general for a range of phosphorus substituents, R^1 and R^2, and strongly electron donating R^3 groups (Table).[7] In all of the cases investigated, little or no Z-isomer was detected in the pre-work up reaction mixtures.

Lower yields of addition products are obtained when R^3 is a weakly electron withdrawing group and also, the yields of addition product fall to 5-10% if there are further substituents at the β-position of the acrylate. In a competition experiment, similar rates of reaction were recorded for addition to α-bromo and α-chloroacrylonitrile and indeed there is little difference between the yields form either series of acrylates.

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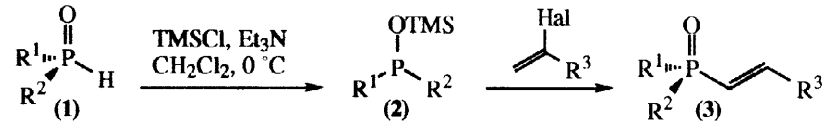
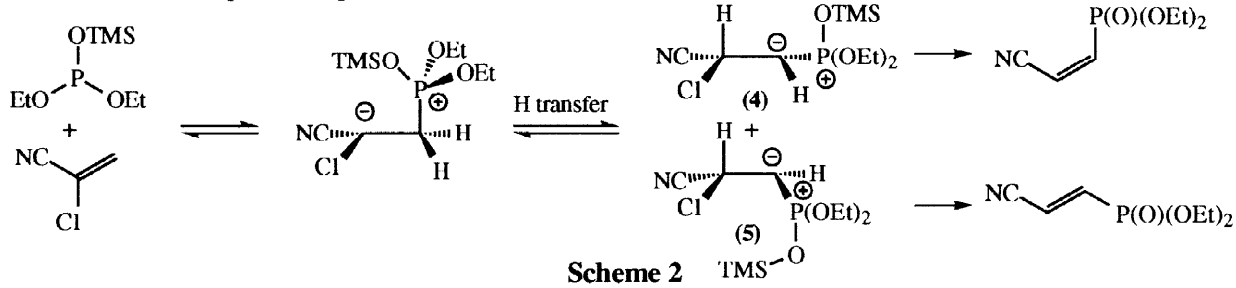


R^1	R^2	R^3	Hal	Yield (%)	δ_P (ppm)	R^1	R^2	R^3	Hal	Yield (%)	δ_P (ppm)
EtO	EtO	CN	Cl	76	10.2	Ph	EtO	CN	Br	65	25.7
MeO	MeO	CN	Br	44	14.6	Ph	EtO	CN	Cl	66	25.7
MeO	MeO	CN	Cl	66	14.6	Ph	EtO	COMe	Br	31	29.2
MeO	MeO	CO_2Me	Br	69	18.0	Ph	EtO	CO_2Me	Br	67	28.3
Ph	Ph	CN	Br	57	21.8	(-)-Menthol	EtO	CN	Cl	55	11.1;10.4
Ph	Ph	CN	Cl	62	21.8	(-)-Menthol	EtO	CN	Br	50	11.1;10.4
Ph	Ph	CO_2Me	Br	51	22.9	(-)-Menthol	EtO	CO_2Me	Br	53	14.3;13.7

Table

As can be seen in the table, the yields of the reaction are generally moderate to good. Not only does the reaction proceeds under very mild conditions, but also, in contrast to two previously reported thermal reactions, the product is exclusively the *trans* isomer.[6,8]

The mechanism of the reaction between diethyltrimethylsilylphophite and α-chloroacrylonitrile is outlined below (Scheme 2).[8] The reaction proceeds via a nucleophilic addition followed by a proton transfer and elimination of TMSCl, to afford the neutral vinylphosphonate. The *trans* selectivity presumably arises because in intermediate (**5**), TMS and halide group are close. It can be argued that either this intermediate is preferred because this proximity allows non-bonding interactions between the groups, or that loss of TMSCl is facilitated in (**5**) because of a concerted pathway concurrently leading to the formation of a P=O and C=C bonds. This rationale is consistent with that proposed to explain the reactivity of silylated phosphites towards imines.[5] An alternative explanation for preference of formation of (**5**) is that this intermediate contains two opposing dipoles whereas in (**4**) the dipoles are parallel.



Scheme 2

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7. *Typical procedure: Addition of diethyl phosphite to α-chloroacrylonitrile.* Chlorotrimethylsilane (0.35 ml, 1.1 eq) was added to a stirred solution of diethyl phosphite (0.35 g, 2.53 mmol) and triethylamine (0.39 ml, 1.1 eq) in dichloromethane (50 ml) maintaineed at 0 °C under an argon atmosphere. α-Chloroacrylonitrile (2.53 mmol) was added after 15 min and the solution was brought to room temperature. After 6 hours, the reaction mixture was poured into water (50 ml) and organic products were extracted with dichloromethane (2 x 75 ml). Organic extracts were dried and evaporated. The residue was distilled in a Kugelröhr (130 °C/0.5 mmHg) to afford a colourless liquid (Found: C, 44.1; H, 6.2; N, 7.0. $C_7H_{12}NO_3P$ requires C, 44.4; H, 6.4; N, 7.4%), ν_{max} 2230 (C≡N), 1603 (C=C), 1258 (P=O) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.33 (6H, dt, *J* 7 Hz, J_P 0.5 Hz, CH_3), 4.13 (4H, ddq, J_P 8Hz, 7 Hz, 1 Hz, CH_2O), 6.30 (1H, dd, *J* 18 Hz, J_P 21 Hz, 1-H), 6.72 (dd, *J* 18 Hz, J_P 15 Hz, 2-H); $\delta_P\{H\}$ (36 MHz, $CDCl_3$) 10.2 ppm; *m/z* (EI) 188 [$(M-H)^+$, 2], 134 [$(M-OEt)^+$, 100].
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