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LETTERS

Acceleration of Nucleophilic Addition to Vinylphosphonates and Vinyl Phosphine Oxides by Chlorotrimethylsilane

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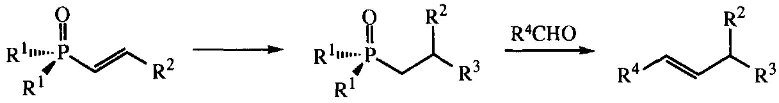
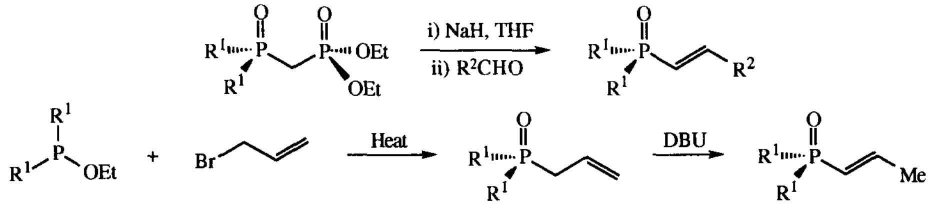
Abstract: Chlorotrimethylsilane significantly accelerates the conjugate addition of alkyl cuprates to vinylphosphonates. © 1998 Elsevier Science Ltd. All rights reserved.

Conjugate addition to α,β-unsaturated phosphonyls is an extremely valuable reaction providing a convenient route to highly branched phosphonates and phosphine oxides which can be utilised in Horner-Emmons reaction (Scheme 1).



Scheme 1

Although the conjugate addition to α,β-unsaturated carbonyls and carboxyls is well explored,[1] there is very little information in the literature regarding conjugate addition to α,β-unsaturated phosphonyls. It has been previously reported that conjugate addition to α,β-unsaturated phosphonyls is inefficient when the β position is substituted.[2] Since chlorotrimethylsilane (TMSCl) has been shown to improve the performances of a variety of catalytic and stoichiometric organometallic reagents in conjugate additions to α,β-unsaturated carbonyl and carboxyls,[3,4] we decided to investigate the influence of this additive on the conjugate addition to α,β-unsaturated phosphonyls with a view to improving the efficiency and hence the synthetic utility of the reaction.

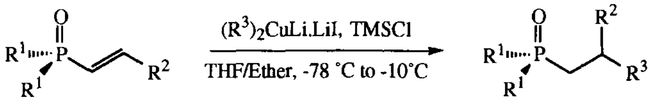


Scheme 2

PII: S0040-4039(98)01612-8

Vinylphosphonates were prepared either by an Arbuzov reaction of the corresponding phosphite and allyl bromide followed by migration of the double bond into conjugation; or from a Horner-Emmons type reaction as shown above (Scheme 2).[5] Cuprate reagents were prepared from the corresponding alkyllithium or Grignard reagent according to standard procedure at -45°C to -30°C. TMSCl (4 equiv.) was added to the cuprate reagent at -78 °C prior to addition of vinylphosphonate. After 1 to 2 hours, the reaction was warmed to -10 °C and quenched. NMR analysis of reaction mixtures indicated a clean reaction but at least four equivalents of cuprate was neccessary for a complete conversion.

The results are summarised below (Table).[6] The yield of typical reactions with no added TMSCl were below 10%. With the addition of TMSCl, the yields of crude reaction mixtures are essentially quantitative (^{31}P NMR), although with diethyl phosphonates, water solubility and difficulty with tlc detection results in lower yields of chromatographically isolated products. With bulky R^2 substituents the reaction was much slower and required a larger excess of cuprate (6-10 equiv.) for completion. For instance, with R^2 as isopropyl, only 20% completion was observed with 4 equiv. of cuprate/TMSCl reagent whereas when the R^2 substituent was phenyl, no addition product was seen with the same excess of the reagent. As expected, an equal mixture of diastereomers are obtained in the reaction of ^{sec}butyl nucleophile.



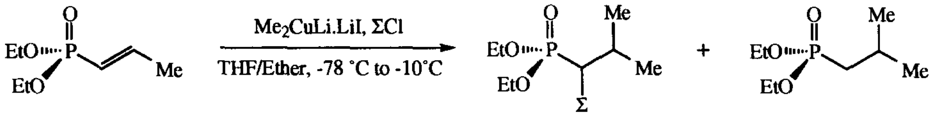
R^1	R^2	R^3	Yield (%)	R^1	R^2	R^3	Yield (%)
EtO	Me	Me	26[a]	Ph	Me	Me	63
EtO	Me	^{n}Bu	34	Ph	Me	^{n}Bu	71
EtO	Me	^{sec}Bu	40	Ph	Me	$HC{=}CH_2$	41
EtO	Me	$HC{=}CH_2$	30[a]	Ph	Me	Ph	52
EtO	Me	Ph	34	Ph	^{n}Pr	Me	42
EtO	^{n}Pr	Me	29	Ph	^{n}Pr	^{n}Bu	72
EtO	^{n}Pr	^{n}Bu	16				

[a] isolated as the α silylated compound.

Table

We used phosphorus NMR to study the reaction of dimethylcuprate with diethyl prop-1-enylphosphonate in the absence and presence of TMSCl. Our study showed that the rate of nucleophilic addition was at least ten times faster at -78 °C in the presence of TMSCl than in the absence of TMSCl. For instance, a typical reaction between cuprate and vinylphosphonate in the presence of TMSCl was complete in half an hour at -78 °C whereas only traces of the product was seen after three hours in the absence of this reagent. Other chlorosilanes, for instance chlorodimethylphenylsilane, also accelerate the rate of addition. On the other hand, addition of lithium cation (in the form of LiBr) to the reaction mixture did not cause rate acceleration confirming that the effect arises from presence of silylating agents.

Interestingly, a common by-product of the additions to diethyl vinyl phosphonate was the corresponding α-silylated phosphonates (Scheme 3). They are detected in the ^{31}P NMR of most crude reaction mixtures as a signal at nearly 4 ppm lower field than the non-silylated product. However, these were produced only in significant quantities (>10%) when the β position substituent is not very sterically demanding (e.g. $R^2 = R^3 =$ Me). Less silylation was seen when bulkier dimethylphenylchlorosilane was used even though the rate acceleration was of the same magnitude as that observed for TMSCl. Also there was no silylation with diphenylphosphine oxides, presumably because of the steric bulk of the phenyl groups. The TMS incorporated phosphonates are easily separated by coloumn chromatography and are always obtained as single diasteromeric compounds based on a sharp signal in ^{31}P NMR, presumably with an *anti* relationship between the silyl and R^3 group. This observation is consistant with the suggestion that α silylation is a secondary process and occurs subsequent to the nucleophilic addition. In other words, rate enhancement must have occurred because there has been a fundamental change in the nature of nucleophilic cuprate reagent in the presence of TMSCl, as proposed by Lipshutz.[4]



$\Sigma = Me_3Si$ 2.75 : 1.0
$\Sigma = MePh_2Si$ 0.15 : 1.0

Scheme 3

In summary, we have demonstrated that addition of chlorotrimethylsilane significantly enhances the rate of conjugate nucleophilic addition of alkylcuprates to vinylphosphonates and hence results in improved yields of the addition product.

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REFERENCES

1. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, 1992. Lee, V. J. in *Comprehensive Organic Synthesis*, Ed by Trost, B. M. and Fleming, I, Pergamon, Oxford, 1991, Vol 4. Schmaltz, H.-G. in *Comprehensive Organic Synthesis*, Ed by Trost, B. M. and Fleming, I, Pergamon, Oxford, 1991, Vol 4. For a review on asymmetric conjugate additions see: Rossiter, B. E. Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
2. Baldwin, I. C.; Beckett, R. P.; Williams, J. M. J. *Synthesis* **1996**, 34-36.
3. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368-3370. Reetz, M. T.; Kindler, A. *J. Chem. Soc., Chem. Commun.* **1994**, 2509-2510. Wipf, P.; Venkatraman, S.; *J. Org. Chem.* **1993**, *58*, 3455-3459.

4. For the role of TMSCl in activation of C=O see: Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087-7090. Bertz, S. H.; Miao, G., Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023-11024. For the role of TMSCl in d-π* stablisation between copper and an enone see: Corey, E. J.; Boaz N. W. *Tetrahedron Lett.* **1985**, *26*, 6015-6018. For a confluent postulate see: Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283-9284.
5. Kiddle, J. J.; Babler, J. H. *J. Org. Chem.* **1993**, *58*, 3572-3574. Savignac, P.; Teulade, M. P.; Aboujaoude, E. E.; Collignon, N. *Synth. Commun.* **1987**, *17*, 1559-1569. For a review see: Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333-349.
6. All compounds were fully characterised. Typical reaction conditions and spectroscopic data are as follows:

   Diphenyl 2-methylpropyl phosphine oxide: MeLi (1.6 M solution in Et_2O, 4.0 mL, 6.6 mmol, 8 eq.) was added to a stirred mixture of CuI (628 mg, 3.3 mmol, 4.0 eq) in dry Et_2O (8 mL) under an Argon atmosphere at -45 °C and the resulting solution was warmed to -35 °C over 10 minutes. The solution was cooled to -78° C and TMSCl (0.4 mL, 3.3 mmol, 4.0 eq.) followed by diphenyl 2-propenyl phosphine oxide (200 mg, 0.8 mmol) in dry THF (8 mL) were added in succession. The stirred reaction mixture was maintained at -78 °C for 1 hour and then warmed to -10° C over half an hour. Saturated ammonium chloride (5.0 mL) was added and the resulting mixture was filtered through florisil with EtOAc (100 mL) as eluent. The filtrate was washed with brine (2 x 25 mL) and dried (Na_2SO_4). Evaporation of solvent followed by chromatography on silica (Merck 9358) using ethyl acetate/petroleum ether (9:1 v/v) as eluent afforded the title compound as a white crystals, m.p. 131-132 °C (Lit. 132.5-134 °C)[7], $\nu_{max.}$ (film) 2872, 1467 cm^{-1}; δ_H (360 MHz, $CDCl_3$) 0.97 [6H, d, J_H 7 Hz, $(CH_3)_2C$], 2.14-2.20 (3H, m, CH and CH_2), 7.44-7.48 (6H, m, aromatic H), 7.71-7.76 (4H, m, aromatic H) ppm; $\delta_P\{H\}$ (145 MHz, $CDCl_3$) 31.5 ppm; δ_C (90.6 MHz, $CDCl_3$) 23.7 [dd, J_P 4 Hz, $(CH_3)_2\underline{C}H$], 24.7 [dq, J_P 9 Hz, $(\underline{C}H_3)_2C$], 38.8 (dt, J_P 71 Hz, CH_2), 128.70 (dd, J_P 11 Hz, aromatic CH), 130.6 (dd, J_P 9 Hz, aromatic CH), 131.5 (dd, J_P 2 Hz, aromatic CH), 134.0 (d, J_P 97 Hz, aromatic C) ppm; *m/z* 258 (M^+, 44), 215 (100); HRMS Calcd for $C_{16}H_{19}OP$ (M^+) 258.1174, found 258.1165.
7. Morrison, D. C. *J. Am. Chem. Soc.* **1950**, *72*, 4820-4821. See also: Buss, A. D.; Warren, S. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2307-2325.