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An Efficient and Practical Synthesis of Diphenyl Cyanomethylenephosphonate: Applications to the Stereoselective Synthesis of *cis*-α,β-Unsaturated Nitriles

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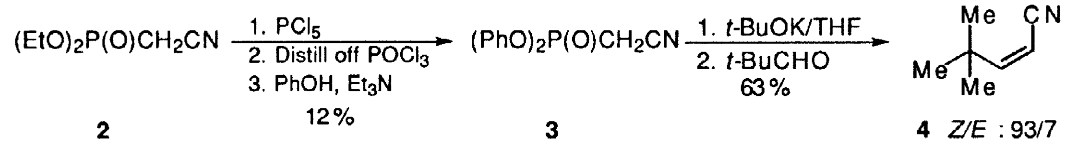
Abstract: Diphenyl cyanomethylenephosphonate $(PhO)_2POCH_2CN$ was prepared as a stable crystalline solid in high yield in a single step from acetonitrile, LDA, and $(PhO)_2P(O)Cl$. The potassium ylide generated from this compound afforded α,β-unsaturated nitriles upon reacting with aldehydes, with a stereoselectivity of 64-100% favoring the *cis*-isomer.

During the course of our study toward finding a practical synthetic process for a pharmaceutical intermediate, the need arose for a *cis*-selective method to install an α,β-unsaturated nitrile moiety. It appeared that the only literature precedents for the selective synthesis of *cis*-1-alkenenitriles from aldehydes are those based on Peterson olefination protocol.[1-6] However, the high cost of Me_3SiCH_2CN or $Me_3SiClCHCN$ and the incompatibility of the very basic anion with sensitive substrates prompted us to search for an alternative.

In light of the recent finding by Ando that a modified Horner-Emmons Wadsworth reagent, $(EtO)_2P(O)CH_2CO_2Et$ (**1**),[7] afforded α,β-unsaturated esters with good *cis*-selectivity upon reacting with aldehydes, we prepared compound **3** in a manner similar to that used for the preparation of **1** (Scheme 1). Indeed, when **6** was sequentially treated with *t*-BuOK and pivaldehyde, compound **4** was obtained in 63% yield with 93% *Z*-selectivity.



Scheme 1

Encouraged by this favorable result, we explored a practical synthesis of **3** in order to address the concerns associated with the preparation of **3** including low overall yield, the use of

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water sensitive solid PCl_5, the necessity to remove corrosive $POCl_3$ by distillation, and the need for a chromatographic purification. Attempts to effect an Arbuzov-type reaction between bromoacetonitrile and diphenylmethyl phosphite resulted in low yield of **3** along with secondary by-product diphenyl methylphosphonate (eqn 1). Nucleophilic substitution of haloacetonitrile with diphenyl phosphite in the presence of a base failed under a variety of conditions due to the propensity of the former being reduced (eqn 1, 2).

$$\mathrm{BrCH_2CN} + \mathrm{(PhO)_2POMe} \xrightarrow{\Delta} \mathrm{(PhO)_2P(O)Me} + \mathrm{MeBr} + \mathbf{3} \qquad (1)$$

$$\mathrm{XCH_2CN} + \mathrm{(PhO)_2P(O)H} \xrightarrow{\text{base}} \mathrm{MeCN} \qquad \mathrm{X = Br, I} \qquad (2)$$

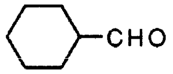
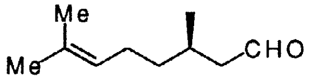
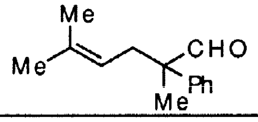
Eventually we found that when the readily available diphenylchlorophosphate was treated with two equivalents of acetonitrile anion[8] followed by an acidic work up, compound **3** was obtained in 69 % isolated yield as a stable solid (eqn 3). It is noteworthy that when pivaldehyde was added directly to the phosphorylation reaction mixture, the putative lithium ylide was found to give 1-alkenyl nitrile with a *Z*/*E* ratio of only 60:40. The effect of countercation is quite pronounced, as in the case of pivaldehyde, the *Z*/*E* ratio deteriorated from 93:7 to 85:15 and 60:40 when *t*-BuOK was replaced with NaH and $LiN(SiMe_3)_2$, respectively.

$$2\ \mathrm{CH_3CN} \xrightarrow[\substack{\text{2. } \mathrm{(PhO)_2P(O)Cl} \\ \text{3. HCl}}]{\text{1. LDA, 2 equiv}} \underset{\mathbf{3}\ 69\%}{\mathrm{(PhO)_2P(O)CH_2CN}} \qquad (3)$$

The scope of this new olefination reagent was briefly explored with a representative array of aldehydes and results are summarized in Table I. As a general trend, bulkier aldehydes offer higher *Z*/*E* selectivity. In the case of entry 7, no *E*-isomer was detectable in the crude reaction mixture by 500MHz ^{1}H NMR.

In summary, we have developed a convenient and practical approach for the selective synthesis of *cis*-alkenyl nitriles. The reagent can be prepared in a highly efficient manner from readily available starting materials. It is worth emphasizing that due to practical concerns, modifiers such as crown ethers which are known to enhance *cis*-selectivity[9] were not employed in these cases. Results related to the effects of solvents, additives, electron density and steric bulk of the aryl ring on the stereoselectivity of the olefination will be reported in due course.

Table I. Cynaomethylenation of Aldehydes

Entry	Aldehyde	Yield, Z-isomer	Yield, *E*-isomer	*Z*/*E* *ratio*
1	$PhCH_2CH_2CHO$	71%	27%	72:28
2	*n*-$C_7H_{15}CHO$	78%	22%	78:22
3		59%	34%	64:36
4	*t*-BuCHO	63%	5%	93:7
5		66%	15%	81:19
6	PhCHO	71%	25%	75:25
7		70%	0%	100:0

EXPERIMENTAL

Diphenyl cyanomethylenephosphonate (3). To a solution of anhydrous MeCN (7.6 mL, 6 g, 146 mmol) in 60 mL of THF was added dropwise a solution of $LiNPr^i_2$ in a mixture of THF, heptane and ethylbenzene (2.0 M, 146 mmol, 73.2 mL, Aldrich) at -78 °C. The resulting light orange slurry was allowed to warm to ambient temperature and then cooled down to -78 °C. A solution of diphenyl chlorophosphate (15.2 mL, 73.2 mmol) in 60 mL of THF was added dropwise. The reaction was complete within 30 min as monitored by ^1H NMR, after which the mixture became homogeneous. The solution was quenched with 300 mL of ice cold 1 N HCl, and extracted with 300 mL of CH_2Cl_2. The methylene chloride layer was then washed successively with 300 mL of 1 N HCl, 300 mL of ice water, and 200 mL of 12.5 % NaCl, dried over $MgSO_4$, and concentrated to afford 19.41 g of oil which was crystallized from heptane/toluene (1:1) to give 13.72 g (68.6 %) of the title compound as a beige granular solid: ^1H NMR ($CDCl_3$): δ 3.19 (d, $J_{H,P}$ = 21 Hz, 2H, $(PhO)_2P(O)C\underline{H_2}CN$), 7.21-7.37 (m, 10H, Ar-$\underline{H}$); ^{13}C NMR($CDCl_3$): δ 16.32 (d, $J_{C,P}$ = 147 Hz, $(PhO)_2P(O)\underline{C}H_2CN$), 118.86 (d, $J_{C,P}$ = 12 Hz, $(PhO)_2P(O)CH_2\underline{C}N$), 120.42 (d, $J_{C,P}$ = 4 Hz, ortho-aromatic $\underline{C}H$), 126.13 (s, para-aromatic $\underline{C}H$), 130.11 (s, meta-aromatic $\underline{C}H$), 149.45 (d, $J_{C,P}$ = 9 Hz, ipso-aromatic $\underline{C}O$); ^{31}P NMR($CDCl_3$): δ 7.27 (t, $J_{H,P}$ = 21 Hz, 1P, $(PhO)_2\underline{P}(O)CH_2CN$). Anal. Calcd. for $C_{14}H_{12}NO_3P$: C, 61.54; H, 4.43, N, 5.13, O, 17.57. Found: C, 61.55, H, 4.57, N, 5.24, O, 17.64.

General Procedure for the Cyanomethylenation of Aldehydes. To a 0.5 M solution of 1 eq of **6** in THF at -78 °C was added dropwise 1 eq of 1.0 M *t*-BuOK/THF under a nitrogen blanket. The solution was stirred for 30 min and aldehyde (1 eq) was added dropwise below -65 °C (solid aldehydes were added as THF solutions). The reaction mixture was stirred at -78 °C for at least 10 min, warmed to and quenched at -25 °C with 25 % NH_4Cl (aq), extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the products, which could be further purified either by column chromatography or by recrystallization.

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