Tetrahedron Letters,Vol.25,No.38,pp 4259-4262,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

2-(DIPHENYLPHOSPHINOYL) PYRROLIDINES; VERSATILE REAGENTS FOR THE SYNTHESIS OF HETEROCYCLIC ENAMINES AND ENAMIDES.

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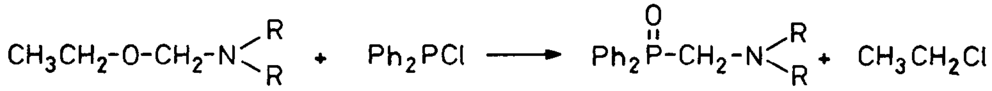
Summary: A method is described for the preparation of N-substituted 2-(diphenylphosphinoyl) pyrrolidines. Application of these phosphine oxides in the Horner-Wittig reaction affords heterocyclic enamines and enamides in good yields.

As part of our continuing interest in the synthetic applications of α-heterosubstituted diphenylphosphine oxides,[1-4] we are investigating the possibility of synthesizing heterocyclic enamines and enamides, versatile intermediates in natural product synthesis,[5,6] by the Horner-Wittig reaction. A recent publication on the synthesis and application of N-carbaethoxy-2-(diphenylphosphinoyl) piperidine[7] prompts us to report our results in the pyrrolidine series.

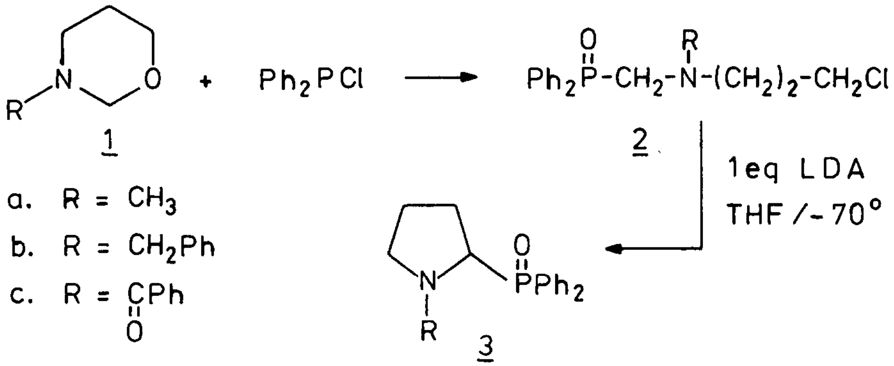
Frequently, diphenylphosphine oxides show superior properties in the (Horner)-Wittig reaction compared to phosphonium salts and phosphonates.[8] This is well demonstrated by α-aminomethyl diphenylphosphine oxides, which are versatile reagents for the synthesis of enamines,[2,3] whereas, in our experience, the corresponding phosphonium salts and phosphonates are not.[2,9]

These α-aminomethyl diphenylphosphine oxides are commonly prepared by an Arbusov reaction of N-ethoxymethylamines with chlorodiphenylphosphine:



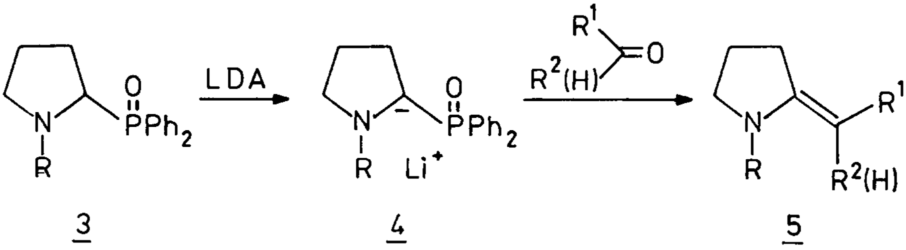
$$CH_3CH_2\text{-}O\text{-}CH_2\text{-}N{<}^{R}_{R} + Ph_2PCl \longrightarrow Ph_2\overset{O}{\overset{\|}{P}}\text{-}CH_2\text{-}N{<}^{R}_{R} + CH_3CH_2Cl$$

Application of this reaction scheme to N-substituted tetrahydro-1,3-oxazines 1 should give rise to ring opened aminomethyldiphenylphosphine oxides 2, bearing a chloro substituent at the right position for nucleophilic ring closure to a pyrrolidine derivative.



a. $R = CH_3$
b. $R = CH_2Ph$
c. $R = C(O)Ph$

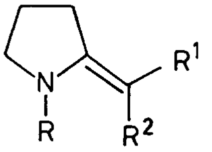
In actuality, mixing equivalent amounts of the readily available[10] tetrahydro-1,3-oxazines 1 and chlorodiphenylphosphine afforded quantitative yields of crystalline ω-chlorosubstituted phosphine oxides 2.[11] The N-alkyl oxazines 1a and 1b reacted smoothly at room temperature; the N-benzoyl derivative 1c required heating at 90 °C for 2 hrs to complete the reaction. Treatment of the phosphine oxides 2 with one equivalent of LDA at -70 °C afforded crystalline 2-(diphenylphosphinoyl) pyrrolidines 3 in yields of 80-90%.[11]



The deeply red coloured anions 4a,b, obtained from the N-alkylpyrrolidine phosphine oxides by adding 1 equiv of LDA to a THF solution at -70 °C, reacted instantaneously at this temperature with aromatic and aliphatic aldehydes to form the lithiated adducts. For completion of the Horner-Wittig reaction, 2 equiv of t-BuOK were added and the mixture was stirred overnight to afford, after the usual work-up procedure, the heterocyclic enamines 5a,b with R^2=H, as shown in Table I (entries 1 to 6). The reaction products consisted only of the more stable E-isomer, probably as a result of isomerisation during work-up.

Since these heterocyclic enamines are rather labile compounds, they were converted into the crystalline perchlorates 6, by addition of perchloric acid to an ethanolic solution of the enamine.[11]

TABLE I : Conversion of carbonyl compounds R^1R^2CO into heterocyclic enamines and enamides.



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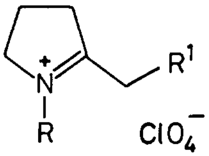

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Entry	R	R^1	R^2	Yield(%)[a]	m.p. (°C)[b]
1	CH_3	Ph	H	81	108 - 109[c]
2	CH_3	p-$MeOC_6H_4$	H	57	87 - 88
3	CH_3	n-C_3H_7	H	65	113 - 115[d]
4	CH_3	CH_3	H	50	203 - 205[e]
5	CH_2Ph	Ph	H	79	195 - 196
6	CH_2Ph	p-$MeOC_6H_4$	H	76	170 - 172
7	COPh	Ph	H	84[g]	143 - 145[f]
8	COPh	C_2H_5	H	87[h]	oil
9	COPh	$-CH_2CH_2\underset{C(CH_3)_3}{CH}CH_2CH_2-$		67	115 - 116
10	COPh	Ph	Ph	78	176 - 178

a. For the enamines (entries 1 to 6), yields and m.p. refer to isolated perchlorates 6.
b. m.p. are uncorrected
c. Lit.[11] : m.p. 109-110 °C
d. Lit.[12] : m.p. 117-118 °C
e. Lit.[12] : m.p. 208-209 °C
f. m.p. of E-isomer, obtained by recrystallization from hexane-CH_2Cl_2 .
g. E/Z ratio 5:2 .
h. E/Z ratio 1:1 .

The N-benzoyl substituted anion 4c is strongly stabilized by dipole interactions,[13] even so a fast reaction was observed with aldehydes at -70 °C. Completion of the Horner-Wittig reaction was easily effected by stirring overnight at room temperature. The resulting enamides are stable compounds and are obtained in good yields as mixtures of E- and Z-isomers (entries 7 and 8).[11] The increased stability of anion 4c allows reaction with carbonyl compounds at higher temperatures and thereby extension of the reaction to ketones. 4-t-Butylcyclohexanone and benzophenone did not add to the anion at -70 °C, but prolonged reaction times at room temperature (48 hrs) afforded the enamides, which were obtained in yields of 67% and 78% respectively, after crystallization (entries 9 and 10).

Application of the novel route to heterocyclic phosphine oxides described in this communication to the synthesis of other N- and O-heterocyclic systems is currently being investigated and will be reported separately.

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ACKNOWLEDGEMENT

The investigations were supported by the Netherlands Foundation for Chemical Research (S.O.N.) with financial aid from the Netherlands Organization for the Advancement of Pure Research (Z.W.O.).

(Received in UK 22 May 1984)