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1,3-DIMETHYL 2-OXO 1,3,2-DIAZAPHOSPHOLIDINE PRECURSOR OF (Z) α,β-UNSATURATED ESTERS.

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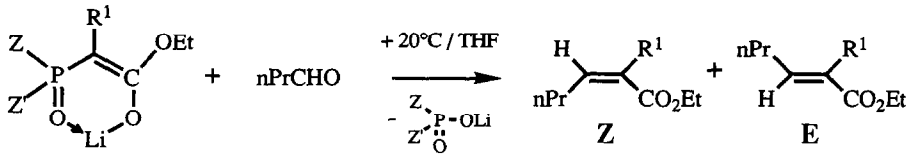
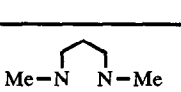
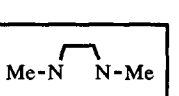
Abstract : α,β-Unsaturated esters of (Z) geometry are selectively obtained from cyclic phosphonocarboxylates derived from N,N'-dimethylethylenediamine.

The Horner-Wittig[1] reaction is a classical method to prepare α,β-unsaturated esters, with predominant (E) geometry. A recent article[2] suggested that a judicious choice of three reaction parameters - cation, temperature, and solvent - suffices to orientate the reaction toward the predominant formation of either the (Z) or the (E) isomer[3]. Still and Gennari[4] showed that the environment of the phosphorus atom could also play a key role. The results described hereafter confirm this.

A preliminary study was realised in THF with the cation Li^+ at 20°C to compare six acyclic and cyclic phosphonic acid esters and amides of different (Z, Z') environment, bearing a R^1 substituent in the α position (Scheme 1).



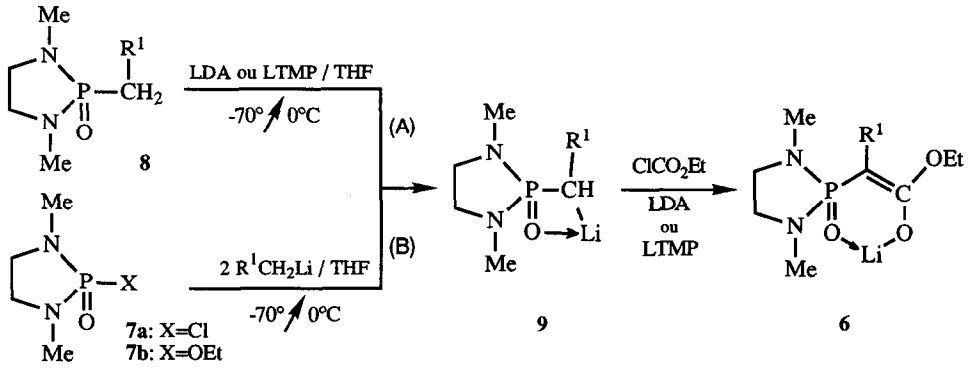
Z = Z' =	$(EtO)_2$			$(Me_2N)_2$		
	1	2	3	4	5	6
Z / E R^1 = nPr	37 / 63	61 / 39	62 / 38	--	--	76 / 24

Scheme 1

Phosphonic acid esters **1**, **2**, and **3** were little or not stereodirective. Phosphonic acid amides **4** and **5** did not react with butyraldehyde. By contrast, **6** reacted with spontaneous elimination of lithiated phosphonic acid amide

(δ ^{31}P +25) as had been shown by Hanessian and coll.[5]. Moreover, the (Z) isomer was obtained predominantly[6]. This unexpected stereodirective effect of the diazaphospholidinyl group prompted us to further investigate its properties.

Alkylation-metalation[7] (route B) of 2-chloro (**7a**) or 2-ethoxy (**7b**) 2-oxo 1,3-dimethyl 1,3,2-diazaphospholidines by 2 equiv. of an alkyllithium, or metalation (route A) by a hindered amide of 2-alkyl 2-oxo 1,3-dimethyl 1,3,2-diazaphospholidine (**8**) yielded stable carbanions (**9**). Treating **9** with ethyl chloroformate in the presence of a lithium amide (LDA or LTMP) afforded lithiated enolates (**6**) (δ ^{31}P +50, singlet) with a variety of R^1 substituents (scheme 2).

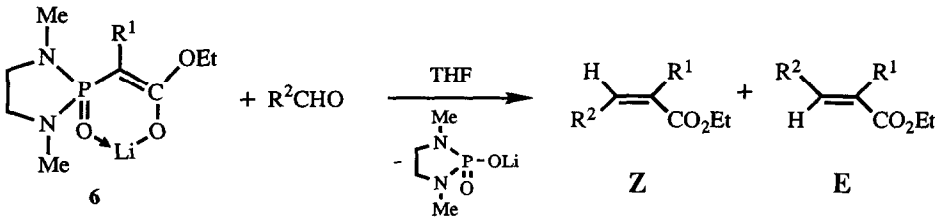


Scheme 2

6 was then reacted with aliphatic aldehydes R^2CHO. The results are summarised in Table 1. Lowering the temperature favoured the formation of the (Z) isomer. However, the size of substituents R^1 and R^2 determined a temperature below which the reaction became extremely slow. With R^1 = H or Me, the reaction could be carried out at -75°C, but with R^1 = Et we had to operate at -30°C, and with R^1 > Et at -20°C. With isobutyraldehyde (R^2 = iPr), it was necessary to run the reaction at +20°C.

It was also found that diluting the reaction medium favoured the formation of the (Z) isomer, probably because of the displacement of an equilibrium between agregated and free **6**. This effect was most important with small R^1 substituents such as H and Me.

Lithium salts , either generated *in situ* (LiCl) or added (LiBr), and the secondary amine (HTMP or HDA) used during the preparation of the lithiated enolates, had only kinetic effects. When the reaction medium contained a lot of lithium salts (e.g. 5 equiv.), we had to use HTMP instead of HDA to run the reaction at the desired temperature.



Entry	R^1	R^2	Starting product	Amine	Yield % crude (dist.)	Z / E ratio[a] crude (dist.)
1[d]	H	nPr	8	HTMP	65	82 / 18
2[d]		iBu	"	"	100	86 / 14
3[d]		nHex	"	"	81 (43)	82 / 18 (90 / 10)
4[d]	Me	nPr	"	HTMP	81 (60)	90 / 10 (91 / 09)
5[b]		iPr	7a	"	93 (57)	92 / 08 (96 / 04)
6[d]		iBu	8	"	93	90 / 10
7[d]		nHex	"	HDA	97 (83)	90 / 10 (95 / 05)
8[b]	Et	iPr	7a	HTMP	78 (56)	96 / 04 (98 / 02)
9[d]		iBu	8	HDA	90 (71)	92 / 08 (93 / 07)
10[d]		nHex	"	HTMP	94 (65)	90 / 10 (93 / 07)
11[b, e]	nPr	Me	7a	HTMP	85 (64)	86 / 14 (90 / 10)
12[c]		nPr	"	"	97 (85)	90 / 10 (94 / 06)
13[b]		iPr	"	"	91 (70)	97 / 03 (98 / 02)
14[d]		iBu	7b	HDA	82 (61)	88 / 12 (91 / 09)
15[c]		nHex	"	HTMP	89	90 / 10
16[b]	nPen	Me	7a	HTMP	100 (51)	89 / 11 (93 / 07)
17[b]		iPr	"	"	98 (54)	95 / 05 (97 / 03)

Table 1

HDA = diisopropylamine ; HTMP = 2,2,6,6-tetramethylpiperidine. *a* : determined by GPC on SE 30 capillary column (the Z isomer is detected before the E isomer) or with 200 MHZ ^{1}H NMR by integrating the signals of the ethylenic protons. *b* : 0.25 M. *c* : 0.12 M. *d* : 0.033 M. *e* : to be kept at -18°C.

When the reaction was finished, the reaction medium was treated with dilute HCl (3 M), transfering both the hindered amine and the diazaphospholidinyl group to the aqueous layer. The acrylic esters were purified by vacuum distillation in a bulb to bulb apparatus (Büchi GKR-50). This technique diminishes the risks of polymerisation due to overheating and allows to enrich the distillate in the (Z) isomer.

We are continuing the investigation of the properties related to this reagent which selectively leads to the formation of (Z) acrylic esters under very ordinary reacting conditions and without any addition of chelating agents.

References and notes :

Preparation of precursors **7a**, **7b**, et **8** has been published[7].

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