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STEREOSELECTIVITY OF WITTIG TYPE OLEFIN SYNTHESIS USING 5 MEMBERED CYCLIC PHOSPHINE OXIDES OR PHOSPHONOUS ACID DIMETHYLAMIDES

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The Horner-Emmons modification of the Wittig reaction-i.e. formation of substituted olefins 1 from phosphonates 2 and carbonyl compounds in basic medium - is a widely used method in organic synthesis[1]. In order to define the factors which influence its stereoselectivity, we have been studying its mechanism[2] - which is related on Scheme I; we have shown[3] that the reversibility factor (k_{-}/k') is of prime importance to determine the E/Z olefin ratio. The formation of Z (E) olefin is favored when the reversibility factor decreases (increases)[2].

To modify k_{-E}/k'_{E} and k_{-Z}/k'_{Z} we might increase (or decrease) the rate of nucleophilic attack of the phosphorus atom in the two intermediate alcoholates 3E and 3Z. This can be achieved by modifying the oxygen atom nucleophilicity according to its association to the cation M^+: the reversibility factor increases when we use Li^+ instead of K^+. It can also be achieved by changing the phosphorus atom electrophilicity. With this purpose in mind, we studied the reaction of aldehydes with two other reagents 4 and 5;

- 5 membered cyclic phosphine oxides 4[4], as it is known for some time that a phosphorus atom, included into a five membered ring is far more electrophilic than open chains analogs[5,6]. A related approach has been previously done for the Wittig reaction by TEBBY and WILSON[7]. We were then expecting a decrease of the reversibility factor.

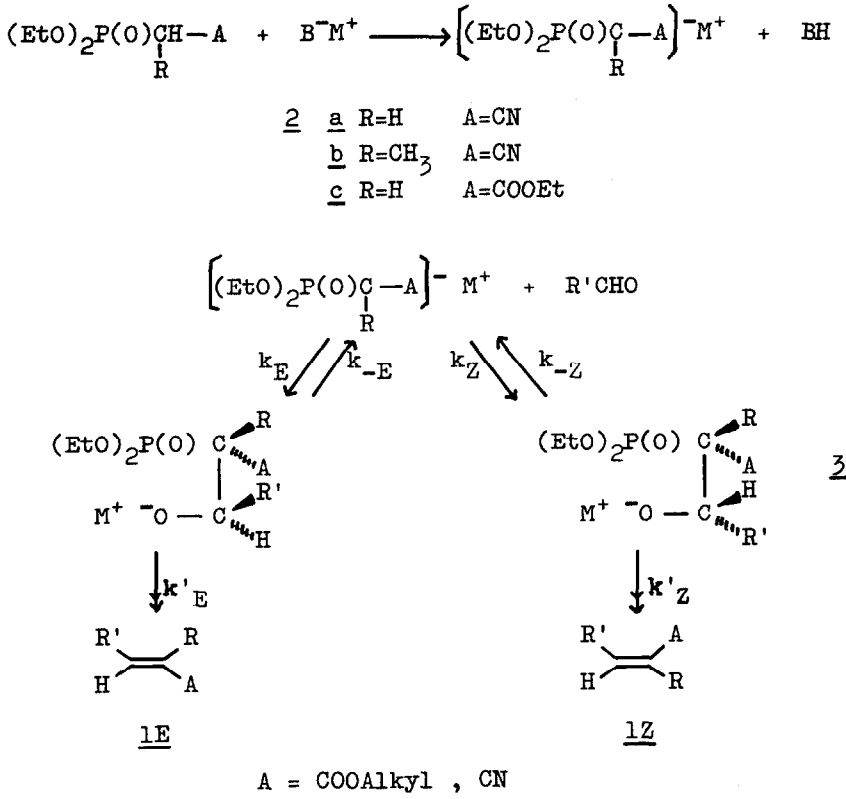
- phosphonic acid dimethylamide 5[8]: the dimethylaminogroup being a better electron donor than the ethoxy one, the phosphorus atom should be less electrophilic. We were then expecting an increase of the reversibility factor.

If the stereoselectivity of the condensation step is not modified by a change of the phosphorus substituants, the formation of 1Z (1E) should be favored in the case of 4 (5) as a reagent and K^+ (Li^+) as an associated cation.

We also studied the reaction of aldehydes with reagent 6 but the change of stereoselectivity observed was not very important (see results in the reference 9).

The reactions are run in THF using equimolar amounts of aldehyde, phosphorus derivative and KOtBu or n.BuLi. The E/Z olefin ratio is determined by

Scheme I

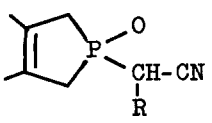


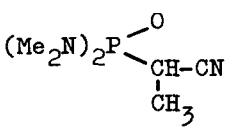
GLC and comparison with standard samples. The results are in the Table.

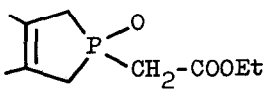
Discussion

In the case of reagents 4 a) if (R=H) we don't see any stereoselectivity change compared to phosphonate 2a, probably due to some epimerisation of the intermediates - contrarily to cyclic phosphonate[10], this reagent does not lead to important amounts of Z olefins; b) when $R=CH_3$, the results are in agreement with our expectations.

- using phospholene 4b, the reversibility factor certainly decreases as there is a very small cation or temperature effect on the stereoselectivity







4 a : R=H
b : $R=CH_3$ [12]

5

6

Table

Formation of ethylenic nitriles 1E and 1Z from aldehydes and phosphonates 2 (A=CN), phospholenes 4 or phosphonamide 5

Exp n°	Aldehyde	Reagent	M^+	t°C	E/Z ratio
1	PhCHO	2a	K^+	+20	80/20 [2a]
2	PhCHO	4a	K^+	+20	80/20
3	PhCHO	2b	K^+	+20	40/60 [2c]
4	PhCHO	2b	K^+	-80	10/90 [2c]
5	PhCHO	2b	Li^+	+65	80/20 [2c]
6	PhCHO	4b	K^+	-80 or +20	53/47
7	PhCHO	4b	Li^+	+65	60/40
8	PhCHO	5	K^+	-80	75/25 [a]
9	PhCHO	5	Li^+	+65	88/12
10	PhCH=CHCHO	2b	K^+	-80	20/80
11	PhCH=CHCHO	2b	Li^+	+65	40/60
12	PhCH=CHCHO	5	K^+	+20	40/60
13	PhCH=CHCHO	5	Li^+	+65 or +20	45/55
14	CH_3CH=CHCHO	2b	K^+	-80	15/85
15	CH_3CH=CHCHO	2b	Li^+	+65	65/35
16	CH_3CH=CHCHO	5	K^+	+20	93/7
17	iPrCHO	2b	K^+	-80 or +20	45/55
18	iPrCHO	2b	Li^+	+20	50/50
19	iPrCHO	4b	K^+	-80 or +20	55/45
20	iPrCHO	4b	Li^+	+20	35/65
21	iPrCHO	5	K^+	-80 or +20	7/93 [b]
22	iPrCHO	5	Li^+	+20	50/50

a) Reaction performed in THF:tBuOH 1:1 mixture. We observed no change of stereoselectivity when reactions with 2b are performed in this solvent mixture.

b) Some isomeric nitrile $\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!C\!=\!CH\!-\!CH_2CN$ ($\sim$ 20%) is also formed.

of the reaction[11].

- using phosphonamide 5, the stereoselectivity increases when the temperature increases or when changing the cation from K^+ to Li^+, therefore the reversibility factor increases as expected. The formation of E isomer is favored whatever the cation is (Li^+, K^+) in comparison with phosphonate 2b, except for isobutyraldehyde. In that case, the results are very difficult to interpret at the present time.

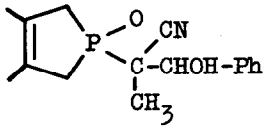
The synthetic implication of these results is the stereoselective obtention of aryl or alkenyl substituted nitriles : E isomer is highly predominating using reagent 5 at room or reflux temperature (exp. 9, 16); Z isomer is predominating using reagent 2b and KOtBu as a base at -80°C

(exp. 4, 10, 14, 21).

A similar approach to this problem has been undertaken by BREUER and BANNET[10]. We thank D[r] BREUER for exchanging information prior to publication.

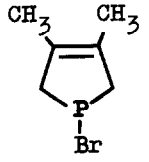
REFERENCES

1. J. BOUTAGY and R. THOMAS, Chem. Rev., 1974, 74, 87.
2. a) B. DESCHAMPS, G. LEFEBVRE and J. SEYDEN-PENNE, Tetrahedron, 1972, 28, 4209; G. LEFEBVRE and J. SEYDEN-PENNE, Chem. Comm., 1970, 1308; b) B. DESCHAMPS, G. LEFEBVRE, A. REDJAL and J. SEYDEN-PENNE, ibid., 1973, 29, 2437; c) A. REDJAL and J. SEYDEN-PENNE, Tetrahedron Letters, 1974, 1733.
3. M. SCHLOSSER, Topics in Stereochemistry, 1970, 5, 1.
4. F. MATHEY, J.P. LAMPIN and D. THAVARD, Canad. J. Chem., 1976, 54, 2402.
5. G. ASKNES and K. BERGESEN, Acta Chem. Scand., 1966, 20, 2508.
6. R.F. HUDSON, Accounts Chem. Res., 1972, 5, 204.
7. I.F. WILSON and J.C. TEBBY, J. Chem. Soc. (C), 1972, 2713.
8. J. BLANCHARD, N. COLLIGNON, P. SAVIGNAC and H. NORMANT, Synthesis, 1975, 655.
9. In the case of esters with phosphonate 2c, KOtBu as a base and aromatic aldehydes, we always obtain E isomer. With reagent 6 and benzaldehyde we obtain 20% Z isomer; with 6 and p.Cl benzaldehyde 10% Z isomer. This reagent is far less interesting than cyclic phosphonate[10] for the synthesis of Z isomers.
10. E. BREUER and D.M. BANNET, accompanying paper.
11. Furthermore, we tried to prepare the hydroxy phosphine oxides 7 (Z or E) working, as previously, with lithium or magnesium derivatives[2]: we could not stop at this stage as either there is no reaction (t° < -40) or it goes to completion and we only obtain cinnamonitriles, indicating thus that k' is quite high.



7, Z or E

12. 4b is prepared with 40% yield by reaction of $BrCH(CH_3)CN$ and



Purification by SiO_2 column chromatography. Elution by a mixture: ethyl acetate-methanol 90:10.