Tetrahedron Letters,Vol.24,No.36,pp 3931-3934,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

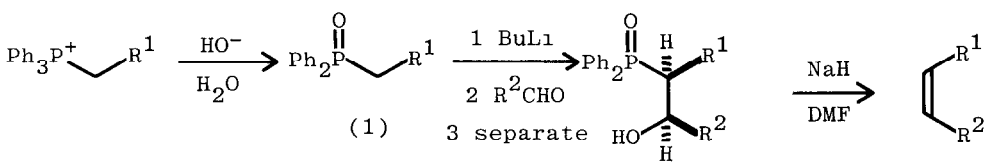
CIS-OLEFINS FROM THE HORNER-WITTIG REACTION; ORIGIN AND OPTIMISATION OF STEREOCHEMISTRY

Antony D. Buss and Stuart Warren*

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW.

Summary: Conditions are described to produce high yields of erythro Horner-Wittig intermediates: stereospecific elimination gives cis-alkenes.

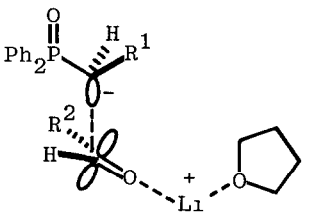
The Horner[1] variant of the Wittig reaction using diphenylphosphinoyl (Ph_2PO) as the anion-stabilising group and butyl-lithium (BuLi) as the base gives erythro intermediates[2] (2) which can be separated by flash column chromatography[3] and crystallisation. Stereospecific elimination[4] (NaH, DMF) gives pure Z-alkenes, easily separated from the water-soluble by-product [$Ph_2PO_2^-$]. This reaction has been applied to the synthesis of single geometrical isomers of dienes,[5] vinyl ethers,[6] allylic amines and amides,[7] and enones.[8] We describe the selection of conditions to maximise erythro selectivity and the effect of substituents R^1 and R^2 upon this selectivity.



erythro-(2)

In hydrocarbon solvents (table 1) there is little stereoselectivity but a dramatic improvement occurs in ethers with the best results in solvents good at complexing lithium and with added complexing agents $Me_2NCH_2CH_2NMe_2$ (TMEDA) or 1,3-dimethyl-2-imidazolidinone[9] (DMI). At about room temperature, even in THF, stereoselectivity is again poor (table 1) but at -78 °C or -100 °C it is good.

We use BuLi in THF at -78 °C unless stereoselectivity is poor enough for -100 °C to be worthwhile (entries 11 and 12, table 1). One possible structure for the transition state (3) has the largest groups (Ph_2PO and complexed Li) anti and R^1 and R^2 anti and gauche.



(3)

Table 1

Effect of Solvent and Temperature on the Formation of (2,R^2=Ph)

Variable	Entry	Condition	R^1	erythro:threo
Solvent	1	pentane	Et	55:45
(all at -78 °C)	2	toluene	Et	58:42
	3	ether	Et	60:40
	4	DME	Et	84:16
	5	THF	Et	85:15
	6	THF + TMEDA	Et	88:12
	7	THF + DMI	Et	88:12
Temperature	8	+10 °C	Et	66:34
(all in THF)	9	-78 °C	Et	88:15
	10	-100 °C	Et	92:8
	11	-78 °C	i-Pr	64:36
	12	-100 °C	i-Pr	83:17

Substituent effects (table 2) can also be explained by this transition state (3). Keeping R^2=Ph and elongating R^1 from Me to n-Bu (entries 1-4) has little effect on the stereoselectivity. Only when R^1 is branched (entries 5-6) does stereoselectivity fall off, and then only significantly when the branch-point is the carbon atom next to the anion site. Clearly R^1 must be large if it is to compete with Ph_2PO as the largest group on C-1 in (3). Increasing the size of R^2 (entries 7-11, table 2) similarly reduces stereoselectivity but the effect is smaller. Large aromatic groups (entry 10) give high stereoselectivity

and even cyclohexyl does not always give a 50:50 mixture. For the alkene of table 1 (R^1=Et, R^2=Ph), the Wittig reaction[10] gives 33-79% yield and from 24:76 to 96:4 Z:E selectivity, depending on the conditions. The highest selectivity is obtained with salt-free ylids.[11]

Table 2

Entry	R^1	R^2	Yield of erythro (2) isolated	erythro: threo[a]	Yield[b] of Z-Alkene
1	Me	Ph	78%	88:12	71% (4)
2	Et	Ph	73%	85:15	79%
3	n-Pr	Ph	73%	85:15	78% (2)
4	n-Bu	Ph	71%	84:16	82% (3)
5	Me_2CHCH_2	Ph	65%	80:20	83% (2)
6	Me_2CH	Ph	54%	64:36	78%
7	Me	2-$MeOC_6H_4$	74%	81:19	83% (2)
8	Me	3-$MeOC_6H_4$	69%	80:20	85% (5)
9	Me	4-$MeOC_6H_4$	81%	87:13	75% (6)
10	Me	c	76%	90:10	84% (4)
11	Me	C_6H_{11}[d]	69%	79:21	79%
12	R[e]	C_6H_{11}[d]	-	50:50[f]	-
13	C_6H_{11}[d]	Me	-	50:50[f]	-

[a] ratio of isolated adducts
[b] yield of E-alkene by g.l.c. in parenthesis
[c] R^2= 3,4-methylenedioxyphenyl
[d] cyclohexyl
[e] R^1=n-Pr, n-Bu, i-Pr, i-Bu.
[f] ratio determined by t.l.c.

The elimination step normally occurs stereospecifically with NaH in DMF or KOH in DMSO. If R^2=Ar, a trace of E-alkene is sometimes formed (table 2) but when R^1=Ar or other conjugating group[4,12] stereospecificity can be lost because of equilibration with starting materials. The synthesis of a pure Z-alkene by the Horner-Wittig reaction is most likely to succeed if large or conjugating groups are placed as R^2 and the reaction is carried out as follows:

BuLi (1.5M solution in hexane) was added from a syringe to a stirred solution of the phosphine oxide in dry THF (freshly distilled from sodium wire) at 0 °C. After 30 min the red solution was cooled to -78 °C and the neat aldehyde added dropwise at such a rate that the solution stayed at -78 °C. The

pale-yellow solution was allowed to warm to room temperature over about 2 h and water was added. The THF was removed under reduced pressure, brine was added, and the solution extracted three times with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated to dryness. The product was separated by flash column chromatography,[3] eluting with ethyl acetate and then acetone. The first diastereoisomer to elute is erythro. Sodium hydride (80% dispersion in oil) was added in one portion to a stirred solution of the erythro adduct in dry DMF. Warming to 50 °C for about 1 h produced a white precipitate (Ph_2PO_2Na). The mixture was cooled and the precipitate dissolved in water. The mixture was diluted with brine and extracted with ether. Washing with water, drying ($MgSO_4$), evaporation, and bulb-to-bulb distillation gave pure Z-alkene.

We thank S.E.R.C. and Glaxo Group Research for grants and Dr Barry Price for many helpful discussions.

References

1. L. Horner, H. Hoffmann, H. G. Wippel, and G. Klahre, Chem. Ber., 1959, **92**, 2499; A. J. Bridges and G. H. Whitham, J. Chem. Soc., Chem. Commun., 1974, 142; Perkin Trans. 1, 1975, 2264.
2. A. D. Buss and S. Warren, J. Chem. Soc., Chem. Commun., 1981, 100.
3. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1978, **43**, 2923.
4. A. D. Buss, S. Warren, J. S. Leake, and G. H. Whitham, J. Chem. Soc., Perkin Trans. 1, in the press.
5. A. H. Davidson and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1976, 639; B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, and S. Ruston, Ibid, 2386; B. Lythgoe, T. A. Moran, J. Tideswell, and P. W. Wright, Ibid, 1978, 590; J. M. Clough and G. Pattenden, Tetrahedron Lett., 1978, 4159; 1979, 5043.
6. C. Earnshaw, C. J. Wallis, and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1979, 3099.
7. D. J. Cavalla and S. Warren, Tetrahedron Lett., 1982, **23**, 4505; 1983, **24**, 295.
8. C. A. Cornish and S. Warren, Tetrahedron Lett., 1983, **24**, 2603.
9. H. Sakurai and F. Kondo, J. Organomet. Chem., 1976, **117**, 149; B. J. Barker, J. Rosenfarb, and J. A. Caruso, Angew. Chem. Int. Ed. Engl., 1979, **18**, 503.
10. H.-J. Bestmann and O. Klein in Methoden der Organischen Chemie (Houben-Weyl), Thieme, Stuttgart, Vol 5/1b, 1972, p. 388.
11. M. Schlosser, G. Müller, and K. F. Christmann, Angew. Chem. Int. Ed. Engl., 1966, 5, 667.
12. J. I. Grayson and S. Warren, J. Chem. Soc., Perkin Trans. 1, 1977, 2263; S. Warren and A. T. Zaslona, Tetrahedron Lett., 1982, **23**, 4167.

(Received in UK 11 July 1983)