Tetrahedron Letters,Vol.26,No.3,pp 311-314,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

THE BETAINE-YLID ROUTE TO TRANS-ALKENOLS

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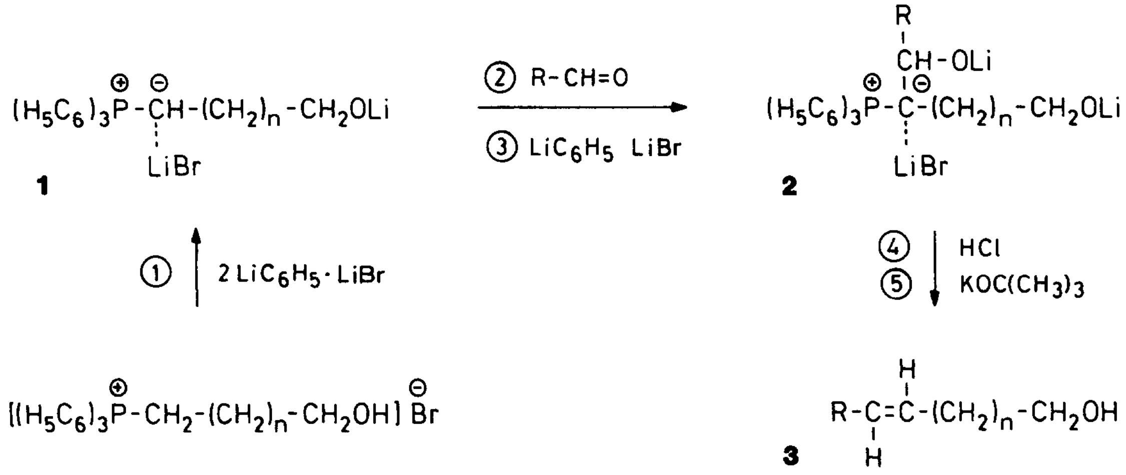
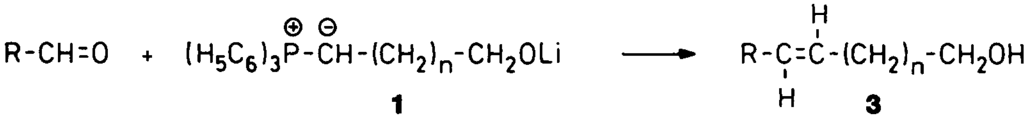
Summary: The trans-selective variant of the Wittig reaction can be successfully applied to the synthesis of alkenol-type pheromones.

The betaine-ylid modification of the Wittig reaction allows the synthesis of *trans*-olefins with an isomeric purity of 99.5% [1]. Until recently, we had investigated only a few functionalized betaine-ylids[2]. We now demonstrate how ω-hydroxyalkyl-triphenylphosphonium bromides of varying chain length can be used in the preparation of alkenols 3 with high *trans*-selectivity (see table). Ylids 1 and betaine-ylids 2 act as key intermediates in this one-pot reaction. The acetates of 3a [3] and 3b [4] and the alcohols 3c [5] and 3d ("codlemone") [6] have pheromone activity.



Sometimes betaine-ylid reactions are considered to be tricky and reported stereoselectivities difficult to reproduce [7]. In most cases such failures can be traced back to the same error : instead of using *self-prepared phenyllithium* [8], the organolithium reagent required for ylid and betaine-ylid generation was purchased. As a matter of fact, commercial solutions of phenyllithium in benzene/diethyl ether mixture (70 : 30 by volume) and butyllithium in petroleum ether, do not contain more than trace amounts of lithium bromide. An over-stoichiometric concentration of the latter, however, is crucial for achieving stereocontrol [1]. Another problem may arise with phosphonium salts carrying a long or bulky hydrocarbon moiety in their side chain. Due to poor solubility of the corresponding betaine/lithium bromide adduct the subsequent betaine-ylid formation may proceed incompletely. This complication can be overcome by increasing the proportion of the tetrahydrofuran which generally serves as a cosolvent besides diethyl ether [9, 10]. The success of *trans*-selective carbonyl olefinations with short-chain ω-lithiooxido ylids again critically depends on the solvent mixture chosen : the tetrahydrofuran /diethyl ether ratio should exceed 3 : 1 and, respectively, 2 : 1 in the case of the 3-lithiooxido-propylid 1a (n+2 = 3) and the 4-lithiooxido-butylid 1b (n+2 = 4) while ratios of 1 : 1 are perfectly convenient with higher homologs such as 1c and 1d (n+2 = 6 or 8).

Table. Straight-chain (*E*)-alkenols 3a - 3d obtained by *trans*-selective Wittig reactions starting with ω-hydroxyalkyl-triphenylphosphonium bromides.



$$R\text{-}CH{=}O + (H_5C_6)_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H\text{-}(CH_2)_n\text{-}CH_2OLi \longrightarrow R\text{-}\underset{H}{C}{=}\overset{H}{C}\text{-}(CH_2)_n\text{-}CH_2OH$$

1 3

aldehyde : cross formula	ylid : n+2	product a)	(*Z*) : (*E*) ratio b)	yield	bp [°C]/ 13 mmHg	n_D^{20}
$C_7H_{14}O$	3	3a	3 : 97	71%	108 - 109	1.4518
$C_6H_{12}O$	4	3b	2 : 98	78%	111 - 113	1.4529
C_3H_6O	6	3c	1 : 99	74%	99 - 101	1.4491
C_4H_6O c)	8	3d [11]	2 : 98	69%	90 - 92 d)	e)

a) All compounds gave satisfactory elemental analyses (± 0.3%) and showed correct spectral data.

b) No gaschromatographic separation of (*Z*)- and (*E*)- 3b ; otherwise : 2 m 10% C-20M, 150°C.

c) Crotyl aldehyde [(*E*)-butenal].

d) 10^{-3} mmHg.

e) Melting range : 31 - 32°C.

Typical working procedure : A solution of 40 mmol phenyllithium in 40 mL of tetrahydrofuran/ diethyl ether mixture (5 : 3 by volume) was added dropwise to a slurry of 8.3 g (20 mmol) of 4-hydroxybutyl-triphenylphosphonium bromide in 60 mL of THF. After 20 min of vigorous stirring at 25°C, the clear red solution was cooled to -75°C and treated with 2,0 g (20 mmol) hexanal. After 20 min at -30°C, again 40 mmol of phenyllithium, dissolved in 40 mL of tetrahydrofuran/ diethyl ether mixture (5 : 3), were added to the cream-colored precipitate. The resulting dark-red betaine-ylid solution was kept 30 min at 25°C and 15 min at -75°C before 10 mL of a 4.2 M solution of HCl in diethyl ether (42 mmol) were added causing immediate decolorization. After addition of 5.0 g (45 mmol) potassium *tert*-butoxide [12] and stirring 1 h at 25°C, the reaction mixture was poured into 25 mL of water and extracted with diethyl ether (2 x 25 mL). After washing, drying and evaporating the organic layers, a semi-solid residue was left which contained much triphenylphosphine oxide and from which the product was extracted with 50 mL pentane. Distillation afforded 2.45 g (*E*)- **3b** as a colorless oil.

> ^{1}H-nmr (360 MHz) of (*E*)- **3b** : 5.47 (1 H, *dt*, *J* 15.3, 5.9); 5.40 (1 H, *dt*, *J* 15.3, 5.9); 3.61 (2 H, *t*, *J* 6.5); 2.49 (1 H, *s*); 2.06 (2 H, *q*, *J* 6.5); 1.97 (2 H, *q*, *J* 6.5); 1.61 (2 H, *p*, *J* 7.1); 1.3 (6 H, *m*); 0.88 (3 H, *t*, *J* 6.9).

For sake of comparison (gc retention times; nmr spectra), the corresponding (*Z*)-isomer was synthetized applying the instant-ylid method [13].

> ^{1}H-nmr (360 MHz) of (*Z*)- **3b** : 5.42 (1 H, *dt*, *J* 10.4, ∿ 6); 5.36 (1 H, *dt*, *J* 10.4, ∿ 6); 3.64 (2 H, *t*, *J* 5.8); 2.12 (2 H, *q*, *J* 6.7); 2.03 (2 H, *q*, *J* 6.7); 2.00 (1 H, *s*, broad); 1.62 (2 H, *p*, *J* 6.9); 1.3 (6 H, *m*); 0.87 (3 H, *t*, *J* 6.8).

Acknowledgment: This work was supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (grant no. 2.635.0-82) and the Ciba-Geigy AG. The latter company notably also offered access to facilities for electrophysiological tests and field trials with some of the prepared samples.

[1] M. Schlosser & K.F. Christmann, *Angew. Chem.* 1966, *78*, 115; *Angew. Chem. Int., Ed. Engl.* 1966, *5*, 126; M. Schlosser & K.F. Christmann, *Liebigs Ann. Chem.* 1967, *708*, 1; M. Schlosser, K.F. Christmann & A. Piskala, *Chem. Ber.* 1970, *103*, 2814; M. Schlosser, *Topics in Stereochem.* 1970, *5*, 1; A.S. Arora & I.K. Ugi in *Houben/Weyl* "Methoden der organischen Chemie", 1972, Vol. *5/1b*, 728, G. Thieme Verlag, Stuttgart.

[2] *E.g.*, 2-hydroxyethyl-triphenylphosphonium bromide was converted into (*E*)-cinnamic alcohol (37%; K.F. Christmann & A. Piskala, 1968/69, unpublished). See also : M. Schlosser & D. Coffinet, *Synthesis* 1971, 380, and previous communications quoted therein.

[3] Pheromone of the sugar beet moth *Scrobipalpa ocellatella* (M. Renou, C. Descoins, J.A. Lallemand, E. Priesner, M. Lettere & M. Gallois, *Z. Angew. Entomol.* 1980, *90*, 275; *Chem. Abstr.* 1980, *93*, 235466 r).

[4] "Confusant" for male insects of the European pine shoot moth *Rhyacionia buoliana* (G.E. Daterman, G.D. Daves & M. Jacobson, *Environ. Entomol.* 1972, *1*, 382).

[5] Important cofactor of the sex attractant of the Mediterranean fruit fly ["Medfly"] *Ceratitis capitata* (M. Jacobson, K. Ohinata, D.L. Chambers, W.A. Jones & M.S. Fujimoto, *J. Med. Chem.* 1973, *16*, 248).

[6] Pheromone of the codling moth *laspeyresia pomonella* (W.L. Roelofs, A. Comeau, A. Hill & G. Milicevic, *Science* 1971, *16*, 297).

[7] See, *e.g.*, F. Camps, J. Coll, G. Fabrias & A. Guerrero, *Tetrahedron* 1984, *40*, 2871.

[8] G. Wittig, *Angew. Chem.* 1940, *53*, 242; H. Gilman & J.W. Morton, *Organic Reactions* 1954, *8*, 286, J. Wiley & Sons, New York.

[9] We are much obliged to Prof.Dr. B.E. McCarry (McMaster University, Hamilton, Ontario, Canada) for informing us about related observations made during his PhD thesis work (carried out under the supervision of Prof. W.S. Johnson at Stanford University).

[10] Phenyllithium can either be prepared directly in tetrahydrofuran (H. Gilman & B.J. Gaj, *J. Org. Chem.* 1957, *22*, 1165) or, if obtained as usual [9], most of the diethyl ether may be removed by distillation before the new solvent is added under cooling. Alternatively, a LiBr-containing solution of *n*-, or *sec*- or *tert*-butyllithium may be prepared by stripping off the hydrocarbon solvent, adding at -80°C some precooled tetrahydrofuran and finally dissolving 1.0 - 1.5 equiv. of anhydrous lithium bromide in this mixture.

[11] In the same way the corresponding 10-fluoro-substituted dienol was synthetized (Huynh Ba Tuong & M. Schlosser, 1977/79 ; biological tests in collaboration with Prof. H.J. Bestmann, Erlangen.

[12] The reprotonation of the equilibrated betaine-ylid (with HCl/diethyl ether) and the elimination of triphenylphosphine oxide after decomplexation of the LiBr-associated betaine thus obtained (with potassium *tert*-butoxide) may be combined into a single operational step : just pouring the reaction mixture into water. This "lazy man's" procedure, however, gives lower yields (∿ 65%) and lower (*Z*/*E*)-ratios (∿ 4 : 96).

[13] B. Schaub, G. Blaser & M. Schlosser, *Tetrahedron Lett.*, preceding communication.

(Received in Germany 8 October 1984)