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Enhanced *cis*-Selectivities in Olefination Reactions Employing Ylids with Modified «Stationary Groups»

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Abstract: While tri*phenyl*phosphonio-ethanide manifests unsatisfactory *cis*-selectivities (84.0–95.5%), tris(*o,o'-difluorophenyl*)- and tri-*o-tolyl*phosphonio-ethanide react with aliphatic or aromatic aldehydes and, respectively, 2-alkenals or 2-alkynals to afford the olefins with *cis*/*trans*-ratios of 99:1 and 96:4 (or better). Tri*phenyl*phosphonio-butanide like other higher-homolog standard ylids shows excellent stereoselectivity (99% *cis*) when condensed with aliphatic aldehydes but fails to produce *cis*-olefins derived from aromatic aldehydes with more than 96% or 97% isomeric purity. In such cases tris(*o,o'-difluorophenyl*)phosphonio-butanide allows to restore a 99% level of selectivity.

As it has become apparent from the preceding communication[1] as well as previous work[2], triphenylphosphonio-*ethanide* reacts with a given aldehyde less *cis*-selectively than do triphenylphosphonio-propanide, -butanide, or the higher ylid homologs. Furthermore, stereoselectivities were found to fall behind if α,β-unsaturated aldehydes (notably alkynals[3]) rather than saturated ones were employed in Wittig reactions (see Table 1). Finally, an α-alkoxy-substituted aldehyde, the 2-(3,4-dihydro-2*H*-pyran)carbaldehyde («acrolein dimer»), was reported to undergo olefination under «salt-free» conditions with only poor stereoselectivity[4]. Improvements were felt to be desirable.

We have already attempted to explain the phenomenon of *cis*-selective olefin formation by a «leeward side approach» of the aldehyde to the ylid when the latter adopts its sterically least hindered conformation[5]. If this model is correct one would expect the *cis*/*trans*-ratios of products to vary considerably if one modifies the permanent substituents at the phosphorus atom, i.e. those which are not delivered to the carbonyl compound but are retained in the final phosphane oxide. «Stationary groups»[2] which are bulkier than the customary phenyl rings, should exert an increased steric pressure and thus enhance the *cis*-selectivity while smaller groups may lower it. Replacement of tri*phenyl*- by tri*alkyl*phosphonio-alkanides led to mainly *trans*-olefins indeed[5].

Now we have converted tri-2-furylphosphane, tri-2-thienylphosphane, tris(*o,o'*-difluorophenyl)phosphane, and tri-*o*-tolylphosphane with ethyl bromide into their phosphonium salts. Ylids were generated with sodium amide in tetrahydrofuran (THF) or diethyl ether (DEE) at 25 °C (1–2 h stirring), the aldehyde was added at −75 °C, and the mixtures were worked up after 1 h at 25 °C. With one exception, all (*Z*/*E*)-ratios were higher than that found with the standard triphenylphosphonio-ethanide. On average the ylids carrying heterocycles as stationary groups raised the *cis*-selectivity by roughly 4.5, the aryl-substituted ones even by more than 6 percentage points (see Table 2).

No such pronounced effects were possible in the series of homologous ylids since triphenylphosphonio-butanide itself approaches in general a 99% *cis*-selectivity provided the aldehyde is added at −75 °C. Under these conditions also the α-oxygen bearing «acrolein dimer» gives not more than trace amounts of the *trans*-isomer.

Table 1. Reaction of triphenylphosphonio-ethanide and its higher homologs with a variety of saturated and unsaturated aldehydes, solutions of the reagents in toluene (or, occasionally, tetrahydrofuran) being mixed at 0 °C: (*Z*/*E*)-ratios of the olefinic products.

$(H_5C_6)_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H\text{-}R' + R\text{-}CH{=}O \longrightarrow R\text{-}CH{=}CH\text{-}R'$

R' \ R	$H_{11}C_5$				
CH_3	91 : 9	87 : 13	87 : 13	79 : 21	-
C_2H_5	96 : 4	96 : 4	-	-	-
C_3H_7	-	96 : 4	-	-	-
C_5H_{11}	-	-	-	-	88 : 12[c]

Table 2. Reaction of triphenyl-, tri-2-furyl-, tri-2-thienyl-, tris(*o,o'*-difluorophenyl)-, and tri-*o*-tolylphosphonio-*ethanide* with a variety of aldehydes which were added to the ylid solutions in THF or DEE at 75 °C: (*Z*/*E*)-ratios of the olefins thus obtained[a–c].

$R''_3\overset{\oplus}{P}\text{-}\overset{\ominus}{C}H\text{-}CH_3 + R\text{-}CH{=}O \longrightarrow R\text{-}CH{=}CH\text{-}CH_3$

R'' \ R	$H_{11}C_5$	$H_7C_3\text{-}C{\equiv}C\text{-}CH$	$H_7C_3\text{-}C{\equiv}C\text{-}$	
	95.5 : 4.5	90.0 : 10.0	84.0 : 16.0	91.5 : 8.5
	97.0 : 3.0	94.5 : 5.5	95.0 : 5.0	94.0 : 6.0
	99.0 : 1.0	97.0 : 3.0	94.5 : 5.5	81.5 : 18.5
	99.0 : 1.0	96.0 : 4.0	92.5 : 7.5	99.0 : 1.0
	98.0 : 2.0	96.5 : 3.5	96.0 : 4.0	94.5 : 5.5

[a] The reactions were carried out on a 5 mmol scale and the products analyzed by gas chromatographic comparison with authentic samples, usually on two columns of different polarity (3 m 5% silver nitrate + benzyl cyanide on 10% Carbowax 20M; 2 m 10% SE-30; 2 m 10% Carbowax 20M; 30 m capillary OV-1701). Yields were determined applying the technique of an «internal standard» and corrected by means of calibration factors. They fell in the range between 54% and 97%, in general aryl-substituted ylids giving high, furyl- or thienyl-substituted ylids (due to their unsufficient chemical stability) only moderate yields. To check on the reproducibility, all reactions were repeated once, twice or three times and the reaction mixture of each individual run was injected at least three times into the gas chromatograph. Although accuracy and reproducibility were actually better, all (*Z*/*E*)-ratios were rounded to half-percentage points to take into account possible temperature-profile effects (see footnote[a] to Table 1 of the preceding communication[1]).

[b] New products were prepared on a 25 mmol (minimum) scale and correctly identified by spectra and combustion analyses. The *trans*-isomer was either selectively synthesized via the betaine-ylid or obtained by a non-selective Wittig reaction and subsequent separation.

[c] THF served as the solvent for all reactions involving tri-2-thienylphosphonio-ethanide or benzaldehyde, DEE for the rest.

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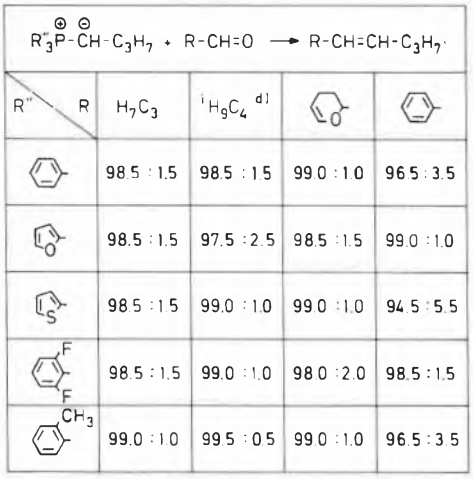
Only *aromatic* aldehydes produce olefins with somewhat diminished (*Z*/*E*)-ratios (typically 96:4 or 97:3). In such cases the 99% *cis*-isomer level may again be reached using the tri-2-furyl- or tris(*o*,*o*′-difluorophenyl)phosphonio-butanide (see Table 3). The phosphonium salt starting materials had been prepared as in the previous cases, just using butyl bromide instead of ethyl bromide.

Table 3. Reaction of triphenyl-, tri-2-furyl-, tri-2-thienyl-, tris(*o*,*o*′-difluorophenyl)-, and tri-*o*-tolylphosphonio-*butanide* with a variety of aldehydes which were added to the ylid solutions in THF or DEE at −75°C: (*Z*/*E*)-ratios of the olefins thus obtained [a–c].



R	H_7C_3	$^iH_9C_4$ [d]		
	98.5 : 1.5	98.5 : 1.5	99.0 : 1.0	96.5 : 3.5
	98.5 : 1.5	97.5 : 2.5	98.5 : 1.5	99.0 : 1.0
	98.5 : 1.5	99.0 : 1.0	99.0 : 1.0	94.5 : 5.5
	98.5 : 1.5	99.0 : 1.0	98.0 : 2.0	98.5 : 1.5
	99.0 : 1.0	99.5 : 0.5	99.0 : 1.0	96.5 : 3.5

[a] See footnote [a] to Table 2.
[b] See footnote [b] to Table 2.
[c] The reactions with butanal were carried out in DEE, all others in THF.
[d] $^iH_9C_4 = (H_3C)_2CH-CH_2$ (isobutyl).

Despite the smaller size of five-membered rings when compared to phenyl groups, the *cis*-selectivity of the furyl- and thienyl-substituted ylids was found to be almost as high and frequently even higher than that of standard triphenylphosphonio-alkanides. This does not necessarily constitute evidence against the «leeward approach model». First, the presence of oxygen or sulfur atoms will give rise to dipolar interactions and polarization transmission which certainly will effect the ylid conformations. Moreover, the stereodiscrimination which operates before or during oxaphosphetane formation is not the sole determining factor. The intermediate may either decompose «forward» to produce an olefin and phosphane oxide or «backward» to revert to its precursors ylid and aldehyde. Reversibility can no longer be neglected if the oxaphosphetane is derived from an aromatic aldehyde[1,6,7]. Since the activation barrier is lower in both directions, *cis*-oxaphosphetanes not only form but also undergo reversible decomposition preferentially. In other words, reversibility undermines *cis*-selectivity. Consequently, tri-2-furylphosphonio-butanide may produce higher proportions of *cis*-olefin than triphenylphosphonio-butanide even if its «intrinsic» stereoselectivity (kinetic *cis*/*trans*-discrimination in the oxaphosphetane-forming step) were inferior[8].

Preparation of phosphonium salts[9]: Tri-2-furylphosphane[10], tri-2-thienylphosphane[11], tris(*o*,*o*′-difluorophenyl)phosphane, and tri-*o*-tolyphosphane[12] were mixed with 2 equivalents of ethyl or butyl bromide and heated to 100°C during 20 h, 2 h, 100 h, and 125 h, respectively. The residues were dissolved in refluxing dichloromethane and crystallized upon addition of hot ethyl acetate. Tris(*o*,*o*′-difluorophenyl)phosphane (*m.p.* 125–127°C after crystallization from hexane) was obtained in 71% yield by reaction of *o*,*o*′-difluorophenyllithium[13] (0.45 mol) with triphenylphosphite (0.15 mol) in THF/DEE mixture.

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[3] In view of contradictory literature findings a re-examination of alkynal olefinations was deemed particularly warranted. When (*tert*-butyldimethylsilyl)propynal was treated with a reactive ylid (having a distant free NH group) *cis*- and *trans*-isomers were produced in a 96:4 ratio despite the presence of lithium bromide (1 equiv.) and the fact that the reagents were mixed at ordinary temperature [S.C. Carey, M. Aratani, Y. Kishi, *Tetrahedron Lett. 26* (1985) 5887]. When 4-(2-tetrahydropyranyl)-2-butynal was reacted with triphenylphosphonio-tridecanide in THF at −30°C and in the presence of lithium bromide (1 equiv.) *cis*-enyne was obtained «exclusively» [G. Cardillo, M. Orena, S. Sandri, C. Tomasini, *Tetrahedron 42* (1986) 917], while the same reaction with 4-(*tert*-butyldimethylsilyl)-2-butynal under otherwise identical conditions was claimed to afford «no detectable amount of *cis*-isomer» [R.S. Garigipati, S.M. Weinreb, *J. Am. Chem. Soc. 105* (1983) 4499]. We find the latter result mysterious.
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[5] M. Schlosser, B. Schaub, *J. Am. Chem. Soc. 104* (1982) 5821.
[6] A. Piskala, A.H. Rehan, M. Schlosser, *Collect. Czech. Chem. Commun. 48* (1983) 3539.
[7] Actually, we believe differences in the *cis*/*trans*-ratios of olefins prepared with the same ylid as mainly originating from a rather irreversible addition of the ylid to ordinary aliphatic aldehydes, say isobutyraldehyde, and a more reversible addition to their aromatic counterparts, say benzaldehyde.
[8] We owe some model calculations to Dr. *E. Moret* of this Department. Making a few reasonable assumptions he concludes that 97.5:2.5 *cis*/*trans*-olefin mixture will result from an initially 99.0:1.0 distribution of *cis*- and *trans*-oxaphosphetanes, if the *cis*-component reverts twice as fast to the precursors, ylid and aldehyde, than it releases the olefin by elimination of phosphane oxide.
[9] Experimental details are described in the Ph.D. thesis of B. Schaub (Université de Lausanne, 1985, 204 pages), a hard-copy of which can be obtained against prepayment of 25.– sFr.
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