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THE WITTIG REACTION OF NON-STABILIZED PHOSPHORUS YLIDES AND AROMATIC ALDEHYDES. STUDIES ON ERYTHRO AND THREO β-HYDROXYPHOSPHONIUM SALTS AND THE PROMOTION OF STEREOCHEMICAL DRIFT BY SYNERGISM BETWEEN DIASTEREOMERS

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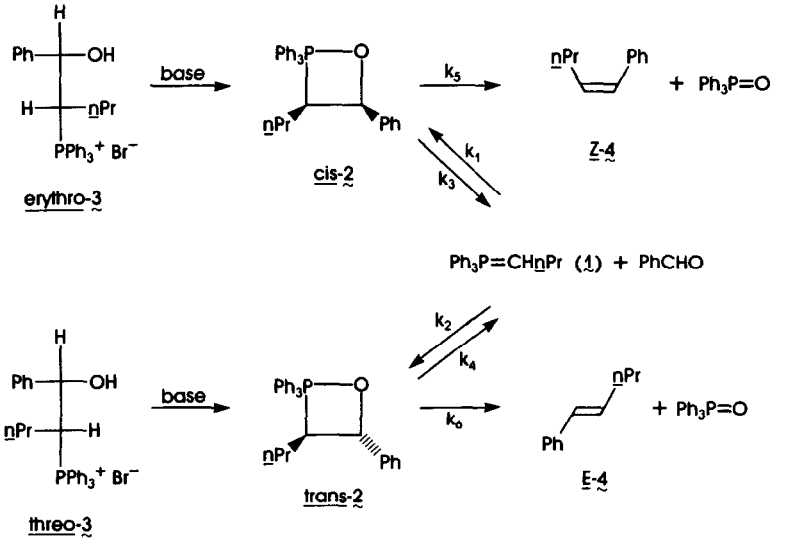
Abstract: In deprotonation studies with isomerically pure erythro-3 and threo-3, "retro-Wittig" reaction was only detected for erythro-3. Mixtures of erythro-3 and threo-3, under lithium salt-free conditions, undergo stereochemical drift because of synergism between diastereomeric oxaphosphetanes cis-2 and trans-2 during their decomposition to alkenes.

Recently, we have observed[1] individual cis and trans oxaphosphetanes in the Wittig reaction of non-stabilized phosphorus ylides and aldehydes by 145.8-MHz ^{31}P and 90.5-MHz ^{13}C NMR.[2] At low temperatures, the time course for all major species in representative Wittig reactions was monitored to obtain relative rates for the various reaction pathways.[1c] For example, in the reaction of butylidenetriphenylphosphorane (1) and benzaldehyde (PhCHO) the following relative rate constants (10^{-5} s^{-1}) were assessed from $^{31}P/^{1}H$ NMR measurements and computational analysis: k_3 = 13.9, k_4 = 0.93, k_5 = 4.8, k_6 = 7.9. The "stereochemical drift" observed, that is the production of more E alkene relative to the amount of trans oxaphosphetane present



initially, was attributed to enhanced reversibility of cis-2 relative to trans-2, in this case a factor of ca. 15. We noted,[3] however, that there is a substantial uncertainty in the k_4 value, because of inherent error in the NMR measurements, which could lead to a distortion of the k_3/k_4 ratio.

To examine further the area of reversibility and stereochemical drift, we have conducted a series of decomposition and decomposition-crossover experiments on diastereomerically pure Wittig intermediates, and on deliberately prepared mixtures, by deprotonation of the corresponding β-hydroxyphosphonium salts, erythro-3 and threo-3. Schlosser and coworkers[4] were the first to use β-hydroxyphosphonium salts as precursors to Wittig intermediates. Their work on a related pair of such salts indicated substantial stereoisomerization of the erythro salt after deprotonation with a lithium base[4a] and minor crossover with m-chlorobenzaldehyde.[4b] In reasonable accord with Schlosser's experiments,[4] we find on deprotonation that {1} pure threo-3 experiences no stereochemical drift while erythro-3 does to some degree, more so with Li present; and {2} pure threo-3 does not afford crossed products with 4-chlorobenzaldehyde while erythro-3 does, more so with Li present. Additionally, we have discovered that stereochemical drift is enhanced, in a concentration-dependent manner, when erythro-3 is deprotonated with a substantial amount of threo-3 (even in the absence of Li salt!!). These results suggest that cis-2 is much more prone to reversal than trans-2, a feature illustrated in our earlier kinetic studies but probably underestimated in the computational analysis.[1c]

Isomerically pure erythro-3 and threo-3 (both >99% stereochemically pure by 360-MHz ^{1}H NMR and 90.5-MHz ^{13}C NMR; structure of threo-3 was confirmed by X-ray analysis) were separately deprotonated and the resultant intermediates (oxaphosphetanes at some stage)[1a] were allowed to decompose either alone or in the presence of 4-chlorobenzaldehyde (crossover experiment). The results of these experiments are collected in the Table (entries 1-9).

With NaHMDS in THF at 23°C, threo-3 led to olefin with complete retention of stereochemistry and erythro-3 resulted in a very slight loss of stereochemical integrity (entries 2 and 1); however, with LiHMDS erythro-3 showed substantial stereochemical drift to E-4 while threo-3 faithfully retained the original stereochemistry (entries 3 and 4). This is consistent with reversibility through carbon-carbon bond cleavage ("retro-Wittig" reaction) insofar as cis-2 (from erythro-3) is expected to produce some trans-2 before its complete decomposition to alkene.[1c] But, it is curious that pure trans-2 (from threo-3) gives only the E alkene, revealing no reversal. (If trans-2 were to revert to ylide 1 and PhCHO to an appreciable degree, then cis-2 and Z alkene, Z-4, would be formed in the recombination process.) In this regard it is notable that PhCHO, which has to arise from "retro-Wittig" reaction, was detected and quantitated (GLC and GLC/MS) in the reactions of erythro-3 but not those of threo-3. Even deprotonation of erythro-3 under lithium salt-free conditions, with NaHMDS, created a small quantity (3%) of PhCHO along with alkenes 4 (92% yield; Z/E = 97:3, reflecting a very small amount of stereochemical drift).

Crossover experiments were conducted with pure salts erythro-3 and threo-3 (entries 5-9). After deprotonation at -78°C in THF, excess 4-chlorobenzaldehyde (4 mol equiv) was added to trap any ylide 1 formed by reversal, then the mixture was allowed to warm slowly to room tem-

perature.[5] In this way cis-2 and trans-2 were generated exclusive of each other (verified by low temperature ^{31}P NMR for the Na reaction)[1a] without any excess aldehyde or ylide present, as there often is in direct Wittig condensations. Erythro-3, but not threo-3, gave mixtures of expected and crossed products with either LiHMDS or NaHMDS. Additionally, PhCHO was detected (GLC) only in the reactions of erythro-3. The minor amount of alkene E-4 in the lithium-base crossover experiment of erythro-3 (Z/E = 96:4), compared to the lithium-base decomposition experiment (entry 3), is partly attributable to the low decomposition temperature (ca. -20°C) in the former case; however, excess aldehyde may also play a role, as suggested by Schlosser[4b] for a related stereochemical discrepancy. Threo-3 did not furnish any crossover products and showed absolutely no stereochemical drift away from trans-2 (^{31}P NMR of Na reaction)[1a] or E-4 during decomposition. In a mixed crossover experiment (entry 9) stereochemical drift was enhanced and crossed products were generated with expected Z/E ratios.

From this data, trans-2 does not appear to undergo "retro-Wittig" reaction, whereas cis-2 does. In our kinetic investigation we had concluded that the rate of conversion of cis-2 to ylide 1 and PhCHO was 7-15 times as fast as that for trans-2,[1c] although the standard deviation for rate constant k_4 was fairly large.[3] The crossover results demonstrate that oxaphosphetane cis-2 reverts much faster than oxaphosphetane trans-2; also, reversion of trans-2 (k_4) must be much slower (at least by a factor of 20) than its decomposition to alkene E-4 (k_6).

Mixtures of erythro- and threo-3 show stereochemical drift to alkene mixtures inordinately enriched in E isomer, without the presence of Li salt (entries 9-14). This is surprising since decomposition of each pure isomer gives almost exclusively the respective alkene (entries 1 and 2). Thus, it appears that stereochemical drift is accentuated when each diastereomer is present originally to a significant extent. Although such "diastereomeric synergism" in the decomposition of cis- and trans-2 might be reasonable with Li present, since there may be lithium-induced aggregates in solution and since stereochemical drift is enhanced by Li salt (qv. ref 1a and 1c and cf. entries 1 and 3), it is more difficult to comprehend for a lithium salt-free reaction. As expected, the cooperativity between the diastereomers is subject to a concentration effect (entries 12-14), stereochemical drift being diminished at higher dilution where there will be less intermolecular interaction. Mixtures of erythro- and threo-3 were deprotonated with NaHMDS at both 23°C and -78°C (entries 10-14); at 0.9 M, less stereochemical drift occurred at the elevated temperature (cf. entries 10 and 12).

Given this unusual result regarding synergism between diastereomers, we re-examined an earlier method[4a] for ascertaining the stereochemical composition of Wittig intermediates, one which involves converting the intermediates to β-hydroxyphosphonium salts with HBr, then decomposing such salts to alkenes (in ether) with potassium t-butoxide. We were able to reproduce this type of deprotonation experiment with 1.5 mol-equiv of sublimed KOtBu, as prescribed; but, mixtures of erythro- and threo-3 yielded alkene mixtures disproportionately enriched in the E alkene when unsublimed or excess KOtBu was used (entries 15-17).

Based on our kinetic studies[1c] and the experiments discussed herein (as well as in ref 4), reversibility of cis oxaphosphetanes derived from non-stabilized phosphorus ylides and aromatic aldehydes is much more facile than reversibility of trans oxaphosphetanes. Also,

cis and trans oxaphosphetanes interact synergistically (via some yet-undefined mechanism[6]), during their decomposition to alkenes, to form excessive amounts of E alkene.[7]

References and Notes

1. (a) Reitz, A. B.; Mutter, M. S.; Maryanoff, B. E. J. Am. Chem. Soc. 1984, 106, 1873. (b) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. Ibid. 1985, 107, 217. (c) Maryanoff, B. E.; Reitz, A. B.; Mutter, M. S.; Inners, R. R.; Almond, H. R., Jr. Ibid. 1985, 107, 1068.
2. Oxaphosphetanes were previously observed in such Wittig reactions by 40.5-MHz ^{31}P NMR, as sole intermediates (diastereomers unresolved): Vedejs, E.; Meier, G. P.; Snoble, K. A. J. J. Am. Chem. Soc. 1981, 103, 2823.
3. Reference 1c, microfilm supplement.
4. (a) Schlosser, M.; Christmann, K. F. Justus Liebigs Ann. Chem. 1967, 708, 1. (b) Piskala, A.; Rehan, A. H.; Schlosser, M. Coll. Czech. Chem. Commun. 1983, 48, 3539.
5. A competition experiment with ylide 1, PhCHO, and 4-chlorobenzaldehyde showed no significant difference between reaction rates.
6. Since the amount of stereochemical drift is rather small in terms of energetics (less than 0.7 kcal/mol), it is probably unreasonable to construct a detailed mechanistic rationale.
7. (a) Studies on solvent- and concentration-dependent effects in the Wittig reaction will be reported separately: Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E., manuscript in preparation. (b) Double-labeling (of both ylide and aldehyde portions) crossover experiments with erythro-3 or threo-3 and erythro-1-hydroxy-1-(4-chlorophenyl)-2-butyltriphenylphosphonium bromide supported the above observations; details will be reported later.

Table[a]

Entry	e-3/t-3	Base[b]	T (°C)	Conc (M)[c]	Z-4/E-4 (% yield)	Z/E for crossover (%)	% PhCHO
1	100:0	NaHMDS	23	0.2	97:3 (92)	--	3
2	0:100	NaHMDS	23	0.2	0:100 (74)	--	0
3	100:0	LiHMDS	23	0.2	62:38 (95)	--	2
4	0:100	LiHMDS	23	0.2	1:99 (72)	--	0
5[d]	100:0	NaHMDS	-78→23	0.1	96:4 (60)	85:15 (16)	18
6[d]	0:100	NaHMDS	-78→23	0.1	0:100 (90)	(0)	0
7[d,e]	100:0	LiHMDS	-78→23	0.1	96:4 (45)	76:24 (3)	17
8[d]	0:100	LiHMDS	-78→23	0.1	0:100 (80)	(0)	0
9[d]	56:44	NaHMDS	-78→23	0.1	41:59 (78)	83:17 (16)	10
10	56:44	NaHMDS	23	0.9	51:49 (74)	--	--
11	56:44	NaHMDS	23	0.02	55:45 (85)	--	--
12[f]	56:44	NaHMDS	-78→23	0.9	42:58 (74)	--	--
13	56:44	NaHMDS	-78→23	0.1	49:51 (57)	--	--
14	56:44	NaHMDS	-78→23	0.02	57:43 (84)	--	--
15	56:44	KOtBu[g]	23	0.17	54:46 (93)[h]	--	--
16	56:44	KOtBu[i]	23	0.17	44:56 (95)	--	--
17	50:50	KOtBu[g,j]	23	0.36	32:68 (56)	--	--

(a) e and t = erythro and threo. Reactions were conducted in THF, except for those with KOtBu, which were in ether (entries 15-17). Salts deprotonated at -78°C were stirred for 20 min before addition of 4-chlorobenzaldehyde. Alkene isomer ratios and yields are from GLC analysis (3% SE-30 on Chromasorb Q) by using Ph_2CH_2 as a reference, except for entries 5-9, which were referenced to the 4-chlorobenzaldehyde (corrected for the small amount consumed). (b) HMDS = hexamethyldisilazide. 1.1 mol-equiv of base was employed for entries 1-14. (c) Based on the amount of salt and solvent, assuming complete deprotonation. (d) This is a crossover experiment; the crossed products are Z/E-1-(4-chlorophenyl)-1-pentene. (e) Five independent experiments gave similar results. (f) The isomer ratio is an average of two experiments (±5%). (g) 1.5 mol-equiv of base. (h) No concentration dependence was observed (0.07-0.5 M). (i) 5.0 mol-equiv of base. (j) Unsublimed KOtBu.

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