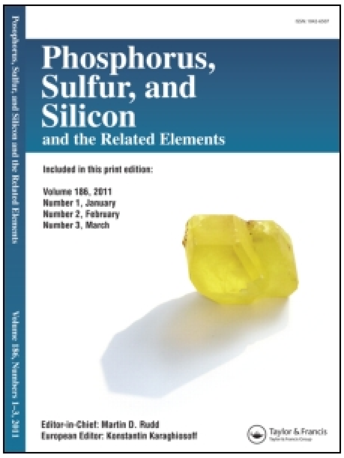

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REACTION OF LITHIUM-ALLYLPHOSPHONIC-BIS-(DIMETHYLAMIDE) WITH SCHIFF BASES. TEMPERATURE AND STERIC EFFECT ON THE REGIOSELECTIVITY

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The reaction of lithium-allylphosphonic-bis-(dimethylamide) **1** with aromatic Schiff bases **2a–e** is studied. It is found that mainly mixtures of α and γ adducts or, in some cases, only γ adducts are formed, the ratio $\alpha:\gamma$ depending on the reaction conditions as well as on the steric effect of the substituents in the Schiff base. In the most cases pure α and γ adducts are isolated by recrystallisation of the crude products.

INTRODUCTION

The ambident reagent lithium-allylphosphonic-bis-(dimethylamide) **1** has been investigated as olefinating reagent in reaction with aldehydes and ketones,[1] where the ratio of the obtained adducts α and γ has been found to depend mainly on steric factors. The influence of the same factors as well as the electronic one on the $\alpha:\gamma$ ratio has been studied in more details in the addition reaction of the analogous allylphosphonic esters[2,3] and allylphosphine oxides[4,5] with aldehydes and ketones.

RESULTS

In the present work we report the results of our investigations on the reaction of the lithium reagent **1** with aromatic Schiff bases **2a–e** with respect to the synthetical scope of the reaction as well as to the influence of the reaction conditions and the effects of the substituents in the Schiff bases on the regioselectivity.

The reaction was carried out in THF or ether at −70°C for 5 hours (method A), or 1 hour at −70°C and then 1 hour at −50°C (method B), or 5 hours at −50°C (method C), α and γ or only γ adducts being formed according to the Scheme 1.

With the Schiff basees **2b** and **2c** by method A only γ adducts **3b** and **3c** in 80% yields were isolated, while in all other cases mixtures of γ and α adducts, i.e., N,N,N′,N′-tetramethyldiamides of 4-arylamino-4-aryl-1-butene-1- and 3-phosphonic acids **3** and **4**, respectively, are obtained in total yields 23–85% (Table I).

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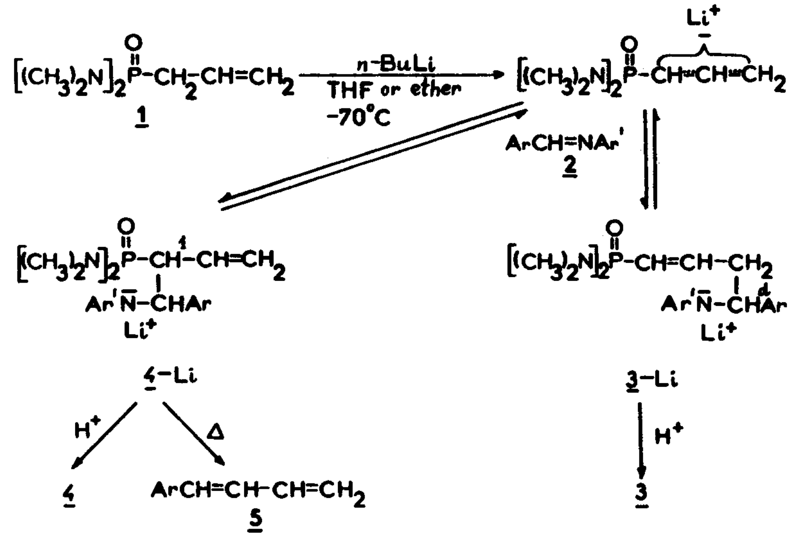


	Ar	Ar'
2,3,4a	C_6H_5	C_6H_5
b	C_6H_5	C_6H_4-Cl-/2/
c	C_6H_5	$C_6H_3Cl_2$-/2,4/
d	C_6H_5	C_6H_4-Cl-/4/
e	4-Cl-C_6H_4	C_6H_5

SCHEME 1

The ratio $\alpha:\gamma$ as listed in Table I was determined on the basis of the integral intensity in the ^{1}H NMR spectra of the product mixtures for the signals as follows: $\delta = 3.14$ for H^1 in **4b, c** and $\delta = 4.32$–4.65 for H^d in **3b, c** and $\delta = 3.60$–3.62 for H^1 in **4a, d, e** and $\delta = 4.38$–4.40 for H^d in **3a, d, e**. After washing and recrystallisation of the mixtures usually the less soluble α adducts, or—when highly predominant—γ adducts in pure state were isolated (Table II). Their yields in relation to the starting isomer mixtures are shown in Table I. The structure of the isolated pure α and γ adducts is supported by their IR and ^{1}H NMR spectra (see the data in Tables II, III).

DISCUSSION

1. Influence of the Substituents in the Schiff Base

With Schiff bases **2a**, **2d** and **2e**, non-containing ortho substituents in the aniline nucleus, at -70°C in THF (method A) the ratio $\alpha:\gamma$ is approximately 1 : 1. With a chlorine atom in ortho position (**2b, 2c**) the reaction becomes highly regioselective, γ

TABLE I

Total yields and $\alpha:\gamma$ ratio of the adducts depending on the reaction conditions

Experiment	Schiff base	Solvent	Method	Ratio ($\alpha:\gamma$)	Yield % ($\alpha+\gamma$)	Isolated pure isomer %*
1	**2a**	THF	A	1 : 1	58	α40
2	**2a**	THF	C	2.5 : 1	not isolated	—
3	**2a**	THF	B	2 : 1	63	α60
4	**2a**	ether	B	1 : 5	45	γ75
5	**2a**	ether	B*	1.5 : 1	40	α55
6	**2b**	THF	A	0 : 1	80	γ90
7	**2b**	THF	C	1 : 3	79	γ75
8	**2c**	THF	A	0 : 1	80	γ90
9	**2c**	THF	C	1 : 4	85	γ80
10	**2d**	THF	A	1 : 1	51	α40
11	**2d**	THF	C	3 : 1	40	α70
12	**2d**	THF	B	2 : 1	41	α60
13	**2d**	ether	B	1 : 2	23	α30
14	**2e**	THF	A	1 : 1	51	α40
15	**2e**	THF	C	2 : 1	not isolated	—

*Related to the starting mixture $\alpha+\gamma$ adduct.

isomeric adducts (E)-**3b** and (E)-**3c** being exclusively obtained. It can be assumed that this is due to the steric effect of the ortho substituent. Thus, no or low regioselectivity at −70°C is observed when the chlorine atom is in para position.

2. *Influence of the Temperature and the Solvent*

In all cases the rise of the reaction temperature from −70°C (method A) to −50°C (method B and especially method C) leads to increase of the ratio $\alpha:\gamma$. Thus, in THF solution with non-ortho substituted bases **2a**, **2d** and **2e** the ratio $\alpha:\gamma$ goes up from 1 : 1 to 2 : 1 and even 3 : 1 (compare experiments 1 with 3 and 2; 10 with 12 and 11; 14 with 15; Table I). The effect is the same with the ortho substituted bases **2b** and **2c**, where the ratio $\alpha:\gamma$ increases from 0 : 1 to 1 : 3 and 1 : 4, respectively. These results show, that at −70°C the reaction is entirely (in the cases of **2b** and **2c**) or predominantly kinetically controlled, while at −50°C the reaction seems to be more reversible and the thermodynamically more stable α adducts are formed to a higher degree. This conclusion is confirmed by experiments with prolonged reaction time at −50°C, where the ratio $\alpha:\gamma$ increases significantly (see experiments 4 and 5, 2 and 3, 11 and 12, Table I).

When ether instead of THF as solvent is used, the reaction at −50°C seems to be less reversible, γ adducts being predominantly formed (compare experiments 3 with 4, 12 with 13, Table I). By prolonging the reaction with the base **2a** at −50°C the ratio $\alpha:\gamma$ increases from 1 : 5 to 1.5 : 1, i.e. near to that in THF (method C) (compare experiments 4 and 5, Table I).

The ^{1}H NMR (multiplicity of N—CH_3 signals) and TLC data show, that with the bases **2a**, **2d** and **2e** mixtures of erythro and threo **4** are obtained, while with the ortho substituted bases **2b** and **2c** only one of the diastereomers **4b** and **4c** is formed stereoselectively.

TABLE II

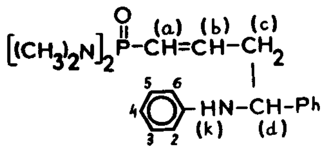
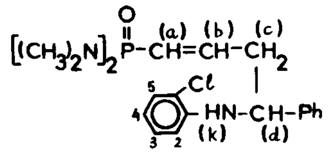
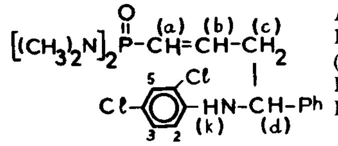
Physical constants, analytical and IR spectral data of the adducts 3 and 4

			Elemental Analysis calc. (found) %				
Compound	M.p. °C		C	H	N	P	IR (nujol)
3a	105–107	$C_{20}H_{28}N_3PO$	67.21	7.88	11.75	8.66	970–980 cm^{-1} (ν_{P-N}); 1175 cm^{-1} ($\nu_{P=O}$);
		(357.39)	(66.99)	(8.11)	(11.52)	(8.60)	1610–1645 cm^{-1} ($\nu_{C=C}$); 3300 cm^{-1} (ν_{N-H})
3b	113–115	$C_{20}H_{27}N_3POCl$	61.31	6.93	10.72	7.90	970–980 cm^{-1} (ν_{P-N}); 1170–1195 cm^{-1} ($\nu_{P=O}$);
		(391.81)	(61.62)	(7.24)	(10.62)	(7.53)	1645–1655 cm^{-1} ($\nu_{C=C}$); 3300 cm^{-1} (ν_{N-H})
3c	157–158	$C_{20}H_{26}N_3POCl_2$	56.35	6.14	9.85	7.26	965–975 cm^{-1} (ν_{P-N}); 1175–1190 cm^{-1} ($\nu_{P=O}$);
		(426.28)	(56.69)	(6.35)	(10.00)	(7.51)	1610–1640 cm^{-1} ($\nu_{C=C}$); 3300 cm^{-1} (ν_{N-H})
4a	152–154	$C_{20}H_{28}N_3PO$	67.21	7.88	11.75	8.66	970–980 cm^{-1} (ν_{P-N}); 1175–1195 cm^{-1} ($\nu_{P=O}$);
		(357.39)	(67.27)	(7.99)	(11.56)	(8.63)	1610–1645 cm^{-1} ($\nu_{C=C}$); 3325 cm^{-1} (ν_{N-H})
4d	165–167*	$C_{20}H_{27}N_3POCl$	61.31	6.93	10.72	7.90	970 cm^{-1} (ν_{P-N}); 1165–1185 cm^{-1} ($\nu_{P=O}$);
	185–188	(391.81)	(61.02)	(6.82)	(10.56)	(7.80)	1610–1640 cm^{-1} ($\nu_{C=C}$); 3320 cm^{-1} (ν_{N-H})
4e	148–149*	$C_{20}H_{27}N_3POCl$	61.31	6.93	10.72	7.90	970 cm^{-1} (ν_{P-N}); 1155–1170 cm^{-1} ($\nu_{P=O}$);
	169–172	(391.81)	(61.48)	(6.95)	(10.50)	(8.22)	1610–1645 cm^{-1} ($\nu_{C=C}$); 3300 cm^{-1} (ν_{N-H})

*Melting points of crystals (without preliminary powdering). The sharp melting points in two regions show that the substances are mechanical mixtures of pure diastereoisomers.

TABLE III

^{1}H NMR spectral data of the adducts **3***

Compound	^{1}H NMR ($CDCl_3$)
3a 	*100 MHz*: 2.44d and 2.48d (12 H, N—CH_3, $^3J_{PH}$ = 10 Hz); 2.57–2.80 (m, 2 H, H^c); 4.04 (b, 1 H, H^k); 4.42 (t, 1 H, H^d, $^3J_{dc}$ = 6 Hz); 5.60 (dd, 1 H, H^a, $^3J_{ab}$ = 17 Hz, $^2J_{PH}$ = 20 Hz); 6.40–7.20 (m, 11 H, H^b, H^2, H^3, H^4, H^5, H^6, Ph)
3b 	*250 MHz*; 2.56d and 2.58d (12 H, N—CH_3, $^3J_{PH}$ = 10.5 Hz); 2.66–2.88 (m, 2 H, H^c); 4.50–4.65 (m, 1 H, H^d); 4.74 (d, 1 H, H^k, $^3J_{kd}$ = 6.5 Hz); 5.84 (dd, 1 H, H^a, $^3J_{ab}$ = 17 Hz, $^2J_{PH}$ = 20 Hz); 6.37 (d, 1 H, H^2); 6.58 (t, 1 H, H^4); 6.67–6.79 (m, 1 H, H^b); 6.96 (t, 1 H, H^3); 7.23–7.42 (m, 6 H, H^5 and Ph)
3c 	*100 MHz*: 2.48d and 2.52d (12 H, N—CH_3, $^3J_{PH}$ = 10 Hz); 2.63–2.80 (m, 2 H, H^c); 4.32–4.50 (m, 1 H, H^d); 4.62 (d, 1 H, H^k, $^3J_{kd}$ = 6 Hz); 5.75 (dd, 1 H, H^a, $^3J_{ab}$ = 18 Hz, $^2J_{PH}$ = 20 Hz); 6.20 (d, 1 H, H^2), 6.40–6.65 (m, 1 H, H^b); 6.70–6.90 (m, 1 H, H^3); 7.10–7.30 (m, 6 H, H^5, Ph)

*The complete interpretation of the ^{1}H NMR spectra of the α adducts **4** did not succeed because the diastereoisomeric mixtures of erythro and threo are not till now separated. For determination of the $\alpha : \gamma$ ratio the signals ^{1}H (m, 100 MHz) were used as follows: **4a**: 3.62; **4b**: 3.14; **4c**: 3.14; **4d**: 3.60; **4e**: 3.60.

3. *Olefination of the α Adducts*

The olefination of the α adduct obtained from **1** and **2b** succeeded only when the reaction mixture formed at −50°C (containing lithium salts **3b**–Li and **4b**–Li) is refluxed in benzene for 2½ hours. In this way (E)-1-phenyl-1,3-butadiene **5b** was obtained in 30% yield with respect to the total starting reaction mixture ($\alpha + \gamma$). The olefin formation in this case proceeds according to the mechanism, proposed by L. Horner[6] for the reaction of PO-activated olefination, as we have shown for other tetramethyldiamidophosphonate carbanions with Schiff bases.[7] An attempt to realize Corey's thermolysis of the corresponding protonated form **4b** did not succeed, probably due to the weaker protonodonating ability of the N—H group compared with the OH group in the analogous α-hydroxy adducts obtained from **1** and carbonyl compounds.[1]

EXPERIMENTAL

The *n*-buthyllithium was commercial "Merck-Schuchardt" (15%-solution in hexan). THF, used as a water free solvent was treated with $LiAlH_4$ and after distillation was boiled with Na in the presence of benzophenone. The qualitative TLC investigations were carried out on silica gel 60 F_{254} (aluminum sheets "Merck") using hexan–acetone 1 : 1 as a mobile phase (for adducts) and hexan (for olefins). The IR spectra were measured on a "Zeiss" UR-10 spectrometer, the ^{1}H NMR spectra on a JEOL-JNM-100 and Bruker WM-250 spectrometer at normal probe temperature in $CDCl_3$. The chemical shifts are relative to internal TMS or HMDSO.

GENERAL PROCEDURE OF WORK

To a solution of **1** (5 mmole) in 5–10 ml anhydrous THF (or ether), cooled to $-70°C$, buthyllithium (5 mmole, 15% in hexan) diluted with 4–8 ml THF (ether) was added under argon. After stirring for 30 minutes at this temperature, Schiff base **2** (5 mmole) in 7–10 ml THF (ether) was added and the stirring continued for 5 hours at $-70°C$ (method A) or 1 hour at $-70°C$ and 1 hour or 5 hours at $-50°C$ (method B or B*, respectively) or 5 hours at $-50°C$ (method C). The mixture was hydrolysed with 10 ml water, then extracted with CH_2Cl_2 (3 × 20 ml), the extracts were washed with water (2 × 2 ml) and dried over magnesium sulfate. After evaporation of the solvent, the residue was examined by ^1H NMR and TLC for determination of the ratio $\alpha : \gamma$. The crude product was washed with hexan, than with ether/hexan 1 : 3 and recrystallized from ether.

OLEFINATION OF 4-LI

The reaction mixture from method C was brought to room temperature, THF distilled off and replaced by 10 ml anhydrous benzene. The mixture was refluxed for $2\frac{1}{2}$ hours, then hydrolyzed with 10 ml water. The formed two layers were separated and the water layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic solutions were washed with water (2 × 2 ml), dried over anhydrous magnesium sulfate and distilled at reduced pressure.

Yield of 1-phenylbutadiene: 0.2 g (30%); b.p. 83–85°C (145 Pa) $N_D^{25} = 1.6082$.

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