Tetrahedron Letters,Vol.29,No.30,pp 3647-3650,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REACTIONS OF 2-AZA-PENTADIENYL ANIONS WITH CARBONYL COMPOUNDS: REGIOSELECTIVITY

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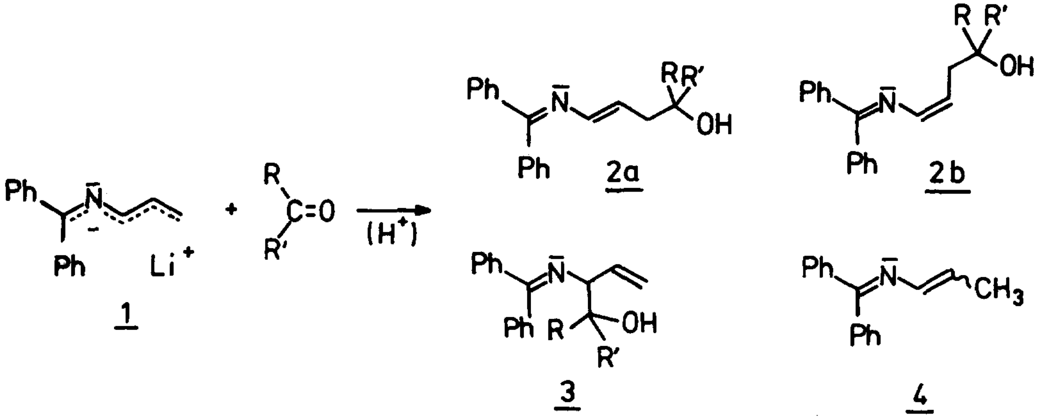
Abstract: 2-Aza-pentadienyl anions **1** are easily prepared by deprotonation of N-allylic imines. They react with carbonyl compounds yielding 3- and 5-substituted 2-aza-pentadienyl derivatives **2** and **3**, depending on the reaction conditions.

In aza-pentadienyl anions one of the CH-units of pentadienyl anions is replaced by the more electronegative nitrogen atom. The magnitude of this electronic perturbation depends on the position of the nitrogen atom and has important consequences on reactivity and chemical properties of the resulting anions. In 1- and 3-azapentadienyl anions the nitrogen atom is favourably located at a place with high electron density in the HOMO. However, in 2-aza-pentadienyl anions the perturbation is situated at a node position of the HOMO; according to ab initio calculations (GAUSSIAN 82[1]) this unfavourable position leads to a higher ground state energy (E_{rel} = 18.1 kcal/mol at 3-21+G//3-21+G[2]) and corresponding increased reactivity, compared to 1-aza-pentadienyl anions (E_{rel} = 0.0 kcal/mol) and 3-aza-pentadienylanions (E_{rel} = 5.3 kcal/mol).

For synthetic purposes, 2-aza-pentadienyl anions are of considerable interest as polyfunctional d^3 and d^5 reactive intermediates for C-C-bond formation reactions. In this communication we report our results of a study on the regiochemistry of the quenching reaction of 2-aza-pentadienyl anions with carbonyl compounds. Electrocyclization reactions of 2-aza-pentadienyl anions are other valuable possibilities, leading to heterocyclic systems[3,4].

N-allylic imines - easily prepared from carbonyl compounds and allylamine - are readily deprotonated using metallated amines. In this paper we concentrate on the chemistry of the 1,1-diphenyl-2-aza-pentadienyl system obtained from benzophenone and allylamine[5]. The metallation reaction is carried out at -78°C in THF using 1.1 molequivalents of base. After warming up to -20°C[6] the solution of the deep red coloured anion **1** is cooled down to -78°C. Extensive ^1H- and ^{13}C-NMR investigations have shown, that this lithium compound **1** adopts exclusively the all-trans W-conformation (^{1}H-NMR coupling constants and NOE experiments[7,8]). Treatment of the reaction mixture with a diluted solution of the carbonyl compound, aqueous work up (sat. $NaHCO_3$ solution) and HPLC separation (Si-60 (Merck), hexane/ethylacetate 9:1) yield the 2-aza-pentadienyl derivatives 2a, 2b and 3.

$$Ph_2C{=}O + H_2\bar{N}{-}CH_2{-}CH{=}CH_2 \xrightarrow[-H_2O]{} Ph_2C{=}\bar{N}{-}CH_2{-}CH{=}CH_2 \xrightarrow{-H^+}$$



In table 1 the results of several quenching experiments under standard conditions are summarized. The yields of the isolated products are generally quite good. The quenching reactions using less reactive ketones are regioselective, yielding only the products 2a resulting from an attack in 5-position of

Table 1: Reactions of 1,1-diphenyl-2-aza-pentadienyl-lithium 1 with carbonyl compounds: Yields (%) of isolated products (standard conditions: -78°C, THF, LDA)

R,R'	2a	2b	3	Total Yield
Ph,Ph	82	-	-	82
Fluorenyl	78	-	-	78
Ph,CH_3	61	-	-	61
tBu,CH_3	83	-	-	83
$-(CH_2)_5-$	41	4	37	82
CH_3,CH_3	21	4	34	59
C_9H_{14} (Adamantanon)	48	5	20	72
tBu,tBu	-	-	-	0
H,Ph	24	-	28+20 a)	72
H,$CH(CH_3)_2$	6	-	64 b)	70

a) diastereomers b) diastereomers (not separated) the anion. However, the more reactive aliphatic ketones form under standard conditions the products 2a and small amounts of their stereoisomers 2b, together with the nonconjugated diastereomeric products 3 of an attack in 3-position. Aldehydes also form mixtures of 3- and 5-substituted products.

Several experiments were performed to optimize the reaction conditions to improve the regioselectivity of the reactions with cyclohexanone and aldehydes. Temperature of addition, solvent and complexing agents were varied

Table 2: Reactions of 1,1-diphenyl-2-aza-pentadienyl anions with carbonyl compounds: Influence of variation of reaction conditions; relative yields of products 2, 3 and 4 (NMR integration)

R,R'	Base	Temp. (°C)	Solv.	Complexing Agent	Yield 2a	% 3	4
$-(CH_2)_5-$	LDA	-78	THF	-	55	45	-
	LDA	0	THF	-	41	59	-
	LDA	-78	THF	-	45	-	55 a)
	KOtBu	-78	THF	-	-	-	100
	KDA	-78	THF	-	-	-	100
	LDA	-78	THF	HMPA	72	28	-
	LDA	0	THF	HMPA	32	-	68
	LDA	-78	THF	TMEDA	60	40	-
	LDA	0	THF	TMEDA	41	59	-
	LDA	-78	Hexane	-	43	57	-
	LDA	0	Hexane	-	29	71	-
H,Ph	LDA	-78	THF	-	33	67	-
	LDA	0	THF	-	29	71	-
	LDA	-78	THF	DMEU	53	47	-
	LDA	-78	THF	HMPA	100	-	-
	LDA	0	THF	HMPA	-	-	- b)
H,CH_2Ph	LDA	-78	THF	-	-	-	100
$H,CHPh_2$	LDA	-78	THF	-	-	-	100
H,CH_2CH_3	LDA	-78	THF	-	7	93	-
	LDA	-78	THF	HMPA	75	-	25
$H,CH(CH_3)_2$	LDA	-78	THF	-	8	92	-
	LDA	-78	THF	DMEU	46	54	-
	LDA	-78	THF	HMPA	74	6	20

a) 9h reflux temperature b) polymerization

HMPA: hexamethyl phosphoroustriamide DMEU: 1,3-dimethylimidazolidin-2-one (table 2). In these experiments (relative yields are given, calculated from NMR integration) occasionally the rearranged starting material 4 was obtained as an additional product. As it can be seen from the table the regiochemistry of the quenching reaction can be influenced. Best yields of products of type 2 are obtained using LDA as a base at low temperature in THF with additional HMPA; TMEDA and DMEU are less effective. In order to obtain good yields of the thermodynamically less stable product 3 (kinetic controll) LDA, low temperatures and apolar solvents (hexane) should be used. Thus, there are several possibilities to influence regioselectivity, but in many cases careful separation of the isomeric products remains necessary.

Aqueous hydrolysis of the imine C=N bond of compounds 2 produces valuable synthetic building blocks: from the 2-aza-butadienes 2 2-hydroxyfuran derivatives[9] may be obtained, which result from the cyclization reaction of intermediate, hardly isolable γ-hydroxy aldehydes. Further investigations on azapentadienyl anions are in progress.

We thank the Fonds der Chemischen Industrie, Frankfurt, for financial support and the BASF AG, Ludwigshafen, for generous gifts of chemicals.

Dedicated to Professor A.R.Katritzky,FRS, on the occasion of his 60th birthday

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7) ^{1}H-NMR data for 1,1-diphenyl-2-aza-pentadienyl-lithium 1 (all-trans) (400 MHz, d_8-THF, -61°C): 3.73 (d, ^3J(H5cis-H4) = 10.64 Hz, 1H, H5cis), 3.95 (d, ^3J(H5trans-H4) = 16.07 Hz, 1H, H5trans), 6.45 (ddd, ^3J(H3-H4) = 9.64 Hz, 1H, H4), 7.03 (d, 1H, H3), 6.19 - 7.23 (m, 10H, Ph) ppm.
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(Received in Germany 18 April 1988)