1,3-ANIONIC CYCLOADDITIONS OF 2-AZAALLYLLITHIUM COMPOUNDS TO ETHYLENE. SYNTHESIS OF 2,5-DIARYLPYRROLIDINES

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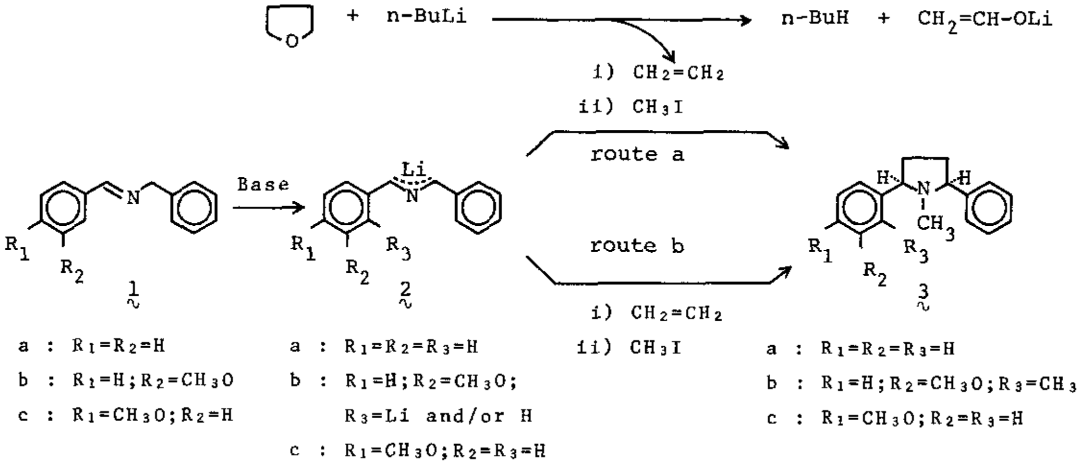
Abstract — Anionic cycloaddition of 1,3-diaryl-2-azaallyllithiums with the ethylene formed in situ by the cleavage of THF by n-butyllithium gave cis-2,5-diarylpyrrolidines in synthetically useful yields. The same cycloadducts were obtained from the reaction of **2a** and **2c** with ethylene itself.

It has been recently demonstrated by the pioneering studies of Kauffmann et al.[1] and others[2] that 2-azaallyllithium compounds undergo 1,3-anionic cycloaddition reactions with conjugated or activated olefins to afford pyrrolidine derivatives. However, alkenes with unstrained isolated double bond have been believed not to be attacked by these 2-azaallyllithium compounds.[1a,c] During the course of other studies we had an occasion to note that when the Schiff base **1b** was treated with an excess of n-butyllithium in THF, a pyrrolidine derivative **3b** was formed although in a low yield. It is well known[3] that THF is cleaved by n-butyllithium to afford ethylene and the lithium enolate of acetaldehyde. It was therefore anticipated that the formation of the product might be rationalized in terms of the reaction of the 2-azaallyllithium compound with the ethylene derived in situ from THF (vide infra). This finding led us to investigate the reaction more closely, since there was a possibility that it would provide a convenient and direct[1d,6] method for the synthesis of certain 2,5-disubstituted pyrrolidine derivatives. We now report that cis-2,5-diarylpyrrolidines are formed in synthetically useful yields by anionic cycloaddition of 1,3-diaryl-2-azaallyllithiums with a simple unactivated olefin, ethylene.

Treatment of the Schiff bases **1** in THF with an excess of n-butyllithium at low temperature[4] resulted in a formation of deep red solutions of **2**,[1c,5] which were allowed to stand at room temperature. The products were characterized as their



Scheme

N-methyl derivatives. Thus, quenching of the reaction mixture with methyl iodide afforded the pyrrolidines 3 (Scheme, route a). The following procedure for the preparation of 3a is illustrative. To a solution of 1a in THF under nitrogen at -78°C was added n-butyllithium in hexane (3.2 equiv) and the resulting solution was stirred at room temperature for 24 h. Treatment of the reaction mixture with methyl iodide (3.3 equiv, -78°C (2.5 h) then up to -35°C) followed by quenching (sat. aq. NH_4Cl) and extraction (ether) furnished an oil, which was heated under reflux in 5% hydrochloric acid. The aqueous layer, obtained after washing of the crude reaction mixture with ether, was extracted with CH_2Cl_2. The CH_2Cl_2 solution was concentrated, made basic with 10% KOH and extracted with ether. After drying ($MgSO_4$) and concentration, there was obtained an oil, from which 3a was

Table I. Formation of 2,5-Diarylpyrrolidines from 1 via Route a

entry	Schiff base	ratio n-BuLi/ 1	temp.	time,h	product	isolated yield,[a]%
1	1a	3	r.t.	12	3a	43
2	1a	3	r.t.	24	3a	61
3	1b	3	r.t.	12	3b[b]	19
4	1b	4	r.t.	38	3b	40(53)
5	1c	3	r.t.	37	3c[c]	78(82)
6	1c	4	r.t.	36	3c	49(66)

[a] Yields determined by GLC are given in parentheses. [b] mp 95.5-96.5°C;MS (m/e) : 281(M^+,40%). [c] mp 48.5-49.5°C;MS (m/e): 267(M^+,58%).

isolated by column chromatography (silica gel, benzene) in a yield of 61%, mp 66 - 67°C (lit.[6] mp 60°C). The results are summarized in Table I.

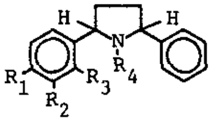
Effects of the reaction time and the amount of n-butyllithium on the reaction can be seen from Table I. An increase in the amount of the base sometimes resulted in a decrease in the yield of a cycloadduct, as was the case in the reaction of 1c (entry 6). This was probably due to an increased formation of a simple addition product (N-benzyl-N-methyl-1-(p-methoxyphenyl)pentylamine; 26%, GLC). In regard to the reaction temperature, it was found that at higher temperature (50°C) formation of a cycloadduct (2,5-diphenylpyrrolidine) reached a maximum (43%, GLC) in a certain time and further continuation of the reaction was ineffectual.

The results (entry 2,4 and 5) indicate that 2,5-diarylpyrrolidines containing some substituents on an aromatic ring can be readily prepared in satisfactory yields by taking advantage of the cleavage reaction of THF by n-butyllithium. It is of interest to find that the yield of 3 (R_1= CH_3O;R_2= CH_3;R_3= H) was not more than 6% (GLC; entry 6) whereas the ortho-methylated cycloadduct 3b was the dominant product (entry 3 and 4) under the reaction conditions employed.

Taking account of the reported stereospecific cis additions[1] of 1,3-diphenyl-2-azaallyllithium to conjugated alkenes, it is reasonable to infer that cis cycloaddition products can be obtained from the reactions in the present investigation. Breuer et al.[6] have prepared cis- and trans-1-methyl-2,5-diphenylpyrrolidines by the reaction of 1-benzoyl-2-phenylcyclopropane with N-methylformamide and assigned the stereochemistry of these compounds based on the ^{1}H nmr spectral behaviour of these stereoisomers. By comparison of the ^{1}H nmr spectral data of 3a given in Table II with the chemical shift values reported for the corresponding cis isomer, the configuration of 3a was thus determined to be cis. That 3b and 3c also have the cis configuration was deduced on the basis of the observation, as well as the above consideration, that the corresponding chemical shift values for these compounds were very similar to those for 3a (Table II).

It was reasonably assumed that the formation of pyrrolidine derivatives in the above reaction was due to the reaction of 2 with the ethylene formed in situ by the reaction of THF with n-butyllithium present in excess, since no trace of a cycloadduct was detected in either a similar reaction of 1a performed in diglyme as a solvent or the reaction of 2a in THF, in which 2a was prepared from 1a using LDA (1 molar equiv) as a base and allowed to react at room temperature for 17 h.

Table II. Chemical Shifts of α-Protons of 2,5-Diarylpyrrolidines



compd				chemical shift[a], δ (TMS)	
R_1	R_2	R_3	R_4	$CDCl_3$	$CDCl_3$ + TFA-d
H	H	H	H[b,c]	4.25 (4.25)	4.91 (5.00)
H	H	H	CH_3 (3a)	3.35 (3.34)	4.36 (4.45)
H	CH_3O	CH_3	CH_3 (3b)	3.41, 3.68	4.45, 4.87
CH_3O	H	H	H[b]	4.24	5.11
CH_3O	H	H	CH_3 (3c)	3.34	4.34

[a] Literature values (ref 6) for the corresponding cis isomers are given in parentheses. [b] Obtained by quenching the reaction mixture with H_2O. [c] The hydrochloride, mp 221-222°C (lit.[7] mp 224.7-225.5°C).

In order to prove this assumption a reaction of 2a with ethylene itself was undertaken (Scheme, route b). Thus, into a solution of 2a in THF, prepared by adding 1a to LDA (1.1 equiv) in THF at -70°C, was bubbled ethylene gas at room temperature for 18 h. Quenching with methyl iodide (4.6 equiv, -48°C then up to 18°C, 1.5 h) followed by the workup as described above gave a cycloadduct (14%) which was identical in every respect with 3a obtained in the above reaction. Similarly, 3c was isolated in a yield of 30%[8] in an analogous reaction of 2c with ethylene (r.t., 8 h).

It is clearly demonstrated by the present investigation that 1,3-diaryl-2-aza-allyllithiums add to ethylene to give cycloaddition products in synthetically useful yields. Further application of this approach to the preparation of other pyrrolidine derivatives is in progress.

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8. The experiment has not been optimized, but the basic fraction, obtained originally as a mixture of hydrochlorides by extraction with CH_2Cl_2, contained two cycloaddition products, **3c** (70%) and 2-(p-methoxyphenyl)-5-phenylpyrrolidine (23%)(GLC).

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