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ADDITION AND METALLATION IN THE REACTION OF n-BUTYL-LITHIUM WITH 2-FERROCENYLPYRIDINE

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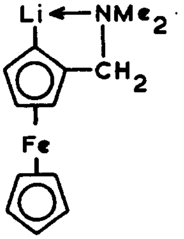
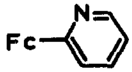
A number of N,N-dialkylarylmethylamines including benzyldimethylamine (2), dimethylaminomethylferrocene (I), (3), N-(ferrocenylmethyl)piperidine (4), and N-(ferrocenylmethyl)pyrrolidine (4), have been shown to undergo specific 2-lithiation by n-butyl-lithium in ether-hexane. Thus the amine (I) gave the lithio-amine (I') and this intermediate was condensed with benzophenone and other electrophilic reagents to afford the corresponding 1,2-disubstituted ferrocenes (3). The addition of organoalkali metal reagents to the carbon-nitrogen bond in pyridine to give the 2-substituted pyridine is well known (5), for example n-butyl-lithium affords 2-butylpyridine.

$FcCH_2NMe_2$

I



I'

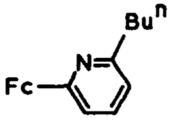


II

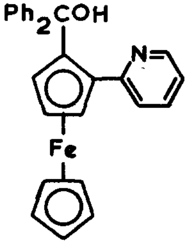
$Fc = C_{10}H_9Fe$

We have examined the reaction between 2-ferrocenylpyridine (II) and n-butyl-lithium in which either metallation at the 2-position of the ferrocene ring or addition across the carbon-nitrogen double bond, or both, might occur. An excess of n-butyl-lithium in hexane was added to an ethereal solution of the amine (II) at room temperature and the mixture examined for the addition reaction by hydrolysis. Thus any species lithiated only in the ferrocene rings would revert to the starting material whilst the product of the addition reaction would be isolated as 2-butyl-6-ferrocenylpyridine (III). The results are recorded in Table 1(b) and show a steady increase with time in the yield of the butylated amine (III) a brown oil, b.p. 149-151°/0.1mm.

The extent of the ferrocene ring metallation reaction was determined by quenching



III



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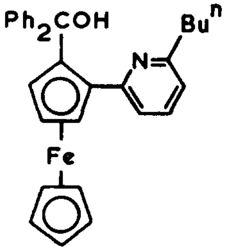
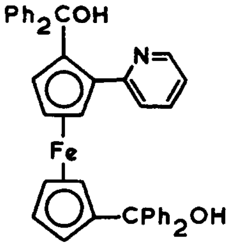
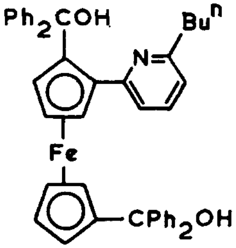


V



VI



VII

the same lithiation mixture with an excess of benzophenone and subsequent hydrolysis. The products (III-VII) were separated by chromatography on alumina and the yields of the products are recorded in Table 1(a). After one hour the 2-benzophenone adduct (IV), m.p. 217-218° was isolated in 82% yield together with a total of 10% of the butylated amines (III) and (V) m.p. 121-122.5° whereas after 21 hours the yield of the adduct (IV) had decreased to 36% and that of the butylated amines (III) and (V) had increased to a total of 32%. After the longer reaction times appreciable quantities of the dibenzophenone adducts (VI) m.p. 221-222° and (VII) m.p. 133.5-134.5° were also isolated.

TABLE 1

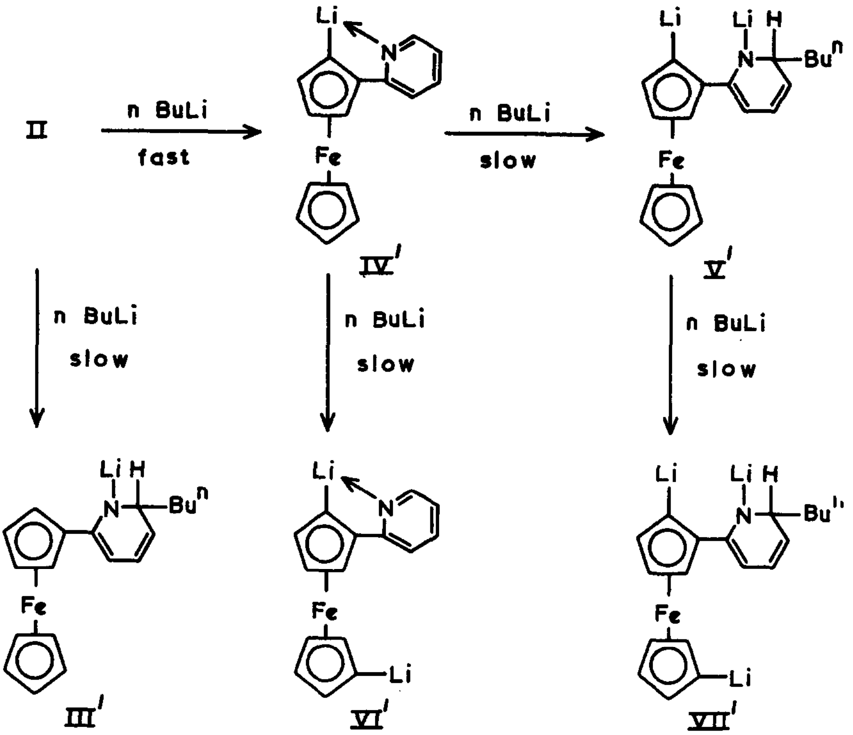
Yields (%) of Products from Reaction between 2-Ferrocenylpyridine and n-Butyl-lithium after (a) Reaction with Benzophenone then Hydrolysis; (b) Hydrolysis.

	Time	Product					
		(II)	(III)	(IV)	(V)	(VI)	(VII)
(a)	1 hr.	0	3	82	7	trace	trace
	6	0	1	51	13	12	7
	11.5	0	9	41	20	16	5
	21	0	8	36	24	9	9
(b)	1	76	6				
	6	51	22				
	11.5	40	30				
	21	37	35				

The structures proposed for the products (III-VII) were supported by their elemental analyses and by their proton magnetic resonance and infrared absorption spectra.

Thus it appeared that the initial reaction was a rapid and specific 2-lithiation to afford the lithio-amine (IV'). That lithiation was complete within one hour was shown by our failure to recover any of the starting amine (II) from the metallation mixture after reaction with benzophenone, whilst it was recovered from the metallation mixture after direct hydrolysis. Competing with and subsequent to this metallation reaction was the slow addition of the reagent to the carbon-nitrogen bond of the pyridine residue. Superimposed on these two reactions was the very slow metallation of the unsubstituted rings of the lithio-amines (IV') and (V') to afford the lithio-amines (VI') and (VII') respectively. A simplified outline of the reactions that probably occur in the metallation mixture is presented in Scheme A.

In this investigation a three-fold molar excess of n-butyl-lithium over the amine (II) was used and the di-and tri-lithio-amines (V', VI' and VII') were found not to be in excess over the mono-lithio amines (III' and IV') after reaction for 21 hours. Previously.the tendency of mono-carbanions to be thermodynamically preferred over dicarbanions in the metallation of ferrocene (6) has been observed whilst



SCHEME A

monoalkylferrocenes (7) preferentially afforded the corresponding dicarbanions. The initial rapid and specific 2-lithiation of the amine (II) may be attributed, in part, to stabilisation of the electropositive lithium by coordination of the unshared electron pair on the adjacent nitrogen as in (IV') and to the electronic effect of the pyridine residue. The recently described 2-lithiation of diphenylacetylene (8) might be subject to a similar explanation where the acetylenic π-electrons stabilise the neighbouring lithium.

Preliminary experiments (9) have shown that analogues of the amine (II) such as 2-ferrocenylquinoline undergo lithiation at the 2-position of the ferrocene nucleus with n-butyl-lithium. Therefore the metallation of ferrocenes with an sp^2 hybridised nitrogen atom, as well as those with an sp^3 nitrogen (3) in the position β to the ring will be expected to provide convenient intermediates in the synthesis of the corresponding 1,2-disubstituted ferrocenes.

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