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Regioselective Thermal Cyclization of N-Aryl-4-chloro-1-aza-1,3-butadiene Derivatives. A Short and Efficient Synthesis of Dibenz[c,h]acridines

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Dibenz[c,h]acridines have been synthesised in good yields by thermal cyclization (140-180°C) of N-aryl-4-chloro-1-aza-1,3-buta-diene derivatives followed by dehydrogenation.

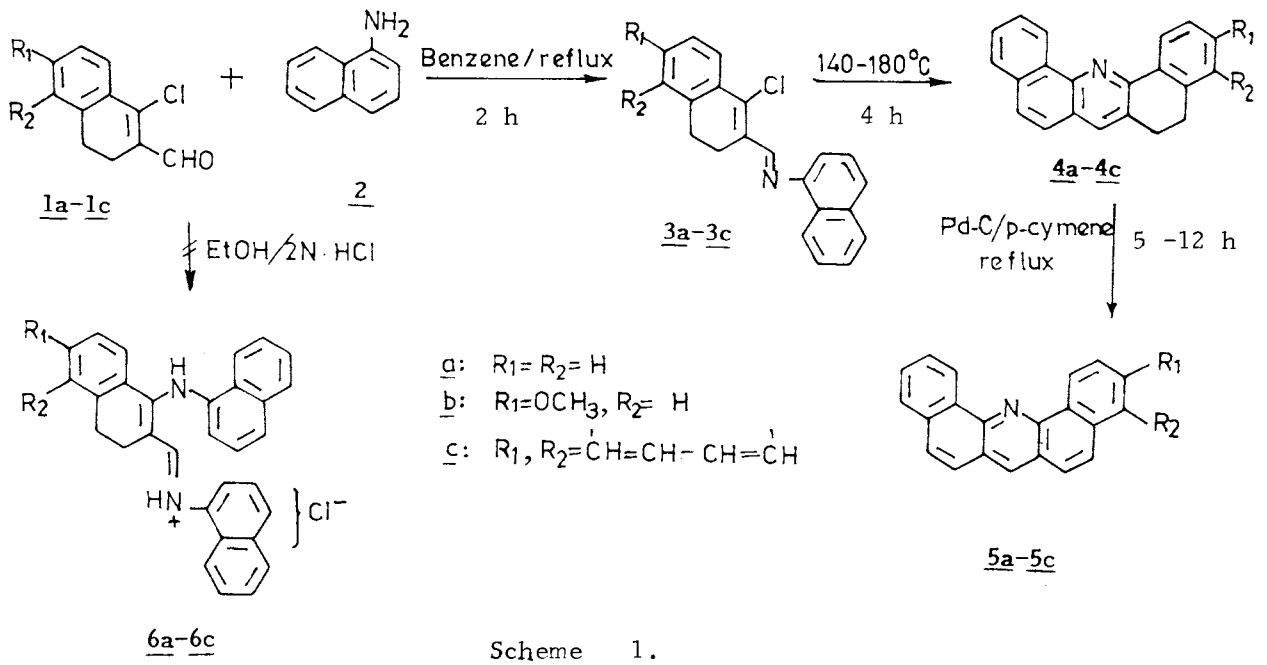
Dibenz[c,h]acridines possess an unique structural feature, where the 'N' atom is located near two bay regions,[1a,b] which induces carcinogenic activities according to Pullman's theory [2] and will serve as very good models to study the electronic effect of 'N' on the mutagenic/carcinogenic activities of Polycyclic Azaarenes (PAA). The literature survey reveals that only few syntheses[3-5] of dibenz[c,h]acridines are known and all of these methods suffer from poor yields (cf.10-30%) and longer time of reactions.

The thermal cyclization of anilhydrochlorides[6a,b] to produce PAA, have already been proved to be an efficient method. Recently we have reported the synthesis of some dibenz[a,h]acridines through the regioselective thermal cyclization of enaminoiminehydrochlorides which in turn were obtained from the reaction of suitable α,β-unsaturated chloroaldehydes and 2-naphthylamine.

Surprisingly, in an attempt to prepare dibenz[c,h]acridine following the above method, we found that the reaction of the chloroaldehyde (1) and 1-naphthylamine under identical condition[7] did not produce any anil derivatives (6) but only the N-aryl-4-chloro-1-aza-1,3-butadiene derivative (3) was produced. This is presumably due to increased "peri effect'" in 1-naphthyl moiety. Replacement of the solvent from EtOH to benzene, refluxing, and use of chloroaldehyde and 1-naphthylamine in the ratio 1:1 or 1:2 produced only the Schiff's base (one equivalent of amine remained unreacted in the latter case). The compound (3) when heted at 140-180° C produced only the dihydrodibenz[c,h]acridines (4) in good yield. The mechanism of the reaction is uncertain, however since the yields of the reaction are greater than 60%, so the cyclization involves no disproportionation reaction. Probably, the reaction passes via a rearranged intermediate (7). However, we could not isolate/prepare the intermediate (7) to prove the authenticity of the pathway.

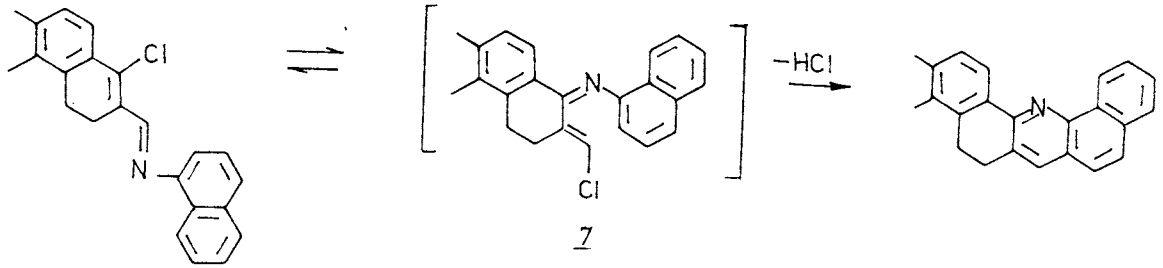
In general, addition of another equivalent of 1-naphthylamine in heating the Schiff's base (3) produced the same product and it has no effect in improving the

yield, except in the case of methoxy derivative 3b where use of the second



Scheme 1.

equivalent of amine improved the yield of 4b by trapping liberated HCl and reducing the amount of tarry products. However heating of the Schiff's base (3) with 1-equivalent of 2-naphthylamine resulted in a dramatic change and in this case the product isolatedd was exclusively dihydrodibenz[a,h]acridine (8) and no dihydrodibenz[c,h]acridine (4) was found in the reaction mixture. Probably,reaction here passes through anilhydrochloride intermediate which formed at higher temperature and is cyclized therein (Scheme 2).

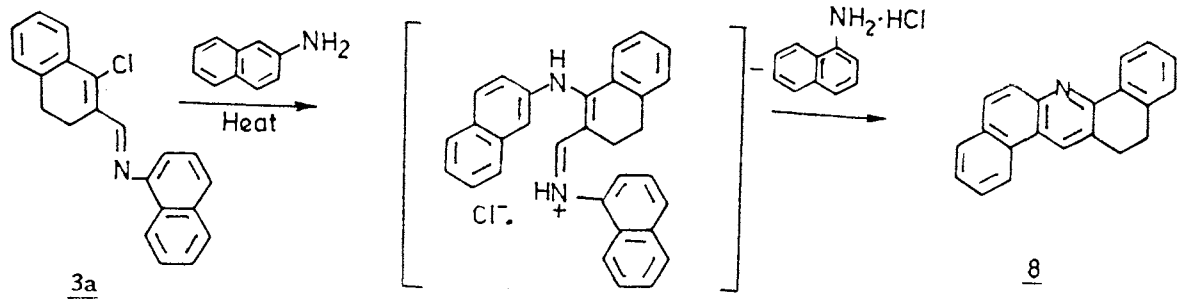


Aromatization of 4 with Pd-C (10%) in refluxing p-cymene produced 5 in very good to excellent yields. The compounds were characterized by comparison with authentic sample, spectral data as well as elemental analyses.

Table 1.

Compound No. (Nature)	MP °C	Yield %	IR cm^{-1}	^1H NMR ($CDCl_3$)	Mass(m/z)
3a (Yellow solid)	110-111 (Pet.ether 60-80°C	92	1590, 1610	2.8-3.35(m,4H), 7.0-7.9(m,10H), 8.4(dd,1H), 9.0(s,1H)	319(M^+2), 317(M^+), 316,282,280, 175,154,141, 127.
3b (Yellow solid)	161-162 (Al_2O_3/ benzene)	86	1585, 1610	2.8-3.4(m,4H),3.9(s,3H),6.9 (d,1H, J≈2.5 Hz), 7.12(dd,1H, J≈2.5 Hz), 7.4-8.0(m,7H), 8.4 (dd,1H, J≈3.5 Hz), 9.0(s,1H)	-
3c (Yellow solid)	175-176 (Pet.ether + benzene)	94	1590, 1610	3.1-3.5(m,4H), 7.1(d,1H),7.2 (d,1H), 7.4-8.28(m,10H), 8.4 (dd,1H, J≈3.5 Hz), 9.1(s,1H).	-
4a (Colourless solid)	154-155 (lit.[5] 141) (silica gel/pet. ether + benzene,10:1)	81 (79)[a]	-	2.9-3.25(m,4H), 7.25(d,1H), 7.35(t,1H), 7.45(t,1H), 7.6-7.8 (m,4H), 7.9(d,1H), 7.95(s,1H), 8.75(d,1H), 9.5(d,1H).	282(M^+1), 281(M^+), 280,279,278 140,139,126.
4b (Pinkish white)	115-116 (silica gel/ pet.ether + benzene,10:1)	35 (61)[a]	-	2.88-3.28(m,4H), 3.9(s,3H), 6.82(d,1H, J≈3 Hz), 7.04(dd,1H, J≈3 Hz), 7.6-8.0(m,5H), 7.9 (s,1H), 8.76(d,1H, J≈9 Hz),9.52 (dd,1H, J≈3 Hz)	-
4c (Colourless solid)	206-207 (Al_2O_3/pet. ether + benzene)	72 (73)[a]	-	3.2-3.6(m,4H), 7.5-8.3(m,11H), 9.04(d,1H, J≈9 Hz), 9.56(dd,1H, J 3≈Hz).	-
5a (Yellowish white solid)	193-194 (EtOH + benzene) (lit.[5] 191)	94	-	7.75-7.95(m,10H), 8.62(s,1H), 9.75(d,2H, J≈9 Hz).	280(M^+1), 279(M^+), 278,140,139, 138,126
5b (Yellowish white solid)	132-133 (Al_2O_3/benzene)	84	-	4.0(s,3H), 7.3(d,1H, J≈3 Hz), 7.5(dd, 1H, J≈3 Hz), 7.8-8.0 (m,7H), 8.52(s,1H), 9.64(d,1H, J≈9 Hz), 9.70(dd,1H, J≈3 Hz).	-
5c (Yellowish white solid)	206-207 (Benzene + EtOH)	89	-	7.8-8.2(m,10H), 8.7(s,1H), 8.8(m,2H), 9.8(m,2H).	-

a) Yields when heated with one equivalent of 1-naphthylamine.
(All the compounds gave satisfactory elemental analysis).



3a 8

Scheme 2.

The methoxy derivative (5b) will be further used for the preparation of the oxidative metabolite-3,4-dihydroxy-3,4-dihydrodibenz[c,h]acridine following the standard method already developed in this laboratory.

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