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Some new aspects of benzyne and radical mediated cyclisations

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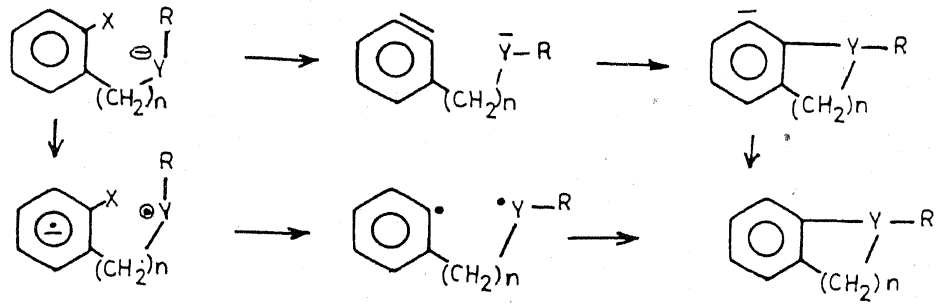
Abstract. KNH_2/NH_3 cyclisations of some alkoxy substituted arylhalides proceed in poor yields. This shortcoming may be overcome by the use of LDA/THF to effect the ring closure which may occur through benzyne or radical intermediates. Besides ortho halogenated dihydroanils and amides, the cyclisation of the benzylamine Schiff bases also provides a convenient route to isoquinoline alkaloids.

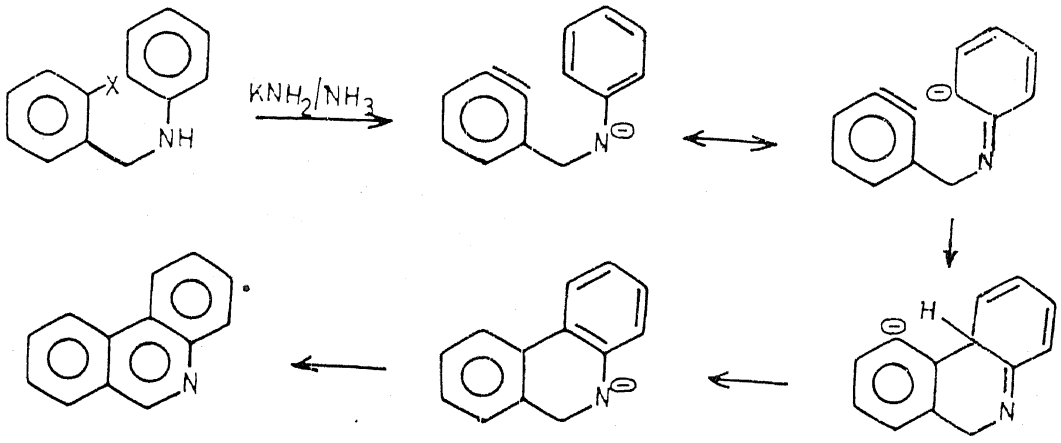
Keywords. Benzyne intermediates; radical intermediates; cyclisation; isoquinoline alkaloids.

1. Introduction

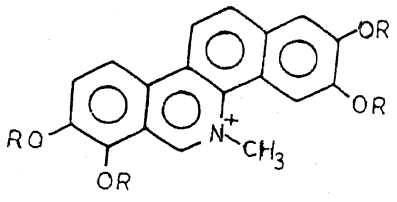
Base promoted cyclisation of aryl halides having a nucleophile bearing side chain in the ortho position is a useful synthetic method (Bunnet *et al* 1963; Kessar 1978; Semmelhack *et al* 1975). For such cyclisations, involvement of both benzyne and radical anion ($S_{RN}1$) (Bunnet 1978, an intermolecular electron transfer is shown in the chart below, but a chain mechanism initiated by external electron transfer can also operate) intermediates has been invoked. Since the publication of our earlier article on the subject (Kessar 1978), many examples bringing out the subtle role of substrate structure and reaction conditions have been uncovered. In the present review, attention is focussed on these aspects and the coverage is primarily restricted to the author's own findings.



Dihydroanils can be cyclised with KNH_2/NH_3 to give phenanthridines in excellent yields and benzyne intermediacy in this reaction has been firmly established (Kessar *et al* 1973a).



The cyclisation was used as a key step in the synthesis of a variety of polynuclear heterocycles including some azasteroids (Kessar *et al* 1973b) and naphthyridine alkaloids (Kessar *et al* 1976). It also provided a very convenient route to benzo[c]phenanthridine alkaloids (Kessar *et al* 1974; Gillespie *et al* 1974). However, cyclisation yields were good (80%) for the 7,8-oxygenated alkaloids (3) but were poor (10%) for the 8,9-oxygenated alkaloids (4). The same trend was observed in cyclisation to the corresponding phenanthridines.



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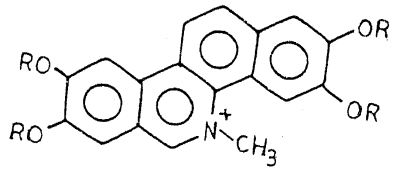

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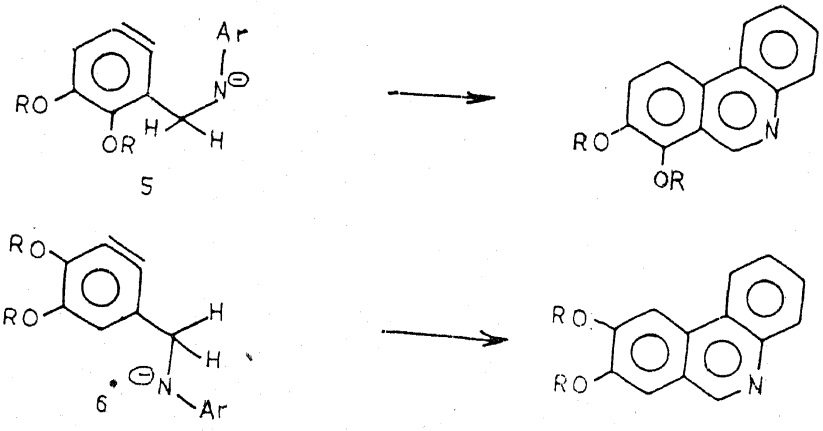
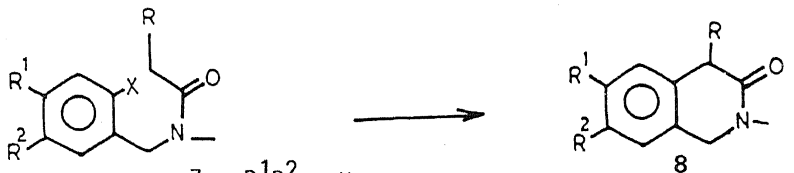


It is known (Biehl and Razzuk 1987) that due to inductive withdrawal of charge and polarisation of the benzyne bond, alkoxy groups render arynes more reactive and consequently less selective towards nucleophiles. Thus in KNH_2/NH_3 promoted reactions amination through the more abundant solvent molecules often predominates. On this basis poor yields could be expected in cyclisation of 5 and 6, though more so for the latter in which the alkoxy groups are placed unsymmetrically. Further, in 5 the alkoxy substituent ortho to the side chain may force it into a conformation suitable for cyclisation. This steric symphoric effect of bringing the

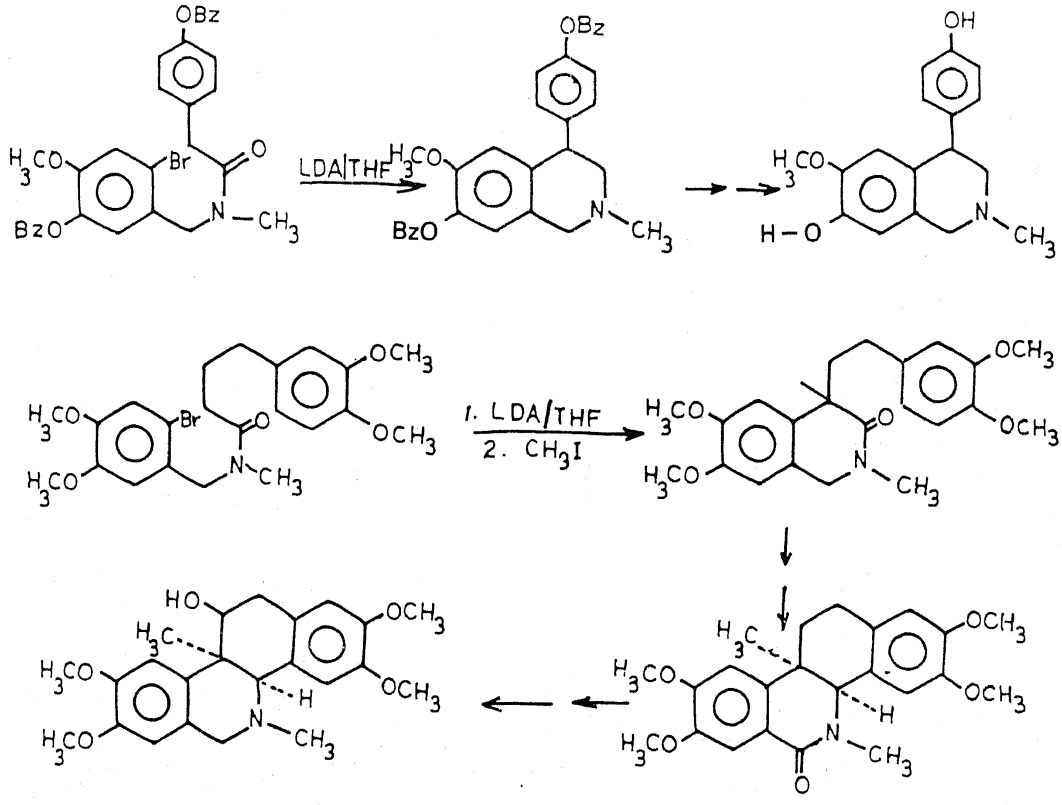
reactive sites together could be responsible for good cyclisation yields with substrates of type 5 inspite of their alkoxy substituents.



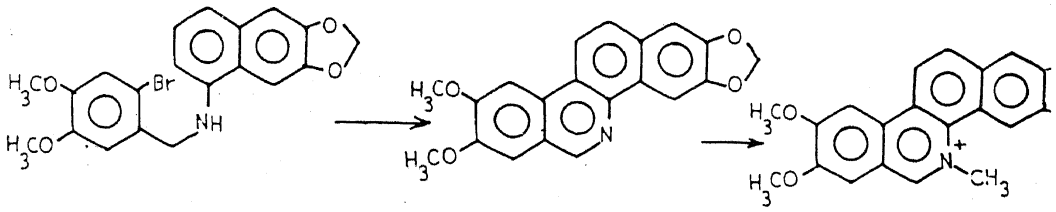
7a, R^1R^2 = H
b R^1R^2 = alkoxy

The deleterious effect of 3,4-alkoxy substituents on the benzyne cyclisation seems to be fairly general. Unsubstituted amide 7a could be easily cyclised with KNH_2/NH_3. But when the same reaction was attempted with 7b, to synthesise some alkaloids (vide infra), only amination products were obtained. Whatever the reason for it, a solution to this shortcoming of the benzyne cyclisation was highly desirable. In fact many natural products readily accessible through this route have the unsuitable substitution pattern.

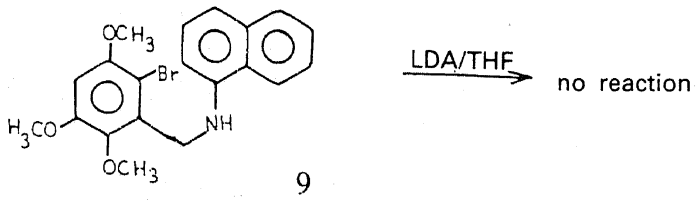
We argued that lowering the reaction temperature, decreasing the concentration of the competing external nucleophile and increasing its bulk may tilt the scales in favour of ring closure even with unselective benzynes. Preliminary results were rather discouraging. Changing from KNH_2/NH_3 at $-33°$ to LDA/THF at $-78°$, resulted in a sharp decrease in the cyclisation yield from 7a. Nevertheless, there were reasons to believe (vide infra) that an improvement may occur with the dialkoxy substrate 7b. Treatment of 7b with LDA/THF at $-78°$ indeed gave a good yield of 8a. This procedure was then used for the synthesis of cherylline (Kessar *et al* 1981) and corynoline type alkaloids as shown below.



When the LDA/THF modification was applied to the cyclisation of dialkoxy anils, equally gratifying yield improvement (from 15% to 90% for 4) was observed. The alkaloid nitidine has now been synthesised very efficiently by this procedure (unpublished work from our laboratory). This is of special interest because of the importance of such substituted benzo c phenanthridines in cancer chemotherapy (Gillespie *et al* 1974).



The dramatic yield improvement in going from KNH_2/NH_3 to LDA/THF for the cyclisation of dialkoxy substrates made us wonder if a change from a benzyne to a radical mediated reaction pathway had occurred. It has been shown that aryl halides can react with LDA/THF by benzyne as well as radical mechanisms (Tanaka *et al* 1987).



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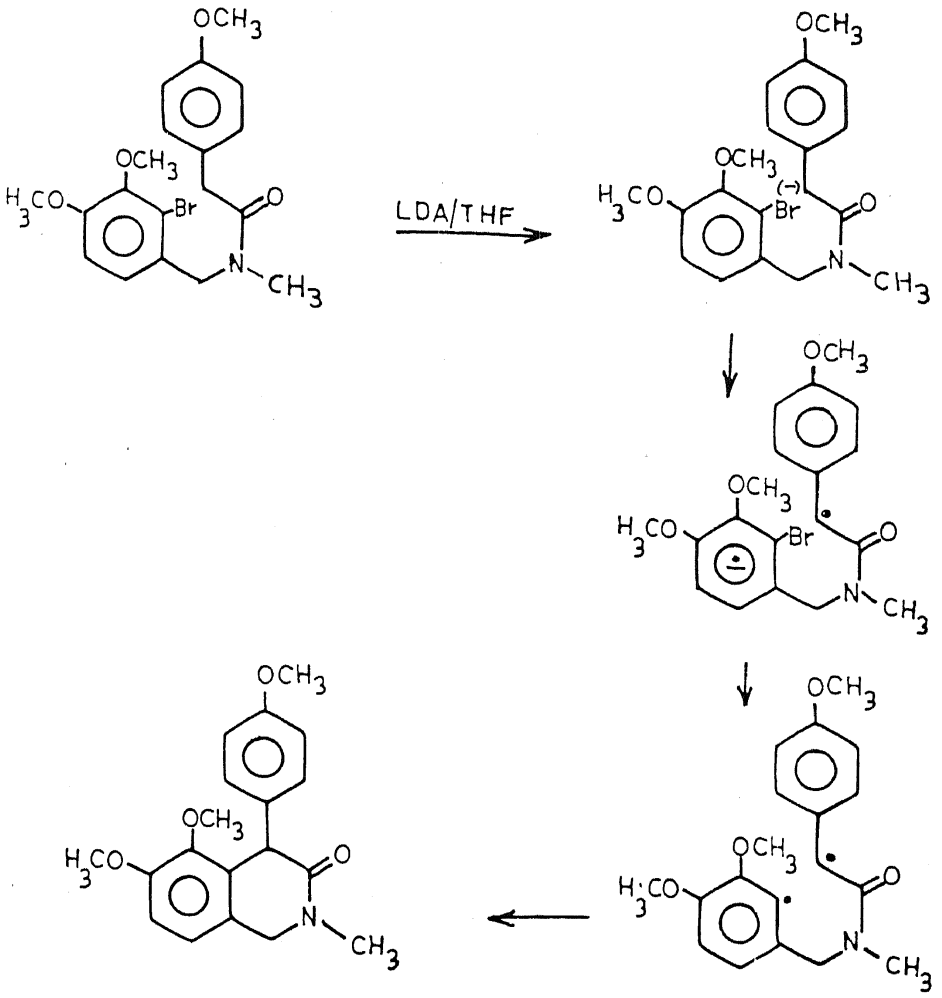
In this context the trimethoxy compound 9 in which benzyne formation is blocked was synthesised. On exposure to LDA/THF it was recovered unchanged (unpublished work from our laboratory) showing that a radical ion mechanism does not operate. Thus cyclisation of dihydroanils with LDA/THF may be assumed to proceed through a benzyne intermediate as established earlier for KNH_2/NH_3 conditions. If so, the glaring difference in the cyclisation of unsubstituted and 4,5-dialkoxy aryl halides under the two conditions may seem puzzling. It can, however, be understood in terms of the position of attack by the external nucleophile. In the benzyne 10, due to the directing effect of the alkoxy substituents, attack at the meta position is favoured but is subject to steric hindrance by the adjoining side chain. The smaller amide ion or ammonia can approach this position readily but with the bulkier diisopropyl amide ion the reaction is sterically inhibited leaving the field open for ring closure. In the unsubstituted benzyne 11, amination can occur away from the side chain and the use of LDA offers no advantage. In fact the cyclisation yield is lowered probably because of the greater reactivity of diisopropyl amide ions towards benzyne.

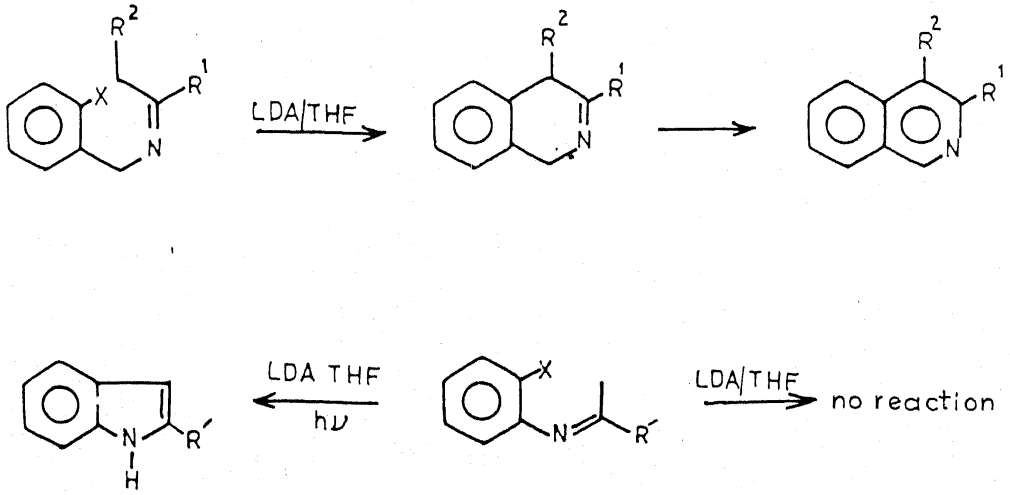
10 11

While investigating the mechanism of LDA/THF cyclisation of amides, unexpected results have been encountered. The amide 12 afforded the cyclic product 13 (unpublished work from our laboratory). Since both the positions ortho

to the halogen are blocked here, a non-benzyne cyclisation mechanism has to be invoked. It may involve electron transfer intramolecularly as shown, or from an external source. It is not yet established whether in the absence of a blocking group, the cyclisation of halogenated amides occurs through a benzyne or a radical mechanism. For the corresponding five-membered ring closures, the recent work of



Wolfe and others (Goehring *et al* 1985) has shown involvement of both the mechanisms under different reaction conditions.



We have also investigated in our laboratory intramolecular reactions of azaallylic anions with aryl halides. Here we find that cyclisation to a six-membered ring occurs in the dark while irradiation is necessary for five-membered ring formation. Again, mechanistic dichotomy may be present. Anyway, the former reaction provides a convenient routed to 3 or 4 substituted isoquinoline alkaloids like corydamine and macrostomine.

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References

Biehl E R and Razzuk A 1987 *J. Org. Chem.* **52** 2619
Bunnett J F 1978 *Acc. Chem. Res.* **411**
Bunnett J F, Flynn R R and Skorez 1963 *J. Org. Chem.* **28** 1
Gillespie J P, Amros L G and Stermitz F R 1974 *J. Org. Chem.* **39** 3239
Goehring R R, Sachdeva Y P, Pisipati J S, Sleevi M C and Wolfe J F 1985 *J. Am. Chem. Soc.* **107** 435
Kessar S V 1978 *Acc. Chem. Res.* **11** 283
Kessar S V, Gopal R and Singh M 1973a *Tetrahedron* **29** 167
Kessar S V, Gupta Y P, Pahwa P S and Singh P 1976 *Tetrahedron Lett.* 3207
Kessar S V, Parkash N and Joshi J S 1973b *J. Chem. Soc., Perkins Trans.* **1** 1158
Kessar S V, Singh M and Balakrishnan P 1974 *Indian J. Chem.* **12** 323
Kessar S V, Singh P, Chawla R and Kumar P 1981 *J. Chem. Soc., Chem. Commun.* 1074
Semmelhack M F, Chong B P, Stanffer R D, Rogerson T D, Chong A and Jones L D 1975 *J. Am. Chem. Soc.* **97** 2507
Tanaka Y, Tsujimoto K and Qhashi M 1987 *Bull. Chem. Soc. Jpn.* **60** 788