Tetrahedron Letters No.18, pp. 1991-1995, 1966. Pergamon Press Ltd.
Printed in Great Britain.

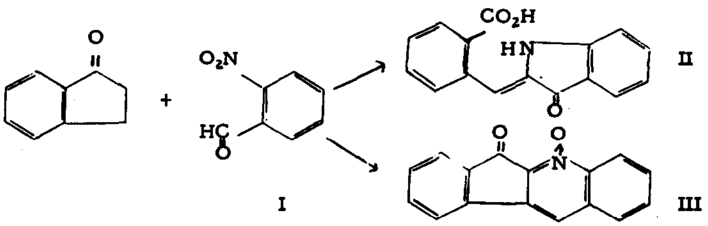
INTERMOLECULAR CARBANION ATTACK ON THE NITRO GROUP,[1]

Alfred Hassner and D.R. Fitchmun
Department of Chemistry
University of Colorado, Boulder, Colorado

(Received 13 December 1965; in revised form 9 March 1966)

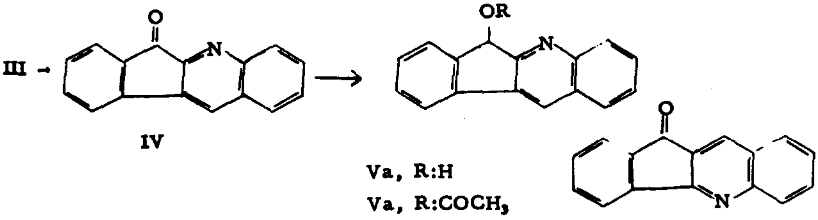
Aldol type condensations of methylene ketones with aldehydes under basic conditions, leading to α, β-unsaturated ketones, are well established organic reactions. Although the nitro group rivals the aldehyde function in polarity and intramolecular attack of enolates on nitro groups has been observed[2], intermolecular aldol type condensations on a nitro group, leading to nitrones, have apparently not been reported.

We are now reporting the formation of nitrone III by base catalyzed condensation of 1-indanone with o-nitrobenzaldehyde (I). The accompanying reaction product is indoxyl acid II (50% yield)[3], resulting from aldol condensation followed by intramolecular enolate attack on the nitro group. The yield of III can be raised to 50 % by conducting the condensation of 1-indanone with I in the presence of one equivalent of potassium hydroxide in methanol at 20°.



The structure of III, an orange neutral compound M.P. 242-243°, was indicated by elemental analysis, spectra, chemical conversions and independent synthesis of its desoxy derivative IV.

The n.m.r. spectrum of III indicates solely the presence of aromatic protons and the infrared absorption (in K Br) at 1725 (s, C=O), 1670 (w, C=N), 1325 (s, N→O) is consistent with structure III. The u.v. spectrum ($\lambda_{max}^{CH_3OH}$, 225, 285, 300 and 335 mμ; ε31, 200, 46, 700,53, 200 and 13,400) of the compound suggests a highly conjugated polycyclic system. Reduction of the N-oxide III with triethylphosphite gave in quantitative yield quinoline IV (m.p. 190-192°). The alternate structure VI (m.p. 175°)[4] was excluded by independent synthesis of IV (m.p. 190-191°), through ring closure of 2-carboxy-3-phenyl quinoline.[5,6] The presence of a carbonyl group in III was further verified by reduction with sodium borohydride to alcohol Va (m.p. 189-190°) which gave an acetate Vb (m.p. 123-123.5°) and was reoxidized to III.

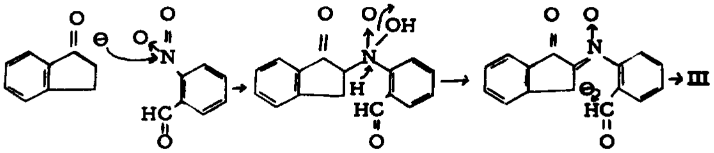


IV

Va, R:H
Va, R:$COCH_3$

VI

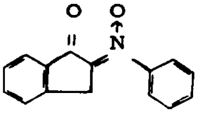
1-Indanone is known to undergo aldol condensation with aldehydes exclusively at the 2-position.[7] The formation of III, therefore, suggests a condensation of the enolate of 1-indanone at the nitro group of o-nitrobenzaldehyde (I), leading to a nitrone intermediate VIII, in which the benzylic hydrogens are activated sufficiently to be abstracted by base and to allow a subsequent intramolecular aldol condensation to take place.



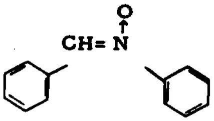
VII VIII

It is remarkable that, in the synthesis of III, intramolecular attack by the carbanion at the nitro group successfully competes with the usual attack at the aldehyde function. In fact, Grignard reagents prefer attack at the aldehyde to the exclusion of attack at nitro functions.[8] In many cases nucleophiles instead of attacking the nitro group choose to add in a 1,4-manner to unsaturated or aromatic nitro compounds.[9,10]

Although there are a number of examples reported[11] for carbanion attack on nitro groups, these generally do not lead to nitrone formation nor are they mentioned as possible methods of nitrone synthesis.[12] The reason became apparent upon investigation of the stability of nitrones towards base. Thus nitrone X, m.p. 128-129°, is decomposed within 5 minutes in dilute alcoholic potassium hydroxide - conditions for formation of III.



X



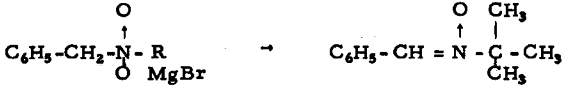
XI

Nitrone XI is likewise unstable in potassium hydroxide solution. Among the decomposition products of XI are benzaldehyde as well as nitrobenzene suggesting that nitrone formation might be reversible.

These results coupled with the fact that simple nitrobenzenes do not react with 1-indanone suggest that, in analogy with aldol formation, condensation of the nitro group is reversible (i.e. formation of VII). Nitrones can be obtained in cases where they have imparted stability towards base, as in the conversion to a pyridine N-oxide (i.e. III).

Encouraged by the results with 1-indanone, we investigated the possibility of synthesizing nitrones by intermolecular attack of simple carbanions on nitro compounds. This task is complicated by the ease of aci-salt formation from nitro compounds containing α-hydrogens and by the fact that, as has been shown recently by Russell and co-workers,[13] carbanions undergo facile electron transfer in the presence of nitro compounds as acceptors. Indeed, phenyl sodium reacts with nitrobenzene or with 2-methyl-2-nitropropane in an electron transfer reaction.[14] Ethylmagnesium bromide reacts with nitrobenzene in the same manner.

The reaction of phenylmagnesium bromide with phenyl-nitromethane leads merely to the aci-salt of the latter. However, benzylmagnesium bromide reacts with nitro compounds, including nitrobenzene, apparently by carbanion attack on the nitro group, to give intermediate insoluble salts of type XII. Careful hydrolysis of these salts leads to nitrones. In this manner nitrones XI and XIII were prepared in yields of 30 to 50%. The reason why benzyl carbanions seem to have a smaller tendency to undergo electron transfer reactions than other carbanions, might be due to the fact that energetically the conversion of a carbanion to the corresponding free radical is less favorable in the benzyl case than in the alkyl or phenyl cases.



$$C_6H_5\text{-}CH_2\text{-}\overset{\overset{\displaystyle O}{\uparrow}}{\underset{\displaystyle O\ MgBr}{N}}\text{-}R \rightarrow C_6H_5\text{-}CH=\overset{\overset{\displaystyle O}{\uparrow}}{N}\text{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\displaystyle CH_3}{C}}\text{-}CH_3$$

XII XIII

Acknowledgement: Support of this investigation by Public Health Service Grant CA-4474, from the National Cancer Institute is gratefully acknowledged.

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