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A NOVEL SYNTHESIS OF INDOLE DERIVATIVES VIA A CLAISEN REARRANGEMENT

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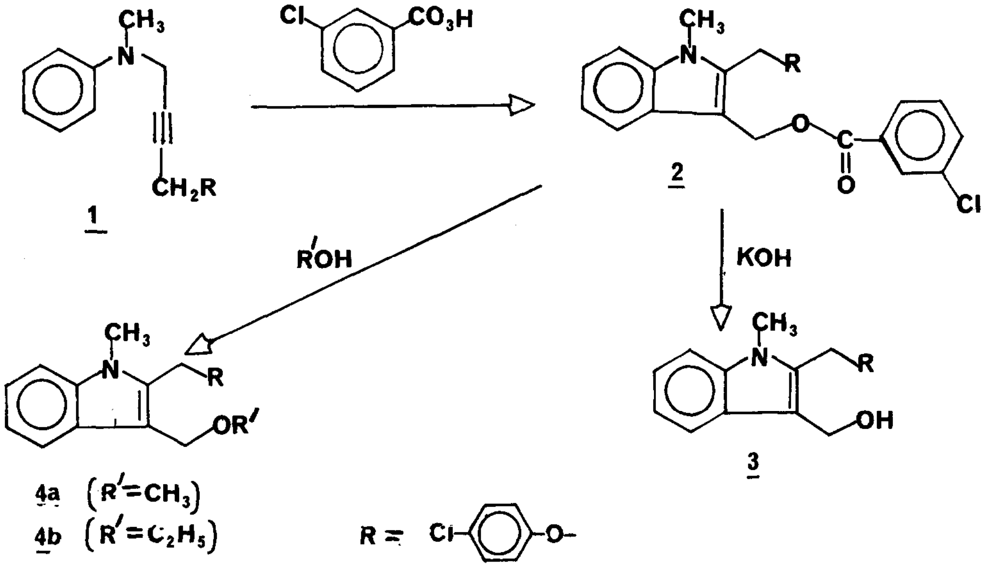
We wish to report a facile thermal rearrangement of an N-aryl propynylamine oxide to an indole. The present study, to our knowledge, is the first report of such a rearrangement.

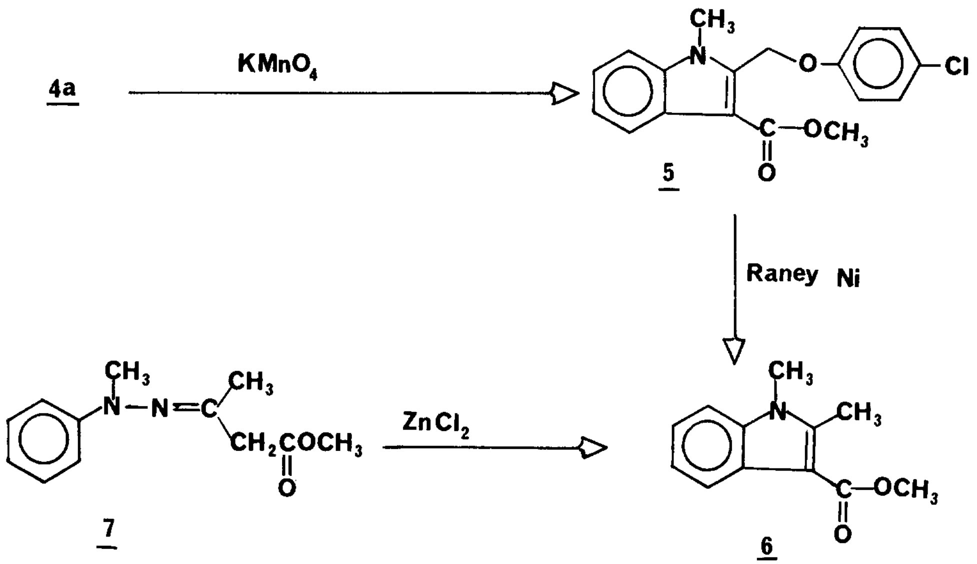
Compound 1 (89.5%; m.p. 76-77)[2] was prepared by the condensation of 1-(4-chlorophenoxy)-4-chloro-2-butyne[3] with two moles of N-methylaniline in refluxing n-butanol. Oxidation of 1 with one equivalent of m-chloroperoxybenzoic acid[4] (MCPBA) in methylene chloride at room temperature over 12 hours gave a high yield of 2 (81%; m.p. 142-43). Alkaline hydrolysis of 2 gave m-chlorobenzoic acid and the alcohol 3 (77%; m.p. 131-32). Alcoholysis of 2 in refluxing alcohol gave the 3-alkoxymethyl indole derivatives 4a (90.5%; m.p. 101-102) and 4b (85%; m.p. 90-91).

Scheme I



The following series of reactions supports structural assignments for the indole derivatives (2, 3 and 4). Oxidation of 4a with $KMnO_4$ in refluxing acetone gave the corresponding 3-carbomethoxy indole 5 (40%; m.p. 157-158). Effective cleavage of the p-chlorophenoxy moiety of 5 with Raney Nickel in refluxing 2-butanol afforded 1,2-dimethyl-3-carbomethoxy indole 6 (45%; m.p. 141-142). Fischer cyclization of 7 (54%; m.p. 65-66) in refluxing cumene (dry) and anhydrous zinc chloride resulted in a direct synthesis of 6 (24.8%; m.p. 141-42). Mixed melting point, ir, nmr and mass spectrum showed the two products to be identical.

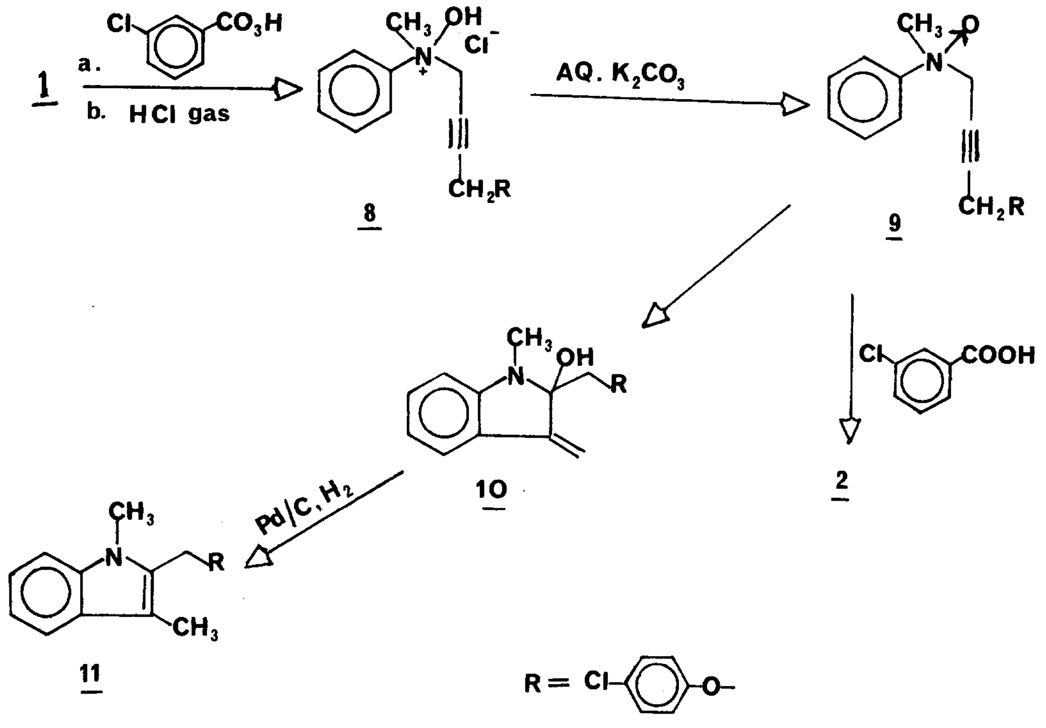
Scheme II



The intermediacy of the N-oxide 9 in the above rearrangement (1 to 2) was demonstrated as follows. Treatment of 1 with one equivalent of MCPBA in benzene at room temperature (5-10 minutes) followed by bubbling gaseous HCl into the solution produced the N-oxide hydrochloride 8 (90%; m.p. 128-130 (dec.); ir(KBr): $-\overset{+}{N}-OH$, 2500 cm^{-1}). Treatment of 8 with aqueous potassium carbonate liberated the N-oxide 9 (88.4%; m.p. 61-62) which is extremely labile. Consequently the ir, nmr[5] spectrum and elemental analysis were difficult to obtain. Proof that the N-oxide mediated the formation of 2 became available when an equimolar amount of 9 and m-chlorobenzoic acid in methylene chloride were stirred for 12 hours at room temperature to produce 2 in 76% yield. This was confirmed by comparison of the product with authentic sample of 2.

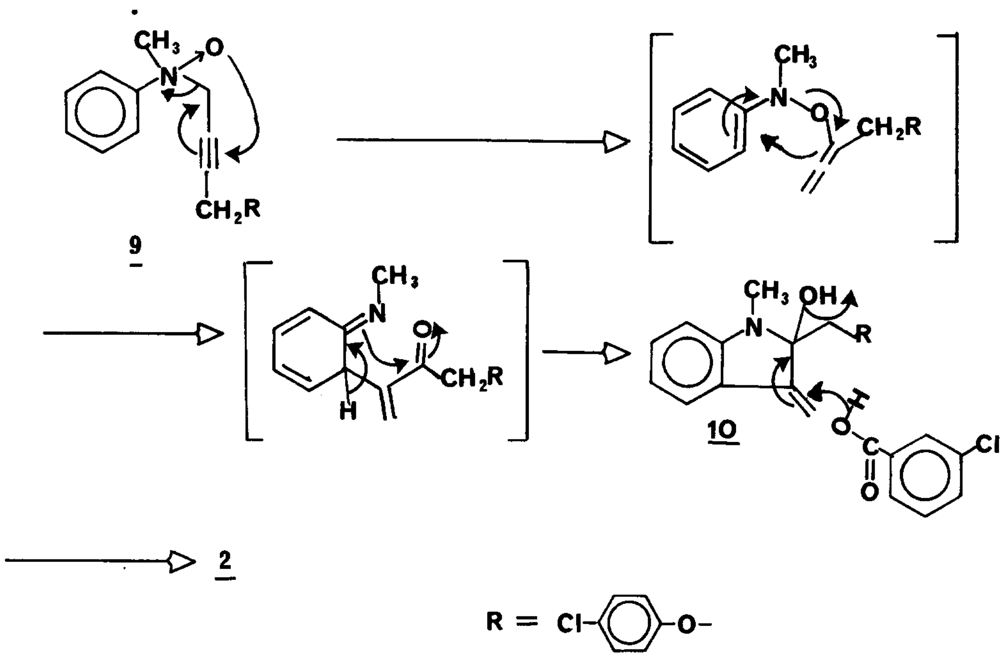
The facility of the rearrangement (1 to 2) is striking. The 3-methylene indoline derivative 10 (viscous oil)[6] is produced by simply dissolving the N-oxide in common organic solvents (benzene, carbon tetrachloride, chloroform, methylene chloride, acetone, ether) at room temperature. Hydrogenation of 10 employing Pd/C catalyst in methanol at room temperature gave the 3-methyl indole derivative 11 (65%; m.p. 131-132) via elimination of water from the initial reduction product.

Scheme III



The mechanism suggested here closely parallels the o-Claisen rearrangement of aryl-prop-2-ynyl sulfoxides[3,7] with the added feature of the acid catalyzed allylic rearrangement[8] of the 3-methylene indoline 10.

Scheme IV



Acknowledgments: We are grateful to Professor C. D. Hurd for helpful comments.

References and footnotes

1. NSF Undergraduate Research Participant; Summer, 1972.
2. All new compounds reported in this study gave excellent elemental analyses and exhibited the proper ir, nmr and mass spectrum unless otherwise stated.
3. K. C. Majumdar and B. S. Thyagarajan, Int. J. Sulfur Chem., A, 2, 93 (1972).
4. m-Chloroperoxybenzoic acid was used as obtained from Aldrich Chemical Co., Inc.
5. When the N-oxide 9 is mixed with benzoic acid, the mixture dissolved in $CDCl_3$ and the nmr spectrum is run instantaneously, then one observes the distinct pattern characteristic of the methylene protons - the same as seen in compound 1.
6. Compound 10 was too labile to be characterized by elemental analysis. However, excellent spectroscopic support came from ir, nmr and mass spectral data.
7. K. C. Majumdar and B. S. Thyagarajan, J. C. S. Chem. Comm., 83 (1972).
8. B. El-osta, K. C. Majumdar and B. S. Thyagarajan, J. Hetero. Chem., 10, 107 (1973).