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INDOLINE VS. BENZAZEPINE RING FORMATION VIA INTRAMOLECULAR ARYLATION OF N-PHENETHYL ENAMINONES

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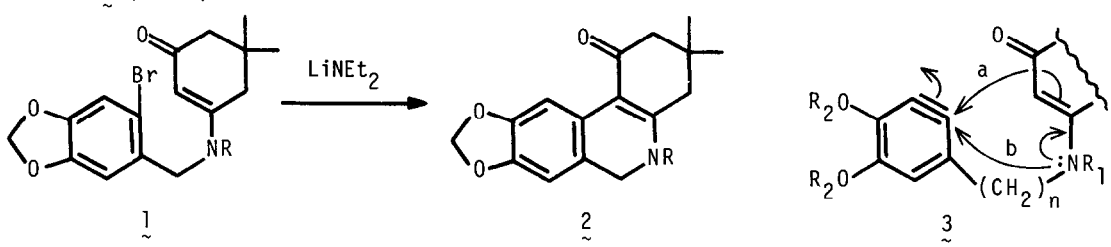
The enaminone[1] system ($>N_a-C_b=C_c-C_d=O_e$) consists of three functional groups, i.e. amino, double bond, and carbonyl, and shows interesting and sometimes complicated reactivity with five reaction sites (a—e). Recent reviews[2] indicated that in contrast to a number of the alkylation and acylation of enaminones, no report of the arylation had appeared. Thus we recently described an intramolecular C-arylation (on site c) of N-benzyl enaminones 1 (R = H, C_2H_5) involving benzyne intermediates 3 (n = 1) according to the following scheme (path a).[3] This work prompted us to attempt investigating the comparative ease of seven- (via path a) vs. five-membered ring (via path b) on the competing cyclization of N-phenethyl analogs of 1 involving benzyne intermediates 3 (n = 2).

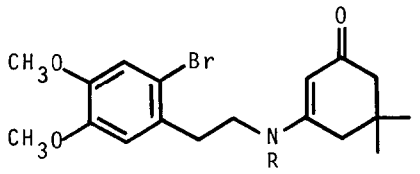


1 2 3

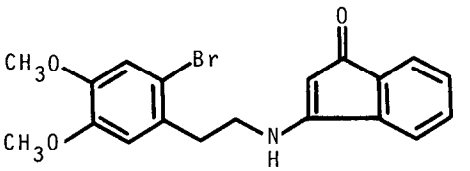
Condensation of dimedone with 2-bromo-4,5-dimethoxyphenethylamine gave the bromoenaminone 4a (mp 167—168 °C). Upon treatment of 4a with lithium diethylamide in ether—THF at room temperature for 1 h, N-arylation leading to five-membered ring proceeded predominantly to give the indoline derivative 6 as a sole product in 65% yield [mp 142—143 °C; IR[4] 1720 (C=O), 1610 cm^{-1} (C=C); NMR[5] δ 1.13 (s, 6 H), 2.21 and 2.61 (each s, 2 H), 5.40 (s, 1 H, vinylic H), 6.72 (s, 2 H, aromatic H)] rather than the azepine ring formation which is expected to arise from the C-arylation on the site c in the enaminone system. In a similar manner, 5 was cyclized to 7 with the five-membered ring as well in 49% yield [mp 143—145 °C; IR 1650 (C=O), 1570 cm^{-1} (C=C); NMR δ 3.15 and 4.45 (each t, 2 H, J = 8 Hz), 5.46 (s, 1 H, vinylic H), 6.75 and 6.85 (each s, 1 H, aromatic H)]

The preferential formation of the five-membered rings via nucleophilic attack by the nitrogens onto the benzynes was not necessarily expected result, since the basicity of the nitrogen in the enaminones is further reduced than in the enamines which are less basic than the corresponding saturated tertiary amines.[6] In an anticipation of obtaining the benzazepine, we then considered the use of a tertiary enaminone as a substrate with no hydrogen on the nitrogen to replace. Thus N-alkylation of 4a with ethyl iodide and sodium hydride in hot toluene gave the desired enaminone 4b in 74% yield [oil; IR 1610 (C=O), 1560 cm^{-1} (C=O); NMR δ 5.17 (s, 1 H, vinylic H)]. Treatment of 4b similar to that described for 4a resulted in N-arylation followed by C-N bond cleavage,

affording 1-ethyl-5,6-dimethoxyindoline (8) in 50% yield [oil; NMR δ 1.17 (t, 3 H, J = 7 Hz), 3.77 and 3.83 (each s, 3 H), 6.18 and 6.73 (each s, 1 H); MS m/e 207 (M^+, 62%), 192 (100%)].



4a, R = H
4b, R = C_2H_5



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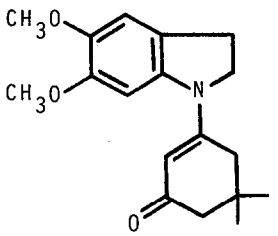

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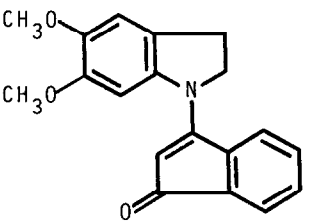

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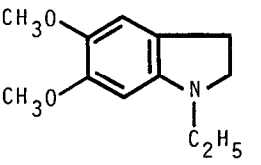

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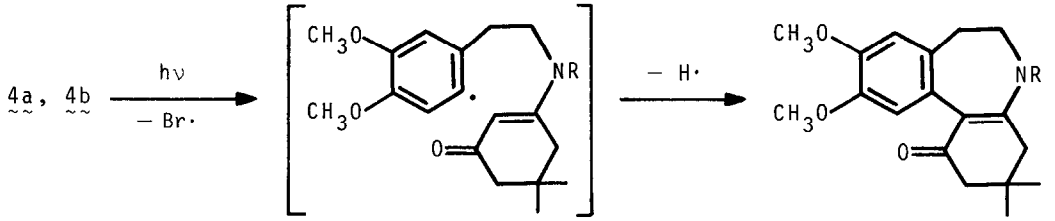
Ring closure to the benzazepine was successfully attained by an alternative intramolecular arylation[7] via photolysis as follows rather than the benzyne reaction. Upon Pyrex-filtered irradiation of 4a in dioxane—acetonitrile containing triethylamine, the C-arylation smoothly proceeded to give the benzazepine 9a in 91% yield [mp 229—230 °C; IR 3420 (NH), 1615 (C=O), 1575 cm^{-1} (C=O); NMR δ 1.10 (s, 6 H), 3.83 (s, 6 H), 6.12 (s, 1 H, 8-H), 7.08 (s, 1 H, 11-H)]. Similar irradiation of 4b gave 9b in 94% yield [oil; NMR δ 1.15 (s, 6 H), 1.16 (t, 3 H, J = 7 Hz), 3.25 (q, 2 H, J = 7 Hz), 3.85 (s, 6 H), 6.53 (s, 1 H, 8-H), 6.91 (s, 1 H, 11-H)].



9a, R = H
9b, R = C_2H_5

REFERENCES AND NOTES

(1) For designation, "enaminone" has been recommended[2b] instead of "enamino ketone" or "β-amino-α,β-ansaturated ketone" since the compounds rarely show the physical or chemical properties normally associated with ketones.
(2) (a) T. Nishino, C. Kajima, and Y. Omote, J. Synth. Org. Chem. Jpn., 34, 526 (1976); (b) J. V. Greenhill, Chem. Soc. Rev., 16, 277 (1977).
(3) H. Iida, Y. Yuasa, and C. Kibayashi, J. Am. Chem. Soc., 100, 3598 (1978).
(4) All IR spectra were determined in $CHCl_3$ solutions.
(5) All NMR spectra were determined in $CDCl_3$ solutions.
(6) G. H. Alt in "Enamines: Synthesis, Structure, and Reactions", A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, p 116.
(7) Intramolecular arylation of haloenaminones in a similar fashion has been studied in our laboratory: H. Iida, T. Takarai, and C. Kibayashi, J. Org. Chem., 43, 975 (1978).

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