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INTRAMOLECULAR Cα- AND Cγ-ALKYLATIONS OF TERTIARY ENAMINONES. FACILE ROUTES TO FUNCTIONALIZED INDOLE RING SYSTEMS

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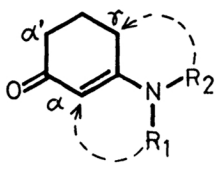
Under the suitably controlled conditions, the tertiary enaminones undergo intramolecular ring formation at Cα and Cγ to give 1-(2-bromo-4,5-methylenedioxybenzyl)tetra(or hexa)hydro-4(or 6)-oxo-indoles which can serve as potential precursors to lycoranes.

Tertiary enaminones are known to have three active reaction sites, Cα, α', and γ, in electrophilic alkyl substitution reaction under strongly basic conditions.[1,2] Therefore, if the substituents attached to the nitrogen, i.e. R_1 and R_2 in 1, undergo the intramolecular C–C bond construction at Cα and/or Cγ (and Cα' in a special case) there is an ample opportunity of providing a variety of suitably functionalized fused heterocycles. From this point of view, we considered utilizing 1 with appropriate N-substitutions for the synthesis of N-benzylindole derivatives which are expected to be utilized as potential precursors to some lycoranes derived from Amaryllidaceae alkaloids.[3] Our procedure constitutes three different modes of intramolecular cyclization of enaminones which was efficiently achieved by the combination of the selection of the substrates and specifying the reaction conditions.



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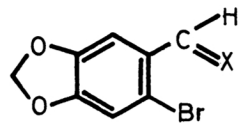
Reduction of the Schiff base (3),[4,5] prepared from 2-bromo-4,5-methylenedioxybenzaldehyde (2) and aminoacetaldehyde diethylacetal (benzene, reflux, 3 h), with $NaBH_4$ in EtOH (r.t., 4 h, then 60 °C, 1 h) afforded the benzylaminoacetal (5)[6] in 71% yield.[7] Condensation of 5 with cyclohexa-1,3-dione (benzene, reflux, 24 h) gave the tertiary enaminone (8)[8] in 60% yield. On treatment of 8 with 6N

HCl at room temperature for 24 h, intramolecular C–C bond formation at the α position of the enaminone moiety followed by aromatization with loss of ethanol occurred to furnish 1-(2-bromo-4,5-methylenedioxybenzyl)-4,5,6,7-tetrahydro-4-oxoindole (12) [mp 150–151 °C (benzene–hexane); NMR ($CDCl_3$) δ 1.96–2.62 (6H, m, 3 x CH_2), 4.86 (2H, s, $ArCH_2N$), 5.82 (2H, s, OCH_2O), 5.99 (1H, s, aromatic H), 6.46 (2H, s, 2 x aromatic H), 6.89 (1H, s, aromatic H); IR ($CHCl_3$) 1640 cm^{-1} (C=O)] in 68% yield.

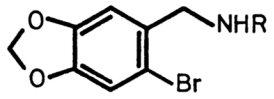
Second procedure for intramolecular cyclization at the α position was then carried out as follows: the Schiff base (4),[9] prepared from 2 and 2-aminoethanol (benzene, reflux, 2 h), was reduced with $NaBH_4$ (EtOH, r.t., 2 h) to give the benzylaminoalcohol (6)[10] in 89% yield. Compound 6 was also available via usual N-alkylation of the benzylamine (7)[11] with 2-chloroethanol. Condensation of 6 with cyclohexa-1,3-dione (benzene, reflux, 4 h) gave the tertiary enaminone (9)[12] in 75% yield, which was treated with PBr_3 in $CHCl_3$ (0 °C, 20 h, then 55 °C, 1 h) to afford the bromide (10)[13] in 75% yield. Reaction of the bromide (10) with $AgClO_4$ in boiling acetonitrile for 4 days followed by separation by column chromatography (silica gel, $CHCl_3$) led to the formation of the 2,3,4,5,6,7-hexahydro-4-oxoindole (13) [mp 142–143 °C (acetone–hexane); NMR ($CDCl_3$) δ 1.89–3.66 (10H, m, 5 x CH_2), 4.33 (2H, s, $ArCH_2N$), 5.98 (2H, s, OCH_2O), 6.62 and 7.00 (1 H each, s, aromatic H); IR ($CHCl_3$) 1590 (C=O), 1555 cm^{-1} (C=C)] in 18% yield and its aromatic analog (12) (15% yield) presumably formed via oxidative aromatization.



2: X = O

3: X = $NCH_2CH(OEt)_2$

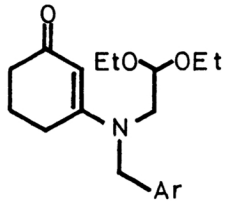
4: X = NCH_2CH_2OH



5: R = $CH_2CH(OEt)_2$

6: R = CH_2CH_2OH

7: R = H



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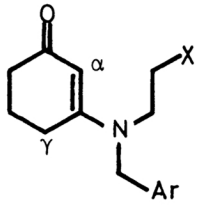
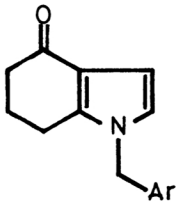


9: X = OH

10: X = Br

11: X = Cl



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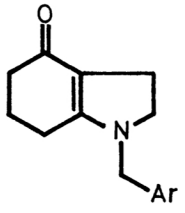

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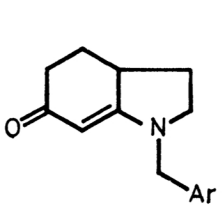

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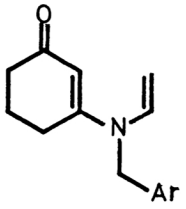

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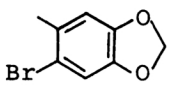
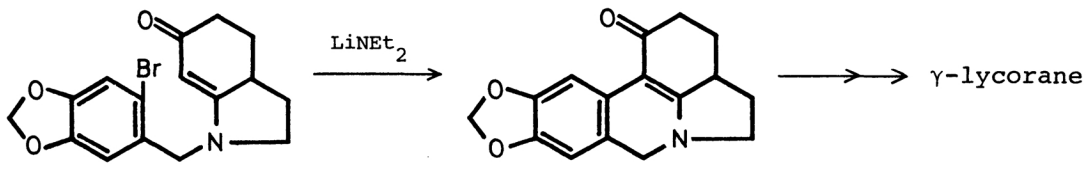
Ar = 

On the other hand, when the bromide (10) was treated with lithium diisopropylamide (1 equiv., - 78 °C, 3 h, then r.t., 15 h), intramolecular alkylation took place at the γ position to give the 2,3,3a,4,5,6-hexahydro-6-oxoindole (14) [mp 157–158 °C ($CHCl_3$–hexane) (lit.[14] mp 157–158 °C)] in 20% yield accompanied with the N-vinyl compound (15)[15] in 28% yield. When the chloride (11),[16] prepared from 9 ($SOCl_2$, benzene, r.t.), was used instead of the bromide (10) as a substrate in this reaction, the major product was the N-vinyl compound (15)[17] (40% yield).

These hydroindoles, which are hardly available by alternative routes via conventional indole ring formation, are of synthetic value, since they still contain the reactive enaminone grouping in each molecule; they possess the ability to undergo successive functionalization at Cα, α', or γ thus being able to act as potential precursors to the pyrrolophenanthridine ring system. In fact, it has been demonstrated by us that one of these hydroindoles, i.e. 14, is subject to intramolecular electrophilic α-arylation via an aryne intermediate, which is a highly electrophilic species, to yield the phenanthridone (16) as versatile intermediate in the synthesis of γ-lycorane.[11]



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References and Notes

1) M. Yoshimoto, N. Ishida, and T. Hiraoka, Tetrahedron Lett., 1973, 39 and references cited therein.

2) For a recent work on α'- and γ-substitutions, see G. V. Grishina, A. I. Vovk, and V. M. Potapov, Khim. Geterotsiklich Soedin, 1979, 1565 [C.A., 92, 215237t (1980)].

3) K. Kotera, Tetrahedron, 12, 248 (1961).

4) Satisfactory elemental analyses were obtained for all new compounds reported.

5) 3: bp 150–152 °C (0.13 mmHg); IR (neat) 1625 cm^{-1} (C=N).

6) 5: bp 156–159 °C (0.08 mmHg); NMR ($CDCl_3$) δ 1.20 (6H, t, J = 6.5 Hz, 2 x $OCH_2\underline{CH_3}$), 1.70 (2H, d, J = 5.5 Hz, NCH_2CH), 3.36–3.85 (4H, m, 2 x OCH_2CH_3), 3.78 (2H, s, $ArCH_2N$), 4.60 (1H, t, J = 5.5 Hz, $CH(OEt)_2$), 5.92 (2H, s, OCH_2O), 6.89 and 6.97 (1H each, s, aromatic H).

7) All yields refer to isolated and purified materials.

8) 8: oil; NMR ($CDCl_3$) δ 1.23 (6H, t, J = 6 Hz, 2 x $OCH_2C\underline{H}_3$), 1.83–2.76 (6H, m, 3 x CH_2), 3.40–3.78 (6H, m, 3 x CH_2), 4.52 (2H, s, $ArC\underline{H}_2N$), 4.65 (1H, t, J = 6 Hz, $C\underline{H}(OEt)_2$), 5.20 (1H, s, vinylic H), 5.95 (2H, s, OCH_2O), 6.46 and 7.00 (1H each, s, aromatic H); IR ($CHCl_3$) 1590 (C=O), 1540 cm^{-1} (C=C) [for IR absorptions characteristic for the enaminone group, see C. A. Grob and H. J. Willkens, Helv. Chim. Acta, 50, 725 (1967)].

9) 4: mp 115–117.5 °C (MeOH); IR (nujol) 3165 (OH), 1640 cm^{-1} (C=N).

10) 6: mp 118–119.5 °C (benzene); NMR ($CDCl_3$) δ 2.69 (2H, t, J = 5 Hz, $NC\underline{H}_2CH_2$), 3.60 (2H, t, J = 5 Hz, $CH_2C\underline{H}_2OH$), 3.72 (2H, s, $ArC\underline{H}_2N$), 5.89 (2H, s, OCH_2O), 6.81 and 6.93 (1H each, s, aromatic H); IR ($CHCl_3$) 3430 cm^{-1} (OH).

11) H. Iida, Y. Yuasa, and C. Kibayashi, J. Org. Chem., 44, 1074 (1979).

12) 9: mp 165–167.5 °C (acetone–hexane); NMR ($CDCl_3$) δ 1.79–2.56 (6H, m, 3 x CH_2), 3.36–3.83 (4H, m, $N(C\underline{H}_2)_2OH$), 4.47 (2H, s, $ArC\underline{H}_2N$), 5.15 (1H, s, vinylic H), 5.90 (2H, s, OCH_2O), 6.44 and 6.95 (1H each, s, aromatic H); IR ($CHCl_3$) 3300 (OH), 1595 (C=O), 1545 cm^{-1} (C=C).

13) 10: mp 145–147.5 °C (acetone–hexane); NMR ($CDCl_3$) δ 1.88–2.58 (6H, m, 3 x CH_2), 3.33–3.79 (4H, m, $N(CH_2)_2Br$), 4.47 (2H, s, $ArC\underline{H}_2N$), 5.20 (1H, s, vinylic H), 5.95 (2H, s, OCH_2O), 6.46 and 7.01 (1H each, s, aromatic H); IR ($CHCl_3$) 1600 (C=O), 1540 cm^{-1} (C=C).

14) H. Iida, Y. Yuasa, and C. Kibayashi, Synthesis, 1977, 879.

15) 15: mp 146–148 °C; NMR ($CDCl_3$) δ 1.92–2.70 (6H, m, 3 x CH_2), 4.25 (1H, d, J = 4 Hz, $\underset{N}{\overset{H}{\rangle}}C{=}C\langle\overset{H}{\underline{H}}$), 4.44 (1H, s,* $\underset{N}{\overset{H}{\rangle}}C{=}C\langle\overset{H}{\underline{H}}$), 5.26 (1H, s, vinylic H), 5.91 (2H, s, OCH_2O), 6.34 (1H, s, aromatic H), 6.68–7.09 (1H, m, $NC\underline{H}{=}CH_2$), 7.00 (1H, s, aromatic H) [* cf. C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Vol. III, 127D (1974)]; IR ($CHCl_3$) 1610 (C=O and vinyl C=C), 1560 cm^{-1} (enaminone C=C).

16) 11: mp 158–159 °C (acetone–hexane); NMR ($CDCl_3$) δ 1.87–2.58 (6H, m, 3 x CH_2), 3.65 (4H, s, $N(CH_2)_2Cl$), 4.49 (2H, s, vinylic H), 5.96 (2H, s, OCH_2O), 6.48 and 7.02 (1H each, s, aromatic H); IR ($CHCl_3$) 1600 (C=O), 1540 cm^{-1} (C=C).

17) This compound is labile on prolonged exposure to air or storage in organic solvents and was alternatively formed by heating 11 with NaH in DMF for 1 h in 82% yield.

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