N-Protecting Group Dependent Aromatization of 3-Pyrroline Systems to Pyrroles

Kwang-Youn Ko*, Key-In Lee, Jae Hak Kim, Myung Hee Jung, and Wan-Joo Kim

Korea Research Institute of Chemical Technology, Daedeog-Danji 305-606. *Received November 23, 1989*

Five-membered nitrogen heterocycles such as pyrroles and indoles are present in a number of natural products such as alkaloids, and drugs.[1] Therefore, novel methodology for the synthesis of pyrroles continues to receive significant attention. Particularly useful classical methods are the Paal-Knorr synthesis, the Hantzsch synthesis, the Knorr synthesis, and the Feist synthesis.[2] Also, recently reported methods include the intramolecular ene strategy developed by Oppolzer,[3] the electrophilic promoted cyclizations of unsaturated amines,[4] the 1,3-dipolar cycloaddition method,[5] the tandem cationic aza-Cope-Mannich cyclization method[6] and the transition metal-catalyzed cyclization of unsaturated amines.[7]

Besides the synthetic methods mentioned above, the oxidative aromatization of more highly reduced nonaromatic heterocycles is often used for the preparation of aromatic nitrogen compounds such as pyrroles and especially, indoles, isoindoles and carbazoles ring system.[2b] As the oxidants, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[8] chloranil, manganese dioxide,[9] palladium on carbon, and sulfur are used.[10]

Here we report the N-protecting group dependent aromatization of 3-pyrrolidines using pyridinium dichromate (PDC).[11]

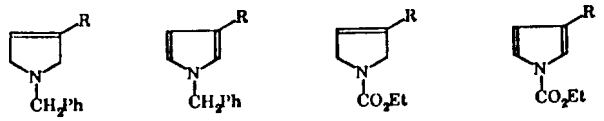
When 1-benzyl-3-hydroxymethyl-3-pyrroline (1)[12] was oxidized with PDC in dichloromethane in a hope of preparing 3-formyl-3-pyrroline (2), 3-formyl-3-pyrrole (3) was instead obtained in 65% yield as evidenced by proton NMR and mass spectra.[14] Also, the oxidation using DDQ (refluxing in benzene) or manganese dioxide gave the same result. However, aldehyde 2 could be obtained in 50% yield by Swern oxidation[15] (dimethyl sulfoxide/trifluoroacetic anhydride/triethylamine).[16]

In the case of 3-carboethoxy derivative 4,[13] the oxidation with PDC or DDQ gave the aromatized product 5 in 60-70% yield.[17]

Later, we examined the effect of N-protecting group by changing to N-ethoxycarbonyl group having electron withdrawing ability. Thus, the oxidation of 3-hydroxymethyl-3-pyrroline (6)[18] with PDC or Swern's reagent gave only the non-aromatized aldehyde (7), mp. 82-83 °C in 60% and 85% yield.[20] In contrast, DDQ oxidation of alcohol 6 and ester 8 gave the aromatized aldehyde 9[21] (80% yield) and ester 10,[22] mp 41-3 °C (90% yield), respectively.

The above results can be summarized as follows; DDQ aromatizes both N-benzyl and N-ethoxycarbonyl-3-pyrrolines to pyrroles with concomitant oxidation of side-chain hydroxyl group. However, in PDC oxidation only N-benzyl-3-pyrrolines are aromatized to pyrroles with sidechain oxidation and in Swern oxidation no aromatization occurs in both cases.

This dichotomy in PDC oxidation may be explained by



(1) R = CH_2OH (2) R = CHO (4) R = CO_2Et (3) R = CHO (5) R = CO_2Et (6) R = CH_2OH (7) R = CHO (8) R = CO_2Et (9) R = CHO (10) R = CO_2Et

postulating that PDC is mild enough to aromatize only 3-pyrrolines whose nitrogen atom is protected with electron donating benzyl group.[23]

In conclusion, PDC may be used as a new aromatization reagent of 3-pyrroline systems and further study is required to examine the potential and limitation of this reagent for the aromatization of non-protected pyrrolines and pyrrolines protected with other groups, and other reduced ring system such as dihydroindoles and tetrahydrocarbazoles.

References

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12. Compound 1 was prepared by the dehydration (acetyl chloride, then potassium carbonate in DMF) of known 1-benzyl-3-carboethoxy-4-hydroxy pyrrolidine[13] followed by the diisobutylaluminum hydride (DIBAL-H) reduction of the resulting 3-pyrroline (4).
13. E. Jaeger and J. H. Biel, *J. Org. Chem.*, **30**, 740 (1965).
14. Proton NMR ($CDCl_3$, 300 MHz) δ 9.69 (s, 1H), 7.35-7.30 (m, 4H), 7.16-7.13 (m, 2H), 6.70-6.68 (m, 1H), 6.64-6.63 (m, 1H), 5.06 (s, 2H); MS (70 eV), *m/e* 65 (14), 91 (100), 185 (71); IR ($CHCl_3$) 1665 cm^{-1}.
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16. Proton NMR ($CDCl_3$, 60 MHz) δ 9.56 (s, 1H), 7.13 (s, 5H), 6.65 (m, 1H), 3.73 (s, 2H), 3.60 (s, 4H).
17. Proton NMR ($CDCl_3$, 300 MHz) δ 7.35-7.20 (m, 4H), 7.13-7.09 (m, 2H), 6.62-6.59 (m, 2H), 5.00 (s, 2H), 4.24 (q, 2H, J = 7 Hz), 1.30 (t, 3H, J = 7 Hz); IR ($CHCl_3$) 1690 cm^{-1}.
18. Compound 6 was prepared from the DIBAL-H reduction of the known ester 8.[19]
19. (a) T. L. Macdonald and B. A. Narayanan, *J. Org. Chem.*, **48**, 1131 (1983); (b) Y.-H. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).
20. Proton NMR ($CDCl_3$, 300 MHz) δ 9.77 (s, 1H), 6.88-6.82 (m, 1H), 4.48-4.42 (m, 2H), 4.39-4.34 (m, 2H), 4.17 (q, 2H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz); IR ($CHCl_3$) 1700, 1680 cm^{-1}.
21. Proton NMR ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 7.92 (apparent t, 1H, $J \approx 2$ Hz), 7.32 (dd, 1H, J = 2, 3 Hz), 6.67 (dd, 1H, J = 1.5, 3 Hz), 4.48 (q, 2H, $J \approx 7$ Hz), 1.44 (t, 3H, J = 7 Hz); IR ($CHCl_3$) 1750, 1670 cm^{-1}.
22. Proton NMR ($CDCl_3$, 300 MHz) δ 7.87 (apparent, t, 1H, $J \approx 2$ Hz), 7.24 (dd, 1H, J = 2, 3 Hz), 6.62 (dd, 1H, J = 1.5, 3 Hz), 4.44 (q, 2H, J = 7 Hz), 4.29 (q, 2H, J = 7 Hz), 1.43 (t, 3H, $U \approx 7$ Hz), 1.35 (t, 3H, J = 7 Hz); IR ($CDCl_3$-$CHCl_3$) 1740, 1720 cm^{-1}.
23. Oxidation is defined as loss of electron, so the electron rich nitrogen atom is more labile to oxidation.