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NITROGEN ASSISTED ENOL ETHER FORMATION

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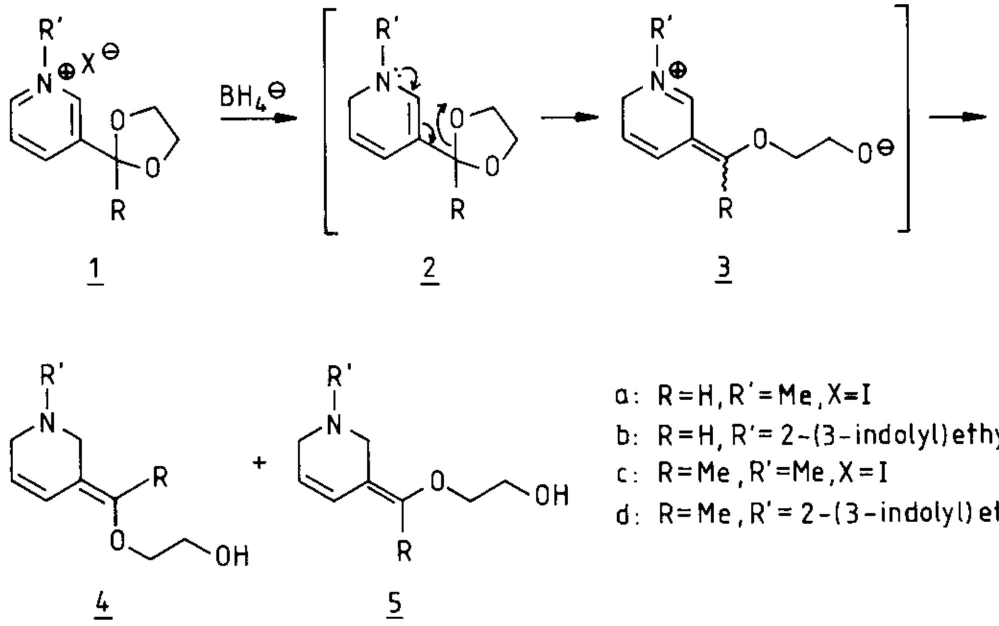
Abstract - A nitrogen assisted enol ether formation via cyclic acetal ring opening is described.

There are only a very few special cases known, where enol ethers are formed via cyclic acetal ring opening.[1] We have found that treatment of N-alkyl salts of 3-formyl- and 3-acetylpyridine acetals 1a-1d with $NaBH_4$ yields enol ethers 4a-d and 5a-d, respectively.

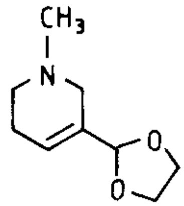
The mechanism of the transformation can be explained by the formation of 1,6-dihydrointermediate 2 in which the nitrogen assisted acetal ring opening takes place (Scheme 1). The reaction is completed by the reduction and protonation of the formed iminium species 3.



a: R=H, R'=Me, X=I
b: R=H, R'=2-(3-indolyl)ethyl, X=Br
c: R=Me, R'=Me, X=I
d: R=Me, R'=2-(3-indolyl)ethyl, X=Br

Scheme 1

3-Formylpyridine acetal methiodide 1a[2] was reduced with $NaBH_4$ in the usual manner (ethanol, 0^oC). In addition to the normal reduction product 6[3], two stereoisomers, 4a[4] (trans) and 5a[5] (cis), with an exocyclic double bond were formed via acetal ring opening.



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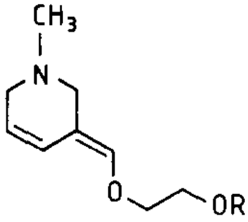
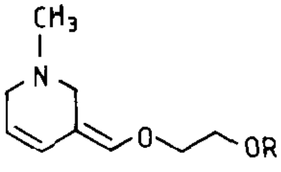


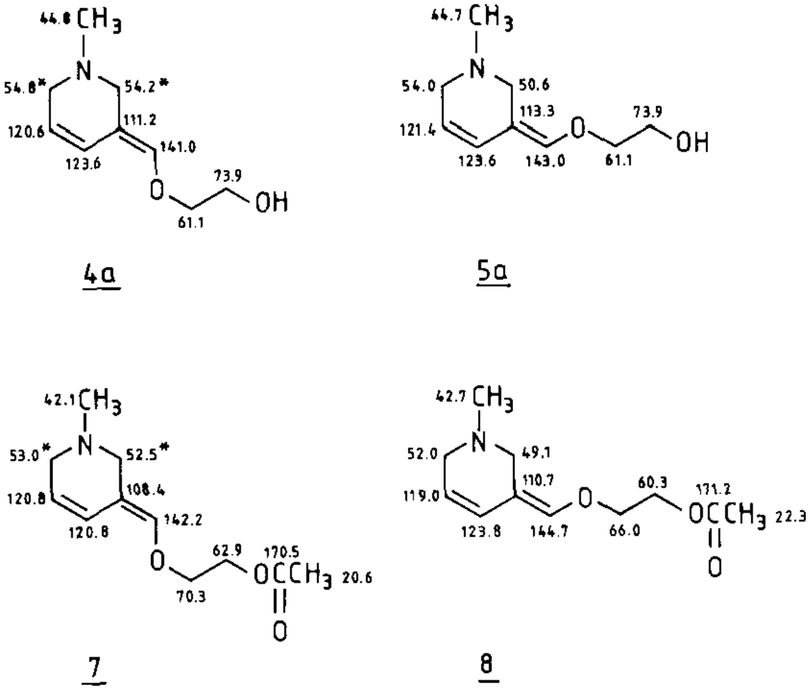
4a (R=H)
7 (R=Ac)



5a (R=H)
8 (R=Ac)

The ratio of the trans- and cis-isomers 4a and 5a was ca. 5:1, determined from NMR spectra. The stereochemistry of the major isomer was assigned trans on the basis of ^{13}C NMR chemical shifts (Fig. 1): the carbon atoms in the exocyclic double bond of the cis-isomer were expected to possess lower field signals.

Isomers 4a and 5a were both quite unstable and so they were converted to their more stable acetates 7[6] and 8[7] (for their ^{13}C NMR data, see Fig. 1).



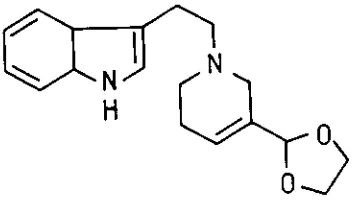
4a

5a

7

8

Fig. 1.



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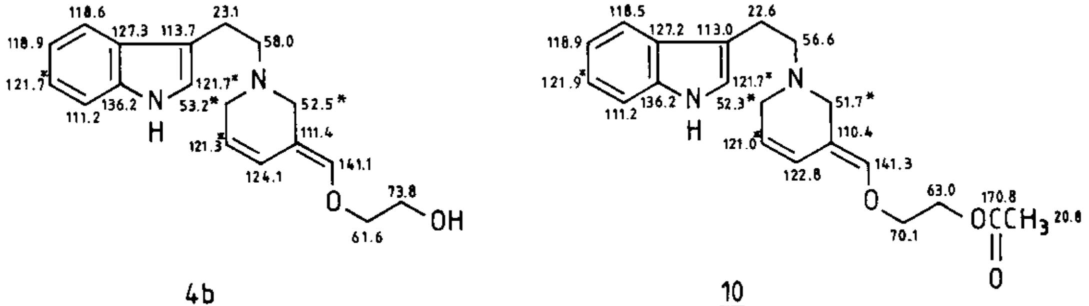
The reduction of the tryptophyl salt 1b gave, besides tetrahydropyridine 9[8], the expected enol ether 4b[9] (trans; traces of the cis-isomer 5b were detected).

This compound was also more conveniently handled as its acetate 10.[10] The ^{13}C NMR chemical shifts of the trans-isomer 4b and the acetate 10 are given in Fig. 2.



4b

10

Fig. 2.

The acetal ring opening was found to take place in a similar manner in the carbonyl protected keto series, i.e. starting from 3-acetylpyridine. Its ketal methyl salt 1c yielded the isomeric mixture 4c and 5c (total yield 35%, ratio ca. 4:3). Similarly, its ketal tryptophyl salt 1d afforded the isomeric mixture 4d and 5d (total yield 40%, ratio ca. 4:3).

REFERENCES AND NOTES

1. E.g. for the reaction of 2-substituted 1,3-dioxolanes with Grignard reagents leading to 2-hydroxyalkyl enol ethers, see G. Westera, C. Blomberg and F. Bickelhaupt, J. Organomet. Chem., 1978, 144, 291.
2. M. Lounasmaa, T. Tamminen and R. Jokela, Heterocycles, 1985, 23, 1735.
3. Compound 6: Yellow oil, yield ~ 40 %. IR (ν cm^{-1}, $CHCl_3$): 2900 (st), 2810 (st), 2400 (w), 1720 (m), 1680 (w), 1660 (w). ^1H NMR (δ, $CDCl_3$): 5.94 (1H, br s), 5.17 (1H, s), 3.92 (4H, br s), 2.94 (4H, m), 2.50 (2H, m), 2.36 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 133.4 (s), 125.0 (d), 104.5 (d), 64.8 (t) (2C), 51.4 (t) (2C), 45.5 (q), 25.3 (t). MS (EI 70 eV, m/z): 169 (M^+, 50), 124 (73), 96 (100).

4. Compound 4a: Colourless oil, yield $\sim$ 20 %. IR (ν cm^{-1}, CHCl$_3$): 3300 (st), 2950 (st), 2800 (st), 1660 (st), 1610 (m). ^{1}H NMR (δ, CDCl$_3$): 6.56 (1H, d, J_{AB} = 10.5 Hz), 5.94 (1H, br s), 5.62 (1H, d, J_{AB} = 10.5 Hz), 3.77 (4H, m), 2.98 (4H, m), 2.34 (3H, s). ^{13}C NMR (δ, CDCl$_3$): see Fig. 1. MS (EI, 70 eV, m/z): 169 (M^{+}, 50), 124 (100), 122 (25), 108 (15), 94 (95).

5. Compound 5a: Colourless oil, yield $\sim$ 4 %. IR (ν cm^{-1}, CHCl$_3$): 3300 (st), 2800 (st), 1660 (st). ^{1}H NMR (δ, CDCl$_3$): 6.56 (1H, d, J_{AB} $\sim$ 10 Hz), 6.10 (1H, br s), 5.61 (1H, d, J_{AB} $\sim$ 10 Hz), 3.76 (4H, m), 2.98 (4H, m), 2.34 (3H, s). ^{13}C NMR (δ, CDCl$_3$): see Fig. 1. MS (EI, 70 eV, m/z): 169 (M^{+}, 50), 124 (100).

6. Compound 7: Yellow oil, yield 90 %. IR (ν cm^{-1}, CHCl$_3$): 3050 (st), 1740 (m), 1680 (m). ^{1}H NMR (δ, CDCl$_3$): 6.58 (1H, d, J_{AB} = 10.2 Hz), 5.96 (1H, br s), 5.60 (1H, d, J_{AB} = 10.2 Hz), 4.11 (4H, m), 3.20 (4H, m), 2.44 (3H, s), 2.07 (3H, s). ^{13}C NMR (δ, CDCl$_3$): see Fig. 1. MS (EI, 70 eV, m/z): 211 (M^{+}, 26), 124 (100), 96 (24), 87 (35).

7. Compound 8: Yellow oil, yield 90 %. IR (ν cm^{-1}, CHCl$_3$): 3100 (st), 1740 (m), 1680 (m). ^{1}H NMR (δ, CDCl$_3$): 6.60 (1H, d, J_{AB} $\sim$10 Hz), 6.16 (1H, br s), 5.60 (1H, d, J_{AB} $\sim$10 Hz), 4.10 (4H, m), 3.20 (4H, m), 2.44 (3H, s), 2.05 (3H, s), ^{13}C NMR (δ, CDCl$_3$): see Fig. 1. MS (EI, 70 eV, m/z): 211 (M^{+}, 30), 124 (100).

8. Compound 9: Yellow foam, yield $\sim$ 50 %. IR (ν cm^{-1}, CHCl$_3$): 3350 (m), 3030 (st), 1710 (w), 1660 (st), 1610 (m). ^{1}H NMR (δ, CDCl$_3$): 8.81 (1H, br s), 7.60-7.00 (4H, m), 6.87 (1H, d, J = 2 Hz), 5.95 (1H, br s), 5.18 (1H, s), 3.87 (4H, s), 3.15-2.65 (8H, m), 2.22 (2H, m). ^{13}C NMR (δ, CDCl$_3$): 136.0 (s), 133.3 (s), 127.1 (s), 125.8 (d), 121.7 (d), 121.3 (d), 18.6 (d), 118.4 (d), 113.4 (s), 110.9 (d), 104.6 (d), 64.9 (t) (2C), 58.8 (t), 49.6 (t) (2C), 25.3 (t), 22.8 (t). MS (EI 70 eV, m/z): 298 (M^{+}, 35), 170 (40), 168 (100), 144 (23), 130 (19), 108 (51).

9. Compound 4b: Yellow foam, yield $\sim$ 25 %. IR (ν cm^{-1}, CHCl$_3$): 3300 (st), 2950 (st), 1665 (st), 1620 (m). ^{1}H NMR (δ, CDCl$_3$): 8.42 (1H, br s), 7.60-7.10 (4H, m), 6.97 (1H, d, J = 2 Hz), 6.60 (1H, d, J_{AB} = 10.7 Hz), 5.91 (1H, br s), 5.67 (1H, d, J_{AB} = 10.7 Hz), 3.80 (4H, br s), 3.30-2.80 (8H, m). ^{13}C NMR (δ, CDCl$_3$): see Fig. 2. MS (EI, 70 eV, m/z): 298 (M^{+}, 10), 168 (35), 144 (22), 130 (48), 108 (95), 84 (100).

10. Compound 10: Yellow oil, yield 90 %. IR (ν cm^{-1}, CHCl$_3$): 3300 (m), 3010 (st), 1720 (st), 1660 (m). ^{1}H NMR (δ, CDCl$_3$): 8.74 (1H, br s), 7.65-7.10 (4H, m), 6.97 (1H, d, J = 2 Hz), 6.59 (1H, d, J_{AB} = 9.7 Hz), 5.83 (1H, br s), 5.63 (1H, d, J_{AB} = 9.7 Hz), 4.05 (4H, m), 3.30-2.90 (6H, m), 2.20 (2H, m), 2.04 (3H, s). ^{13}C NMR (δ, CDCl$_3$): see Fig. 2. MS (EI, 70 eV, m/z): 340 (M^{+}, 80), 300 (20), 253 (18), 226 (22), 211 (32), 210 (50), 168 (95), 142 (20), 130 (100).

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