Tetrahedron Letters No. 36, pp 3453 - 3456. 0040-4039/79/0901-3453$02.00/0

NOVEL N-ALKYLATION OF A SCHIFF BASE WITH ELECTRON-DEFICIENT OLEFINS

Yujiro Nomura*, Takashi Bando, Yoshito Takeuchi, and Shuji Tomoda
Department of Chemistry, College of General Education, The University of Tokyo
Komaba, Meguro, Tokyo 153, JAPAN

Summary: The reaction of 2,3,4,5-tetrahydropyridine with electron-deficient olefins such as methyl acrylate, acrylonitrile, and N-phenylmaleimide, provided 1-(2-methoxycarbonylethyl)-5-[1-(2-methoxycarbonylethyl)-2-piperidyl]-1,2,3,4-tetrahydropyridine, 1-(2-cyanoethyl)-5-[1-(2-cyanoethyl)-2-piperidyl]-1,2,3,4-tetrahydropyridine, and 2-(2-methoxypiperidino)-N-phenylsuccinimide, respectively, in high yields.

2,3,4,5-Tetrahydropyridine (1), a cyclic Schiff base, which also has biological importance as a precursor of various alkaloids,[1] is labile as monomeric form (1).[2] If the trimer (3)[2]– monomer (1) equilibrium and imine (1) – enamine (2) tautomerism[3], [5] in the reaction conditions are taken for granted, one can expect reaction modes of 1 as a Schiff base having enolizable hydrogens.[4]

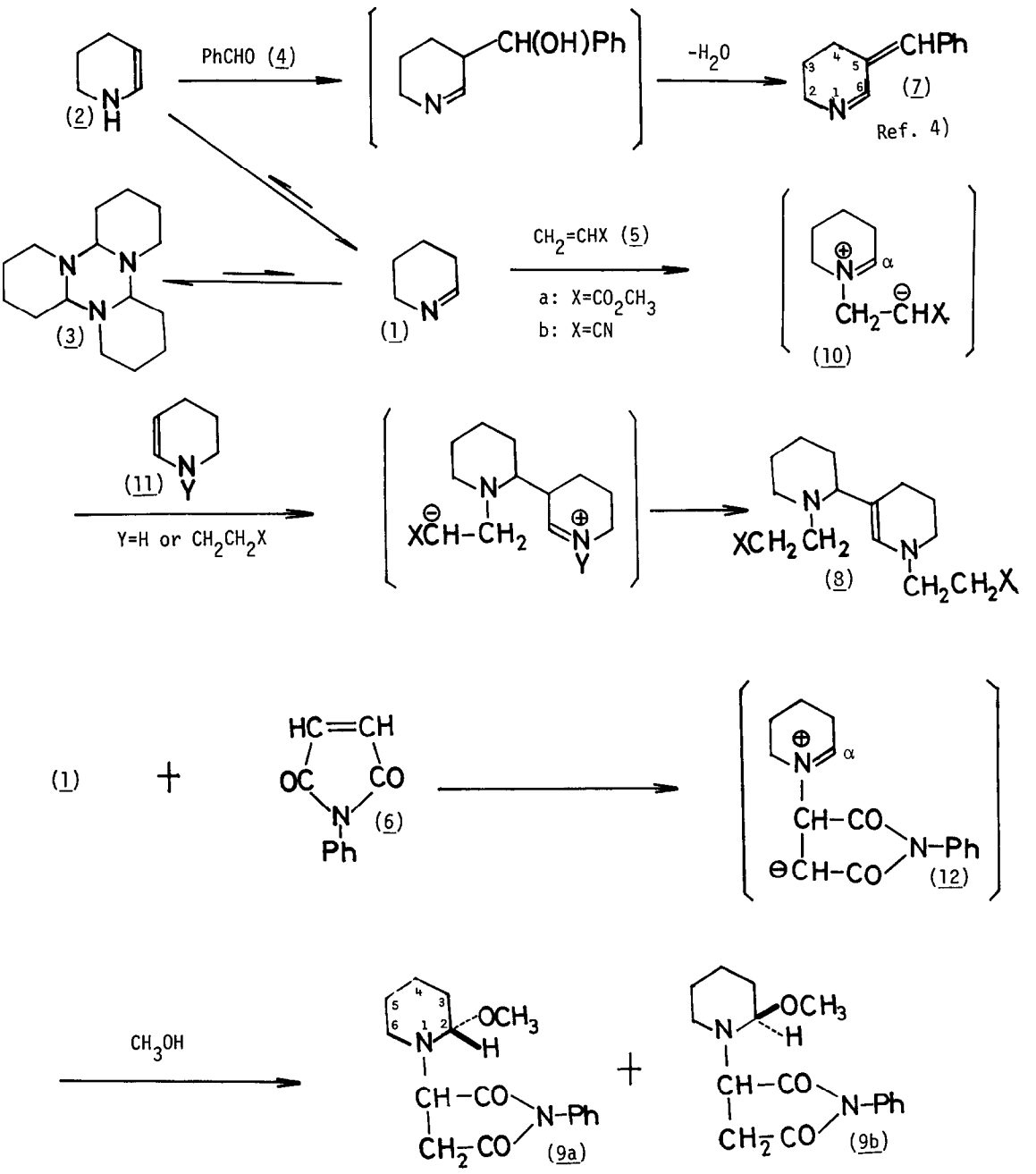
Whereas electron-deficient acetylene derivatives can react with Schiff bases at nitrogen atom even when hydrogen atoms exist next to the imino group,[5] it has hitherto been demonstrated that electron-deficient olefins afford C-alkylated products exclusively in every case already known.[3] In this communication, we wish to report novel N-alkylation reactions of a cyclic Schiff base (1) with typical electron-deficient olefins such as methyl acrylate, acrylonitrile, and N-phenylmaleimide.

A solution of 2,3,4,5-tetrahydropyridine trimer (α-isomer) (3) (1.25 g, 0.005 mol) and methyl acrylate (5a) (1.72 g, 0.020 mol) in absolute methanol (50 ml) was stirred for 48 h at room temperature under nitrogen. Evaporation of the solvent provided spectrally pure 1-(2-methoxycarbonylethyl)-5-[1-(2-methoxycarbonylethyl)-2-piperidyl]-1,2,3,4-tetrahydropyridine (8a)[6] (2.55 g, 100 % yield). Acrylonitrile (5b) reacted similarly with 3 to give 5-(2-piperidyl)-1,2,3,4-tetrahydropyridine derivative (8b)[7] in 100 % yield.

The structures of these products were determined by spectroscopy and most explicitly by an independent synthesis involving mercuric acetate oxidation of methyl 3-piperidinopropionate or 3-piperidinopropiononitrile.[8]

These reactions can be rationalized only if an initial attack of the olefin on the nitrogen atom of 1 affords a zwitterionic intermediate 10. Subsequent attack of an enamine 11 on α-carbon of 10 will afford tetrahydroanabasine derivatives (8). Although it is impossible to decide whether N-alkylation of enamine 11 (Y=H) with another molecule of the electrophilic olefins (5) precedes nucleophilic attack of 11 (Y=H) to 10 or vice versa, the initial N-alkylation reaction of 1 makes a remarkable contrast to the case of ordinary Schiff bases having hydrogen atoms next to

the imino group in which exclusive β-carbon alkylation always takes place.[3)]



The intermediate formation of 10 was further demonstrated by the reaction of 1 with N-phenylmaleimide.

Thus, N-phenylmaleimide (6) (2.60 g, 0.015 mol) reacted with 3 (1.25 g, 0.005 mol) in methanol (30 ml) under identical conditions. Purification of the product with column chromatography on silica gel gave a solvent-incorporated adduct, 2-(2-methoxypiperidino)-N-phenylsuccinimide (diastereomeric mixture 9a and 9b; 47 and 21 % yield, respectively).[9]

The structure of 9a was identified as follows. The mass spectrum and elemental analysis established its molecular formula as $C_{16}H_{20}N_2O_3$. ^{1}H-Off-resonance ^{13}C-NMR spectrum indicated, besides phenyl carbons, ten peaks which contained two carbonyl, one methoxyl, two methyne and five methylene carbons.

The structure of 9b was similarly assigned on the basis of spectral data which resemble those of diastereomeric 9a in many respects.[9]

The stereochemistry about C-2 of the piperidine ring in 9a and 9b was confirmed by the ^{13}C-NMR chemical shifts based on the fact that replacement of the equatorial hydrogen atom at C-4 of t-butylcyclohexane by a hydroxyl group results in a low-field shift of C-4 carbon by 43.2 ppm and in case of an axial hydroxyl group by 37.8 ppm.[10]

Compared with intermediate (10), the α-position of 12 is much more conjested by the larger substituent, making the attack of less bulky methanol more favourable instead of enamine corresponding to 11.

In conclusion, what is unusual in our reactions is therefore the formation of the N-alkylated products (8) and (9) from 1 and electron-deficient olefins, in sharp contrast to exclusive C-alkylation of typical aliphatic imines containing enolizable hydrogens.[3] This anomaly is most likely associated with the cyclic structure of 1.

From a synthetic point of view, it should also be noted here that the quantitative formation of compound 8, which possesses Δ^2-tetrahydroanabasine skeleton,[6), 7)] is considered to be important in connection with naturally occurring alkaloids such as adenocarpine[1] or (+)-N'-methylammodendrine.[11]

Reference and Notes

1) E. Leete, Acc. Chem. Res., 4, 100(1971), and references cited therein; R. B. Herbert, "The Alkaloids", M. F. Grundon Ed., The Chemical Society, 1976, p. 1-15, and references cited therein; W. M. Golebiewski and I. D. Spenser, J. Am. Chem. Soc., 98, 6726(1976).

2) C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, Justus Liebigs Ann. Chem., 559, 1(1948).

3) R. W. Layer, Chem. Rev., 63, 489(1963), and references cited therein; M. Pfau and C. Ribière, J. Chem. Soc., Chem. Commun., 1970, 66; idem, Bull. Soc. Chim. Fr., 1971, 2584; K. C. Brannock, A. Bell, R. D. Burpitt, and C. A. Kelly, J. Org. Chem., 29, 801(1964); K. Takahashi, A. Miyake, and G. Hata, Bull. Chem. Soc. Jpn. 45, 2212(1972).

4) This postulation was clearly demonstrated by the reaction of trimer (3) with benzaldehyde (4) in absolute methanol for 48 h at room temperature under nitrogen resulting in the exclusive formation of 5-benzylidene-2,3,4,5-tetrahydropyridine (7) in 44 % yield.
7; colourless needles, Mp. 36–38 °C; ^{13}C-NMR($CDCl_3$): δ(TMS) 21.53(t), 24.95(t), 49.49(t),

128.09(d), 128.40(d), 129.47(d), 131.58(s), 135.84(s), 136.51(d), 163.73(d); ^{1}H-NMR($CDCl_3$): δ(TMS) 1.71(q, J=7 Hz, 2H), 2.70(t, J=7 Hz, 2H), 3.72(t, J=7 Hz, 2H), 6.64(s, 1H), 7.36(s, 5H), 7.96(s, 1H); IR(neat); 1613(conjugated C=N), 760, 698 cm^{-1}; MS: M^{+}= 171; Anal. Found(Calcd.): C 84.04(84.21), H 7.73(7.60), N 8.29(8.19).

This reaction is in line with observations for the reaction of azomethines derived from aliphatic carbonyl compounds with enolizable protons: T. M. Patrick Jr., J. Am. Chem. Soc., 74, 2984 (1952).

5) R. Huisgen and K. Herbig, Justus Liebigs Ann. Chem., 688, 98(1965); A. de Savignac and A. Lattes, Bull. Soc. Chim. Fr., 1970, 4476.

6) 8a; pale yellow oil (purified by silica gel column chromatography); ^{13}C-NMR($CDCl_3$): δ(TMS) 20.44(t), 22.60(t), 24.95(t), 25.96(t),31.18(t), 32.29(t), 32.67(t), 47.08(t), 49.86(t), 51.01(t), 51.31(q: OCH_3), 51.52(q: OCH_3), 52.92(t), 68.24(d), 111.03(s), 132.86(d), 172.67 (s: C=O), 173.33(s: C=O); ^{1}H-NMR($CDCl_3$): δ(TMS) 3.69(s, 3H), 3.71(s, 3H), 5.84(s, 1H); IR(CCl_4): 1743(C=O), 1735(C=O), 1658(C=C) cm^{-1}; M.W. (determined by cryoscopy): 310 ($C_{18}H_{30}N_2O_4$= 338).

7) 8b; colourless oil (purified by silica gel column chromatography); ^{13}C-NMR($CDCl_3$): δ(TMS) 14.96(t), 16.44(t), 20.47(t), 22.49(t), 24.79(t), 25.94(t), 32.17(t), 46.96(t), 49.65(t), 50.92(t), 52.84(t), 67.47(d), 111.25(s), 118.57(s: CN), 119.53(s: CN), 132.14(d); ^{1}H-NMR($CDCl_3$): δ(TMS) 5.92(s, 1H); IR(neat): 2458(CN), 1660(C=C) cm^{-1}; Anal. Found(Calcd.): C 70.53(70.59), H 9.05(8.82), N 20.32(20.59).

8) N. J. Leonard and F. P. Hauck Jr., J. Am. Chem. Soc., 79, 5279(1957); N. J. Leonard and A. G. Cook, J. Am. Chem. Soc., 81, 5627(1959).

9) 9a; colourless needles, Mp. 103 °C; ^{13}C-NMR($CDCl_3$): δ(TMS) 22.76(t), 25.16(t), 28.97(t), 35.21(t), 48.28(t), 51.74(d), 61.14(d), 77.70(q: OCH_3), 124.56(d: phenyl), 126.31(d: phenyl), 128.92(d: phenyl), 134.28(s: phenyl), 171.35(s: C=O), 171.97(s: C=O); ^{1}H-NMR($CDCl_3$): δ(TMS) 1.00–2.20(m, 6H), 2.20–3.30(m, 4H), 3.52(m, 1H), 3.72(s, 3H), 4.10(m, 1H), 7.00–7.80(m, 5H); IR(neat): 1735(C=O), 1728(C=O), 1598, 1500, 1123, 774, 698 cm^{-1}; MS: M^{+}= 288; Anal. Found(Calcd.): C 66.97(66.67), H 7.24(6.94), N 9.90(9.72).

9b; pale yellow oil; ^{13}C-NMR($CDCl_3$): δ(TMS) 20.92(t), 21.83(t), 27.75(t), 34.77(t), 46.07(t), 51.92(d), 58.54(d), 74.51(q: OCH_3), 122.66(d: phenyl), 125.78(d: phenyl), 129.19(d: phenyl), 136.42(s: phenyl), 171.31(s: C=O), 172.04(s: C=O); ^{1}H-NMR($CDCl_3$): δ(TMS) 1.10–2.20(m, 6H), 2.50–3.10(m, 4H), 3.50(s, 1H), 3.69(s, 3H), 4.20(m, 1H), 7.00–7.90(m, 5H); IR(neat): 1375(C=O), 1710(C=O), 1598, 1500, 1122, 758, 692 cm^{-1}.

10) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, J. Am. Chem. Soc., 92, 1338(1970).

11) W. L. Fitch, P. M. Dolinger, and C. Djerassi, J. Org. Chem., 39, 2974(1974).

(Received in Japan 2 April 1979)