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2H-PYRROLO[3,4-b]PYRIDINE AND 2H-PYRROLO[3,4-c]PYRIDINE: SYNTHESIS OF THE PARENT RING SYSTEM AND THE DIELS-ALDER REACTION

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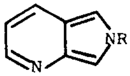
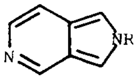
Summary: 2H-Pyrrolo[3,4-b]pyridine (1) and 2H-pyrrolo[3,4-c]pyridine (2) were prepared and reacted with N-phenylmaleimide to give Diels-Alder adducts.

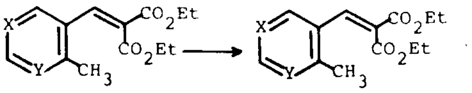
2H-Pyrrolo[3,4-b]pyridine (1) and 2H-pyrrolo[3,4-c]pyridine (2)[1] are aza-analogues of the highly labile isoindole system. The insertion of the extra nitrogen atom in 1 and 2 was expected to make the system thermodynamically more stable, also reducing the reactivity of the pyrrole moiety towards electrophilic attack. However, the parent compounds 1 and 2 are still unknown. Only the 2-methyl derivatives 3 and 4 have been prepared,[2,3] but the methods can not be easily modified for the preparation of the parent systems 1 and 2. In this letter, we now report the first synthesis of 1 and 2 based on our new method,[4] and their Diels-Alder reaction with N-phenylmaleimide.



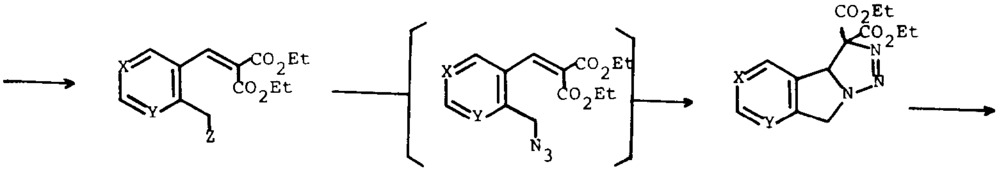
1 R=H
3 R=CH$_3$



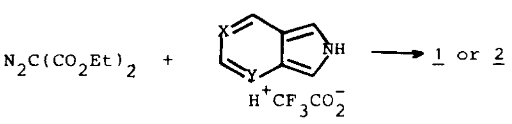
2 R=H
4 R=CH$_3$



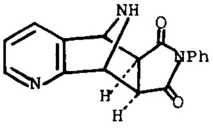
5 X=C, Y=N
6 X=N, Y=C
7 X=C, Y=N→O
8 X=N→O, Y=C



9 X=C, Y=N, Z=Cl
10 X=N→O, Y=C, Z=Br
11 X=N, Y=C, Z=Br
12 X=C, Y=N
13 X=N, Y=C
14 X=C, Y=N
15 X=N, Y=C



16 X=C, Y=N
17 X=N, Y=C



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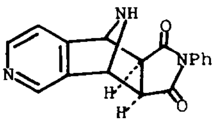

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MCPBA oxidation of 5[5] or 6[6] afforded pyridine oxide 7 or 8. Treatment of 7 with phenylsulfonyl chloride gave chloride 9 (66%). Reaction of 9 with NaN_3 in DMF gave 12, which immediately underwent intramolecular 1,3-dipolar cycloaddition to afford triazoline 14 directly (85%). On the other hand, bromination of 8 with NBS gave bromide 10 (84%). Bromide 10 was reduced with PCl_3 to give 11 (80%). Reaction of 11 with NaN_3 gave triazoline 15 (91%) via 13. The 1,3-dipolar cycloreversion reactions of 14 and 15 were effected with 2.5 equiv of triflouroacetic acid in ether to give diethyl diazomalonate and salts 16 and 17 respectively (74% and 80%).[7] Treatment of salts 16 and 17 with saturated Na_2CO_3 solution followed by extraction with CH_2Cl_2 gave free base 1 (81%) and 2 (77%).[8] Compound 1 is much less stable than 2 at room temperature. Treatment of salt 16 or 17 with 1.2 equiv of Et_3N (generating 1 and 2 in situ) in the presence of 1.2 equiv of N-phenylmaleimide in ether at room temperature for 16, or in refluxing THF for 17, gave the exo-adduct 18 or 19[9] in 64% and 96% yield respectively. Extension of this methodology for the preparation of other iso-condensed heteroaromatic pyrroles is under current investigation.

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References and Notes

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(5) Compound 5 was prepared by Knoevenegel condensation from 2-methylpyridine-3-carboxaldehyde: E. B. Sanders, H. V. Secor, and J. I. Seeman, J. Org. Chem., 1978, 43, 324.

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(7) NMR data for salt 16: ^1H NMR (400 MHz, DMSO-d_6) δ 7.31(dd, J=8.5 and 5.2 Hz, H_6), 7.74(br s, $H_{1\ or\ 3}$), 7.89(br s, $H_{3\ or\ 1}$), 8.74(d, J=5.2 Hz, $H_{5\ or\ 7}$), 8.81(d, J=8.5 Hz, $H_{7\ or\ 5}$), and 13.81(br s, NH). ^{13}C NMR(100.6 MHz, DMSO-d_6) δ 108.11(C_6, d), 116.65($C_{1\ or\ 3}$, d), 117.99 δ ($C_{3\ or\ 1}$, d), 120.83($\underline{C}F_3CO_2^-$, q), 122.94($C_{3a\ or\ 7a}$, s), 130.47($C_{7a\ or\ 3a}$, s), 144.40($C_{5\ or\ 7}$, d), 146.16($C_{7\ or\ 5}$, d), and 162.95 ($CF_3\underline{C}O_2^-$, q). UV(MeOH): λ_{max} (log ε) 225.8(4.40), 279.2(3.50), 290.6 (3.46), 357.6(3.37). NMR data for salt 17: ^1H NMR(400 MHz, DMSO-d_6) δ 7.75(br s, H_1), 7.80(d, J=7 Hz, H_7), 7.95(d, J=7Hz, H_6), 8.32(br s, H_3), 9.50(s, H_4), 11.45(br s, NH), ^{13}C NMR(100.6 MHz, DMSO-d_6) δ 111.69(C_7, d), 117.22($\underline{C}F_3CO_2^-$,q), 117.32(C_6, d), 117.41($C_{3a\ or\ 7a}$, s), 120.25($C_{1\ or\ 3}$, d), 122.61($C_{7a\ or\ 3a}$, s), 123.77($C_{3\ or\ 1}$, d), 143.39(C_4,d), 158.63($CF_3\underline{C}O_2^-$,q). UV(EtOH): λ_{max}(log ε) 342.8(3.59), 223.2(4.49).

(8) NMR data for 1: ^1H NMR (400 MHz, $CDCl_3$) δ 6.87(dd, J=3.9 and 8.4 Hz, H_6), 7.21(d, J=1.7Hz, H_1), 7.45(br s, H_3), 7.99(d, J=8.4Hz, H_5), 8.43(dd, J=1.7 and 3.9 Hz, H_7), 12.30(br s, NH). NMR data for 2: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24(s, H_1), 7.40(d, J=7Hz, H_6), 7.47(s, H_3), 7.92(d, J=7Hz, H_7), 9.10(s, H_4), 9.95(br s, NH).

(9) NMR data for 18: ^1H NMR (400 MHz, $CDCl_3$) δ 2.55(br s, 1H), 2.99(d, J=6.9Hz, 1H), 3.08(d, J=6.9Hz, 1H), 4.92(s, 1H), 4.99(s, 1H), 7.06(dd, J=7.4 and 5.1 Hz, 1H), 7.28-7.49(m, 5H), 7.59(d, J=7.4 Hz, 1H), 8.30(dd, J=5.1 and 1.3 Hz, 1H). NMR data for 19: ^1H NMR (400 MHz, $CDCl_3$) δ 2.65(br s, 1H), 2.96(d, J=6.9 Hz, 1H), 3.01(d, J=6.9 Hz, 1H), 5.00(s, 1H), 5.07(s, 1H), 7.27-7.51(m, 6H), 8.48(d, J=5.0Hz, 1H), 8.62(s, 1H).

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