SYNTHESIS AND 1,3-DIPOLAR CYCLOADDITION OF 3-HYDROXY-5-METHOXY-PYRIDINIUM N-IMINE

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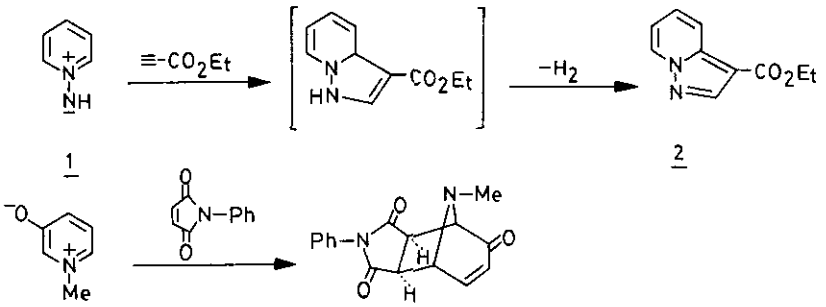
Abstract ——— The synthesis and 1,3-dipolar cycloaddition of 3-hydroxy-5-methoxypyridinium N-imine (12) is described. Compound 12 was found to undergo 1,3-dipolar cycloaddition reaction with ethyl propiolate to give ethyl 8-amino-4-methoxy-2-oxo-8-azabicyclo[3.2.1]oct-3,6-diene-6-carboxylate (13) and ethyl 4-hydroxy-6-methoxypyrazo[1,5-a]pyridine-3-carboxylate (14).

Pyridinium N-imine (1) was found to undergo 1,3-dipolar cycloaddition with ethyl propiolate to give ethyl pyrazo[1,5-a]pyridine-3-carboxylate (2).[1] In addition, 1-methyl-3-oxidopyridinium (3) reacts as a 1,3-dipole across the 2- and 6-positions with the N-phenylmaleimide to give cycloadduct (4).[2]



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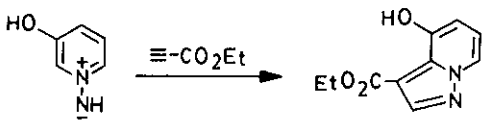
The reaction attitude of 3-hydroxypyridinium N-imine (5) is marked contrast to that of the betaine 3, 1-methyl-3-oxidopyridinium, which undergoes 1,3-dipolar cycloaddition with ethyl propiolate to give the ethyl 4-hydroxypyrazo[1,5-a]pyridine-3-carboxylate (6).[3]



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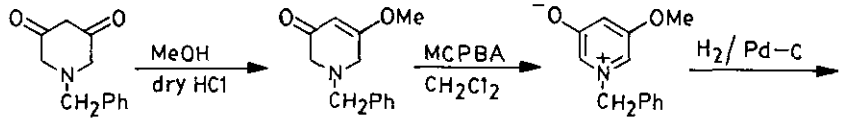
In order to enhance the 1,3-dipolar reactivity of the betaine 5, we have prepared 3-hydroxy-5-methoxypyridinium N-imine (12) from the known 1-benzylpiperidine-3,5-dione (7).[4]



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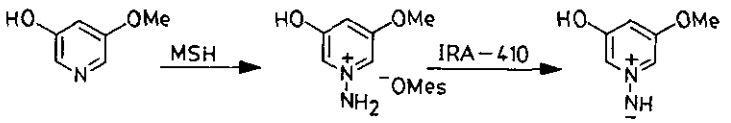

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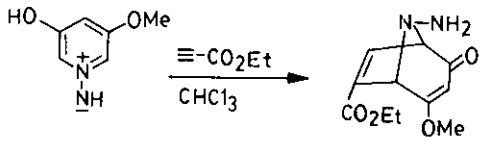
Compound 7 was converted into 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine (8) by treatment with dry methanol and hydrogen chloride gas in 67% yield. When the enol ether 8 was treated with m-chloroperbenzoic acid (MCPBA) in methylene chloride, 1-benzyl-5-methoxy-3-oxidopyridinium (9) was obtained quantitatively as hygroscopic crystals. Debenzylation of 9 by catalytic hydrogenolysis over 5% palladium-carbon in methanol at room temperature gave 3-hydroxy-5-methoxypyridine (10) in 84% yield. Stirring of 10 with O-mesitylenesulfonylhydroxylamine (MSH)[5] in methylene chloride at 0°C gave 1-amino-3-hydroxy-5-methoxypyridinium mesitylenesulfonate (11) in 68% yield. After treatment of 11 with IRA-410 in methanol solution gave 3-hydroxy-5-methoxypyridinium N-imine (12) in quantitative yield.

1,3-dipolar cycloaddition of 12 with ethyl propiolate in refluxing chloroform for 4 h gave ethyl 8-amino-4-methoxy-2-oxo-8-azabicyclo[3.2.1]oct-3,6-diene-6-carboxylate (13) in 30% yield.



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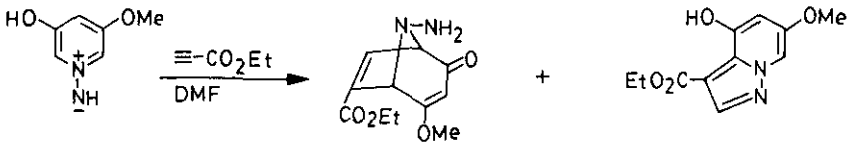
However, when the betaine 12 reacted with ethyl propiolate at room temperature in N,N-dimethylformamide (DMF) for 14 h to give cycloadducts 13 in 10% yield and ethyl 4-hydroxy-6-methoxypyrazo[1,5-a]pyridine-3-carboxylate (14) in 12% yield, respectively.



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Thus it has been demonstrated that chloroform is superior to DMF when 3-hydroxy-5-methoxypyridinium N-imine (12) reacts as a 1,3-dipole across the 2- and 6-positions with the ethyl propiolate to give cycloadduct 13.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured with a Hitachi EPI G-2 spectrophotometer in chloroform unless otherwise specified, uv spectra with a Hitachi 124 spectrophotometer in ethanol, and mass spectra with a Hitachi RMU-6D mass spectrometer at 70 ev. Pmr spectra were obtained with a Hitachi R 20A spectrometer in the solvents indicated. Chemical shifts and coupling constants were measured in ppm (δ) and J (Hz) with respect to TMS.

1-Benzyl-5-methoxy-3-oxidopyridinium Betaine (9): To a solution of 1-benzyl-3-methoxy-5-oxo-3,4-dehydropiperidine (8) (400 mg, 1.84 mmol) in methylene chloride (20 ml), m-chloroperbenzoic acid (544 mg, 3.15 mmol) was added under ice-cooling. The mixture was stirred for 1 h and concentrated in vacuo to give a syrup, which was subjected to IRA-410 through a methanol solution to give 380 mg (96%) of 9 as hygroscopic crystals. An analytical sample of mp 60-61°C was obtained as colorless prisms by crystallization from petroleum ether; pmr (deuteriochloroform): δ 3.79 (s, 3H, OCH_3), 5.19 (s, 2H, CH_2Ph), 6.79 (t, 1H, J=2 Hz, H-4), 6.90 (t, 1H, J=2 Hz, H-2), 7.18 (t, 1H, J=2 Hz, H-6), 7.73 (s, 5H, ArH); ir: ν 1575, 1570 cm^{-1}; uv: λ 236, 255, 268, and 333 nm. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found : C, 72.68; H, 6.05; N, 6.72.

3-Hydroxy-5-methoxypyridine (10): Compound 9 (380 mg, 1.77 mmol) was submitted to the standard catalytic hydrogenolysis over 5% palladium-carbon (60 mg) in methanol (40 mg) at room temperature for several hours. After removal of palladium-carbon by filtration, the filtrate was concentrated under reduced pressure to give a solid, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give 184 mg (84%) of 10. An analytical sample of mp 147.5-148.5°C was obtained by crystallization from ethanol; pmr (DMSO-d_6): δ 3.77 (s, 3H, OCH_3), 6.79 (t, 1H, J=2.5 Hz, H-4), 7.76 (d, 2H, J=3 Hz, H-2 and H-6); ir: ν 1580, 1520, 1430, 1360, and 1325 cm^{-1}; uv: λ 221, 286 nm. Anal. Calcd. for $C_6H_7NO_2$: C, 57.59; N, 11.19. Found: C, 57.49; H, 5.69; N, 11.03.

1-Amino-3-hydroxy-5-methoxypyridinium Mesitylenesulfonate (11): To a solution of 10 (300 mg, 2.40 mmol) in methylene chloride-ethanol (5:1, 20 ml), a solution of O-mesitylenesulfonate (877 mg, 2.40 mmol) in methylene chloride (20 ml) was added dropwise. After stirring at room temperature for 1 h, ether (10 ml) was added. The insoluble material was isolated by filtration, which was recrystallized from methanol-ethyl acetate to give 554 mg (68%) of 11, mp 158.5-159.5°C; pmr (DMSO-d_6): δ 2.18 (s, 3H, CH_3-4'), 2.50 (s, 6H, CH_3-2', 6'), 3.89 (s, 3H, OCH_3), 6.78 (s, 2H, H-3', 5'), 7.26 (t, 1H, J=2 Hz, H-4), 7.98 (t, 1H, J=2 Hz, H-2), 8.13 (t, 1H, J=2 Hz, H-6), 8.45 (bs, 2H, NH_2); ir: ν 3240, 1595, 1535, 1430, 1360, and 1325 cm^{-1}; uv: λ 228, 262, 302, and 328 nm. Anal. Calcd. for $C_{15}H_{20}N_2O_5S$: C, 52.93; H, 5.92; N, 8.23. Found: C, 52.80; H, 5.95; N, 8.26.

3-Hydroxy-5-methoxypyridinium N-Imine (12): Treatment of 11 (500 mg, 1.47 mmol) with IRA-410 through a methanol solution to give 200 mg (97%) of 12 as a crystalline solid. An analytical sample of mp 173-174°C was obtained by crystallization from ethanol; pmr (DMSO-d_6): δ 3.70 (s, 3H, OCH_3), 6.33 (t, 1H, J=2 Hz, H-4), 6.95-7.10 (m, 2H, H-2, H-6), 7.75 (bs, 2H, NH and OH); ir: ν 3270, 3210, 1720, 1595, 1575, and 1530 cm^{-1}; uv: λ 234, 326 nm. Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.76; N, 19.99. Found: C, 51.54; H, 5.62; N, 19.86.

Ethyl 8-Amino-4-methoxy-2-oxo-8-azabicyclo[3.2.1]oct-3,6-diene-6-carboxylate (13): To a solution of 12 (150 mg, 1.07 mmol) in chloroform (10 ml), ethyl propiolate (105 mg, 1.07 mmol) was added. The mixture was refluxed for 4 h and concentrated under reduced pressure to give a residue, which was subjected to column chromatog-

raphy on silica gel with chloroform-hexane-methanol (20:20:1) as an eluting solvent to give 77 mg (30%) of 13, mp 120-121°C; pmr (deuteriochloroform): δ 1.30 (t, 3H, J=7 Hz, OCH_2CH_3), 3.40 (bs, 2H, NH_2), 3.77 (s, 3H, OCH_3), 4.21 (q, 2H, J=7 Hz, OCH_2CH_3), 4.37 (s, 1H, H-5), 4.46 (d, 1H, J=2 Hz, H-1), 5.48 (bs, 1H, H-3), 6.77 (d, 1H, J=2 Hz, H-7); ir: ν 1720, 1645, and 1605 cm^{-1}; uv: λ 246 nm. Anal. Calcd. for $C_{11}H_{15}N_2O_4$: C, 55.22; H, 6.32; N, 11.71. Found: C, 55.34; H, 6.23; N, 11.85.

Ethyl 4-Hydroxy-6-methoxypyrazo[1,5-a]pyridine-3-carboxylate (14): To a solution of 12 (150 mg, 1.07 mmol) in N,N-dimethylformamide (10 ml), ethyl propiolate (105 mg, 1.07 mmol) was added. The mixture was stirred at room temperature for 14 h and concentrated in vacuo to give a syrup, which was subjected to column chromatography on silica gel with ethyl acetate-hexane (1:6) as eluting solvents to give 26 mg (10%) of 13 and 30 mg (12%) of 14, respectively. An analytical sample of mp 136-137°C was obtained by crystillization from benzene; pmr (deuteriochloroform): δ 1.43 (t, 3H, J=7 Hz, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 4.40 (q, 2H, J=7 Hz, OCH_2CH_3), 6.57 (d, 1H, J=2 Hz, H-5), 7.72 (d, 1H, J=2 Hz, H-7), 8.14 (s, 1H, H-2), 11.50 (s, 1H, OH); ir: ν 1640 cm^{-1}; uv: λ 229, 234, 266, 275, 286, 321, and 335 nm. Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.81; H, 5.24; N, 11.75.

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