A FORMATION OF PYRROLO[2,1-a]ISOQUINOLINE DERIVATIVES BY THE REACTION OF ISOQUINOLINE N-OXIDES WITH ETHYL PROPIOLATE

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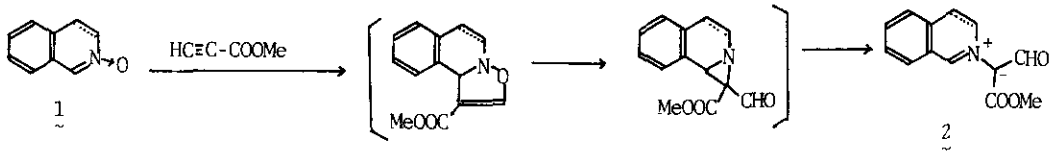
Abstract ——— Diethyl pyrrolo[2,1-a]isoquinoline-1,3-dicarboxylates were obtained by the reaction of the corresponding isoquinoline N-oxides with ethyl propiolate.

The cycloaddition reaction of nitrones with acetylene derivatives is recognized as the most versatile method for the synthesis of 4-isoxazolines[1], which have been proposed as reactive transients, first-formed intermediates. In many cases, these isoxazolines are easily convertible to ketoaziridines and 2-oxazolines[1] and the primary reactions are masked by the subsequent changes[2,3,4]. The reaction of isoquinoline N-oxides (1) and methyl propiolate afforded the stable azomethine ylides (2) through ring opening of ketoaziridine rearrangement[5,6]. We have investigated the similar reaction in the expectation that the pyrrolo[2,1-a]isoquinoline derivatives (3) or azetino[2,1-a]isoquinolines (4) might be obtained by the successive reaction of azomethine ylide intermediates with methyl propiolate. We wish to report the results of our studies in this paper.



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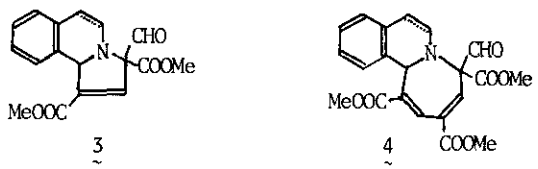

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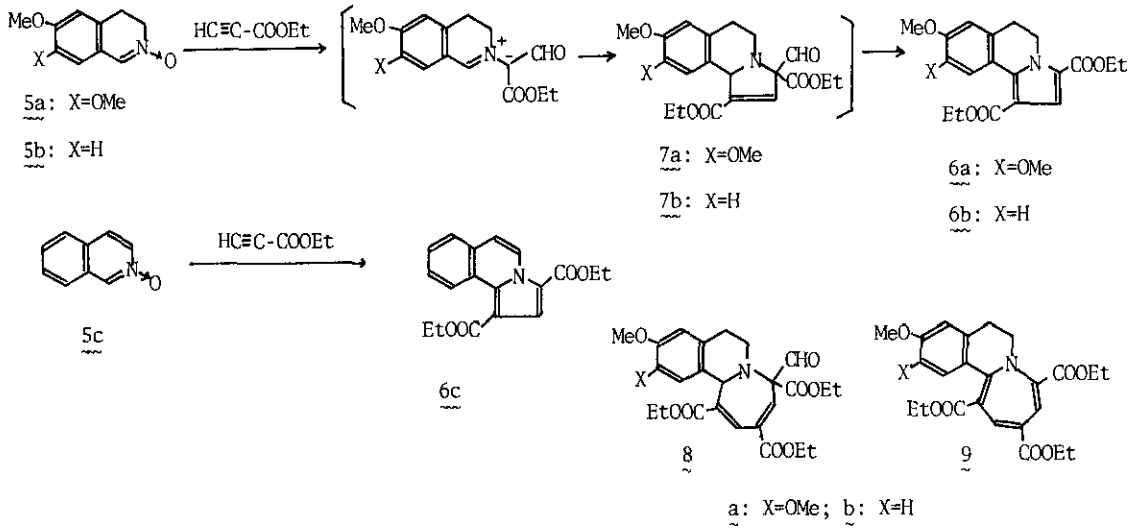
3,4-Dihydro-6,7-dimethoxyisoquinoline N-oxide (5a)[7], mp 189-191°C, prepared by oxidation of 3,4-dihydro-6,7-dimethoxyisoquinoline[8] with m-chloroperbenzoic acid in methylene chloride, was treated with ethyl propiolate (2.5 equi mol) in benzene at room temperature for 14 h, followed by heating under reflux for 3 h to give diethyl 5,6-dihydro-8,9-dimethoxypyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (6a)[9] in 35 % yield, mp 129-131°C. The product was easily obtained in a pure state by column chromatographic separation using benzene as an eluent. Upon heating a solution of the reaction mixture in benzene for 10 h without allowing to stand at room temperature, the yield of the product increased to 45 %. By this improved manner, 3,4-dihydro-6-methoxyisoquinoline-N-oxide (5b)[10] as an oil, obtained from 3,4-dihydro-6-methoxyisoquinoline[11] by the method as 5a, was condensed with ethyl propiolate (2.5 equi mol) to yield diethyl 5,6-dihydro-8-methoxypyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (6b)[12] in 30 % yield, mp 115-117°C. Furthermore, the reaction of isoquinoline N-oxide (5c)[13] with ethyl propiolate (2.5 equi mol) afforded the similar results and diethyl pyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (6c)[14] was obtained in 15 % yield, mp 127-128°C. Apparently, the formation of 6a and 6b can be accounted for the thermal decomposition of the azomethine ylide-ethyl propiolate adduct (7a) and (7b), respectively as shown in the following scheme. In these reactions, the formation of azepino[2,1-a]isoquinoline derivatives (8) or (9) was not observed even in the presence of excess ethyl propiolate.



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7. m/e 207 (M^+); ^{1}HNMR ($CDCl_3$) δ 3.13 (2H, t, J=8 Hz), 3.90 (3H, s), 3.93 (3H, s), 4.08 (2H, t, J=8 Hz), 6.70 (1H, s), 6.80 (1H, s), 7.70 (1H, s).
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9. m/e 373 (M^+); ^{1}HNMR ($CDCl_3$) δ 1.52 (6H, t, J=7.5 Hz, 2xCH_3CH_2-), 2.99 (2H, t, J=6 Hz), 3.96 (3H, s), 4.01 (3H, s), 4.37 (4H, q, J=7.5 Hz, 2xCH_3CH_2-), 4.66 (2H, t, J=6 Hz), 6.82 (1H, s), 7.57 (1H, s), 8.49 (1H, s).
10. m/e 177 (M^+); ^{1}HNMR ($CDCl_3$) δ 3.12 (2H, t, J=7.5 Hz), 3.82 (3H, s), 4.05 (2H, t, J=7.5 Hz), 6.80 (1H, d, J=2 Hz), 6.82 (1H, d,d, J=2 and 8 Hz), 7.12 (1H, d, J=8 Hz), 7.77 (1H, s).
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12. m/e 343 (M^+); ^{1}HNMR ($CDCl_3$) δ 1.34 (6H, t, J=7.5 Hz, 2xCH_3CH_2-), 2.98 (2H, t, J=7 Hz), 3.84 (3H, s), 4.33 (4H, q, J=7.5 Hz, 2xCH_3CH_2-), 4.59 (2H, t, J=7 Hz), 6.79 (1H, d, J=2 Hz), 6.90 (1H, d,d, J=2 and 8 Hz), 7.51 (1H, s), 8.52 (1H, d, J=8 Hz).
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14. m/e 311 (M^+); ^{1}HNMR ($CDCl_3$) δ 1.43 (3H, t, J=7.5 Hz), 1.47 (3H, t, J=7.5 Hz), 4.76 (2H, q, J=7.5 Hz), 4.78 (2H, q, J=7.5 Hz), 7.18 (1H, d, J=7 Hz), 7.58-7.76 (3H, m), 8.07 (1H, s), 9.43 (2H, d, J=7 Hz), 9.97-9.83 (1H, m).

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