Reaction of Diethyl Malonate with 3-Amino-4-carbethoxy-3-Pyrroline – a new Synthesis of Pyrrolo[3,4-b]pyridines

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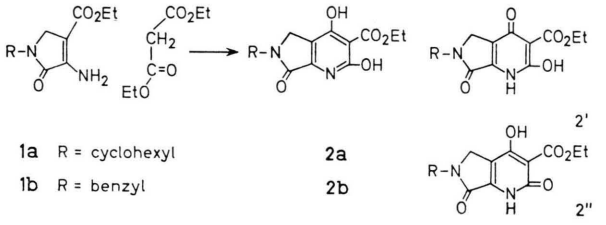
3-Amino-4-carbethoxy-3-pyrrolines, Pyrroline derivative, Diethyl malonate, Pyrrolo[3,4-b]pyridine

Few references have appeared in the literature to the preparation of derivatives of pyrrolo[3,4-b]-pyridine. Almost without exception, the methods for synthesis of this ring system utilise quinolinic acid as the starting material and construct the pyrrole ring in a sequence of several steps[1].

In the course of our work on this class of compounds[2], a convenient synthesis was developed using 3-amino-4-carbethoxy-1-substituted-3-pyrrolines[3] (**1**) as starting materials. For this purpose, these compounds were condensed with diethyl malonate in the presence of sodium ethoxide to give 6-substituted-2,4-dihydroxy-3-carbethoxy-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-7-ones (**2**). Support for the assigned structures has been obtained from analytical and spectroscopic data. However, results to date do not permit an unambiguous choice among the possible tautomeric forms 2, 2′ and 2″.



1a R = cyclohexyl **2a**
1b R = benzyl **2b**

The products were sufficiently acidic to dissolve in aqueous sodium carbonate solution, but appeared to react slowly with aqueous sodium bicarbonate. The NMR do not reveal a signal which could be assigned to a proton bound to carbon at the 3-position of the pyridine ring; the ketonic tautomer 2‴ does not seem to be present.

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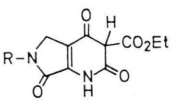

2‴

In a typical run, equimolar quantities of 3-amino-4-carbethoxy-2-oxo-1-substituted-3-pyrroline (**1**) and diethyl malonate and sodium ethoxide were heated without solvent at a temperature of 125–130° for 30 h in vacuo. The mixture was diluted with water and acidified with 6 N hydrochloric acid. The product was collected by filtration, washed and recrystallized from suitable solvents.

The ready availability of 3-amino-4-carbethoxy-3-pyrroline derivatives and their facile condensation with malonic ester to yield the pyrrolo[3,4-b]pyridines promises to be an alternate method to this class of compounds.

2a: Yield 74.5% from **1a**,
m.p. 235–237 °C (from ethanol).

Analysis: $C_{16}H_{20}N_2O_5$ (320.24)

Calcd	C 59.84	H 6.41	N 8.76,
Found	C 59.99	H 6.29	N 8.75.

NMR($CDCl_3$-trifluoroacetic acid – 4:1) τ 5.3–5.7 (q, 2, $-C\underline{H}_2CH_3$) 5.53 (s, 2, methylene at position-5), 5.8 (m, 1, methine of cyclohexyl) 7.9–8.8 (m, 10, cyclohexyl), 8.48–8.7 (t, 3, $-CH_2C\underline{H}_3$).
IR (Nujol) μ 3.15, 5.85, 5.87, 5.95, 6.05, 6.10.

2b: Yield 85.4% from **1b**,
m.p. 206–207 °C (from ethanol-acetic acid-water).

Analysis: $C_{17}H_{16}N_2O_5$ (328.31)

Calcd	C 62.19	H 4.91	N 8.53,
Found	C 61.99	H 5.18	N 8.34.

NMR ($CDCl_3$-Trifluoroacetic acid – 4:1) τ 2.7 (s, 5, aromatic) 5.2 (s, 2, methylene at position-5), 5.3–5.7 (q, 2, $-C\underline{H}_2CH_3$), 5.65 (s, 2, benzylic methylene), 8.45–8.75 (t, 3, $-CH_2C\underline{H}_3$).
IR (Nujol) μ 3.16, 5.80, 5.87, 5.95, 6.05, 6.10.

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[2] R. MADHAV, Synthesis, in press.
[3] P. L. SOUTHWICK and G. H. HOFMAN, J. org. Chemistry **28**, 1332 [1963]. M. FRISHBERG, Ph. D. Thesis, Carnegie-Mellon University, 1972; See R. MADHAV, R. F. DUFRESNE, and P. L. SOUTHWICK, J. Heterocyclic. Chem., **10**, 225 [1973] for the use of 3-Arylamino-4-carbethoxy-3-pyrroline derivatives in the synthesis of pyrrolo[3,4-b]quinoline.