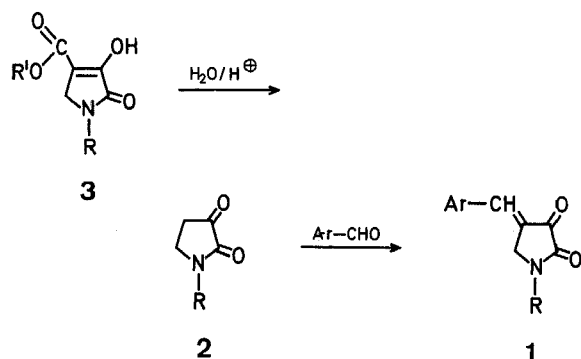


# A New Synthesis of Compounds in the 5*H*-Pyrrolo-[3,4-*b*]pyridine Series

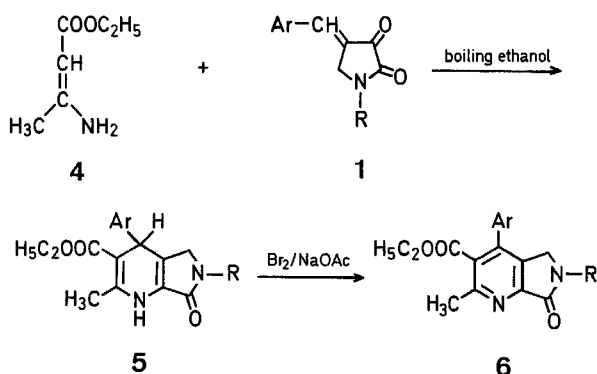
R. MADHAV

Mellon Institute, Carnegie-Mellon University,  
Pittsburgh, Pennsylvania 15213, U.S.A.

4-Benzylidene derivatives of 1-substituted-2,3-dioxopyrrolidines (**1**) are very easily obtained<sup>1</sup> from the condensation of aromatic aldehydes with 1-substituted-2,3-dioxopyrrolidines (**2**), compounds which can be obtained by hydrolysis and decarboxylation of readily accessible enols of the 1-substituted-4-alkoxycarbonyl-2,3-dioxopyrrolidines (**3**)<sup>2</sup>.

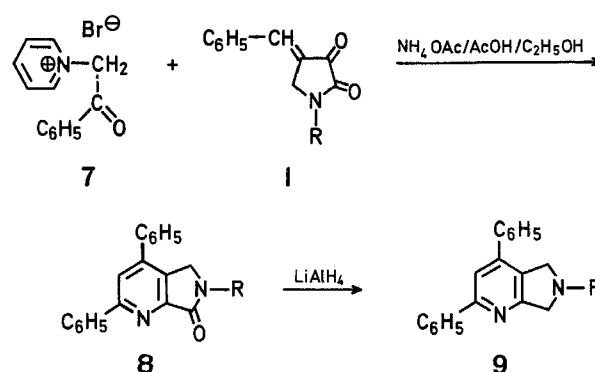


The 4-benzylidene derivatives **1** are a potentially useful source of bicyclic and polycyclic systems incorporating a pyrroline ring fused across the 3,4-positions. A previously described example is the formation of derivatives of pyrrolo-[3,4-*d*]pyrimidine by reaction of the benzylidene compounds **1** with guanidine<sup>3</sup>. The present work demonstrates the facile synthesis of 6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine derivatives from compounds of the type **1**. Compounds in the pyrrolo[3,4-*b*]pyridine series had previously been obtained only from quinolinic acids<sup>4</sup>.



The first route consisted in condensing the benzylidene derivatives **1** with ethyl β-aminocrotonate (**4**) in refluxing ethanol to yield the non-aromatized adducts **5** which were converted to 4-aryl-3-ethoxycarbonyl-2-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine derivatives (**6**) upon treatment with bromine and sodium acetate.

The second method, originally developed by Kröhnke<sup>5</sup>, which uses phenacylpyridinium bromide (**7**) was applied to the benzylidene derivatives **1** to give compounds of the type **8**.



The reaction was carried out in ethanol/acetic acid containing ammonium acetate. Both of these methods give good yields and the products could be isolated with ease. All new compounds gave correct elemental analysis (see Tables 1 and 2) and the spectral (I.R. and <sup>1</sup>H-N.M.R.) data were consistent with the assigned structures.

Typical runs have been described for the preparation of **6** and **8**.

## Preparation of 6-Substituted 4-Aryl-3-ethoxycarbonyl-2-methyl-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridines (**6**); General Procedure:

The 1-substituted 4-arylidene-2,3-dioxopyrrolidine (**1**; 0.01 mol), ethyl acetoacetate (0.01 mol), and conc. aqueous ammonia (1 ml) were refluxed in absolute ethanol (10 ml) for 3 hr. The reaction mixture was poured into a large volume of water (200 ml). The solid which separated was filtered out, washed with water, and dried. The crude solid (3.0 g) was treated with anhydrous sodium acetate (1.5 g) and bromine (0.8 g; 0.2 mol) in acetic acid (25 ml) under reflux for 2 hr. The reaction mixture was diluted with water (300 ml) and the product was collected by filtration, washed with water, and crystallized from ethanol/water.

Table 1. 6-Substituted 4-Aryl-3-ethoxycarbonyl-2-methyl-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridines (**6**) prepared

Ar	R	Yield (%)	m. p.	Elemental Analyses				
<b>6a</b>		63	202–203°	C <sub>23</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub> (378.5)	calc. 72.99 found 72.78	H 6.93 6.78	N 7.40 7.14	
<b>6b</b>		69	183–185°	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub> (408.5)	calc. 70.56 found 70.61	H 6.91 7.20	N 6.86 6.78	
<b>6c</b>		74	231–232°	C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O <sub>5</sub> (423.5)	calc. 65.23 found 65.49	H 5.95 6.23	N 9.92 9.65	
<b>6d</b>	<i>t</i> -C <sub>4</sub> H <sub>9</sub>	78	218–220°	C <sub>21</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub> (352.4)	calc. 71.57 found 71.76	H 6.86 7.07	N 7.95 7.83	
<b>6e</b>	-CH <sub>2</sub> -	93	174–175°	C <sub>24</sub> H <sub>22</sub> N <sub>2</sub> O <sub>3</sub> (386.4)	calc. 74.59 found 74.42	H 5.74 5.95	N 7.10 7.10	

**Table 2.** 6-Substituted 2,4-Diaryl-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridines (**8**) prepared

	R	Yield (%)	m. p.	Elemental Analyses				
<b>8a</b>	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	61	235–236°	C <sub>25</sub> H <sub>24</sub> N <sub>2</sub> O (368.5)	calc. found	C 81.49 81.61	H 6.57 6.32	N 7.60 7.45
<b>8b</b>	—CH <sub>2</sub> —C <sub>6</sub> H <sub>5</sub>	49	182–183°	C <sub>26</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> <sup>a</sup> (394.5)	calc. found	C 79.41 79.16	H 5.64 5.62	N 6.92 7.10

<sup>a</sup> Analyzed as a hydrate.**Preparation of 6-Substituted 2,4-Diaryl-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridines (**8**); General Procedure:**

The 1-substituted 4-benzylidene-2,3-dioxopyrrolidine (**1**; 0.005 mol), phenacylpyridinium bromide (**7**; 0.005 mol), and ammonium acetate (1.0 g) were refluxed in ethanol/acetic acid (20 ml/1 ml) for 3 hr. The reaction mixture was poured into water (200 ml) and extracted with ethyl acetate (3 × 50 ml). The ethyl acetate layer was washed with water, dried with anhydrous sodium sulfate, and evaporated to obtain the product. Crystallization of the crude material was effected from ethyl acetate/petroleum ether (b. p. 30–60°).

**6-Cyclohexyl-2,4-diphenyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine (**9a**):**

A suspension of compound **8a** (0.9 g) in dry tetrahydrofuran (100 ml) was reduced with lithium aluminum hydride (1.0 g) under reflux in a nitrogen atmosphere for 20 hr. The excess lithium aluminum hydride was decomposed by the addition of aqueous sodium sulfate. The inorganic salts were removed by filtration and the clear filtrate was concentrated to give a viscous oil; yield 0.3 g. The product was characterized by preparation of its picrate; m. p. 189–190° (from ethanol).

C<sub>31</sub>H<sub>29</sub>O<sub>7</sub>N<sub>5</sub> calc. C 63.80 H 5.01 N 12.00  
(583.6) found 63.56 4.99 11.71

The author is grateful to Dr. Philip L. Southwick for his interest in this work.

Received: June 9, 1973

- <sup>1</sup> P. L. Southwick, E. F. Barnas, *J. Org. Chem.* **27**, 98 (1962).  
P. L. Southwick, N. Latif, B. M. Fitzgerald, N. M. Zaczek, *J. Org. Chem.* **31**, 1 (1966).  
B. M. Fitzgerald, *Ph. D. Thesis*, Carnegie Institute of Technology, Pittsburgh, 1965.  
C. A. Snyder, *Ph. D. Thesis*, Carnegie-Mellon University, Pittsburgh, 1969.
- <sup>2</sup> P. L. Southwick, R. T. Crouch, *J. Amer. Chem. Soc.* **75**, 3413 (1953).
- <sup>3</sup> P. L. Southwick, G. H. Hofmann, *J. Org. Chem.* **28**, 1332 (1963).
- <sup>4</sup> Z. J. Vejdeck, M. Protiva, *Česk. Farm.* **13**, 76 (1964); *C. A.* **60**, 10662 (1964).  
W. L. F. Armarego, B. A. Milloy, S. C. Sharma, *J. Chem. Soc. [C]* **1972**, 2485.
- <sup>5</sup> W. Zecher, F. Kröhnke, *Chem. Ber.* **94**, 690 (1961).