

## Pyrroles and Pyrazolines from the Ring Closure of Azines

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Alkyl substituted pyrroles and pyrazolines are obtained in good yields by catalytic ring closure of azines, using nickel or cobalt (II) halides as catalysts. The specificity of the reaction is determined by the structure of the azines and a notable exception is discussed.

The synthesis of pyrroles and pyrazolines has been the object of extensive studies and various preparative methods have been described in the past.

The most general method for pyrazoline synthesis is the reaction of hydrazines with  $\alpha,\beta$ -unsaturated aldehydes and ketones (1) (2) or by displacement of halogen or dialkylamino groups from  $\beta$ -substituted carbonyl compounds (3) (4). These reactions generally lead to *N*-substituted pyrazolines and are often inadequate for the preparation of *N*-unsubstituted compounds because the reactions with hydrazine itself are more complex and lead to poor reaction conditions and low yields (5). Certain substituted pyrazolines were also obtained from the reaction of ketazines with maleic or oxalic acid (6). Pyrroles, which are generally synthesized by condensation of  $\alpha$ -aminoketones with  $\alpha$ -methylene ketones (7) and also by condensation of  $\gamma$ -diketones and ammonia or primary amines (8), were also reported to have been prepared from azines of enolizable ketones by catalytic ring closure with zinc chloride following a mechanism analogous to Fischer's indole synthesis (9). The scope of these reactions was not defined but the competing formation of pyrroles and pyrazolines during the ring closure of aliphatic azines was reported (10).

We have found that various alkyl substituted pyrroles and pyrazolines can be prepared systematically by catalytic ring closure of ketazines and aldazines using nickel or cobalt (II) halides as catalysts. The reactions occur at temperatures ranging from 20 to 200°, they appear to be specific and the structure of the compounds resulting from the cyclizations depends upon the structure of the azines used as starting materials. Selective structural changes in the azine may direct the reaction towards the formation of either pyrroles or pyrazolines.

When treated with nickel or cobalt (II) halides, symmetric alkyl azines containing at least one methyl group adjacent to the nitrogen bonded carbon atom invariably form substituted 2-pyrazolines. As shown in Table I, acetaldazine readily forms 5-methyl-2-pyrazoline, acetone azine forms 3,5,5-trimethyl-2-pyrazoline and butanone

azine forms 3,5-diethyl-5-methyl-2-pyrazoline.

On the other hand, if the symmetric azine contains at least one methylene group adjacent to the nitrogen bonded carbon atom, but no adjacent methyl group, the cyclization is accompanied by quantitative elimination of one molecule of ammonia and yields substituted pyrroles as major reaction products. Thus, 3-pentanone azine forms 2,5-diethyl-3,4-dimethyl pyrrole, propionaldazine forms 3,4-dimethyl pyrrole and cyclohexanone azine forms

TABLE I

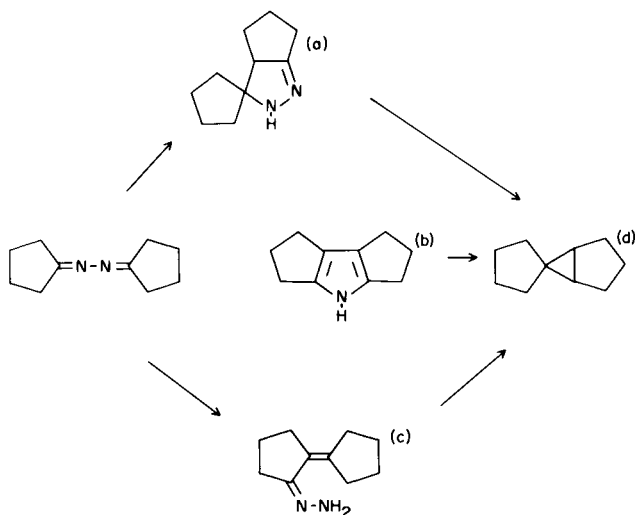
Starting Material	Resulting Compound	Yield %
		69
		77
		72
		55
		50
		63

octahydrocarbazole in high yields. The latter compound was obtained earlier by a similar ring closure of cyclohexanone azine with hydrochloric acid (11) and zinc chloride (12).

Whenever both a methyl and a methylene group are concurrently adjacent to the nitrogen bonded carbon atom, as in the case of butanone azine, the methyl group prevails and the intermediate transition metal complex favors the formation of a pyrazoline.

The formation of pyrroles is obviously more laborious and since the catalyst causes extensive hydrogen abstraction to take place, the elimination of ammonia is accompanied by the formation of polymeric materials which reduces the yields.

Cyclopentanone azine is an interesting exception to this rule and contrary to the expected pyrrolic structure the ring closure leads to spiro bicyclo[3.1.0]hexane-6,1'-cyclopentane (d) as the major reaction product. According to previous work (13) one could expect 3,4-trimethylene-5,5-tetramethylene-2-pyrazoline (a) to be a more likely intermediate than 2,3-trimethylene-4,5-trimethylene pyrrole (b) since no spirododecane can be obtained from octahydrocarbazole. However, (a) could not be prepared by using the synthetic method described for the six membered ring analog (13) and since cyclopentanone hydrazone as well as cyclopentadiene were isolated along with the spirodecane, it is reasonable to assume that an intermolecular mechanism, yet undetermined, intervenes in this particular reaction. The formation of the intermediate pyrazoline (a), then, may not necessarily be involved but 2-cyclopentylidene cyclopentanone hydrazone (c), which is known to form the spirodecane easily (14), may possibly be the intermediate.



The formation of hydrazone further indicates that the initial cleavage of the azine, in presence of a nickel or

cobalt (II) halide, to form pyrazolines or pyrroles is also occurring at the C=N bridge and not exclusively at the N-N bridge as suggested earlier (10) (15).

## EXPERIMENTAL

### 3,5,5-Trimethyl-2-pyrazoline.

A reaction mixture consisting of 112 g. of acetone azine and 0.5 g. of cobalt (II) bromide was kept under agitation at 200° for 24 hours. Upon fractional distillation, 86 g. (77% yield) of pure 3,5,5-trimethyl-2-pyrazoline was isolated, m.p. -8°, b.p. 160-160°.

*Anal.* Calcd. for C<sub>6</sub>H<sub>12</sub>N<sub>2</sub>: C, 64.28; H, 10.80; N, 25.00. Found: C, 64.32; H, 10.75; N, 24.95.

H-NMR on Varian HA-100D in deuteriochloroform (in ppm delta) 1.18 (6 H's); 1.85 (3 H's); 2.30 (2 H's); 4.92 (1 H).

### 3,4-Dimethyl-2,5-diethylpyrrole.

To a solution of 168 g. of 3-pentanone azine in 250 ml. of *o*-xylene was added 0.5 g. of cobalt (II) iodide and the reaction mixture was refluxed for 24 hours. The xylene was evaporated and upon vacuum distillation, 75 g. (50% yield) of 3,4-dimethyl-2,5-diethylpyrrole was isolated, b.p. 55-155°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>17</sub>N: C, 79.40; H, 11.32; N, 9.27. Found: C, 79.50; H, 11.29; N, 9.29.

### Octahydrocarbazole.

A mixture of 192 g. of cyclohexanone azine and 1.0 g. of anhydrous nickel chloride was maintained under agitation at 200° for 24 hours. Upon cooling the recrystallization of the reaction mixture from petroleum ether yielded 110 g. (63%) of pure octahydrocarbazole m.p. 100-101°, picrate m.p. 134-135°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>17</sub>N: C, 82.24; H, 9.76; N, 7.99. Found: C, 81.88; H, 9.69; N, 7.99.

### Spiro bicyclo[3.1.0]hexane-6,1'-cyclopentane.

One hundred g. of cyclopentanone azine and 0.5 g. of cobalt (II) chloride was kept at reflux under agitation for 72 hours. Upon cooling, fractional distillation on a spinning band column led to the isolation of 35 g. (42% yield) of the pure spirodecane as the major reaction product, m.p. -46°, b.p. 196°; n<sup>25</sup> 1.4820.

*Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>: C, 88.24; H, 11.76. Found: C, 87.85; H, 11.93.

Infrared spectra was recorded on a Perkin Elmer Infracord 337, potassium bromide wafer (in cm<sup>-1</sup>), 3003 vs and 1000 m, characteristic of the cyclopropyl group (16).

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