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Synthesis of 5-Oxo-2-pyrazoline-4-carboxaldehydes

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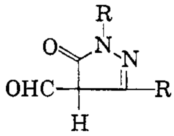
A practical synthesis for 5-oxo-2-pyrazoline-4-carboxaldehydes from *N,N*-dimethylformamide, phosphoryl chloride, and 2-pyrazolin-5-ones was developed. The preparations of several of these aldehydes are described. These aldehydes readily underwent intermolecular condensation on heating.

The 4-formyl derivatives of 2-pyrazolin-5-ones have been known for some time. These compounds have the following general formula:



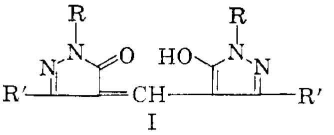
R = H, alkyl, or aryl
R′ = alkyl or aryl

The first reference to a compound of this type appeared in *Monatschefte für Chemie* in 1910.[1] The preparation involved the hydrolysis of the reaction product of 3-methyl-1-phenyl-2-pyrazolin-5-one and 2-phenyliminopseudoindoxyl.

In 1937, Passerini and Cassini reported a synthesis which involved hydrolysis of the reaction product of the pyrazolinone and phenyl isocyanide.[2] In 1940, Losco obtained a 12% yield of the 3-methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde by treating the pyrazolinone with chloroform.[3]

None of these syntheses affords a practical source of these aldehydes. However, a fairly recent modification of the Vilsmeier reaction has been applied with considerable success. This reaction involved the action of a complex of *N,N*-dimethylformamide and phosphoryl chloride on the pyrazolinone. The use of this synthetic method gave the aldehydes in good yields and used inexpensive, readily available reagents.

Characterization of these aldehydes presented something of a problem. They have a well known tendency to condense and give

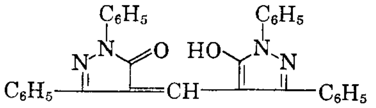


I

R = H, alkyl, or aryl
R′ = alkyl or aryl

This condensation occurred on heating the aldehyde in a solvent or heating the solid aldehyde to its melting point. Consequently, the melting point determinations were sometimes difficult. In some cases, the determinations were perfectly straightforward; in others, it was hard to obtain a clear-cut melting point. This tendency to condense to the methylidynedipyrazolinone caused difficulties in obtaining analytically pure samples. It was desirable to heat the pyrazolinecarboxaldehyde during recrystallization as briefly as possible to reduce the intermolecular reaction.

This purification problem is readily apparent when the results of the recrystallization of one of these aldehydes from naphtha and Methyl Cellosolve are compared. Where 5-oxo-1,3-diphenyl-2-pyrazoline-4-carboxaldehyde was obtained as the crude reaction product, it melted at 134.5–150.5°. When this product was recrystallized once from naphtha, the melting point was 146.5–148.5°. The nitrogen analysis on this recrystallized sample was slightly high. When the crude sample was recrystallized from Methyl Cellosolve, using only a minimum boiling time, the product melted at 248–249°. This was the same as the melting point of



II

A melting point determination of a mixture of this recrystallized sample with an authentic sample of II showed no depression. The quantitative analysis of the recrystallization product from Methyl Cellosolve for carbon, hydrogen, and nitrogen showed excellent agreement with the theoretical values calculated for II.

When 3-methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde was recrystallized from Methyl Cellosolve, the product was the corresponding monoenol form of methylidynedipyrazolinone, as shown by melting point determination of a mixture of the product with a known sample of I (R = C_6H_5, R′ = CH_3). Actually, a good yield of the condensation product was obtained when the Methyl Cellosolve solution was heated less than five minutes.

It is interesting to note that recrystallization of the 3-isobutyl-5-oxo-2-pyrazoline-4-carboxaldehyde did not cause this condensation to occur.

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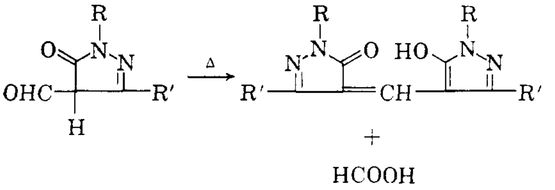
(1) A. Felix and P. Friedlander, *Monatsh. Chem.*, **31**, 55–79 (1910).

(2) M. Passerini and V. Cassini, *Gazz. chim. ital.*, **67**, 332–336 (1937).

(3) G. Losco, *Gazz. chim. ital.*, **70**, 284–286 (1940).

The condensation proceeded as follows:



When a sample of the 3-methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde was dissolved in cold Methyl Cellosolve, the solution had a *p*H of ~7. After the solution was heated for one minute in the steam bath, the *p*H was 3–4, indicating the formation of the formic acid.

EXPERIMENTAL

The 3-methyl-1-phenyl-2-pyrazolin-5-one was obtained from Eastman Kodak Co. and used without further purification. All of the other 2-pyrazolin-5-ones used were synthesized from the appropriate substituted hydrazines and acyl- or aroyl-acetic esters.

3-Methyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde. A mixture of 87 g. (0.50 mole) of 3-methyl-1-phenyl-2-pyrazolin-5-one and 100 ml. of *N*,*N*-dimethylformamide was cooled to 0° in an ice-acetone bath. Then, 55 ml. (~ 92 g., 0.60 mole) of phosphoryl chloride was added dropwise at such a rate as to maintain the temperature between 10° and 20°. After the addition was complete, the reaction mixture was heated on the steam bath for 1.5 hr. The mixture was then poured into 2 l. of ice-water mixture. The resulting mixture was allowed to stand overnight at room temperature. The solid product was collected by filtration, washed with water, and dried. The yield was 87.4 g. (86.5%), m.p. 174–175°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.8; H, 4.98. Found: C, 65.4; H, 5.16.

When a sample of this aldehyde was recrystallized from Methyl Cellosolve—heating only long enough to effect solution—I(R = C_6H_5, R′ = CH_3) was formed in 67% yield. This sample melted at 180–181°. An authentic sample of I (R = C_6H_5, R ′ = CH_3) melted at 180–181°,[4] as did a mixture of these two materials.

5-Oxo-3-phenyl-2-pyrazoline-4-carboxaldehyde. A mixture of 32 g. (0.20 mole) of 3-phenyl-2-pyrazolin-5-one and 40 ml. of *N*,*N*-dimethylformamide was cooled to 0°. Then 22 ml. (0.24 mole) of phosphoryl chloride was added dropwise between 25° and 35°. When the addition was complete, the reaction mixture was heated for 1.5 hr. on the steam bath. The reaction mixture solidified during this period. The mixture was then chilled and water was added to the reaction flask to facilitate removal of the product. The reaction mixture in 500 ml. of water was allowed to stand overnight at room temperature. The product was then collected by filtration, washed with water, and dried. The yield was 37.2 g. (99%), m.p. 273.5–277°.

When this aldehyde was recrystallized from an ethyl alcohol–methanol mixture, the melting point of the recrystallized sample was 282–284°.

Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.43; H, 4.44; N, 15.25.

3-Isobutyl-5-oxo-1-phenyl-2-pyrazoline-4-carboxaldehyde. 3-Isobutyl-1-phenyl-2-pyrazolin-5-one (14.0 g., 0.067 mole) was treated in the same molar proportions and using the same conditions as Ex. 1. The yield was 14.6 g. (90%), m.p. 120–121°.

A sample was recrystallized from naphtha. This sample melted at 120–121°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 69.0; H, 6.57; N, 11.5. Found: C, 68.96; H, 6.77; N, 11.64.

3-Isobutyl-5-oxo-2-pyrazoline-4-carboxaldehyde. 3-Isobutyl-2-pyrazolin-5-one (14.0 g., 0.1 mole) was treated in the same molar proportions and using the same conditions as Ex. 1, except that the temperature during the addition rose for a short time to 65°. Yield: 11.4 g. (68%), m.p. 272–275°.

Recrystallization of this aldehyde from naphtha or Methyl Cellosolve resulted in simple purification. No condensation was noted. The melting point of the recrystallized samples was 282–284.°

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.15; N, 16.7. Found: C, 57.17; H, 7.15; N, 16.93.

5-Oxo-1,3-diphenyl-2-pyrazoline-4-carboxaldehyde. 1,3-Diphenyl-2-pyrazolin-5-one (47.4 g., 0.20 mole) was treated in the same molar proportions and using the same conditions as Ex. 1. Yield: 38 g. (72%), m.p. 134.5–140.5°.

When the product was recrystallized once from naphtha, the melting point was 140–143°. The analysis indicated 11.09% nitrogen, as opposed to a theoretical value of 10.60%.

When recrystallized once from Methyl Cellosolve, the product melted at 250.5–251°. This was the same as the melting point of II. A melting point of a mixture of these two samples showed no depression.

Anal. Calcd. for $C_{31}H_{22}N_4O_2$: C, 77.1; H, 4.68; N, 11.73. Found: C, 77.06; H, 4.88; N, 11.60.

The values were calculated for II.

KINGSPORT, TENN.

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[4] B. Schiedt, *J. prakt. Chem.*, **157**, 222 (1940).