The Preparation of Substituted 1,2,4-Triazolines and Substituted Picolinic Acid Methylene Hydrazides by the Action of Certain Carboxamide Hydrazones with Ketones

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The action of certain ketones with carboxamide hydrazones, yielding, depending on conditions, 1,2,4-triazolines or substituted picolinic acid methylene hydrazides, has been investigated. Also the preparation of 3-substituted-5-phenyl-1,2,4-triazines from the action of phenyl glyoxal and certain carboxamide hydrazones is described.

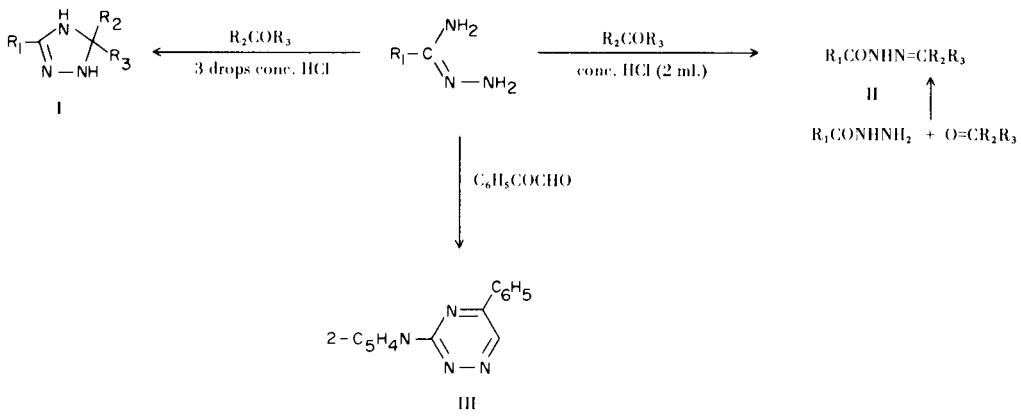
In previous communications (1,2) was described the action of diketones and of aldehydes on certain carboxamide hydrazones (hydrazidines) to yield respectively, 1,2,4-triazines and 1,2,4-triazolines. Recently the action of a monoketone, acetophenone, with picolinamide hydrazone in presence of a trace of hydrochloric acid to form 5-methyl-5-phenyl-3-(2-pyridyl)-Δ^2-1,2,4-triazoline has been described (3).

In an attempt to provide compounds with the capability of chelating Fe(II) and Cu(I) we have prepared a series of triazolines (I) containing the ferroin group by this method, using the ketones acetophenone and 2-acetyl pyridine with various hydrazidines. From 2-benzoyl pyridine and from di(2-pyridyl)ketone, however, a triazoline could be obtained in only one case (XII).

When the concentration of hydrochloric acid was increased triazolines were obtained only when the reactants were 2-acetylpyridine with 4-phenylpicolinamide hydrazone (IX) and 2-(1,10-phenanthroline)carboxamide hydrazone (X). Under these conditions due to hydrolysis of the hydrazidine the following combinations yielded substituted picolinic acid methylene hydrazides (II): 2-acetylpyridine + picolinamide hydrazone (XIII); 2-benzoylpyridine + picolinamide hydrazone (XIV) and its 4-methyl (XV) and phenyl (XVI) derivatives: di(2-pyridyl)ketone + picolinamide hydrazone (XVII). The structure of these was confirmed in the case of XIII, XIV, and XVII by synthesis from picolinic acid hydrazide and the appropriate ketone.

In addition to the above mentioned hydrazides, the 2-pyridyl hydrazone of di(2-pyridyl)ketone was also prepared. All of these compounds give a deep ferroin test.

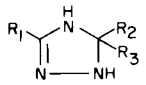
The preparation of 3-(2-pyridyl)-5-phenyl-1,2,4-triazine (III) and proof of its structure have previously been described (4,5). In this laboratory a number of these phenyl triazines have been prepared in which instead of 2-pyridyl, 4-methyl-2-pyridyl, 4-phenyl-2-pyridyl, 2-(1,10)-phenanthrolyl and 6-(2,2′)bipyridyl have been introduced. These all yield deep ferroin tests.



I II III

TABLE I

5,5,3-Trisubstituted-Δ^2-1,2,4-triazolines



	R_1	R_2	R_3	Yield %	M.p., °C	Crystallization Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IV	4-CH_3-2-C_5H_3N	CH_3	C_6H_5	64.7	82	methanol	$C_{15}H_{16}N_4$	71.40	6.39	22.20	71.59	6.49	22.22
V	4-C_6H_5-2-C_5H_3N	CH_3	C_6H_5	66.7	130	ethanol	$C_{20}H_{18}N_4$	76.41	5.77	17.82	76.02	5.71	18.04
VI	2-(1,10)-phenanthrolyl	CH_3	C_6H_5 (a)	62.0	217-218	aq. ethanol	$C_{21}H_{17}N_5$	74.32	5.05	20.63	74.13	4.87	20.90
VII	2-C_5H_4N	CH_3	2-C_5H_4N	58.4	107-108	methanol	$C_{13}H_{13}N_5$	65.26	5.48	29.27	65.17	5.55	29.45
VIII	4-CH_3-2-C_5H_3N	CH_3	2-C_5H_4N	71.9	172-173	ethanol	$C_{14}H_{15}N_5$	66.38	5.97	27.65	66.57	5.82	27.69
IX	4-C_6H_5-2-C_5H_3N	CH_3	2-C_5H_4N	81.7	134	ethanol	$C_{19}H_{17}N_5$	72.36	5.43	22.21	72.73	5.45	21.87
X	2-(1,10)-phenanthrolyl	CH_3	2-C_5H_4N	33.2	180-181 (b)	aq. ethanol	$C_{20}H_{16}N_6$	70.57	4.74	24.69	70.66	4.58	24.97
XI	6-(2,2′-bipyridyl)	CH_3	2-C_5H_4N	53.3	92-93	aq. ethanol	$C_{18}H_{19}N_2O$ (c)	64.46	5.71	25.06	64.21	5.29	25.12
XII	2-(1,10)-phenanthrolyl	C_6H_5	2-C_5H_4N	27.3	176-177	ethanol	$C_{25}H_{18}N_6$	74.11	4.51	20.88	73.96	4.42	20.92

(a) Dried at 110°. Loss 11.47%. (b) Dried at 100°. (c) Monohydrate.

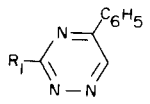
TABLE II

Substituted Picolinic Acid Methylene Hydrazides
$R_1CONHN = CR_2R_3$

	R_1	R_2	R_3	Yield %	M.p., °C	Crystallization Solvent	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XIII	2-C_5H_4N	CH_3	2-C_5H_4N	30.8	196-197	methanol	$C_{13}H_{12}N_4O$ (a)	64.99	5.03	23.32	65.10	5.07	23.49
XIV	2-C_5H_4N	C_6H_5	2-C_5H_4N	19.1	183-184	methanol	$C_{18}H_{14}N_4O$ (b)	71.51	4.67	18.53	71.42	4.65	18.72
XV	4-CH_3-2-C_5H_3N	C_6H_5	2-C_5H_4N	22.7	184-185	methanol	$C_{19}H_{16}N_4O$	72.14	5.10	17.71	71.76	5.07	17.86
XVI	4-C_6H_5-2-C_5H_3N	C_6H_5	2-C_5H_4N	21.5	163-164	methanol	$C_{24}H_{18}N_4O$	79.54	5.01	15.46	79.64	4.92	15.47
XVII	2-C_5H_4N	2-C_5H_4N	2-C_5H_4N	28.9	168	methanol	$C_{17}H_{13}N_5O$	67.32	4.32	23.09	67.46	4.43	23.09

TABLE III

3-Substituted-5-phenyl-1,2,4-triazines



	R_1	Yield %	M.p., °C	Crystallization Solvent	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XVIII	4-CH_3-2-C_5H_3N	43.8	111-112	benzene-pet ether	$C_{15}H_{12}N_4$	72.58	4.87	22.57	72.64	5.12	22.54
XIX	4-C_6H_5-2-C_5H_3N	51.6	183	ethanol	$C_{20}H_{14}N_4$	77.40	4.55	18.05	76.95	4.62	18.33
XX	2-(1,10)phenanthrolyl	63.6	254	ethanol	$C_{21}H_{13}N_5$	75.21	3.91	20.88	74.76	4.13	21.19
XXI	6-(2,2′-bipyridyl)	67.7	196	methyl cellosolve	$C_{19}H_{13}N_5$	73.30	4.21	22.49	72.92	4.16	22.83

EXPERIMENTAL

Preparation of 5,5,3-Trisubstituted-Δ^2-1,2,4-triazolines.

To a mixture of 0.006 mole each of the appropriate carboxamide hydrazone and ketone and 25 ml. of absolute ethanol was added 3 drops of concentrated hydrochloric acid. After refluxing for 20 hours, the solvent was removed and the residue neutralized with potassium carbonate solution. The resulting solid was then crystallized from the solvent indicated in Table I.

Preparation of Substituted Picolinic Acid Methylene Hydrazides.

The procedure was the same as above except that 2 ml. of concentrated hydrochloric acid was used. The crystallization solvents are shown in Table II.

Preparation of 3-Substituted-5-phenyl-1,2,4-triazines.

A mixture of 0.006 mole of phenylglyoxal monohydrate and the appropriate carboxamide hydrazone and 25 ml. of ethanol was heated at reflux for 3 hours. After removal of the solvent, the residue was crystallized from the solvent indicated in Table III.

Synthesis of Substituted Picolinic Acid-Methylene Hydrazides (XIII, XIV, and XVII).

A mixture of 0.007 mole each of picolinic acid hydrazide and the appropriate ketone and 20 ml. of ethanol was heated at reflux for 2.5 hours. After evaporation of solvent, the residue was crystallized from the solvent indicated in Table II and was identical with the compound described therein.

Preparation of 2-Pyridylhydrazone of Di(2-pyridyl ketone).

A mixture of 1 g. of 2-hydrazinopyridine, 1.8 g. of di(2-pyridyl)ketone and 25 ml. of ethanol was heated under reflux for 6 hours. After evaporation of solvent, the residue was crystallized from methanol, yielding 1.6 g. (64.0%) of pure product.

Anal. Calcd. for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.32; H, 4.70; N, 25.82.

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