1,2,4-Triazoles and 1,3,4-Oxadiazoles from *N*-Acylhydrazidines

P. M. Hergenrother

Polymer Sciences Laboratory, Boeing Scientific Research Laboratories

The preparation of 1,2,4-triazoles and 1,3,4-oxadiazoles through intermediate *N*-acylamidrazones (*N*-acylhydrazidines) has been known for many years (1-4). More recently, Saga and Shono (5) have reported on the reaction of oxalamidrazone with various carboxylic acid chlorides to obtain *N*-acylamidrazones which they subsequently converted to the corresponding 1,2,4-triazoles and/or 1,3,4-oxadiazoles.

It was of interest to prepare a series of *N*-acylhydrazidines and study their conversion to 1,2,4-triazoles and/or 1,3,4-oxadiazoles as represented in the reaction scheme. This work was performed to obtain information regarding reaction conditions necessary for polymer formation (6) from the reaction of 2,6-pyridinediyl dihydrazidine with isophthaloyl chloride and to obtain model compounds to aid in polymer identification.

The *N*-acylhydrazidines were prepared in essentially quantitative yields by low temperature solution condensation in polar solvents such as *N*-*N*-dimethylacetamide and hexamethylphosphoramide or by the interfacial method. Quantitative conversion of the *N*-acylhydrazidines to 1,3,4-oxadiazoles was effected at elevated temperature in solu-

REACTION SCHEME

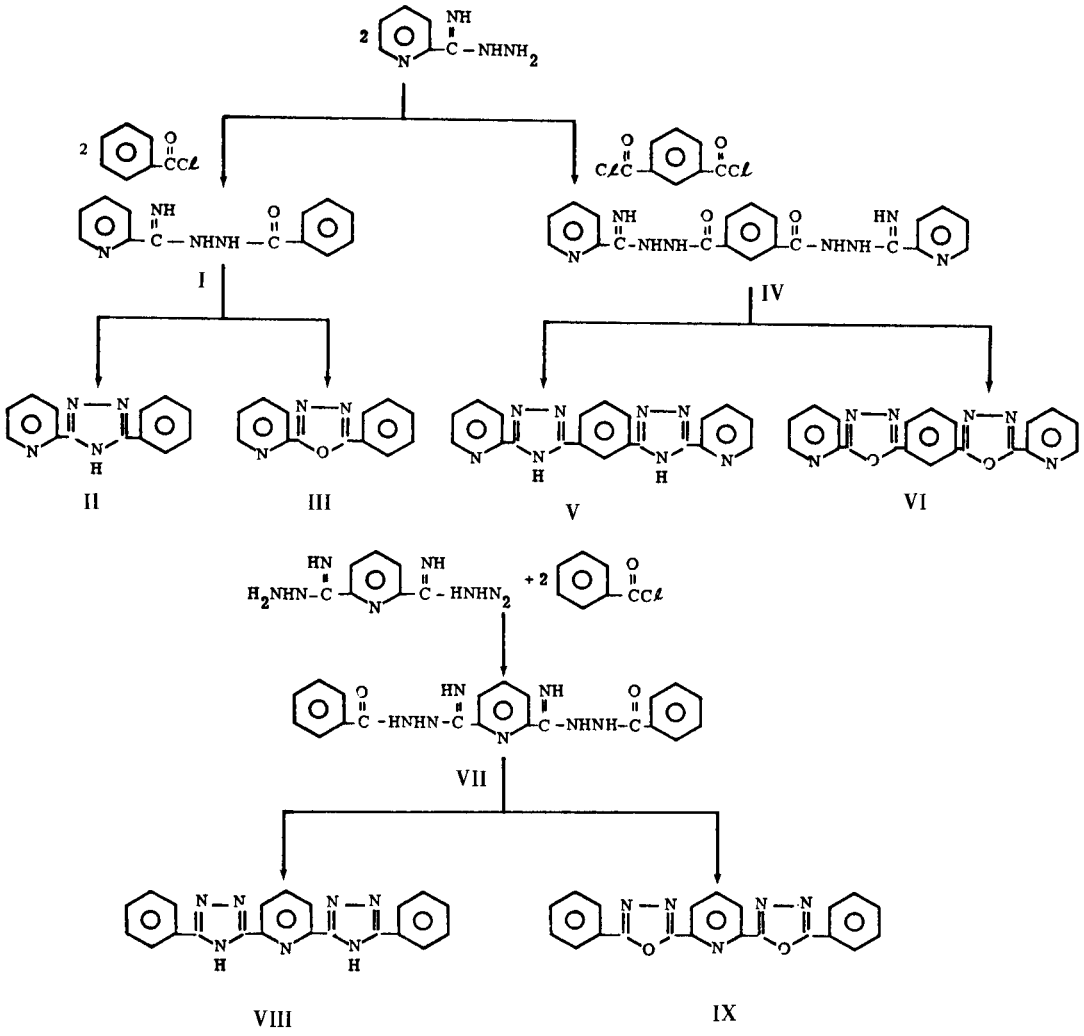

TABLE I

Characterization of Compounds

Compound	M.p., °C	Formula	Elemental Analysis (a) %C	%H	%N	%O	Ultraviolet λ max, mμ	Spectrum (b) ε
N-Benzoyl(2-pyridyl) hydrazidine (I)	208.5-209.5 dec.	$C_{13}H_{12}N_4O$	64.72 (64.98)	5.02 (5.04)	23.32 (23.32)	6.86 (6.66)	267	22,600
2-(2-Pyridyl)-5-phenyl-1,2,4-triazole (II)	211.5-212.5 (c)	$C_{13}H_{10}N_4$	70.16 (70.25)	4.51 (4.54)	25.07 (25.21)	--- ---	264 295	14,600 18,000
2-(2-Pyridyl)-5-phenyl-1,3,4-oxadiazole (III)	123.5-124.5	$C_{13}H_9N_3O$	69.82 (69.94)	4.00 (4.06)	18.88 (18.84)	7.30 (7.17)	241 271 314	5,500 12,300 26,100
N,N'-Isophthaloyl bis [(2-pyridyl) hydrazidine] (IV)	278-279 dec.	$C_{20}H_{18}N_8O_2$	59.47 (59.69)	4.55 (4.51)	27.81 (27.85)	--- ---	262	31,500
3,3'-*m*-Phenylene bis[5-(2-pyridyl)-1,2,4-triazole] (V)	326.5-327.5	$C_{20}H_{14}N_8$	65.33 (65.56)	3.82 (3.85)	30.74 (30.59)	--- ---	248 289	25,900 44,800
2,2'-*m*-Phenylene bis[5-(2-pyridyl)-1,3,4-oxadiazole] (VI)	241-242.5	$C_{20}H_{12}N_6O_2$	64.95 (65.21)	3.15 (3.28)	22.63 (22.82)	--- ---	234 264 301	14,900 21,500 51,800
N,N'-Dibenzoyl(2,6-pyridinediyl) dihydrazidine dihydrate (VII)	229-230.5 dec.	$C_{21}H_{23}N_7O_4$	57.48 (57.65)	4.98 (5.30)	22.49 (22.42)	--- ---	270	33,400
3,3'-(2,6-Pyridinediyl) bis[5-phenyl-1,2,4-triazole] (VIII)	296-297	$C_{21}H_{15}N_7$	69.18 (69.02)	4.10 (4.14)	27.00 (26.84)	--- ---	265 338	34,600 22,300
2,2'-(2,6-Pyridinediyl) bis[5-pnenyl-1,3,4-oxadiazole] (IX)	267.5-268.5	$C_{21}H_{13}N_5O_2$	68.44 (68.66)	3.43 (3.57)	18.96 (19.02)	--- ---	278 349	28,500 30,700

(a) Theoretical values reported in parenthesis. (b) Measured in sulfuric acid. (c) Lit. (9) m.p. 212°.

tion using strong acids such as dichloroacetic, trifluoroacetic, phosphoric, or sulfuric. This was evidenced by pouring the dichloroacetic acid or trifluoroacetic acid solution into cold anhydrous methanol and analyzing the resulting filtrate for water. Since no water due to cyclization was found, it was concluded that in the presence of strong acids, quantitative conversion of the N-acylhydrazidines to 1,3,4-oxadiazole occurred. This was further supported by the nmr spectra of the crude products which indicated no detectable 1,2,4-triazole.

Although the *N*-acylhydrazidines could be readily converted to the corresponding 1,3,4-oxadiazole at elevated temperature (100°) in sulfuric acid, degradation occurred as indicated by uv and nmr spectroscopy when the *N*-acylhydrazidine was allowed to stand at ambient temperature in sulfuric acid. The degradation products appeared to be predominantly a mixture of 1,3,4-oxadiazole resulting from cyclization and hydrazidine and carboxylic acid resulting from cleavage of the *N*-acylhydrazidine.

Under an inert atmosphere at elevated temperature (250° to 300°) in a melt or in refluxing solvents such as *N*-methylpyrrolidone, *m*-cresol, or hexamethylphosphoramide, the intermediate *N*-acylhydrazidines were converted predominantly to 1,2,4-triazoles. Analysis of the trapped exit gases revealed small amounts of ammonia which are evolved during the cyclization of the *N*-acylhydrazidine to 1,3,4-oxadiazole. The amount (0.8 to 3.6%) of ammonia appeared to be dependent upon the heating rate. Introduction of a tube containing the *N*-acylhydrazidine under nitrogen into a preheated oil bath at 300° generally resulted in the maximum (3.6%) evolution of ammonia. Whereas, when a *m*-cresol solution was heated from ambient temperature to reflux, the minimum (0.8%) evolution of ammonia was usually observed.

All compounds appeared to be hygroscopic with the relative affinity for hydration decreasing from *N*-acylhydrazidine to 1,2,4-triazole to 1,3,4-oxadiazole. In most instances, drying at 100-120° for 4 hours under high vacuum removed the hydrated water except for *N,N'*-dibenzoyl-2,6-pyridinediyl dihydrazidine (VII). Drying to temperatures as high as 200° failed to achieve complete removal of the tightly bound water.

Other means of converting the *N*-acylhydrazidines to 1,3,4-oxadiazole or 1,2,4-triazole such as refluxing in acetic anhydride, thionyl chloride, or in *m*-cresol containing a catalytic amount of *p*-toluenesulfonic acid were given a cursory examination but the resulting crude products were either very impure or not the desired compound. For example, 3-(2-pyridyl)-5-methyl-1,2,4-triazole was obtained as the major component in the product formed when *N*-benzoyl (2-pyridyl) hydrazidine (I) was refluxed in acetic anhydride. This was demonstrated by preparing an authentic sample of 3-(2-pyridyl)-5-methyl-1,2,4-triazole from the reaction of 2-pyridyl hydrazidine and acetyl chloride and comparing the properties of the two samples. No attempt was made to isolate and characterize the other components since that was beyond the scope of this immediate work.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ultraviolet spectra (in sulfuric acid) were obtained on a Cary 14 recording spectrophotometer. Elemental Analyses were determined by Galbraith Laboratories, Inc., Knoxville, Tennessee.

2-Pyridyl Hydrazidine.

This reactant was synthesized following the procedure of Case (7) and obtained as white needles, m.p. 95-96° [lit. (7) m.p. 95-96°].

2,6-Pyridinediyl Dihydrazidine.

This compound was prepared through a known procedure (8) as pale yellow needles, m.p. 231-232° dec.

Anal. Calcd. for $C_7H_{11}N_7$: C, 43.51; H, 5.74; N, 50.76. Found: C, 43.76; H, 5.75; N, 50.70.

Since the experimental procedures for the preparation of the individual groups of compounds, the *N*-acylhydrazidines (I, IV, VII), the 1,2,4-triazoles (II, V, VIII), and the 1,3,4-oxadiazoles (III, VI, IX) are essentially identical, the synthesis of a representative series from the reaction of 2,6-pyridinediyl dihydrazidine and benzoyl chloride is presented.

N,N'-Dibenzoyl(2,6-pyridinediyl) Dihydrazidine Dihydrate (VII).

To a slurry of 2,6-pyridinediyl dihydrazidine (1.93 g., 0.01 mole) and anhydrous sodium carbonate (2.22 g., 0.02 mole) in *N,N*-dimethylacetamide (30 ml.) at 0°, a solution of benzoyl chloride (2.80 g., 0.02 mole) in *N,N*-dimethylacetamide (15 ml.) was added dropwise during 0.5 hour. The pale yellow reaction mixture was stirred at ambient temperature for 3 hours, followed by pouring into ice water to precipitate a pale yellow solid. The isolated solid was washed with water followed by drying *in vacuo* over phosphorus pentoxide at 80° for 4 hours to yield 4.1 g. (94% yield) of *N,N'*-dibenzoyl(2,6-pyridinediyl) dihydrazidine dihydrate (VII), m.p. 229-230.5° dec. (Table I).

In the interfacial method, a solution of benzoyl chloride (2.80 g., 0.02 mole) in methylene chloride (30 ml.) was added rapidly to a vigorously stirred solution of 2,6-pyridinediyl dihydrazidine (1.93 g., 0.01 mole) and sodium carbonate (2.22 g., 0.02 mole) in water (100 ml.). A yellow solid began to precipitate immediately. The reaction mixture was stirred for 10 minutes and filtered. The resulting pale yellow solid was washed with water and dried *in vacuo* over phosphorus pentoxide at 80° for 4 hours to yield 3.95 g. (90% yield) of Compound VII, m.p. 229-231° dec.

3,3'-(2,6-Pyridinediyl)bis[5-phenyl-1,2,4-triazole] (VIII).

N,N'-Dibenzoyl(2,6-pyridinediyl) dihydrazidine dihydrate (1.0 g.) was dissolved in *m*-cresol (25 ml.) and refluxed for 0.5 hour under nitrogen. The resulting clear yellow solution was concentrated by simple distillation to about 7 ml. and diluted with methanol. Further dilution with water gave a white precipitate which was isolated and dried in air at 60°. The resulting white solid (0.82 g., 93% yield) melted at 216.5-218° dec., for the monohydrate of 3,3'-(2,6-pyridinediyl)bis[5-phenyl-1,2,4-triazole].

Anal. Calcd. for $C_{21}H_{17}N_7O$: C, 65.78; H, 4.47; N, 25.57.

Found: C, 65.76; H, 4.32; N, 25.78.

Further drying at 120° *in vacuo* for 4 hours provided the anhydrous material, m.p. 293-296°, which was recrystallized from a mixture of methanol and water to yield an amorphous white solid, m.p. 296-297° (Table I).

Thermal cyclization of the *N*-acylhydrazidines *via* melt technique was performed in the following manner. *N,N'*-Dibenzoyl-2,6-pyridinediyl dihydrazidine dihydrate (1.0 g.) in a polymerization tube under nitrogen was introduced into a preheated oil bath at 300°. A clear tan melt formed immediately with the evolution of volatiles. After maintaining at 300° for 0.5 hour, the resulting tan solid (0.87 g., 100% yield) softened at 288° and melted at 292-296°. The tan solid was recrystallized from a mixture of methanol and water to yield 3,3'-(2,6-pyridinediyl)bis[5-phenyl-1,2,4-triazole] (VIII) as a white solid, m.p. 295.5-297°, after drying at 120° *in vacuo* for 4 hours.

2,2'-(2,6-Pyridinediyl)bis[5-phenyl-1,3,4-oxadiazole] (IX).

N,N'-Dibenzoyl(2,6-pyridinediyl) dihydrazidine dihydrate (1.0 g.) was dissolved in trifluoroacetic acid (20 ml.) and refluxed for 4 hours under nitrogen. The resulting clear orange solution was poured into ice water to precipitate a white solid which was successively washed with aqueous sodium carbonate and water followed by drying at 120° *in vacuo* for 4 hours. The resulting white solid (0.80 g., 95% yield), m.p. 260-263°, was recrystallized from methanol to give white crystals of 2,2'-(2,6-pyridinediyl)bis[5-phenyl-1,3,4-oxadiazole] (IX), m.p. 267.5-268.5° (Table I).

3-(2-Pyridyl)-5-methyl-1,2,4-triazole.

A solution of acetyl chloride (1.57 g., 0.02 mole) in *N,N*-dimethylformamide (20 ml.) was added during 10 minutes to a solution of 2-pyridyl hydrazidine (2.72 g., 0.02 mole) in *N,N*-dimethylformamide (40 ml.) containing sodium carbonate (3.3 g., 0.31 mole) at 10°. The resulting yellow reaction mixture was stirred at ambient temperature for 0.5 hour followed by pouring onto ice to precipitate *N*-acetyl-(2-pyridyl) hydrazidine as a white solid (1.98 g., 56% yield), m.p. 211-212° dec.

Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.64; H, 5.51; N, 31.29.

N-Acetyl(2-pyridyl) hydrazidine (1.0 g.) was refluxed in *m*-cresol (20 ml.) for 0.5 hour followed by concentrating the clear pale yellow solution to dryness *in vacuo*. The residual tan solid (0.85 g., 94% yield), m.p. 162-164°, was recrystallized from *n*-hexane to provide 3-(2-pyridyl)-5-methyl-1,2,4-triazole as white needles, m.p. 166-167°

Reaction of *N*-Benzoyl(2-pyridyl) Hydrazidine in Acetic Anhydride.

N-Benzoyl(2-pyridyl) hydrazidine (1.0 g.) was refluxed in acetic anhydride (25 ml.) under a drierite tube for 18 hours. The resulting clear yellow solution was concentrated *in vacuo* to dryness to yield a tan residual solid which exhibited softening and melting from about 50° to 150°. Recrystallization from *n*-hexane (60 ml.) provided white needles (0.45 g., 67% yield) of 3-(2-pyridyl)-5-methyl-1,2,4-triazole, m.p. 165-166.5°.

Anal. Calcd. for $C_8H_8N_4$: C, 59.98; H, 5.04; N, 34.98. Found: C, 59.87; H, 5.14; N, 34.89.

Mixed melting point with an authentic sample of 3-(2-pyridyl)-5-methyl-1,2,4-triazole was 165-167°. When *N*-benzoyl (2-pyridyl) hydrazidine was stirred in acetic anhydride for 18 hours at ambient temperature, no detectable change was observed.

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