Intramolecular Nucleophilic Cyclization of a Carboxylic Acid Hydrazide Under Mild Acid Conditions

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Phthaloyl-2′-nitrophenylhydrazide undergoes ring closure involving nucleophilic attack of the hydrazide on the carboxylic acid in dilute aqueous acid solution to form the corresponding *N*-substituted phthalimide. Structure of the resulting phthalimide was unequivocally confirmed by ^{13}C-nmr.

J. Heterocyclic Chem., 14, 349 (1977).

Since 1,2-disubstituted hydrazides are relatively weak bases (1), especially when one of the substituents is an acyl moiety (2), they would not be expected to undergo a facile intramolecular nucleophilic cyclization. However, several reports appear in the literature (3,4) describing this type of cyclization under strong acid conditions, although structural confirmation of the reported products was not presented in these early reports.

We now wish to report the unusual intramolecular nucleophilic cyclization of a 1,2-disubstituted acyl hydrazide to yield exclusively an *N*-substituted phthalimide under mild acid conditions with conclusive proof of the structure of the product by fourier transform ^{13}C-nmr.

In acidic aqueous solution, phthaloyl-2′-nitrophenylhydrazide **1** cyclizes intramolecularly to form *N*-2′-nitroanilinophthalimide **2**. This reaction was observed to proceed in dilute aqueous hydrochloric acid (0.1 *N*) to yield **2** as yellow crystals, which by conventional elemental analysis used in the initial reports (3,4) would give data consistent with either **2** or **3**. However, by examination of the FT ^{13}C-nmr spectrum of the isolated material and the starting material **1**, the product was conclusively demonstrated to have structure **2**. If the compound represented by **3** had been the correct structure, two carbonyl signals would clearly result from the inherrent dissymmetry of the 2-[*N*-(2′-nitrophenyl)]-1,4-phthalazindione structure, as in the analogous model system 2-methyl-1,4-napthaquinone. In contrast, **2** gave only one carbonyl signal for the symmetrical *N*-substituted phthalazine ring as observed in other *N*-substituted phthalazines (5). Complete ^{13}C-nmr signal assignments were made on the basis of calculated chemical shifts (6,7) where possible and were aided by off-resonance decoupled spectra. Also employed were several model compounds which included:

Scheme I

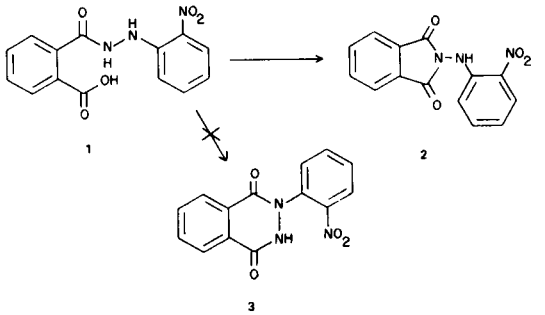
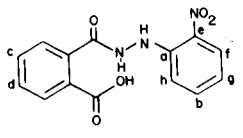
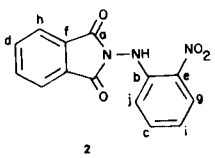


Table I

25.2 MHz ^{13}C-nmr Spectra of Phthaloyl-2′-nitrophenyl Hydrazide (**1**) and *N*-2′-Nitroanilinophthalimide (**2**) in DMSO-d_6



1



2

signal	obs.	calc.	signal	obs.	calc.
	169.4	****	a	165.8	****
	168.6	****	b	143.2	146.5
a	146.4	146.5	c	136.5	134.8
b	137.4	134.8	d	135.0	136.1
c,d (a)	132.4	132.1, 133.4	e	132.6	132.0
	131.1 (b)		f	129.8	131.1
	130.7 (b)		g	125.8	124.2
	130.3 (b)		h	123.6	123.3
e	129.0	132.0	i	119.2	119.8
f	126.4	124.2	j	114.8	112.9
g	118.7	119.8			
h	116.3	112.9			

(a) Listed respectively. (b) Could not be unambiguously assigned.

2-nitrophenylhydrazine; benzoylhydrazide; phenylhydrazine and *N*-(2-bromoethyl)phthalimide.

The rate of this cyclization was also examined and does not appear to be appreciably affected by the hydrogen-ion concentration of the system over the range of 0.1 to 0.5 *N*; k_{obs} (average value) = 3.09 x 10^{-3} sec^{-1} with a standard deviation of 0.45 x 10^{-3} sec^{-1}. It is, however, likely that the driving force of the cyclization is the very low solubility of the product which crystallizes from the reaction mixture on cyclization.

It is further interesting to note that when the cyclization of **1** was carried out under somewhat stronger conditions in boiling acetic acid that **2** was still formed rather than the 1,4-phthalazindione as previously reported (3,4).

Finally, since this cyclization was initially observed to occur in dilute hydrochloric acid, under conditions similar to those of human gastric fluid, the possibility of similar reactions occurring in pharmaceutical agents containing hydrazide noieties should be considered.

EXPERIMENTAL

All ^{13}C-nmr spectra were recorded on a Varian XL-100 spectrometer operating at 25.2 MHz, equipped with a Nicolet TT-100 Data System. Fixed operating parameters were: sweep width, 6025 Hz; pulse width, 12.5 usec; pulse delay, 10.000 sec; acquisition time 0.33997 sec. All samples were prepared, including model compounds, in d_6-dimethylsulfoxide as approximately 20% solutions and chemical shifts are reported relative to the central signal of the DMSO multiplet (δ 39.6).

Phthaloyl-2'-nitrophenylhydrazide (**1**).

This compound was synthesized by adding phthalic anhydride (0.01 mole) in benzene solution dropwise to a stirred suspension of 2-nitrophenylhydrazine (0.016 mole) in benzene. The resulting mixture was allowed to stand at room temperature for one hour. The precipitate was collected by filtration, washed with benzene and dilute hydrochloric acid and then recrystallized from a methanol-water mixture. Yellow-orange crystals were obtained melting at 298° (80% yield).

Anal. Calcd. for $C_{14}H_{11}N_3O_5$: C, 55.81; H, 3.65; N, 13.95. Found: C, 55.81; C, 3.71; N, 13.66.

N-2'-Nitroanilinophthalimide (**2**).

This compound was synthesized either through the cyclization of **1** in boiling acetic acid or through cyclization of 0.1 *N* hydrochloric acid at room temperature to give yields of 72 and 58% respectively.

Anal. Calcd. for $C_{14}H_9N_3O_5$: C, 59.36; H, 3.18; N, 14.84. Found: C, 59.30; H, 3.06; N, 14.70.

REFERENCES AND NOTES

(1) R. L. Hinman, *J. Org. Chem.*, **23**, 1587 (1958).

(2) N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5115 (1930).

(3) S. Baloniak and R. S. Ludwiczak, *Rocz. Chemi.*, **36**, 411 (1962).

(4) S. Baloniak and R. S. Ludwiczak, *ibid.*, **38**, 373 (1964).

(5) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972, p. 125.

(6) G. C. Levy and G. L. Nelson, *ibid.*, p. 79.

(7) J. B. Stother, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972, p. 196.