New preparation of benzo-2,1,3-oxadiazoles (benzofurazans)[1]

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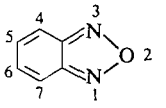
Received March 10, 1970

A new procedure for the synthesis of substituted benzo-2,1,3-oxadiazoles (benzofurazans) has been established. The method involved the pyrolysis of substituted methyl *N*-(*o*-nitrophenyl)carbamates. A possible mechanism for the reaction is outlined.

Canadian Journal of Chemistry, **48**, 3059 (1970)

Previously it was reported (1) that the thermal decomposition of alkyl *N*-(*o*-nitrophenyl)carbamates yielded benzofurazan. Further investigation of the reaction has shown that this relatively simple procedure could be generally applicable as a synthetic route to benz-substituted benzofurazans (Table 1). The only apparent limitation would be the availability of the properly substituted starting carbamates.



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The preferred alkyl carbamate has been shown (1) to be the methyl carbamate. When the alkyl group was ethyl or isopropyl, side reactions involving olefin formation occurred. These were shown to be occurring by passing the gaseous products through a CCl_4–Br_2 solution. When different phenyl carbamates were used, benzofurazan formation was noticeably reduced or failed to occur (Table 2). In making use of this reaction for the preparation of benzofurazans it was necessary to prepare the substituted methyl-*N*-(*o*-nitrophenyl)carbamates. These carbamates were prepared in two different ways depending on the availability of the starting materials. Certain carbamates were readily obtained by reacting substituted *o*-nitroanilines with methyl chloroformate. Other carbamates were prepared by starting with the substituted *o*-nitrobenzoic acid and converting the acid to the acid chloride by using thionyl chloride. The acid chloride was then reacted with sodium azide (Curtius reaction) to yield the substituted *o*-nitrophenylisocyanate. Addition of absolute methanol to the isocyanate gave the substituted methyl carbamate.

In the absence of kinetic data the proposed mechanism is based on product yields (Table 1) and from the results of special reaction mixtures listed in Table 3. Attempts to run kinetics on the reaction in solvents such as diphenyl ether, dimethyl sulfoxide, hexamethylphosphoramide, and benzonitrile yielded only trace amounts of benzofurazans. Two tentative routes which could lead to the final products are shown in Scheme 1.

Both routes *1* and *2* require the formation of a cyclic intermediate; route *1* in the cyclization of the starting urethane and route *2* in the cyclization of the *o*-nitrophenylisocyanate once it has formed. In addition to the carbamate pyrolysis reactions, the following findings are of both preparative and mechanistic interest (Table 3). Pyrolysis of *o*-nitrophenylisocyanate itself resulted in a lower yield of benzofurazan than most of the studied carbamates. Also the yield of product was unaffected by the addition of base. However, addition of base to the pyrolysis of methyl *N*-(*o*-nitrophenyl)isocyanate which should facilitate breakdown of carbamate into isocyanate and alcohol (2) drastically reduced the yield of benzofurazan.

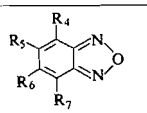
The experimental results obtained would favor the formation of the benzofurazans via route *1*. The cyclic intermediate formed then could break down to a nitrene-type intermediate similar to that proposed by Huisgen (3) as a feasible intermediate when benzofuroxan was formed from *o*-nitrophenyl azide according to eq. 1. Subsequent cyclization of the nitrene intermediate would yield benzofurazan. However, route *2* is probably operative and does lower the yields of benzofurazan due to undesirable side reactions.

[1]Taken from the thesis of Peter A. Forte presented to the Faculty of Graduate Studies, University of Guelph, Guelph, Ontario, as part of the requirements for the degree of Master of Science.

TABLE 1

The preparation of substituted benzofurazans*

Substituents				Melting points (°C)		
R_4	R_5	R_6	R_7	Observed	Reported	% Yield
CH_3	H	H	H	41.5–42.5	44	30
CH_3O	H	H	H	87.5–88.5	89–90	30
H	CH_3O	H	H	98–100	99	20
H	CH_3	H	H	35.5–36.5	37	50
H	H	H	H	51.5–52.5	55	50
H	Cl	H	H	41–42	44	40
H	NO_2	H	H	64–65	65	35
H†	CH_3	CH_3	H	83–85		48
H	H	CH_3	H	35.5–36.5	37	46
H	H	Cl	H	41–42	44	20
H	H	H	CH_3	41.5–42.5	44	50

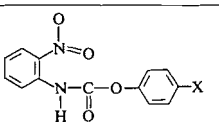
*The general structure was 

†Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 17.35. Found: C, 64.55; H, 5.43; N, 17.09.

TABLE 2

The preparation and decomposition of substituted phenyl *N*-(*o*-nitrophenyl)carbamates*

X	Melting point (°C)	% Composition Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	% Yield benzofurazan
H	93–95	60.46	3.90	10.85	60.16	4.06	11.03	0
CH_3O	157–158	58.33	4.19	9.72	58.48	4.38	9.51	15
O_2N	174–176	51.49	2.99	13.86	51.62	2.64	14.01	0

*General Formula 

All the phenyl-*N*-*o*(nitrophenyl)carbamates were prepared by treating the *o*-nitrophenyl isocyanate with the corresponding phenol.

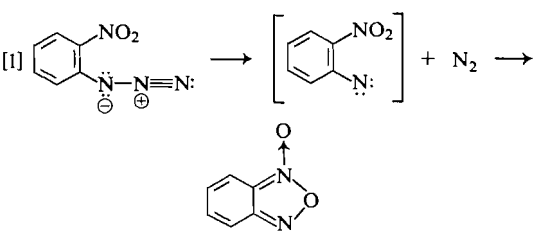
TABLE 3

Special reaction mixtures

Reactant(s)	Reaction temperature* (°C)	% Benzofurazan
o-Nitrophenylisocyanate	255	24†
o-Nitrophenylisocyanate; 18% MeO	190	28
o-Nitrophenylisocyanate; 79% MeO	190	26
Methyl *N*-(*o*-nitrophenyl)-carbamate; 2% MeO	250	20
Methyl *N*-(*o*-nitrophenyl)-carbamate; 70% MeO	200	0

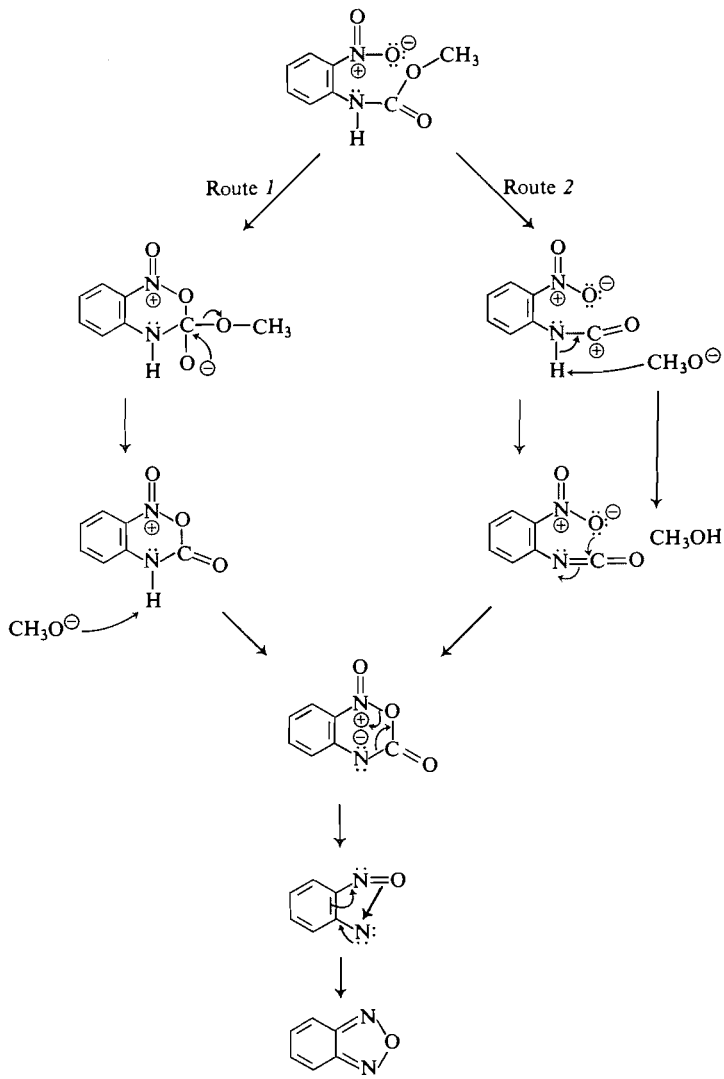
*Reaction temperature is taken as the temperature where the evolution of CO_2 gas is at a constant rate.

†Previously reported (1) as 5%. An improved workup technique raised the yield over a series of runs.



Experimental

All melting points were determined on the Fisher-Johns melting point apparatus and are uncorrected. Analyses were performed by Organic Microanalyses, 5757 Decelles Avenue, Montreal, Quebec. The n.m.r. spectra were measured on a Varian A60A instrument using tetramethylsilane as a standard and the i.r. spectra on a



SCHEME 1

Beckmann IR5A. All product yields are based on an average of at least three runs.

Preparation of Substituted Methyl N-(o-Nitrophenyl)-carbamates

Method A: Preparation of Methyl N-(4-Methyl-2-nitrophenyl)carbamate

In a typical experiment, a slurry of 4-methyl-2-nitroaniline (50.0 g, 0.328 mole) and CCl_4 (400 ml) was made. To this 50.0 ml (61.1 g, 0.650 mole) of methyl chloroformate were added over a period of 30 min. The mixture was stirred continuously at room temperature for an additional hour. Pyridine (26.5 ml, 0.328 mole) was then added over a period of 1 h and the reaction mixture stirred at room temperature for an additional hour. The solid material which separated was removed by filtration. The CCl_4 from the remaining liquid was removed *in vacuo* whereupon an orange–yellow precipitate resulted. Recrystallization of this precipitate from hexane – carbon tetrachloride (9:1) gave 39.0 g (56%) of methyl *N*-(4-methyl-2-nitrophenyl)carbamate, m.p. 104–105° with the following spectral data: n.m.r. ($CDCl_3$) δ 9.54 (1 NH broad singlet which disappears on the addition of D_2O), 7.10–8.51 (3H multiplet), 3.80 (3H singlet), and 2.36 (3H singlet); i.r. (CCl_4) 3325 (—N—H), 1740 (—C(=O)—), and 1250 (—O—CH_3) cm^{-1}.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.48; H, 4.83; N, 13.19.

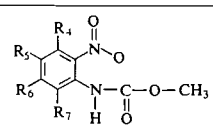
Method B: Preparation of Methyl N-(5-Methyl-2-nitrophenyl)carbamate

The method of McElvain and Carney (4) was followed

TABLE 4

The preparation of methyl *N*-(substituted-2-nitrophenyl)carbamates*

Substituents				Method	Melting point (°C)	% Yield	Analysis: Calcd. (%)			Analysis: Found (%)		
R_4	R_5	R_6	R_7				C	H	N	C	H	N
CH_3	H	H	H	B	48–49.5	75	51.43	4.79	13.33	51.43	4.38	13.51
CH_3O	H	H	H	B	125–127	44	47.79	4.46	12.38	47.78	4.32	12.68
H	CH_3O	H	H	A	100.5–101	60	47.79	4.46	12.38	47.38	4.48	12.51
H	CH_3	H	H	A	104–105	56	51.43	4.80	13.33	51.48	4.83	13.19
H†	H	H	H		51–53	71	48.98	4.11	14.28	48.89	4.01	14.28
H‡	Cl	H	H	A	107.5–108	58	41.67	3.06	12.15	41.36	2.88	12.05
H	NO_2	H	H	B	125–127	58	39.84	2.92	17.42	40.13	3.23	17.66
H	CH_3	CH_3	H	A	81–82.5	57	53.57	5.39	12.49	53.84	5.36	12.31
H	H	CH_3	H	B	59–60	57	51.43	4.79	13.33	51.43	4.70	13.46
H§	H	Cl	H	B	63.5–65.5	24	41.67	3.06	12.15	41.70	2.96	12.01
H	H	H	CH_3	A	133–134	2.5	51.43	4.79	13.33	51.44	4.55	13.66

*The general structure was 

†Reference 1 for preparation.
‡Analysis for Cl: Calcd., 15.37; Found, 15.65.
§Analysis for Cl: Calcd., 15.37; Found, 15.31.

for the preparation of the acid chloride of 5-methyl-2-nitrobenzoic acid. 5-Methyl-2-nitrobenzoic acid (50.0 g, 0.277 mole) was dissolved in 600 ml of dry benzene and cooled to 13° by a cold water bath. To this solution 93.0 ml (132.0 g, 1.108 mole) of thionyl chloride were added slowly with stirring after which the solution was refluxed gently for 24 h. The solvent and excess thionyl chloride were removed *in vacuo* to give the crude acid chloride which was used in the unpurified form for preparing the isocyanate according to the method of Allain and Bell (5).

Sodium azide (27.0 g, 0.415 mole) was dissolved in 180 ml of distilled water and cooled to 10°. While stirring this solution, the acid chloride (dissolved in 150 ml of reagent acetone) was added at a rate such that the reaction temperature did not exceed 15°. After addition of the acid chloride, the reaction mixture was stirred at 18° for 3 h. A solid formed which was filtered off. The organic layer of the filtrate was separated and the solvent removed *in vacuo* whereupon a solid formed. This solid azide was combined with the original solid and was added in small portions to dry benzene which had been heated initially to 60°. The addition of the azide was exothermic and so no further warming was necessary. After complete addition the solution was allowed to stand at room temperature for 2 h.

To the benzene solution was added 20.0 ml anhydrous methanol and the solution was refluxed for 3 h. The solvent and excess methanol was removed *in vacuo* whereupon an oil resulted. Addition of hot hexane yielded 32.6 g (57%) of methyl *N*-(5-methyl-2-nitrophenyl)-carbamate, m.p. 59–60°, with the following spectral data: n.m.r. ($CDCl_3$) δ 9.90 (1 NH broad singlet which disappears on the addition of D_2O), 5.80–8.40 (3H multiplet), 3.82 (3H singlet), and 2.41 (3H singlet); i.r. (CCl_4) O ‖ 3325 (—N—H), 1745 (—C—), and 1250 (—O—CH_3) cm^{-1}.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.79; N, 13.33. Found: C, 51.43; H, 4.70; N, 13.46.

The remainder of the carbamates were prepared by one of the two methods given. Details are shown in Table 4.

Preparation of Substituted Benzofurazans

The method of preparation of the substituted benzofurazans was identical for all cases. The thermal decomposition of methyl *N*-(4-methyl-2-nitrophenyl)carbamate resulting in the formation of 5-methylbenzofurazan, CO_2, and methanol will be described as a typical method. The remainder of the benzofurazans were similarly prepared and these details are shown in Table 1.

Thermal Decomposition of Methyl N-(4-methyl-2-nitrophenyl)carbamate

Methyl N-(4-methyl-2-nitrophenyl)carbamate (8.9 g, 0.065 mole) was placed in a 50 ml two-necked conical flask fitted with a thermometer and a simple distillation set up consisting of a stillhead, condenser, and receiver. The flask contents were raised to 255° by means of a heating mantel. The evolution of CO_2 gas was detected by use of a limewater solution. After the evolution of gas ceased, the material in the pot was distilled at 0.2 mm pressure. All distillable material came off at a pot temperature less than 169° and solidified in the condenser. This solid was scraped out of the condenser and purified using a Nester-Faust sublimation apparatus. Pure 5-methylbenzofurazan, m.p. 35–36.5° (lit. (8) 37°) was obtained with the following spectral properties: n.m.r.

($CDCl_3$) δ 7.08–7.75 (multiplet) and 2.43 (singlet) with an integrated area ratio of 1:1 respectively; i.r. (CCl_4) showed strong absorption at 1630, 1530, 1460, 1440, 1410, 1370, 1315, 1155, 1040, 1010, 890, and 850 cm^{-1}.

The authors would like to acknowledge the National Research Council of Canada for financial support of this research. We also thank Mr. H. S. McKinnon for running all the n.m.r. spectra.

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