Facile One-Pot Synthesis of 2,1,3-Benzoxadiazole *N*-Oxide (Benzofuroxan) Derivatives Under Phase-Transfer Catalysis[1]

N. R. Ayyangar,* S. Madan Kumar, K. V. Srinivasan

National Chemical Laboratory, Pune 411 008, India

Several 2,1,3-benzoxadiazole *N*-oxide (benzofuroxan) derivatives are synthesized from the corresponding *o*-chloronitrobenzenes in a one-pot operation by stirring with sodium azide in dichloroethane in the presence of benzyl tributylammonium bromide as a phase-transfer catalyst. The moderate reaction conditions enable the isolation of the intermediate reactive azido compounds.

The chemistry of furoxans (1,2,5-oxadiazole *N*-oxides) and benzofuroxans (2,1,3-benzoxadiazole *N*-oxides) has been reviewed recently.[2] Benzofuroxans **3** possess wide ranging biological activity.[2] Vasodilatory activity has been observed in some fused benzofuroxan derivatives.[3] Nitrobenzofuroxan, pyridofuroxan and some fused benzofuroxans have been found to inhibit nucleic acid and protein synthesis in leucocytes.[4,5] Some of these compounds show particular activity against leukaemia,[4] and other forms of cancer cells.[6] Benzofuroxans are also valuable starting materials for the synthesis of biologically active quinoxaline oxides.[7] A variety of applications have been reported for benzofuroxan derivatives in dry battery cells as depolarizing agents,[8] in photopolymerizable compositions as selective inhibitors of thermal polymerization for better resolutions,[9] in compositions useful as inhibitors of styrene polymerization,[10] and in pest control.[11]

Benzofuroxan has been obtained by the oxidation of *o*-quinone dioxime.[12] This method has limited practical utility since the *o*-quinone or its monoxime is not readily available. Generally routes involving *o*-nitroanilines as starting material, are preferred. In one method, *o*-nitroanilines have been oxidized to the corresponding benzofuroxan by alkaline hypochlorite or by phenyliodosodiacetate.[13,14] However, the alkaline oxidation conditions have been shown to have a detrimental effect on the products.[15] The other method, perhaps the most reliable one so far for synthesizing benzofuroxans, is by the decomposition of *o*-nitrophenyl azides usually by pyrolysis or less frequently by photolysis.[16] This method generally involves the synthesis of *o*-nitrophenyl azide by a separate sequence of reactions,[4,17] followed by the isolation and thermolysis of the azides in suitable solvents in another step. We report in this communication, a facile one-pot synthesis of benzofuroxan derivatives starting from easily available *o*-chloronitrobenzenes, possessing electron withdrawing substituent in *para* position to chloro group. The interesting feature of the present method is the nucleophilic substitution of chlorine by azido group followed by *in situ* cyclization under solid-liquid phase-transfer catalysis (PTC) conditions, hitherto not reported in literature. Moreover, the *o*-chloronitrobenzenes are the most likely precursors for the corresponding *o*-nitroanilines (starting materials for other general routes).

Several benzofuroxan derivatives **3a–h** were synthesized from the corresponding *o*-chloronitrobenzenes **1a–h** by stirring them at 60 °C with a suspension of powdered sodium azide in dichloroethane in the presence of benzyl tributylammonium bromide as a phase-transfer catalyst (PTC) (Table 1). The reaction was extended to the synthesis of pyridofuroxan **6** from the corresponding chlorodinitropyridine **4**. The previously unknown benzofuroxans and the new pyridofuroxan **6** have been characterized by spectral data and microanalyses (Table 2). The presence of a weak electron-withdrawing group such as the

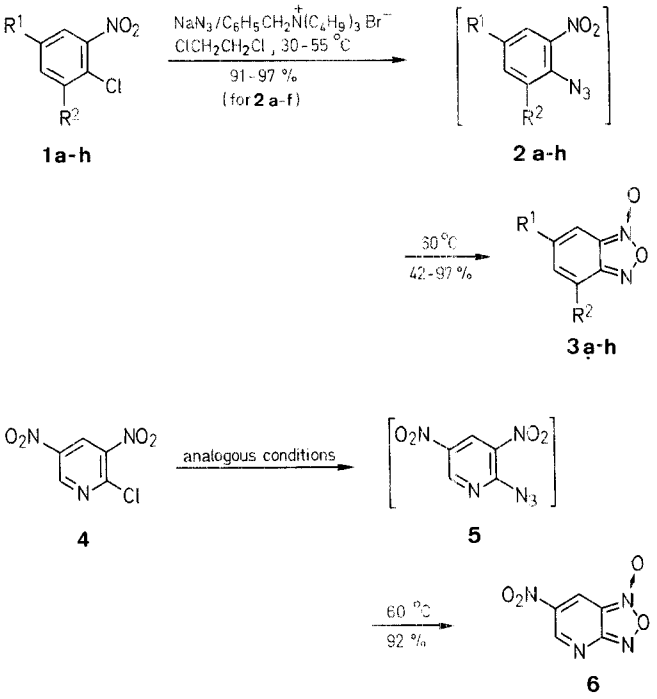

Table 1. 2,1,3-Benzoxadiazole *N*-oxides **3a–h** and [1,2,5]Oxadiazolo-[3,4-*b*]pyridine 1-Oxide **6**

Product	R^1	R^2	Yield[a] (%)	m.p. (°C)	Molecular Formula[b] or Lit. m.p. (°C)
3a	NO_2	H	95	72	72[21]
3b	CHO	H	97	69	68–69[4]
3c	$COCH_3$	H	90	102	$C_8H_6N_2O_3$ (178.2)
3d	COC_6H_5	H	88	142	$C_{13}H_8N_2O_3$ (240.2)
3e	Cl	H	42	49	48[16]
3f	CN	NO_2	92	169	$C_7H_2F_3N_3O_4$ (249.1)
3g	CF_3	NO_2	91	124	126–127[22]
3h	CO_2H	H	88	128	128–129[23]
6	–	–	92	106	$C_5H_2N_4O_4$ (182.1)

[a] Isolated yield.
[b] Satisfactory microanalyses obtained: C ±0.21, H ±0.15, N ±0.32.

chloro, has resulted in lower yields of the benzofuroxan **3e** (42%) (Table 1). However, in the absence of an additional electron-withdrawing substituent at the *para* position to the chloro group in **1**, there was no formation of benzofuroxan.

The concentration profile of the reactants and products in a typical reaction sequence of **1a** to **3a** is shown in Fig. 1. The curves have been plotted by analysing aliquots of reaction mixtures at different intervals of time by TLC/FID. The formation of benzofuroxans **3** from *o*-chloronitrobenzenes **1** at low temperatures favors the concerted elimination of a nitrogen molecule followed by intramolecular cyclization, without the involvement of an intermediate nitrene species. Such mechani-

Table 2. Spectral Data for Compounds **3c**, **d**, **f** and **6**

Product	UV (CH_3OH) λ_{max}(nm) (log ε)	IR (Nujol) ν(cm^{-1})	MS *m/e* (rel. intensity, %)
3c	372 (3.72)	1670, 1600, 1570, 1470, 1450, 1410, 1400, 1370, 1270, 1240, 1160, 1130	178 (43); 162 (19); 147 (44); 103 (65); 77 (44)
3d	372 (3.92)	1650, 1610, 1570, 1530, 1480, 1460, 1370, 1240, 1180	240 (98); 224 (21); 151 (35); 106 (35); 105 (100); 103 (34); 77 (98); 75 (87)
3f	399 (3.04)	1620, 1600, 1590, 1525, 1475, 1380, 1350, 1330, 1115	206 (57); 190 (11); 176 (66); 130 (14); 116 (7); 100 (100); 99 (79)
6	390 (3.26)	3010, 1590, 1530, 1455, 1430, 1340, 1235, 1170, 1060	182 (50); 166 (8); 152 (10); 106 (17); 78 (100)

Table 3. Azides **2a–f**

Product	Reaction Temp. (°C)	Yield[a] (%)	m.p. (°C)	Molecular Formula[b] or Lit. m.p. (°C)	IR (Nujol)[c] ν(cm^{-1})	MS *m/e* (rel. intensity, %)[c]
2a	29	97	66	66–67[20]	—	—
2b	29	96	74	74–75[3]	—	—
2c	50	92	84	$C_8H_6N_4O_3$ (206.2)	2112, 1670, 1600, 1520, 1450, 1350, 1240, 1160, 1010	206 (10); 176 (100); 160 (80); 145 (95); 115 (60); 101 (95)
2d	55	91	105	$C_{13}H_8N_4O_3$ (268.2)	2110, 1645, 1600, 1520, 1435, 1340, 1280, 1155, 1060	268 (10); 240 (100); 224 (42); 149 (21); 105 (35)
2f	50	94	142	$C_7H_2N_6O_4$ (234.1)	2210, 2115, 1610, 1530, 1460, 1340, 1270, 1220, 1100	234 (30); 207 (50); 205 (98); 190 (40); 177 (35); 176 (100); 130 (42); 100 (95)

[a] Yield of isolated Product.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.25, N ±0.36.
[c] Spectral data of only new azides are given.

stic pathways involving azido compounds, occurring at temperatures below that required for the generation of a nitrene species has been shown to follow either a concerted process or one involving an initial 1,3-dipolar cycloaddition, followed by nitrogen loss.[18–20]

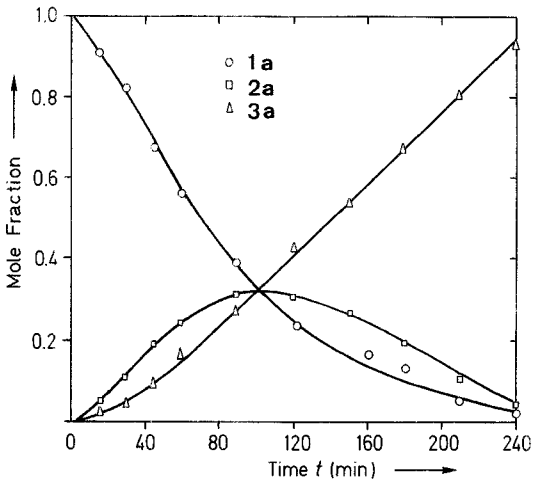

Figure 1. Concentration – Time Curves

In separate experiments, *o*-nitrophenyl azides **2a–f** could be obtained from the corresponding *o*-chloronitrobenzenes in excellent yields by carrying out the reactions under PTC conditions. The moderate PTC reaction conditions enabled us to isolate the reactive azides (Table 3). The reaction of *o*-chloronitrobenzenes **1** with sodium azide in dichloroethane under identical conditions but in the absence of PTC did not yield any *o*-nitrophenyl azides **2**. The unreacted *o*-chloronitrobenzenes **1** could be completely recovered.

To ascertain the role of PTC in the cyclization of the azides to benzofuroxans, two experiments were carried out starting from **2b** at 60 °C in 1,2-dichloroethane as solvent for 4 h both in the presence and absence of PTC. The percentage yield of **3b** against time was plotted (Fig. 2). The data points were generated by withdrawing aliquots of reaction mixture at different intervals and analysing the components by TLC/FID. In the presence of PTC, complete conversion to **3b** could be achieved in 3 h, whereas in the absence of PTC, the conversion of 3 h was to an extent of 85 % only. In the absence of PTC complete conversion could not be ontained even after 4 h (Fig. 2).

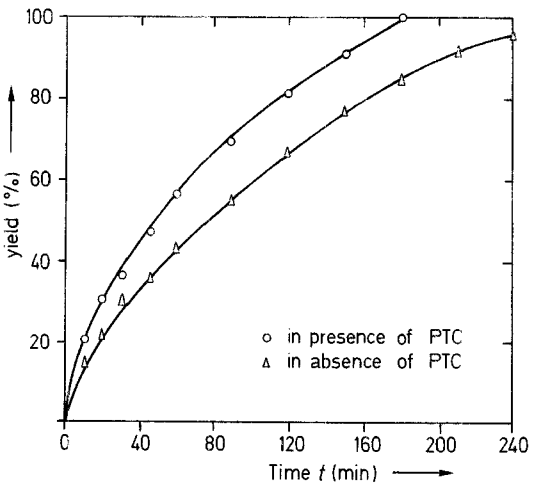

Figure 2. A Plot of Percentage Yield of **3b** From **2b** Against Time

In order to ascertain the effect of temperature in influencing the course of the reaction of **1d** leading either to the azide **2d** or to the cyclized product **3d**, we performed experiments at three different temperatures namely 52.5 °C, 55 °C and 57 °C respecti-

vely for 6 h, following the described general procedure. Care was taken to control temperature within ± 0.1 °C using a constant temperature bath. The products **2d** and **3d** in the reaction mixtures were estimated by TLC/FID analysis. The results are summarized in Table 4. The results indicate that the reaction temperature is a critical parameter determining the selectivity of formation of **2d** or **3d**.

Table 4. Effect of Temperature on the Yield of **2d** and **3d**

Entry No.	Reaction Temp. (°C)	Yield (%)	
		2d	**3d**
1	52.5	96.5	3.3
2	55.2	93.4	5.2
3	57.0	86.5	13.4

In order to compare the performances of other PTC systems, a set of three experiments were performed, starting from **1b** under identical conditions as per the general procedure using 18-crown-6, polyethyleneglycol-1000, and benzyl tributylphosphonium bromide respectively. The unreacted **1b** and the products **2b** and **3b** in the reaction mixture were estimated by TLC/FID analysis. The yield data is recorded in Table 5. A comparison of yield data of **3b** in Tables 1 and 5 indicates that benzyl tributylammonium bromide seems to be an optimal PTC system for the one-pot synthesis of benzofuroxan derivatives.

Features of the present method are:

- one-pot synthesis of benzofuroxans from easily available starting materials in the presence of an optimal PTC system;
- excellent yields of products under moderate reaction conditions;
- moderate reaction conditions which enables the isolation of the intermediate azides in excellent yields;
- shorter reaction times; and
- simple work-up procedures.

Table 5. Effect of Other PTC Systems on the Formation of Benzofuroxan

Entry No.	PTC System	Yield (%)		
		1b	**2b**	**3b**
1	18-Crown-6	–	5.3	94.4
2	Polyethyleneglycol-1000	3.3	8.3	88.5
3	Benzyl tributylphosphonium bromide	–	2.4	91.8

Conversion of *o*-Chloronitrobenzenes 1 to 2,1,3-Benzoxadiazole *N*-oxides 3 and of 2-Chloro-3,5-dinitropyridine (4) to 6-Nitro-[1,2,5]oxadiazolo[3,4-*b*]pyridine 1-Oxide (6); General Procedure:

o-Chloronitrobenzene derivative **1** or pyridine derivative **4** (0.01 mol) and powdered sodium azide (650 mg, 0.01 mol) are added to a vigorously stirred solution of benzyltributylammonium bromide (PTC) (356 mg, 1 mmol) in 1,2-dichloroethane (50 ml). The mixture is slowly heated up to 60 °C in 0.25 h and maintained at 60 °C for 6 h. Complete conversion of the *o*-chloronitrobenzene derivative is confirmed by TLC analysis on silica gel using *n*-hexane/benzene (12:8) as eluent and color development by iodine vapors (the order of elution being chloronitrobenzene **1**, benzofuroxan **3**, followed by the azide **2**). The reaction mixture is cooled to 28 °C and filtered. The filtrate is washed first with 1 normal hydrochloric acid (100 ml) and subsequently with water (50 ml). The organic layer is separated and dried with sodium sulfate. The solvent is distilled on a steam-bath and the residue is crystallized from absolute alcohol to yield the pure benzofuroxan **3** or pyridofuroxan **6**.

Isolation of the Azides **2**: For the conversion to the azides **2**, the reaction mass is stirred at the temperature indicated in the Table 3 for 6 h. Complete conversion of **1** is again confirmed by TLC analysis using the same eluent system as described above. The same isolation procedure as already described is followed. The crude product on crystallization from dichloromethane/ether (1:1) yielded the pure azide **2**.

TLC/FID Estimations:

The TLC/FID estimations of **1**, **2** and **3** were carried out on Iatroscan TH-10 TLC/FID analyser (New-Howells Associates Ltd., U.K.) connected to a two-pen flat-bed type strip chart recorder VP-6621A (National, Japan). A mixture of benzene (Analar grade, British Drug Houses, Ltd.) and *n*-hexane (80:20 v/v) was used for development. An aliquot of reaction mixture (1 ml) withdrawn at different intervals of time was given a wash first with dilute hydrochloric acid (10% w/v, 5 ml) and then with water (5 ml). The samples were spotted in volumes of 1 µl each with a fine microlitre syringe on chromarods. The rods were eluted twice in the development tank for better separation. Standard solutions of the pure components were also spotted and eluted under identical conditions. The estimations were done by calculating the areas under the recorded peaks. Each estimation was a mean of at least four consecutive spottings and elutions.

Received: 4 September 1986
(Revised form: 28 January 1987)

(1) NCL Communication No. 4143.
(2) Gasco, A., Boulton, A.J. *Adv. Heterocycl. Chem.* **1981**, *29*, 252. Ghosh, P.B., Ternai, B., Whitehouse, M.W. *Med. Res. Rev.* **1981**, *2*, 158.
(3) Ghosh, P.B., Everitt, B.J. *J. Med. Chem.* **1974**, *17*, 203.
(4) Ghosh, P.B., Whitehouse, M.W. *J. Med. Chem.* **1968**, *11*, 305.
(5) Ghosh, P.B., Whitehouse, M.W. *J. Med. Chem.* **1969**, *12*, 505.
(6) Barry, V.C., Belton, J.G., Conalty, M.L. *Chemother., Proc-Int. Congr. Chemother. 9th, 1975* **1976**, *8*, 97; C.A. **1977**, *86*, 182960.
(7) Haddadin, M.J., Issidorides, C.H. *Heterocycles* **1976**, *4*, 767.
(8) Hardy, W.B., Parent, R.A. *French Patent* 1 395 886 (1965), American Cyanamid Co.; C.A. **1965**, *63*, 14875.
(9) Nalli, G.R., Pazos, J.F. *German Patent* 2 533 073 (1976) E.I. du Pont de Nemours and Co.; C.A. **1977**, *86*, 180729.
(10) Shimazu, H., Arai, T., Harada, S. *Japan Kokai* 102231, 133931; C.A. **1978**, *88*, 62733, 90234.
(11) Iwamoto, R., Sakata, H., Okumura, K., Honga, A. *Japan Patent* 77 07 055 (1977) Nitto Chemical Industry Co. Ltd.; C.A. **1977**, *87*, 12883d.
(12) Zincke, T., Schwarz, P. *Ann. Chem.* **1899**, *28*, 307.
(13) Green, A.G., Rowe, F.M. *J. Chem. Soc.* **1912**, *101*, 2443.
(14) Boulton, A.J., Middleton, D. *J. Org. Chem.* **1974**, *39*, 2956.
(15) Mallory, F.B., Wood, C.S., Hurwitz, B.M. *J. Org. Chem.* **1964**, *29*, 2605.
(16) Smith, P.A.S., Brown, B.B. *J. Amer. Chem. Soc.* **1951**, *73*, 2435.
(17) Grieco, P., Mason, J.P. *J. Chem. Eng. Data* **1967**, *12*, 623.
(18) Dyall, L.K., Kemp, J.E. *J. Chem. Soc. B.* **1968**, 976.
(19) Dyall, L.K. *Aust. J. Chem.* **1975**, *28*, 2147.
(20) Dyall, L.K. *Aust. J. Chem.* **1977**, *30*, 2669.
(21) Bailey, A.S., Case, J.R. *Tetrahedron* **1958**, *3*, 113.
(22) Ghosh, P.B., Ternai, B., Whitehouse, M.W. *J. Med. Chem.* **1972**, *15*, 255.
(23) Boulton, A.J., Ghosh, P.B., Katritzky, A.R. *J. Chem. Soc. C* **1966**, 971.