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Straightforward one-pot synthesis of benzofuroxans from *o*-halonitrobenzenes in ionic liquids

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Treatment of *o*-halonitrobenzenes with sodium azide in a [empyrr][BF_4]/Bu_4NBr/H_2O system gives benzofuroxans in high yields, with the recovery and reuse of the ionic liquid for at least ten times.

Benzofuroxans (benzo-2,1,3-oxadiazole *N*-oxides) exhibit diverse biological activity and have been extensively investigated as NO-releasing agents, calcium channel modulators, monoamine oxidases inhibitors, herbicides[1] or energetic materials.[2] Among various methods for the preparation of benzofuroxans,[3] thermal cyclization of *o*-nitroaryl azides is most widely used. This reaction is typically carried out at 100–160 °C in toluene, xylene, decalin, DMSO, acetic or propionic acid. The principal drawback of this method is that the starting azides are hazardous compounds and can explode on impact and grinding. In an alternative one-pot approach, a few benzofuroxans were synthesized from the corresponding *o*-chloronitrobenzenes upon nucleophilic substitution with sodium azide in chlorobenzene or dichloroethane under phase transfer conditions.[4] However, many of the reported methods suffer from the following drawbacks: (i) long reaction times, (ii) high temperatures, (iii) application of combustible solvents, (iv) use of toxic and/or explosive reagents, (v) use of uncommon starting materials. Thus, the development of efficient methods for the preparation of benzofuroxans is required.

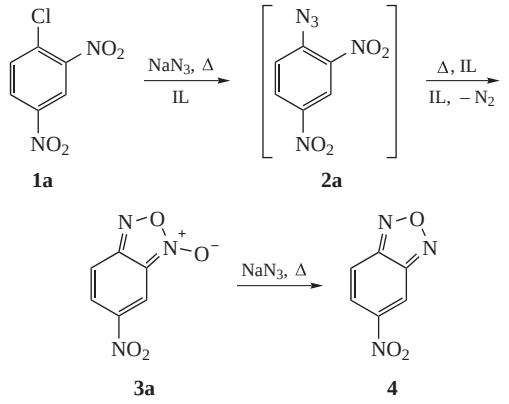
Ionic liquids (ILs) have been widely investigated as substitutes for common solvents in a variety of chemical processes.[5–7] Although many types of reactions have been investigated in ILs, synthesis of benzofuroxan in ILs by thermolysis of *o*-nitroaryl azides, which would either be prepared beforehand or generated *in situ*, are absent from the literature.

Recently, D'Anna *et al.*[8] have reported the nucleophilic aromatic substitution of some activated aryl or heteroaryl halides in ILs ([bmim][BF_4], [bmim][PF_6], [bmim][NTf_2], [bm_2im][NTf_2] and [bmpyrr][NTf_2]), using 1-butyl-3-methylimidazolium azide ([bmim][N_3]) as a nucleophile. More attractive azidation with NaN_3 in IL proceeded slowly giving lower yield of product after 70 h at 25 °C. Note that treatment of *o*-bromonitrobenzene with [bmim][N_3] in [bmim][BF_4] at 60 °C after 24 h provides only 33% conversion whereas the yield of *o*-azidonitrobenzene was 19% only.

Herein, we report a convenient method for the synthesis of a range of benzofuroxans in IL as reaction medium, *o*-nitroaryl halides and NaN_3 being the principal reactants.

We chose the reaction between the commercially available 2,4-dinitrochlorobenzene **1a** and NaN_3 to yield 2,4-dinitroazidobenzene **2a** that can be further transformed to 6-nitrobenzofuroxan **3a** as a model one (Scheme 1).

A variety of ILs and conditions were screened to optimize the yield of furoxan **3a**. The reactions were monitored by measuring the yields of the returned compound **1**, intermediate azide **2**, the target furoxan **3a**,† and benzofurazan byproduct‡ **4**. In this study,§ the best yield (95%) of furoxan **3a** was achieved on treatment of 2,4-dinitrochlorobenzene **1a** with 1 equiv. of NaN_3 at 60 °C for 4 h in [empyrr][BF_4] or [bmim][$MeSO_3$] as the solvent.



Scheme 1

In an attempt to improve the time of conversion and reduce reaction temperature, the azidation was carried out in the presence of phase transfer catalysts (Table 1). We were pleased to see that the use of Bu_4NBr (entries 5 and 9) was effective enough. When a control reaction was run in the presence of water (entries 10–12) and in the absence of a phase transfer catalyst, cyclization also occurred. Small amounts of water (entry 12) was required to shorten the reaction duration time and to provide the highest yield of the product. Finally, we found that combination of both additives, Bu_4NBr and water (entries 13 and 14), improved the reaction rate and the conversion significantly. In practice, after stirring the mixture of compound **1a**, sodium azide and Bu_4NBr with the IL in the presence of 5 vol% of H_2O at 55 °C for ~2 h, the product **3a** was separated by vacuum sublimation.

One important feature of the use of ILs is the possibility of their recycling and reuse. We found that the recycling of [empyrr][BF_4] is feasible for the process herein studied. Recycling reactions were performed at 55 °C for 2 h using 2,4-dinitrochlorobenzene as a model precursor in the [empyrr][BF_4]/H_2O/Bu_4NBr system. After

† The identity of product **3a** was confirmed by NMR spectra, CHN analysis, mp, MS, and comparison with the literature data.[9]
‡ Reduction of benzofuroxans with NaN_3 to benzofurazans was previously reported.[10]
§ See Online Supplementary Materials for more detailed optimization data (Table S1).

Table 1 Preparation of 5-nitrobenzofuroxan **3a** in ILs.[a]

Entry	Additive	IL[b]	*T*/°C	*t*/h	Yield (%)		
					1a	**3a**	**4**
1	Bu_4NBr, 0.5 mmol	[bmpyrr][OTf]	40	9	trace	84	0
2	Bu_4NBr, 0.5 mmol	[bmpyrr][OTf]	50	3	trace	88	2
3	Bu_4NBr, 0.5 mmol	[bmpyrr][OTf]	60	2	0	93	5
4	Bu_4NBr, 0.5 mmol	[bmpyrr][OTf]	70–80	2	trace	71	8
5	Bu_4NBr, 0.1 mmol	[bmpyrr][OTf]	60	3	0	92	5
6	Bu_4NCl, 0.1 mmol	[bmpyrr][OTf]	60	3.5	trace	61	4
7	Bu_4NI, 0.1 mmol	[bmpyrr][OTf]	60	7	trace	47[c]	0
8	Et_3NBnCl, 0.1 mmol	[bmpyrr][OTf]	60	4	trace	91	0
9	Bu_4NBr, 0.1 mmol	[empyrr][BF_4]	55	2	trace	92	0
10	H_2O, 1 ml	[empyrr][BF_4]	60	5.5	7	85	1
11	H_2O, 0.5 ml	[empyrr][BF_4]	60	5.5	trace	88	1
12	H_2O, 0.1 ml	[empyrr][BF_4]	60	3	trace	94	0
13	H_2O, 0.1 ml Bu_4NBr, 0.1 mmol	[empyrr][BF_4]	55	2	0	96	0
14	H_2O, 0.1 ml Bu_4NBr, 0.1 mmol	[bmim][$MeSO_3$]	55	2.5	0	96	0

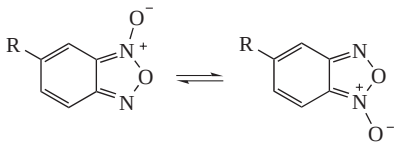
[a] Reaction conditions: 1 mmol of compound **1a** and 1 mmol of NaN_3 in 2 ml of IL indicated. [b] [bmpyrr] is 1-butyl-1-methylpyrrolidinium, [empyrr] is 1-ethyl-1-methylpyrrolidinium, [bmim] is 1-butyl-3-methylimidazolium. [c] Complicated reaction mixture was formed; compound **3a** was isolated by silica gel chromatography.

each cycle, the mixture was diluted with water, the product was filtered and the IL was extracted from water with EtOAc. Then, the IL/EtOAc solution was evaporated, next portions of 2,4-dinitrochlorobenzene and NaN_3 were added to the IL. Note that ten cycles were tested and the isolated yield was high (~95%) in each cycle.

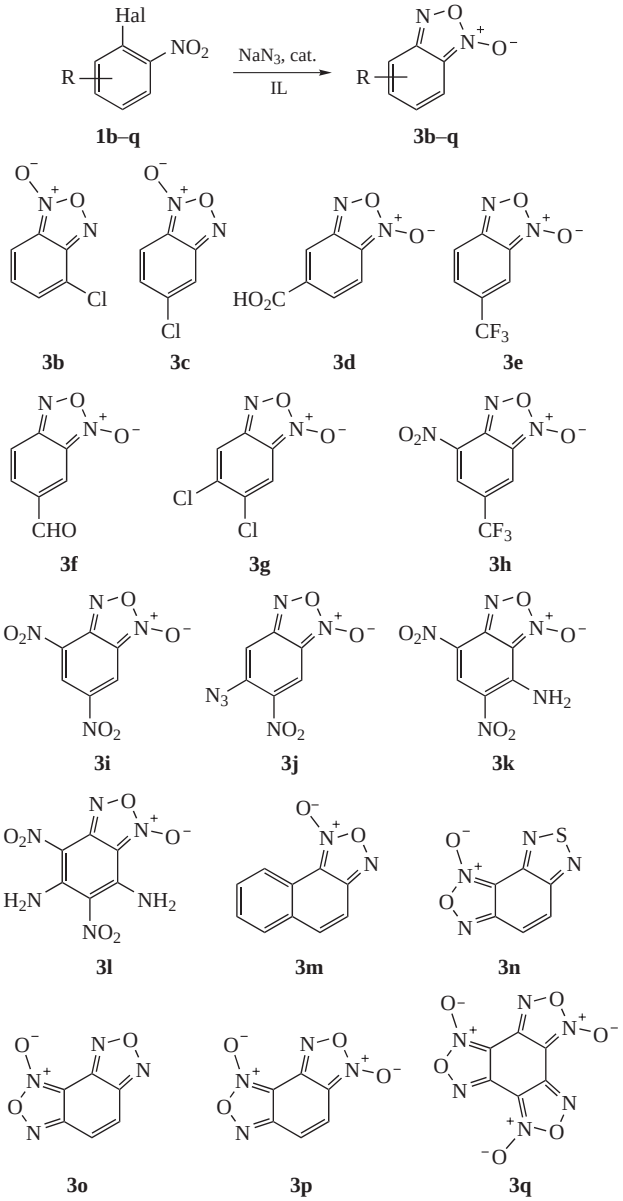
The simple procedure and the mild conditions of this one-pot synthesis provide an easy access to a wide diversity of the benzofuroxan derivatives¶ by reacting a variety of substituted *o*-nitroaryl halides and sodium azide in IL (Scheme 2, Table 2). All substrates bearing electron-withdrawing groups provide high yields of the corresponding furoxans, with the reaction rate being higher when –M effect being greater. Substrates with electron-donating groups (not shown), such as methyl, methoxy and amino, required elevated temperatures (> 150 °C) and gave poor yields of the corresponding benzofuroxans that proved to be unstable and/or inseparable from other side products. Interestingly, substrates bearing both electron-donating and electron-withdrawing groups showed good reactivity (entries 10 and 11). *o*-Nitrohalo derivatives of fused benzene cores were also tested and provided excellent yields of the products (entries 12–15). On using of 1,3,5-trichloro- or trifluoro-2,4,6-trinitrobenzene, three furoxan rings were formed (entry 16).

In conclusion, we have developed a general one-pot procedure for the synthesis of benzofuroxans from *o*-nitroaryl halide and have demonstrated the viability of ionic liquids as a solvent for the process to make it environmentally friendly. The ready availability of starting materials, combined with the high yields

¶ The possible tautomeric equilibria (*N*1- to *N*3-oxide) of benzofuroxan have been the focus of much interest for over some decades.[11] NMR evidences that, at room temperature, many benzofuroxan derivatives in solution exhibit rapid tautomeric equilibrium.



The equilibrium concentrations are dependent on the nature and position of the substituents at the ring, solvent and temperature.



Scheme 2

Table 2 Syntheses[a] of benzofuroxans from the variety of *o*-nitroaryl halides.

Entry	Product	*T*/°C	*t*/h	Yield (%)	Mp/°C
1[b]	**3b**	110	8	81	78 (lit.,[12] 78)
2[b]	**3c**	110	8	86	50 (lit.,[13] 48)
3[b]	**3d**	80	4	85	130 (lit.,[13] 130)
4[b]	**3e**	60	4	96	124 (lit.,[14] 110)
5[b]	**3f**	60	4	91	69 (lit.,[13] 69)
6[b]	**3g**	55	2	87	131 (lit.,[15] 131)
7[b]	**3h**	55	1	93	128 (lit.,[16] 127)
8[c]	**3i**	55	1	93–96	173[e] (lit.,[17] 172)
9[d]	**3j**	60	2	87	89 (lit.,[18] 90)
10[b]	**3k**	55	2	87	272 (lit.,[19] 270)
11[d]	**3l**	55	0.5	96	295[e] (lit.,[19] 292)
12[b]	**3m**	55	2	93	129 (lit.,[20] 125)
13[b]	**3n**	80	2	82	146 (lit.,[21] 175)
14[b]	**3o**	55	1	96	77 (lit.,[22] 53)
15[b]	**3p**	55	1	87	97[e] (lit.,[22] 94)
16	**3q**	55	1	~92	199[e] (lit.,[18] 195)

[a] Reaction conditions: 1 mmol of *o*-nitroaryl halide and 1 mmol of NaN_3 with 0.1 mmol Bu_4NBr in 2 ml of [empyrr][BF_4] with 5 vol% H_2O. In most cases, isolation of benzofuroxans by vacuum sublimation was satisfactory. [b] *o*-Nitroaryl chloride was used as the substrate. [c] Picryl fluoride, chloride and bromide also reacted efficiently under these conditions. [d] Fluoro substrate was the precursor. [e] Recrystallized from HNO_3.

of these reactions, make this approach highly appealing and very practical. Our conditions were designed to minimize the risk of manipulation with dangerous aryl azides often found in more traditional benzofuroxan preparations.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.03.015.

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