Synthesis of chlorofurazans from nitrofurazans

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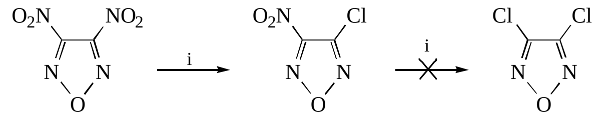
DOI: 10.1070/MC2000v010n02ABEH001250

Furazans bearing one and two chlorine atoms can be easily prepared by nucleophilic displacement of a nitro group at a furazan ring upon treatment with the Vilsmeier reagent.

Although the synthesis of simple furazan building blocks, which can be employed in the preparation of more complex derivatives, is of considerable current interest the chemistry of chlorofurazans (chloro-1,2,5-oxadiazoles) has not been adequately explored. The reported examples of this class of compounds include 3-chloro-4-phenylfurazan,[1,2] isomeric 3-chloro-4-(nitrophenyl)-furazans[3] and 3-chloro-4-(pyrid-3-yl)furazan.[4] However, these starting materials are difficult to obtain. In the context of the use of nucleophilic substitution reactions in the synthesis of furazans,[5–11] we have sought a straightforward and, if possible, general method for the synthesis of halogen derivatives.

A classical procedure for the replacement of a hydroxy group with a chlorine atom at a (hetero)aromatic ring is the treatment of a hydroxy compound by a mixture of phosphorus oxychloride with DMF (the Vilsmeier reagent) or another catalyst. This method was successfully used for the preparation of chloronitrobenzenes[12] and applied to hydroxy-1,3,4-oxadiazoles.[13,14] However, note that our attempts to prepare chlorofurazans by the treatment of available hydroxyfurazans[9,10] with the Vilsmeier reagent were unsuccessful.

We found that a nitro group at a furazan ring[15] underwent displacement by chlorine when heated with the Vilsmeier reagent.[†] A variety of chlorofurazans can be produced in moderate-to-good yields only from 3-nitro-4-R-furazans bearing an electron-withdrawing group R. Thus, when 3,4-dinitrofurazan **1**[16] was treated with the reagent at 30 °C for 24 h, 3-chloro-4-nitrofurazan **2**[‡] was obtained in 62% yield (Scheme 1) and isolated by column chromatography on silica gel, using 30% CH_2Cl_2 in pentane as an eluent. The starting furazan **1** was also recovered in 29% yield. Note that no traces of compound **3** were detected. Our attempts to improve the yield of **2** by changing the reaction time and temperature were unsuccessful. Treatment of **1** with $POCl_3$ in the absence of DMF did not afford chloro products; only the starting compound was detected.

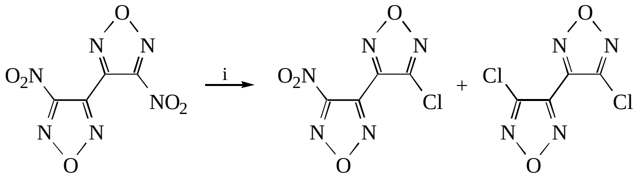


1 **2** **3**

Scheme 1 *Reagents and conditions*: i, $POCl_3$/DMF, 30–60 °C, 24–72 h.

Compound **2** is a highly volatile liquid soluble in all organic solvents. It can be purified by freezing from pentane at –78 °C.

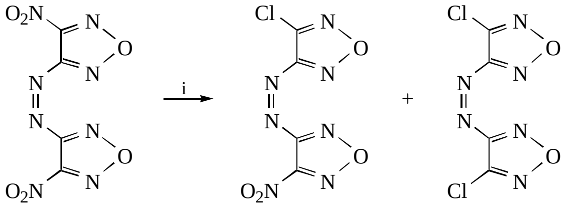
Treatment of 4,4′-dinitrobifurazan **4**[16] with the Vilsmeier reagent at 60 °C for 6 h led to the nucleophilic displacement of nitro groups to yield a mixture of starting compound **4** and chloro derivatives (Scheme 2). The mixture was chromatographed on a column to give compound **4** as the major product (74%) with small amounts of monochlorofurazan **5** (13%) and 4,4′-dichlorobifurazan **6** (2%). Compound **5** was obtained in 37% yield by a similar reaction carried out in the presence of PCl_5. The same reaction gave a higher yield (45%) at 80 °C. Pure product **6** was only obtained in 3% yield by flash chromatography. The low yield is probably due to a substantial loss of volatile compound **6** (evaporation of **6** with CH_2Cl_2 was observed) in the course of separation.



4 **5** **6**

Scheme 2 *Reagents and conditions*: i, $POCl_3$/PCl_5/DMF, 80 °C, 6 h.

When a mixture of 4,4′-dinitroazofurazan **7**[16] and the Vilsmeier reagent with an excess of $POCl_3$ was heated at 80 °C for 6 h, halofurazans **8** and **9** in a ratio of 2 : 1, respectively, were the only products isolated (89%) (Scheme 3). Monochloro and dichloro compounds **8** and **9** were then separated and purified by chromatography on silica gel. The same reaction in the presence of three equivalents of PCl_5 gave 4,4′-dichloroazofurazan **9** as the sole product in 84% yield.



7 **8** **9**

Scheme 3 *Reagents and conditions*: i, $POCl_3$/DMF, 80 °C, 6 h.

The nucleophilic substitution reactions in 4,4′-dinitroazoxyfurazan **10**[16] proceed at the carbon atom bonded to the nitro group proximate to the *N*-oxide of the azoxy group and at the carbon atom bonded to the N(O) atom of the azoxy group.[11] Indeed, treatment of compound **10** with the Vilsmeier reagent

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[†] *General procedure.* Dimethylformamide (0.02 mol for one nitro group) was added dropwise to a solution of a nitrofurazan (0.01 mol) in $POCl_3$ (15 ml). The reaction mixture was heated with stirring for 6–24 h. After cooling, the mixture was poured into ice water and extracted with pentane–CH_2Cl_2. The extracts were washed with water and dried. The crude products were separated by chromatography.

[‡] All chloro compounds gave satisfactory elemental analyses and mass spectra. The structures were also confirmed by IR and NMR spectroscopy.

For **2**: oil, R_f 0.79 (pentane–CH_2Cl_2, 1:1). ^{13}C NMR ($CDCl_3$) δ: 141.9 (C–Cl), 157.2 (C–NO_2). ^{14}N NMR ($CDCl_3$) δ: –45.5 (NO_2, $\Delta\nu_{1/2}$ 10 Hz). IR (ν/cm^{-1}): 1570, 1330 (NO_2), 1610, 1180, 860 (furazan ring). MS, *m/z*: 151, 149 (M^+), 105, 103 ($M^+ - NO_2$), 75, 73, 68.

For **5**: oil. ^{13}C NMR ($CDCl_3$) δ: 137.2 (*C*–CNO_2), 140.5 (C–Cl), 146.2 (*C*–CCl), 158.7 (C–NO_2). ^{14}N NMR ($CDCl_3$) δ: –40.0 (NO_2, $\Delta\nu_{1/2}$ 7 Hz). MS, *m/z*: 218, 216 (M^+).

For **6**: mp 59–61 °C. MS, *m/z*: 208, 206, 204 (M^+).

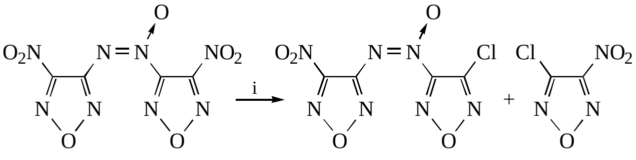
For **8**: oil. ^{13}C NMR ($CDCl_3$) δ: 136.5 (C–Cl), 148.8 (C–NO_2), 151.4, 154.9. ^{14}N NMR ($CDCl_3$) δ: –39.0 (NO_2, $\Delta\nu_{1/2}$ 9.5 Hz). IR (ν/cm^{-1}): 1540, 1360 (NO_2). MS, *m/z*: 247, 245 (M^+).

For **9**: mp 25–26 °C. ^{13}C NMR ($CDCl_3$) δ: 139.7 (C–Cl), 158.5. MS, *m/z*: 234, 235, 236 (M^+).

For **11**: mp 26–27 °C. ^{13}C NMR ($CDCl_3$) δ: 142.1 (C–Cl), 148.0 (*C*–CNO_2), 155.0 (C–NO_2), 156.1 [CN(O)N]. ^{14}N NMR ($CDCl_3$) δ: –38.4 (NO_2, $\Delta\nu_{1/2}$ 13 Hz), –65.2 (N→O, $\Delta\nu_{1/2}$ 28 Hz). IR (ν/cm^{-1}): 1550, 1350 (NO_2), 1580, 1170, 1105, 915, 870 (furazan ring). MS, *m/z*: 263, 261 (M^+).

For **13**: mp 55–56 °C. MS, *m/z*: 185 (M^+), 139 ($M^+ - NO_2$).

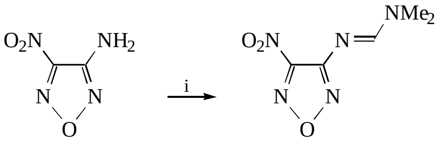
in the above manner afforded 4-chloro-4′-nitroazoxyfurazan **11**§ and 3-chloro-4-nitrofurazan **2**, which resulted from the nucleophilic displacement of an azoxyfurazanyl moiety (Scheme 4), in ~50% yields. The reaction mixture contained none dichloro derivatives such as 4,4′-dichloroazoxyfurazan¶ and 3,4-dichlorofurazan **3**.



10 **11** **2**

Scheme 4 *Reagents and conditions*: i, $POCl_3$/DMF, 80 °C, 6 h.

3-Methyl-4-nitrofurazan remained unaffected under treatment with the Vilsmeier reagent in an excess of $POCl_3$ at 80 °C for 36 h. Under similar conditions, the nitro group of 3-amino-4-nitrofurazan **12** was also unchanged; at the same time, the amino group was transformed to a formamidine moiety (as was observed in nitroanilines[12]) to give compound **13** in quantitative yield (Scheme 5).



12 **13**

Scheme 5 *Reagents and conditions*: i, $POCl_3$/DMF, 80 °C, 6 h.

In conclusion, a simple method for chlorofurazan synthesis has been developed. As a result, key precursors such as 3-chloro-4-nitrofurazan, 4-chloro-4′-nitrobifurazan and 4,4′-dichloroazofurazan can be easily prepared.

This work was supported by the Russian Foundation for Basic Research (grant no. 98-03-33024a).

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§ The identification of the *N*-oxide position was made using selective ^{13}C–{^{14}N} double heteronuclear resonance and by comparison with the published data.[7]

¶ 4,4′-Dichloroazoxyfurazan was prepared by oxidation of azo compound **9** with Caro's acid in 67% yield, mp 75–77 °C.

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Received: 15th December 1999; Com. 99/1576