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Electrophilic Amination of 4-Fluorophenol with Diazenes: A Complete Removal of the Fluorine Atom†

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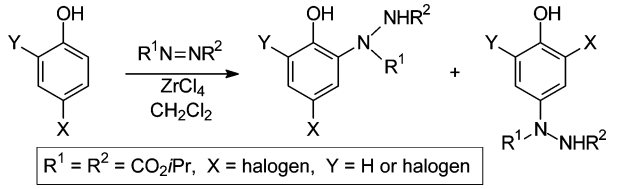
Abstract: The electrophilic amination of 2-fluorophenol, 4-fluorophenol, and 2-chlorophenol was observed to occur as a result of their treatment with diazenes **1**−**4** under mild reaction conditions in the presence of $ZrCl_4$. The products originating from the 2-fluorophenol or 2-chlorophenol can be considered as "normal" products of amination. On the other hand, the 2-chloro-4-amino-substituted phenols obtained from the 4-fluorophenol seem to be formed in a process that involves an *ipso* amination, the complete removal of the fluorine atom, and the introduction of the chlorine atom.

It has been known for 50 years that a halogen atom on the thiophene ring can migrate in the presence of a strong base.[1] A similar observation was reported for the case of halogenated benzenes by Wotiz and Huba.[2] This transformation, also known as the "halogen dance", was later thoroughly investigated by several groups.[3−6] In contrast, acid-promoted halogen migration rarely occurs with aromatic molecules and is limited to bromine[7] and iodine.[8] As a part of our continuing interest in hydrazides[9] and other N−N-containing compounds,[10] we recently reported on the electrophilic amination of 4-halophenols and 2,4-dihalophenols with diisopropyl diazenedicarboxylate in the presence of $ZrCl_4$ as a Lewis acid. In several cases, the reactions led to a mixture of two products that were aminated either at the *ortho* or at the *para* position, with respect to the phenolic OH (Scheme 1).[11] The formation of products bearing the corresponding hydrazino functionality at position 4 indicated that the

SCHEME 1



† Dedicated to Professor Sándor Antus, University of Debrecen, on the occasion of his 60th birthday.

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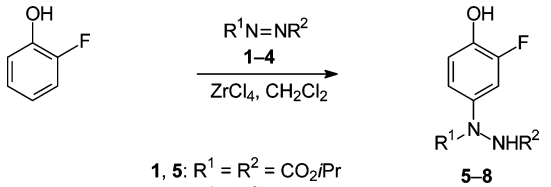
TABLE 1. Electrophilic Amination of 2-Fluorophenol

entry	diazene	time[a] (h)	*T* (°C)	product(s) (yield, %)[b]
1	**1**	4	−62	**5** (83)
2	**2**	4	−62	**6** (89)
3	**3**	4	−62	**7** (86)
4	**4**	6 + 15[c]	−45, rt	**8a** (34)[d] and **8b** (36)[d]

[a] The reactions were performed in CH_2Cl_2, under argon. [b] Isolated yields are given. [c] Reaction mixture was stirred for 6 h at −45 °C, followed by 15 h at rt. [d] Purified by radial chromatography using petroleum ether−ethyl acetate (5:3).

SCHEME 2



1, **5**: $R^1 = R^2 = CO_2iPr$
2, **6**: $R^1 = R^2 = CO_2Et$
3, **7**: $R^1 = R^2 = CO_2Allyl$
4, **8a**: $R^1 = Cl(CH_2)_2NHCO$, $R^2 = CO_2Me$
8b: $R^1 = MeO_2C$, $R^2 = CONH(CH_2)_2Cl$

amination was accompanied by a halogen substitution. We found that the fluorine, the chlorine, the bromine, or the iodine atom migrated under mild reaction conditions. This type of halogen displacement during an electrophilic amination has not been described previously, although the reactions of haloarenes with dialkyl diazenedicarboxylates are well documented.[12]

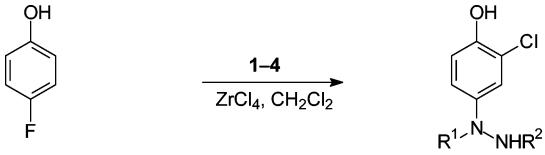
The migration of fluorine on organic substrates has been observed only rarely and has involved the use of high energy intermediates or excited molecules.[13] Soon after our report,[11] Avent and Taylor published a unique 1,3-shift of fluorine on fullerene $C_{60}F_{36}$ at room temperature.[14] In this paper, we present new results related to fluorine removal that will provide some evidence for a plausible reaction pathway. Three halophenols (2-fluorophenol, 4-fluorophenol, and 2-chlorophenol) were used in this study. When electrophilic aromatic substitution is performed on these substrates, the new group is directed primarily to the *para* position, with respect to the phenolic OH, in 2-fluorophenol or 2-chlorophenol, and to the *ortho* position, with respect to the phenolic OH, in 4-fluorophenol.[15] Thus, the amination of 2-fluorophenol with dialkyl diazenedicarboxylates **1**−**3** in the presence of $ZrCl_4$ resulted in the formation of 4-substituted 2-fluorophenols **5**−**7** with high yields (Scheme 2, Table 1, entries 1−3). The reaction is not regioselective in regard to the aminating agent, as shown by the application of an unsymmetrical diazene, namely the diazenecarboxamide **4**, where we isolated regioisomers **8a** and **8b**. It is possible to differentiate between them on the basis of their mass spectra, as we described previously for similar trisubstituted semicarbazides.[16]

TABLE 2. Electrophilic Amination of 4-Fluorophenol and 2-Chlorophenol

entry	phenol	diazene	time[a] (h)	*T* (°C)	product(s) (yield, %)[b]
1	4-F[c]	**1**	4	−65	**9** (66)
2	4-F	**2**	4	−62	**10** (60)
3	4-F	**3**	4	−62	**11** (41)
4	4-F	**4**	6 + 18[d]	−15, rt	**12a** (58) and **12b** (29)
5	2-Cl[e]	**1**	1.5	−42	**9** (89)
6	2-Cl	**2**	4	−62	**10** (95)
7	2-Cl	**3**	4	−62	**11** (78%
8	2-Cl	**4**	6 + 18[f]	−45, rt	**12a** (36) and **12b** (40)

[a] The reactions were performed in CH_2Cl_2, under argon. [b] Yields obtained after radial chromatography using petroleum ether−ethyl acetate (5:3) are given. [c] 4-F: 4-fluorophenol. [d] Reaction mixture was stirred for 6 h at −15 °C, followed by 18 h at rt. [e] 2-Cl: 2-chlorophenol. [f] Reaction mixture was stirred for 6 h at −45 °C, followed by 18 h at rt.

SCHEME 3



9: $R^1 = R^2 = CO_2iPr$
10: $R^1 = R^2 = CO_2Et$
11: $R^1 = R^2 = CO_2Allyl$
12a: $R^1 = Cl(CH_2)_2NHCO$, $R^2 = CO_2Me$
12b: $R^1 = MeO_2C$, $R^2 = CONH(CH_2)_2Cl$

The electrophilic amination of 4-fluorophenol with the diazenes **1**−**4** in the presence of $ZrCl_4$ led to 4-aminated 2-chlorophenols **9**−**12** (Scheme 3, Table 2, entries 1−4). Diazene **4** that reacted through either of the electrophilic nitrogens to give the compounds **12a** and **12b** displayed a certain level of regioselectivity (**12a**/**12b** = 2:1). The products **9**−**12** obviously originated from 4-fluorophenol in a process that included fluorine substitution, followed by the introduction of a chlorine atom. The same products, i.e., phenol derivatives **9**−**12**, were also prepared by a "normal" electrophilic amination from 2-chlorophenol and diazenes **1**−**4** (Table 2, entries 5−8).[17]

To get a better insight into the amination process that involved the removal of the fluorine atom we performed several additional experiments. These experiments showed

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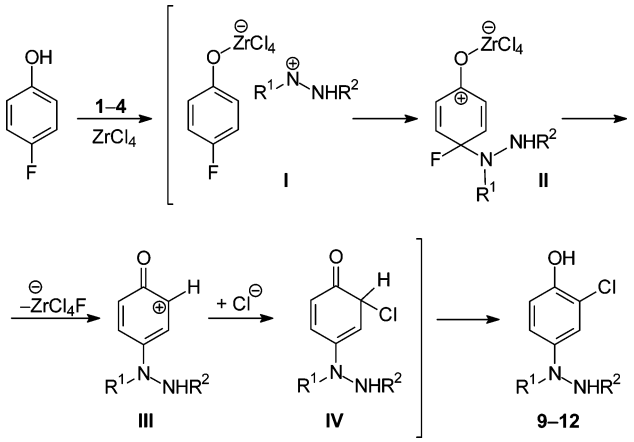
(17) The reaction yields of 4-fluorophenol with dialkyl diazenedicarboxylates **1**−**3** are lower than those of 2-chlorophenol with the same diazenes. In the case of 2-chlorophenol, the reactions are typical electrophilic aromatic substitutions while 4-fluorophenol follows the reaction pathway proposed in Scheme 4. After radial chromatography of the reaction mixtures, obtained from 4-fluorophenol and dialkyl diazenedicarboxylates, a certain amount of an unidentified dark residue (tar) remains at the baseline (sample line) of the silica gel plate. This is the reason for lower yields of products **9**−**11** (Table 2, entries 1−3), prepared from 4-fluorophenol, compared to the yields of the same products that were synthesized from 2-chlorophenol (Table 2, entries 5−7).

SCHEME 4



the following: (i) 4-fluorophenol did not react with $ZrCl_4$ in the absence of diazenes **1**−**4**; (ii) 4-aminated 2-fluorophenols **5**−**8** remained unchanged after being treated with $ZrCl_4$ in CH_2Cl_2 at temperatures and times required for the synthesis of **9**−**12** from 4-fluorophenol and diazenes **1**−**4** in the presence of $ZrCl_4$. The above results allow us to conclude that the substitution of the fluorine atom did not take place either before or after the amination; rather, it took place during this process.

A plausible reaction pathway that would lead from 4-fluorophenol and diazenes **1**−**4** to the products **9**−**12** is proposed in Scheme 4. In the first step, we assume the formation of an ion pair intermediate **I**; similar species containing electrophilic nitrogen were recently proposed for the $ZrCl_4$-mediated intramolecular migration of the imino group of *O*-arylketoximes.[18] In the second step, an *ipso* attack[15] of the nitrogen electrophile at position 4 would give **II**. This latter intermediate could then eliminate $ZrCl_4F^-$, leading to **III**. An anion, $ZrCl_4F^-$, may serve as the source of a chloride ion, this is because the cleavage of the Zr−Cl bond is preferential to the cleavage of the Zr−F bond (bond energies: Zr−Cl, 489.5 kJ mol^{-1}; Zr−F, 646.8 kJ mol^{-1}).[19] Thus, the reaction of the chloride ion with cation **III** would lead to the dienone **IV**, a tautomer of the final product.[20] Steric factors in an ion pair intermediate **I** seem to regulate the outcome of the amination. Thus, sterically hindered electrophilic nitrogen attacks the *para* position that is occupied by a small fluorine atom, rather than by the neighboring $-OZrCl_4^-$ group hindered *ortho* position in **I**. It is in agreement with our previous results showing that a *para* attack of the electrophilic nitrogen becomes disfavored if the bulkier halogen is attached in the place of the fluorine atom. Indeed, predominantly *ortho*-aminated products are formed on reactions of 4-chloro-, 4-bromo-, and 4-iodophenol with diisopropyl diazenedicarboxylate.[11]

In conclusion, 2-fluorophenol, 4-fluorophenol, and 2-chlorophenol reacted with diazenes in $ZrCl_4$-promoted conversions that result in 4-aminated halophenols. The electrophilic amination of 4-fluorophenol with either dialkyl diazenedicarboxylates **1**−**3** or diazenecarboxamide **4**, which led to 4-aminated 2-chlorophenols, indicated that this transformation was accompanied by the removal of fluorine and the subsequent introduction of the chlorine atom. A plausible reaction pathway for the above process is proposed.

Experimental Section

Typical Procedure for the Electrophilic Amination of Halophenols Represented by Entry 2 of Table 2. A solution of diethyl diazenedicarboxylate (**2**, 175 μL, 1.1 mmol) and 4-fluorophenol (112 mg, 1 mmol) in CH_2Cl_2 (7 mL) was added dropwise to a stirred suspension of $ZrCl_4$ (260 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) at −62 °C under an argon atmosphere. After 4 h, the reaction mixture was quenched with water (5 mL) and neutralized with a saturated aqueous solution of $NaHCO_3$. The two phases were separated, and the aqueous solution was extracted with CH_2Cl_2 (4 × 10 mL). The combined extracts were then dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by radial chromatography using petroleum ether−ethyl acetate (5:3) as the eluent to give the product **10** (182.2 mg, 60% yield).

Diisopropyl 1-(3-fluoro-4-hydroxyphenyl)-1,2-hydrazinedicarboxylate[11] (5): mp 126.3−128.5 °C (*n*-heptane−diethyl ether); IR 3307, 2984, 1709, 1529, 1403, 1258, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 6.2 Hz, 6H), 1.28 (d, J = 6.2 Hz, 6H), 5.01 (m, 2H), 5.27 (s, 1H), 6.82 (s, 1H), 6.92 (m, 1H), 7.09 (m, 1H), 7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.84, 21.87, 70.4, 71.2, 112.8 (m), 117.0 (d, J = 2.6 Hz), 121.0 (m), 134.1 (d, J = 8.4 Hz), 142.5 (d, J = 13.7 Hz), 150.3 (d, J = 239.8 Hz), 154.7, 156.1; MS (EI) *m*/*z* 314 (M^+, 73), 228 (28), 186 (100), 141 (50), 61 (35). Anal. Calcd for $C_{14}H_{19}FN_2O_5$: C, 53.50; H, 6.09; N, 8.91. Found: C, 53.76; H, 5.95; N, 8.68.

Diethyl 1-(3-fluoro-4-hydroxyphenyl)-1,2-hydrazinedicarboxylate (6): mp 101−103 °C (petroleum ether−diethyl ether); IR 3229, 2988, 1720, 1682, 1526, 1259, 1069 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 4.23 (q, J = 7.1 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 5.75 (s, 1H), 6.98 (s, 1H), 6.93 (m, 1H), 7.08 (m, 1H), 7.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.29, 14.30, 62.4, 63.2, 113.2 (m), 117.0 (d, J = 2.9 Hz), 121.4 (m), 134.0 (d, J = 8.2 Hz), 142.7 (d, J = 15.5 Hz), 150.3 (d, J = 240.2 Hz), 155.2, 156.4; MS (EI) *m*/*z* 286 (M^+, 45), 214 (96), 141 (100); HRMS calcd for $C_{12}H_{15}FN_2O_5$ 286.0965, found 286.0972. Anal. Calcd for $C_{12}H_{15}FN_2O_5$: C, 50.35; H, 5.28; N, 9.79. Found: C, 50.11; H, 5.67; N, 9.98.

Diallyl 1-(3-fluoro-4-hydroxyphenyl)-1,2-hydrazinedicarboxylate (7): oil; IR 3296, 1707, 1519, 1448, 1391, 1323, 1279, 1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.67 (m, 4H), 5.19−5.38 (m, 5H), 5.90 (m, 2H), 6.90−7.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 66.8, 67.5, 113.4 (m), 117.1 (d, J = 2.9 Hz), 118.2, 118.5, 121.5 (m), 131.5, 131.6, 133.6 (d, J = 8.3 Hz), 143.0 (d, J = 10.9 Hz), 150.3 (d, J = 240.6 Hz), 155.0, 156.1; MS (EI) *m*/*z* 310 (M^+, 37), 225 (88), 181 (75), 111 (100); HRMS calcd for $C_{14}H_{15}FN_2O_5$ 310.0965, found 310.0970. Anal. Calcd for $C_{14}H_{15}FN_2O_5$: C, 54.19; H, 4.87; N 9.03. Found: C, 54.13; H, 5.01; N, 9.12.

Methyl 2-[(2-chloroethyl)aminocarbonyl]-2-(3-fluoro-4-hydroxyphenyl)hydrazinecarboxylate (8a): mp 192−194.5 °C (chloroform−methanol); IR 3379, 3292, 1728, 1650, 1542, 1514, 1443, 1373, 1254 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.33 (m, 2H), 3.59 (m, 2H), 3.61 (s, 3H), 6.90 (m, 2H), 7.13 (dd, J_1 = 12.8 Hz, J_2 = 2.5 Hz, 1H), 7.23 (broad s, 1H), 9.75 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 42.0, 43.1, 52.2, 112.6 (m), 116.9 (d, J = 2.9 Hz), 120.4 (m), 134.1 (d, J = 8.0 Hz), 142.4 (d, J = 12.1 Hz), 149.9 (d, J = 240.2 Hz), 155.9, 156.0; MS (EI) *m*/*z* 305 (M^+, 3), 231 (2), 200 (100), 141 (62), 125 (37); HRMS (FAB) calcd for

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(20) The products **5**−**12** cannot be isolated from the reaction mixture prior to treatment with water. The reason seems to be the formation of 1:1 complex between the product and zirconium halide ($ZrCl_4$ or $ZrCl_3F$). This is also in agreement with the fact that an equimolar amount of $ZrCl_4$ is always required for amination. All attempts to isolate and characterized the above-mentioned complex from a gummy-like material that was insoluble in CH_2Cl_2 failed. The product is easily isolated after treatment of the reaction mixture with water. Under these conditions the hydrolysis of zirconium halide ($ZrCl_4$ or $ZrCl_3F$) takes place.

$C_{11}H_{13}ClFN_3O_4$ 305.0579, found 305.0583. Anal. Calcd for $C_{11}H_{13}ClFN_3O_4$: C, 43.22; H, 4.29; N 13.75. Found: C, 43.32; H, 4.41; N, 13.49.

Methyl 2-[(2-chloroethyl)aminocarbonyl]-1-(3-fluoro-4-hydroxyphenyl)hydrazinecarboxylate (8b): mp 142−145 °C (chloroform−methanol); IR 3316, 1694, 1644, 1584, 1526, 1457, 1379, 1321, 1239, 1109 m^{-1}; ^1H NMR (DMSO-d_6) δ 3.35 (t, J = 6.3 Hz, 2H), 3.58 (t, J = 6.3 Hz, 2H), 3.65 (s, 3H), 6.89 (m, 2H), 7.05 (m, 1H), 7.23 (m, 1H), 8.78 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 41.4, 43.7, 53.2, 112.7 (m), 116.8 (d, J = 3.6 Hz), 120.6 (m), 134.3 (d, J = 7.9 Hz), 142.9 (d, J = 12.7 Hz), 149.8 (d, J = 240.4 Hz), 155.4, 157.1; MS (EI) m/z 305 (M^+, 10), 200 (13), 184 (14), 57 (100). Anal. Calcd for $C_{11}H_{13}ClFN_3O_4$: C, 43.22; H, 4.29; N, 13.75. Found: C, 43.01; H, 4.21; N, 13.49.

Diisopropyl 1-(3-chloro-4-hydroxyphenyl)-1,2-hydrazinedicarboxylate[11] **(9):** mp 120.8−122.3 °C (*n*-heptane−diethyl ether); IR 3295, 2984, 1707, 1518, 1431, 1291, 1272, 1108 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.2 Hz, 6H), 1.28 (d, J = 6.2 Hz, 6H), 5.00 (m, 2H), 5.69 (s, 1H), 6.86 (s, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.24 (broad d, J = 8.7 Hz, 1H), 7.44 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.88, 21.92, 70.3, 71.2, 115.9, 119.5, 125.0, 125.7, 135.0, 150.1, 154.6, 156.0; MS (EI) m/z 330 (M^+, 47), 244 (32), 202 (100), 157 (71), 141 (30). Anal. Calcd for $C_{14}H_{19}ClN_2O_5$: C, 50.84; H, 5.79; N, 8.47. Found: C, 50.76; H, 5.94; N, 8.40.

Diethyl 1-(3-chloro-4-hydroxyphenyl)-1,2-hydrazinedicarboxylate (10): mp 83−86 °C (petroleum ether−diethyl ether); IR 3292, 2986, 1713, 1514, 1429, 1381, 1287, 1250, 1055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 4.23 (q, J = 7.1 Hz, 2H), 4.24 (q, J = 7.1 Hz, 2H), 5.62 (s, 1H), 6.94 (s, 1H), 6.97 (d, J = 8.9 Hz, 1H), 7.25 (dd, J_1 = 8.9 Hz, J_2 = 2.5 Hz, 1H), 7.45 (d, J = 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.25, 14.26, 62.4, 63.2, 116.0, 119.6, 125.3, 126.3, 134.5, 150.6, 155.2, 156.4; MS (EI) m/z 302 (M^+, 33), 230 (60), 157 (100); HRMS calcd for $C_{12}H_{15}ClN_2O_5$ 302.0669, found 302.0672. Anal. Calcd for $C_{12}H_{15}ClN_2O_5$: C, 47.67; H, 5.00; N, 9.27. Found: C, 47.54; H, 5.32; N 9.58.

Diallyl 1-(3-chloro-4-hydroxyphenyl)-1,2-hydrazinedicarboxylate (11): oil; IR (NaCl) 3295, 2952, 1708, 1497, 1423, 1389, 1329, 1281, 1238, 1057 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.67 (m, 4H), 5.18−5.40 (m, 4H), 5.64 (s, 1H), 5.90 (m, 2H), 6.97 (d, J = 8.9 Hz, 1H), 7.07 (s, 1H), 7.25 (m, J = 1 Hz), 7.45 (broad s, 1H); ^{13}C NMR ($CDCl_3$) δ 66.7, 67.4, 116.1, 118.1, 118.4, 119.7, 125.4, 126.5, 131.4, 131.6, 134.2, 150.8, 155.0, 156.0; MS (EI) m/z 326 (M^+, 90), 241 (100), 197 (69), 127 (28); HRMS calcd for $C_{14}H_{15}ClN_2O_5$ 326.0669, found 326.0671. Anal. Calcd for $C_{14}H_{15}ClN_2O_5$: C, 51.46; H, 4.63; N, 8.57. Found: C, 51.59; H, 4.89; N, 8.69.

Methyl 2-[(2-chloroethyl)aminocarbonyl]-2-(3-chloro-4-hydroxyphenyl)hydrazinecarboxylate (12a): mp 167−170 °C (diethyl ether−ethyl acetate); IR 3392, 3242, 1741, 1665, 1624, 1542, 1510, 1285, 1256, 1058 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.37 (m, 2H), 3.59 (m, 5H), 6.90 (d, J = 8.8 Hz, 1H), 7.10 (dd, J_1 = 8.8 Hz, J_2 = 2.6 Hz, 1H), 7.24 (broad t, 1H), 7.32 (d, J = 2.6 Hz, 1H), 9.87 (s, 1H), 10.10 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 42.0, 43.2, 52.2, 116.0, 118.7, 124.5, 126.2, 134.6, 150.8, 155.9, 156.0; MS (EI) m/z 321 (M^+, 20), 285 (4), 216 (100), 157 (61). Anal. Calcd for $C_{11}H_{13}Cl_2N_3O_4$: C, 41.01; H, 4.07; N, 13.04. Found: C, 40.85; H, 4.26; N 12.99.

Methyl 2-[(2-chloroethyl)aminocarbonyl]-1-(3-chloro-4-hydroxyphenyl)hydrazinecarboxylate (12b): mp 124−127 °C (*n*-heptane−ethyl acetate); IR 3312, 1693, 1643, 1582, 1516, 1450, 1379, 1254, 1221, 1061 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.35 (m, 2H), 3.58 (t, J = 6.3 Hz, 2H), 3.64 (s, 3H), 6.90 (s, 1H), 6.91 (d, J = 8.7 Hz, 1H), 7.20 (dd, J_1 = 8.7 Hz, J_2 = 2.6 Hz, 1H), 7.42 (broad s, 1H), 8.80 (s, 1H), 10.19 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 41.4, 43.7, 53.2, 115.9, 118.7, 124.5, 126.4, 134.8, 151.3, 155.4, 157.1; MS (EI) m/z 321 (M^+, 4), 285 (5), 216 (93), 157 (100); HRMS calcd for $C_{11}H_{13}Cl_2N_3O_4$ 321.0283, found 321.0290. Anal. Calcd for $C_{11}H_{13}Cl_2N_3O_4$: C, 41.01; H, 4.07; N, 13.04. Found: C, 41.27; H, 4.14; N 12.88.

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Supporting Information Available: General Experimental Section; synthesis and characterization data of the diazene **4** and its precursor (the corresponding hydrazinecarboxylate). This material is available free of charge via the Internet at http://pubs.acs.org.

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