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Superelectrophilic heterocycles: facile S_NAr–S_EAr couplings involving very weak carbon nucleophiles

Sergey Kurbatov, Pedro Rodriguez-Dafonte, Régis Goumont and François Terrier*
Laboratoire SIRCOB, UMR 8086, Institut Lavoisier-Franklin, University of Versailles, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France. E-mail: terrier@chimie.uvsq.fr

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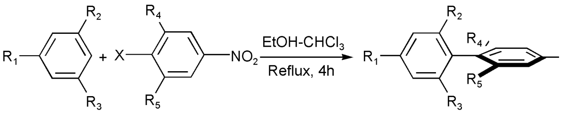
Superelectrophilic halonitro-2,1,3-benzoxadiazoles undergo remarkably facile carbon–carbon couplings with some electron-rich aromatics and heteroaromatics, affording quantitatively products exhibiting an intense visible absorption due to strong intramolecular charge transfer.

Countless examples have been reported where a S_NAr pathway plays a pivotal role in the displacement of a potential leaving group of an electron-deficient aromatic or heteroaromatic substrate by anionic as well as neutral oxygen, sulfur and nitrogen nucleophiles.[1] A number of books and reviews have discussed the synthetic applicability of this mechanism, both in inter- and intra- molecular nucleophilic aromatic substitutions.[1a,d,2] Even though a few S_NAr carbon–carbon couplings have been reported, the evidence is that this mechanism does not apply satisfactorily well with most carbon nucleophiles.[1a] A major factor responsible for this situation is the notable tendency of many carbanions to oxidise, thereby favoring the occurrence of electron-transfer processes. As a result, other strategies have been developed, such as the vicarious and oxidative nucleophilic aromatic substitutions, which allow C–C bond formation at an initially unsubstituted position of an electron-deficient arene or hetarene ring.[3–5]



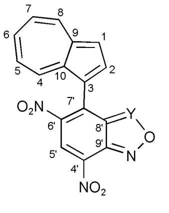
(1)

R_1 , R_2 ,R_3 = NMe_2, piperidino, morpholino, pyrrolidino
R_4, R_5 = NO_2, CO_2Me, H, CN; X= Cl, F

Among the few known S_NAr substitutions involving neutral carbon nucleophiles, the reactions depicted in eqn. 1 are noteworthy since they describe a convenient synthesis of donor–acceptor substituted biphenyls *via* substitution of nitroactivated haloarenes, *e.g.* picryl chloride, by electron-rich aminobenzenes.[6a] In these instances, it is the high carbon nucleophilicity of these substrates – the $\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ value for *C*-protonation of the benzene ring in aqueous solution is 9.62 for 1,3,5-tripyrrolidinobenzene[6b] – that provides the decisive driving force for the substitutions.

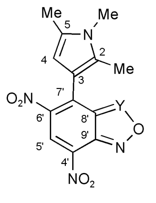
In this paper, we report on our finding that the high electrophilic character of 7-chloro-4,6-dinitro-benzofurazan (DNBZ-Cl) and -benzofuroxan (DNBF-Cl) allows the achievement of remarkably facile S_NAr-type displacements of the chlorine atom by very weak carbon nucleophiles. The reactions of DNBZ-Cl and DNBF-Cl with *N*-methylindole 1 ($\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ = −2.32),[7a] azulene 2 ($\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ = −1.76)[7b] and 1,2,5-trimethylpyrrole 3 ($\mathrm{p}K_\mathrm{a}^\mathrm{CH}$ = −0.49)[7c] have thus been found to proceed smoothly at room temperature in ethanol, affording the expected substitution products S-1a,b, S-2a,b and S-3a,b in excellent yields.† Interestingly, these compounds can also be viewed as being formally the products of S_EAr substitution of the azulene or hetarene moiety of the nucleophiles by the electrophilic DNBZ-Cl and DNBF-Cl substrates.

A most reasonable mechanism for the substitutions is the S_NAr–S_EAr coupling pathway described in Scheme 1 with reference to the *N*-methylindole systems. In this scheme, it is assumed that the initial formation of the zwitterionic Wheland–Meisenheimer intermediates $ZH^\pm$ is followed by rearomatization of the arenonium or hetarenium moiety to give the anionic σ-complexes Z^-, a situation which was shown to prevail in the S_EAr substitutions of a number of indoles or pyrroles by 4,6-dinitrobenzofuroxan (DNBF) to give stable σ-adducts of type 4 in various solvents. Facile loss of chloride ion ($\mathrm{p}K_\mathrm{a}$ = −7) from the adducts Z^- will then afford the substitution products.[8]

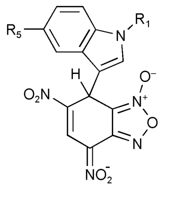


S-2a
S-2b

Y=N
Y=N⁺-O⁻



S-3a
S-3b



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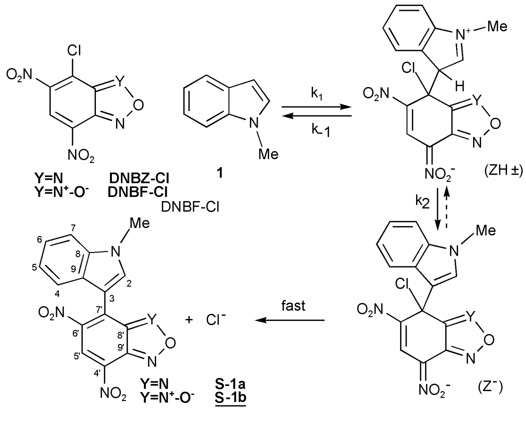
$$k_{\mathrm{obs}} = \frac{k_1k_2}{k_{-1}+k_2}[\mathrm{Nu}] = k[\mathrm{Nu}] \qquad (2)$$

A kinetic study of the reactions has been carried out at 25 °C under pseudo-first-order conditions with respect to the nucleophilic reagent (Nu = 1, 2 or 3) as the excess component in acetonitrile solution. The general expression for the observed rate constant for formation of the products, k_{obs}, as derived from Scheme 1 under the assumption that the zwitterions $ZH^\pm$ are low-concentration intermediates, is given by eqn. 2. In accordance with this equation, excellent straight lines with zero intercepts were obtained in all systems on plotting k_{obs} *vs* the Nu concentration. From the slopes of these plots, the second-order rate constants *k* listed in Table 1 were readily derived. Very importantly, experiments carried out with deuterated nucleophiles, *e.g.* 3-D-*N*-methylindole, did not reveal any significant influence of the nature of the isotopic substitution on the rates of the reactions, *e.g.* k^H/k^D = 1.1 ± 0.1 for the *N*-methylindole reactions. This shows that proton removal from $ZH^\pm$ is rapid and



Scheme 1

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Table 1 Second-order rate constants, k_1, for nucleophilic addition of *N*-methylindole 1, azulene 2 and 1,2,5-trimethylpyrrole 3 to DNBZ-Cl, DNBF-Cl and DNBF in acetonitrile. $T = 25$ °C

	$k = k_1$, mol^{-1} dm^3 s^{-1}			
Nu	pK_a^{Nu}	DNBZ-Cl	DNBF-Cl	DNBF
1	−2.32	1.15	1.02	19.6
2	−1.76	0.56	0.50	5.88
3	−0.49	3.45	9.64	910

that nucleophile addition is the actual rate-limiting step of the substitutions in acetonitrile solution, *i.e.* $k = k_1$.

Consistent with this conclusion, the rate constants k_1 for addition of 1–3 to the chlorine-bearing C-7 carbon of DNBF-Cl are notably lower than those for addition of these nucleophiles to the unsubstituted *C*-7 carbon of DNBF (Table 1).[9] Other structural things being equal, it is a general situation that nucleophilic addition occurs faster at an unsubstituted than a substituted carbon in nucleophilic aromatic substitutions and related σ-complexation processes.[1] More data are needed, however, to delineate the reasons why the present k_1 values for DNBF-Cl and DNBZ-Cl reactions do not parallel the *C*-basicity of the three nucleophiles.

A most important result is that the various products obtained through Scheme 1 exhibit an intense and solvent dependent visible absorption at rather high wavelengths, *e.g.* $\lambda_{max} = 664$ nm (H_2O), $\lambda_{max} = 624$ nm (Me_2SO) and $\lambda_{max} = 609$ nm (heptane) for S-2b. Obviously, a strong intramolecular charge transfer is taking place between the π-system of the aromatic or heteroaromatic donor and the π-system of the benzofurazan or benzofuroxan acceptor, even though the coplanarity of these two moieties is totally precluded by steric effects. Some NMR data provide a suitable illustration of this charge transfer, *e.g.* the H_2 resonance of the indole ring moves strongly to higher frequency on going from the parent substrate 1 ($\delta = 7.09$ ppm) to S-1a ($\delta = 8.30$) or S-1b ($\delta = 7.78$) in $CDCl_3$. In view of these preliminary results, further experimental and theoretical work is currently being carried out to get a better picture of how the extent of the charge transfer is in this series modulated by steric and electronic effects and therefore by the structure and the π-excessive character of the donor system.

Notes and references

† *General procedure*: To a solution of **1**, **2** or **3** (0.2 g,) in EtOH (20 ml) at room temperature was added one equivalent of DNBZ-Cl or DNBF-Cl.[10] The solution turned rapidly green and the reaction mixture was stirred at room temperature for one hour. The precipitate was collected by filtration and then purified by column chromatography (SiO_2–CH_2Cl_2).

S-1a. Dark green solid; yield 86%; mp 248 °C dec.; EI MS: *m*/*z* 339 $[M]^{+\cdot}$, anal. calc. for $C_{15}H_9N_5O_5$: C, 53.10; H, 2.67; N, 20.64. Found: C, 52.98; H, 2.59; N, 20.82%. ^1H NMR ($CDCl_3$, δ): 9.06 (1H, $H_{5'}$, s), 8.30 (1H, H_2, s), 7.51 (1H, H_7, d, $^3J_{7/6}$ 8.1 Hz), 7.43 (1H, H_5, ddd, $^3J_{5/4}$ 8.1 Hz, $^3J_{5/6}$ 8.1, $^4J_{5/7}$ 1.1 Hz), 7.34 (1H, H_6, ddd, $^3J_{6/5}$ 8.1, $^3J_{6/7}$ 8.1, $^4J_{6/4}$ 1.1 Hz), 7.19 (1H, H_4, d, $^3J_{4/5}$ 8.1 Hz), 4.04 (3H, CH_3, s).

S-2a. Dark blue solid; yield 72%; mp 197 °C dec.; EI MS: *m*/*z* 336 $[M]^{+\cdot}$, anal. calc. for $C_{16}H_8N_4O_5$: C, 57.15; H, 2.40; N, 16.66. Found: C, 57.38; H, 2.36; N, 16.38%. ^1H NMR ($CDCl_3$, δ): 9.07 (1H, $H_{5'}$, s), 8.58 (1H, H_4, d, $^3J_{4/5}$ 9.6 Hz), 8.37 (1H, H_2, d, $^3J_{2/1}$ 4.4 Hz), 8.22 (1H, H_8, d, $^3J_{8/7}$ 9.8 Hz), 7.91 (1H, H_6, dd, $^3J_{6/5}$ 9.9, $^3J_{6/7}$ 9.9 Hz), 7.63 (1H, H_1, d, $^3J_{1/2}$ 4.4 Hz), 7.62 (1H, H_5, dd, $^3J_{5/6}$ 9.9, $^3J_{5/4}$ 9.6 Hz), 7.53 (1H, H_7, dd, $^3J_{7/6}$ 9.9, $^3J_{7/8}$ 9.8 Hz).

S-3a. Dark green solid; yield 87%; mp 187 °C dec.; EI MS: *m*/*z* 317 $[M]^{+\cdot}$, anal. calc. for $C_{13}H_{11}N_5O_5$: C, 49.22; H, 3.49; N, 22.07. Found: C, 49.18; H, 3.57; N, 22.21%. ^1H NMR ($CDCl_3$, δ): 8.93 (1H, $H_{5'}$, s), 6.40 (1H, H_4, q, $^4J_{4/CH_3}$ 0.8 Hz), 3.52 (3H, $CH_3{}^1$, s), 2.31 (3H, $CH_3{}^5$, d, $^4J_{CH_{3/4}}$ 0.8 Hz), 2.19 (3H, $CH_3{}^2$, s).

S-1b. Dark green solid; yield 74%; mp 179 °C dec.; EI MS: *m*/*z* 355 $[M]^{+\cdot}$, 339 $[M - O]^{+\cdot}$, anal. calc. for $C_{15}H_9N_5O_6$: C, 50.71; H, 2.55; N, 19.71. Found: C, 50.80; H, 2.48; N, 19.57%. ^1H NMR ($CDCl_3$, δ): 8.89 (1H, $H_{5'}$, s), 7.78 (1H, H_2, s), 7.48 (1H, H_7, d, $^3J_{7/6}$ 7.4 Hz), 7.40 (1H, H_5, ddd, $^3J_{5/4}$ 8.1 Hz, $^3J_{5/6}$ 8.1, $^4J_{5/7}$ 1.1 Hz), 7.29 (1H, H_6, ddd, $^3J_{6/5}$ 8.1, $^3J_{6/7}$ 7.4, $^4J_{6/4}$ 1.1 Hz), 7.15 (1H, H_4, d, $^3J_{4/5}$ 8.1 Hz), 3.98 (3H, CH_3, s).

S-2b. Dark blue solid; yield 80%; mp 204 °C dec.; EI MS: *m*/*z* 352 $[M]^{+\cdot}$, 336 $[M–O]^{+\cdot}$, anal. calc. for $C_{16}H_8N_4O_6$: C, 54.56; H, 2.29; N, 15.90. Found: C, 54.87; H, 2.28; N, 15.62%. ^1H NMR ($CDCl_3$, δ): 8.89 (1H, $H_{5'}$, s), 8.54 (1H, H_4, d, $^3J_{4/5}$ 9.5 Hz), 8.00 (1H, H_8, d, $^3J_{8/7}$ 9.9 Hz), 7.96 (1H, H_2, d, $^3J_{2/1}$ 4.4 Hz), 7.88 (1H, H_6, dd, $^3J_{6/5}$ 9.6, $^3J_{6/7}$ 9.6 Hz), 7.58 (1H, H_5, dd, $^3J_{5/6}$ 9.6, $^3J_{5/4}$ 9.5 Hz), 7.56 (1H, H_1, d, $^3J_{1/2}$ 4.4 Hz), 7.48 (1H, H_7, dd, $^3J_{7/6}$ 9.6, $^3J_{7/8}$ 9.9 Hz).

S-3b. Dark green solid; yield 92%; mp 172 °C dec.; EI MS: *m*/*z* 333 $[M]^{+\cdot}$, anal. calc. for $C_{13}H_{11}N_5O_6$: C, 46.85; H, 3.33; N, 21.01. Found: C, 47.05; H, 3.36; N, 20.99%. ^1H NMR ($CDCl_3$, δ): 8.70 (1H, $H_{5'}$, s), 5.86 (1H, H_4, q, $^4J_{4/CH_3}$ 1.7 Hz), 3.48 (3H, $CH_3{}^1$, s), 2.25 (3H, $CH_3{}^5$, d, $^4J_{CH3/4}$ 1.7 Hz), 2.12 (3H, $CH_3{}^2$, s).

1 (*a*) F. Terrier, in *Nucleophilic Aromatic Displacement*; ed H. Feuer, VCH, New York, 1991; (*b*) J. Miller, in *Aromatic Nucleophilic Substitution*, Elsevier, Amsterdam, 1968; (*c*) J. F. Bunnett, *Rev. Chem. Soc.*, 1958, **12**, 1; (*d*) E. Buncel, M. R. Crampton, M. J. Strauss and F. Terrier, in *Electron-Deficient Aromatic and Heteroaromatic – Base Interactions*, Elsevier, Amsterdam, 1984.

2 C. Paradisi, in *Comprehensive Organic Synthesis*, **vol. 4**, part 2, ed. B. M. Trost, Pergamon Press, Oxford, 1991.

3 (*a*) M. Makosza and K. Stalinski, *Chem. Eur. J.*, 1997, **3**, 3025; (*b*) M. Makosza and K. Wojciechowski, *Liebigs Ann. Chem.*, 1997, 1905.

4 A. R. Katritzky and K. S. Laurenzo, *J. Org. Chem.*, 1988, **53**, 3978.

5 G. Moutiers, R. Goumont, J. Pinson and F. Terrier, *Chem. Eur. J.*, 2001, **7**, 1712.

6 (*a*) F. Effenberger, *Acc. Chem. Res.*, 1989, **22**, 27; (*b*) S. Vogel, W. Knoche and W. W. Schoeller, *J. Chem. Soc., Perkin Trans. 2*, 1986, 769.

7 (*a*) R. L. Hinman and J. J. Lang, *J. Am. Chem. Soc.*, 1964, **86**, 3796; (*b*) J. Schulze and F. A. Long, *J. Am. Chem. Soc.*, 1964, **86**, 4770; (*c*) E. B. Whipple, Y. Chiang and R. Hinman, *J. Am. Chem. Soc.*, 1963, **85**, 26.

8 A situation where loss of chloride would occur in a concerted process with proton loss cannot be firmly rejected.

9 (*a*) F. Terrier, E. Kizilian, J. C. Hallé and E. Buncel, *J. Am. Chem. Soc.*, 1992, **114**, 1740; (*b*) F. Terrier, M. J. Pouet, J. C. Halle, S. Hunt, J. R. Jones and E. Buncel, *J. Chem. Soc., Perkin Trans. 2*, 1993, 1665.

10 (*a*) G. P. Sharnin, F. S. Levinson, S. A. Akimova and R. H. Hasanov, USSR Pat. 657025, 1979 (*Chem. Abstr.*, 1979, **91**, P20519h); (*b*) W. P. Norris, A. Chafin, R. J. Spear and R. W. Read, *Heterocycles*, 1984, **22**, 271.