Tetrahedron 66 (2010) 995–1006

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

S_EAr–S_NAr couplings of indolizines and related pyrrole derivatives with superelectrophilic nitrobenzoxadiazoles

Artem Tatarov [a], Serguey Kurbatov [a], Gennady Borodkin [a], Régis Goumont [b,*], François Terrier [b]

[a] Department of Chemistry, Southern Federal University, 7, Zorge Street, 344090 Rostov-on- Don, Russian Federation
[b] Institut Lavoisier, UMR CNRS 8180, University of Versailles, 45, Avenue des Etats-Unis, 78035 Versailles Cedex, France

ARTICLE INFO

Article history:
Received 8 October 2009
Received in revised form 13 November 2009
Accepted 16 November 2009
Available online 7 December 2009

Keywords:
Indolizine nucleophilicity
Pyrrole nucleophilicity
S_EAr–S_NAr couplings
Superelectrophilic nitrobenzoxadiazoles
Zwitterionic spiro adducts

ABSTRACT

The nucleophilic aromatic substitutions of 7-chloro-4,6-dinitrobenzofurazan (DNBZ-Cl) and 7-chloro-4,6-dinitrobenzofuroxan (DNBF-Cl) with a series of differently substituted indolizines (**5a–f**) and a series of dihyropyrroloisoquinolines (**11a–f**) have been investigated. In accord with previous reports emphasizing the superelectrophilic character of these compounds in σ-complexation processes, DNBZ-Cl and DNBF-Cl react very readily and quantitatively with the weak carbon nucleophiles **5a–f** and **11a–f** at room temperature in acetonitrile. In the case of DNBZ-Cl, the resulting products (**7Z,a–f** and **12Z,a–f**) are those expected from the displacement of the chlorine atom through a S_EAr–S_NAr mechanism. A significant result is that these compounds, despite the lack of coplanarity of the two rings, are characterized by an intense intramolecular charge transfer between the donor pyrrole-type moiety and the electron-deficient acceptor DNBZ moiety. Contrasting with this behaviour, the DNBF-Cl reactions show a totally different pattern, proceeding with loss of the N-oxide functionality and expansion of the pyrrole moiety to afford stable zwitterionic spiro adducts (**8F,a–f** and **13F,a–f**) of a so far unknown type. Rapid NMR recordings have revealed that the formation of these adducts occurs after initial formation of the expected substitution products **7F,a–f** and **12F,a–f**. A mechanism accounting for the overall rearrangement leading to the spirobenzofurazan adducts is suggested. It is based on an initial nucleophilic attack of the oxygen atom of the N-oxide functionality at the electron-deficient and strongly olefinic C–C coupling bond generated by the aforementioned intramolecular charge transfer. This results in the formation of an unstable five-membered isoxazole ring whose decomposition goes along with loss of the N-oxide functionality and enlargement of the pyrrole moiety into a pyridine one. Also discussed are the factors accounting for the high thermodynamic stability of the spiro adducts, and their relevance to the stability of previously reported spiro adducts.

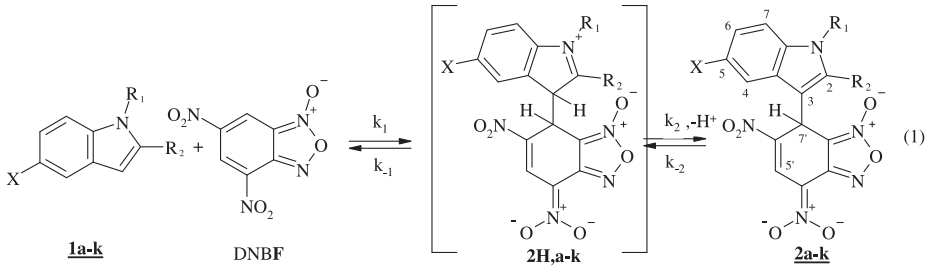
1. Introduction

The field of electrophile–nucleophile combinations has, during the last few years, received a boost with the discovery of a class of electron-deficient aromatic compounds that show increased reactivity in the formation of σ-bonded (Meisenheimer) complexes.[1–14] The high susceptibility of 4,6-dinitrobenzofuroxan (DNBF, 4,6-dinitro-2,1,3-benzoxadiazole-1-oxide) and 4,6-dinitrobenzofurazan (DNBZ, 4,6-dinitro-2,1,3-benzoxadiazole) to react very readily and quantitatively with water,[10,11] or such weak carbon nucleophiles as benzenoid aromatics (phenols, anilines…)[2,3b,15,16] or π-excessive heteroaromatics (indoles, pyrroles, thiophenes, furans…),[1,17,18] is a nice illustration of this behaviour. In all of these reactions, covalent addition of the carbon nucleophile takes place at C-7 of the carbocyclic ring of DNBF and DNBZ to give very stable carbon-bonded σ-adducts. The formation of the DNBF adducts **2a–k** from various indoles (**1a–k**) according to Eq. 1 is a prototype example. Altogether, the results obtained have revealed that the neutral DNBF and DNBZ molecules exhibit an electrophilic reactivity that compares well with that of the positively charged 4-nitrobenzenediazonium cation.[19] The ease of coupling of DNBF and DNBZ with very weak nucleophiles has led to numerous synthetic, analytical and biological applications.[8,20–22]

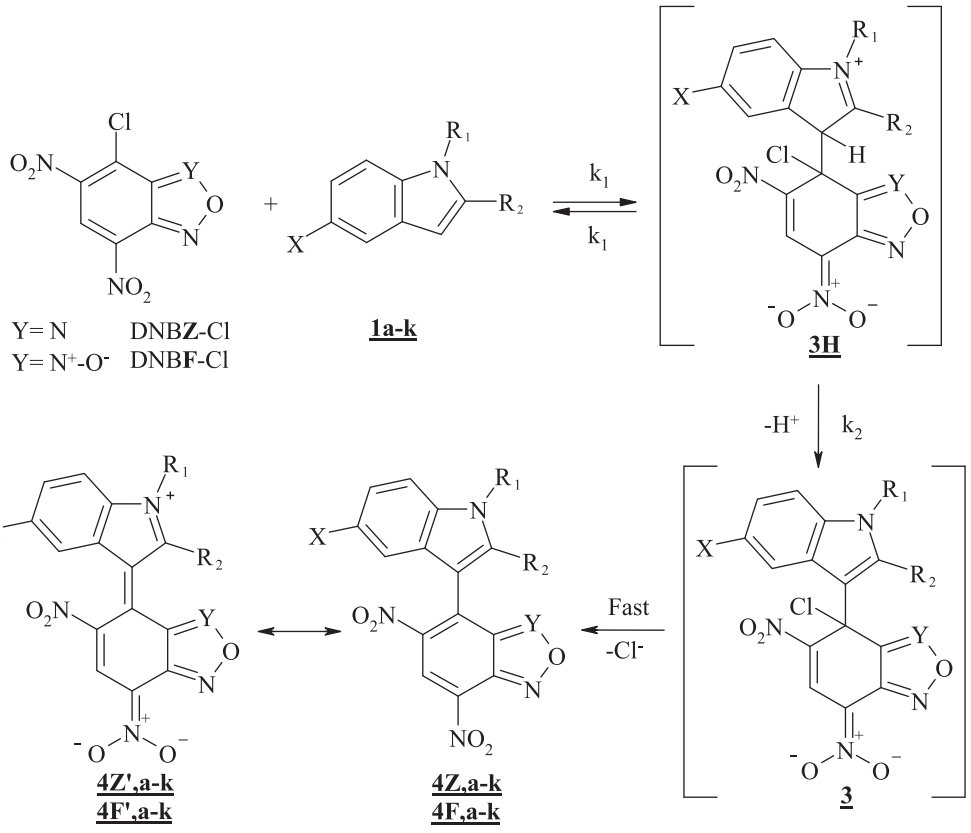
Recently, we have found that the remarkable propensity of DNBF and DNBZ to react in σ-complexation processes extends to nucleophilic aromatic substitutions of the S_NAr type.[23] While only strong carbon bases of $pK_a \geq 9$, e.g., 1,3,5-trispyrrolidinobenzene,[24] react satisfactorily with picryl chloride,[25] the reactions of 7-chloro-4,6-dinitrobenzofurazan (DNBZ-Cl) and—benzofuroxan (DNBF-Cl) have been found to proceed smoothly at room temperature with a large set of indoles and 2-methylindoles (pK_a values in the range −6 to +0.26), affording the related substituted products, i.e., **4Z** and **4F**, in essentially quantitative yields (Scheme 1).[23] An interesting structural property of these products is that a strong intramolecular

* Corresponding author. Tel.: +33 1 39 25 66 56; fax: +33 1 39 25 66 52.
E-mail address: goumont@chimie.uvsq.fr (R. Goumont).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.11.071



with n = a: $R_1 = R_2 = X = H$
b: $R_1 = R_2 = H$, $X = OCH_3$
c: $R_1 = R_2 = H$, $X = CH_3$
d: $R_1 = R_2 = H$, $X = Cl$
e: $R_1 = R_2 = H$, $X = Br$
f: $R_1 = R_2 = H$, $X = CN$
g: $R_1 = CH_3$, $R_2 = X = H$
h: $R_1 = X = H$, $R_2 = CH_3$
i: $R_1 = H$, $R_2 = X = CH_3$
j: $R_1 = H$, $R_2 = CH_3$, $X = OCH_3$
k: $R_1 = H$, $R_2 = CH_3$, $X = Cl$



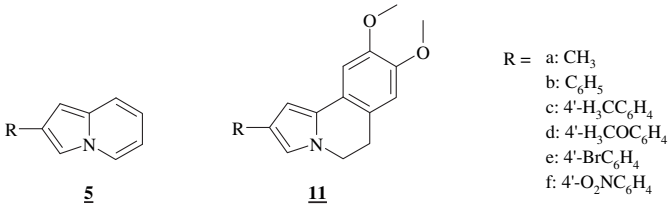
(see equation 1 for the identification of the indoles)

Scheme 1.

charge transfer is taking place between the π-system of the benzofuroxan or benzofurazan acceptor and the π-system of the aromatic or heteroaromatic donor, despite the fact that steric effects preclude a full coplanarity of the two moieties.[23] Similar couplings with 1,2,5-trimethylpyrrole and azulene have also been carried out.[23] Accordingly, the resonance structures **4Z′** and **4F′** must play a major role in determining the reactivity of **4Z** and **4F**.

In an attempt to expand the S_NAr feasibility of C–C couplings, we have become interested in looking at the reactivity of DNBF-Cl and DNBZ-Cl towards various families of carbon nucleophiles. In this paper, we report on the S_NAr reactivity of two families of pyrrole derivatives. The first consists of a series of indolizines, namely **5a**–**f**, whose pK_a values are known to lie in the range of the most basic pyrroles, e.g., pK_a=3.94 for unsubstituted indolizine versus pK_a=3.75 for 2,4-dimethyl-3-ethylpyrrole (kryptopyrrole).[26–28] All pK_a values presented relate to water as solvent and give general indication of relative basicity. The second family includes a series of pyrroloisoquinolines, **11a**–**f**, whose C-basicity is expected to be favoured by the 1,2-dialkylsubstitution of the pyrrole ring. As will be seen, only the DNBZ-Cl reactions

proceeded to give the expected S_NAr products. In the case of the DNBF-Cl systems, the substitution products are not stable, undergoing an unprecedented rearrangement, which is induced by an intramolecular oxygen atom transfer from the N-oxide functionality of the DNBF moiety. A possible mechanism for this rearrangement will be discussed. To be noted is that a preliminary communication dealing only with the reactivity of 2-(4′-bromophenyl)indolizine **5e** and the X-ray determination of the resulting products **7Ze** and **7Fe** has appeared.[29]



5 **11**

2. Results

2.1. Reactions of DNBZ-Cl and DNBF-Cl with indolizines 5a–f

Treatment of DNBZ-Cl with 1 equiv of each of the indolizines **5a–f** in $CHCl_3$ solution produced deep blue-green crystals in rather high yields. Confirming the results obtained previously with 2-(4′-bromophenyl)indolizine **5e**,[29] these solids correspond to the expected S_NAr substitution products **7Z,a–f** Eq. 2. Of particular significance is that **7Z,a–f** exhibit an intense visible absorption at very high wavelengths, e.g., λ_{max}=780 nm for **7Ze** in $CHCl_3$. This points to a very strong intramolecular charge transfer from the donor indolizine moiety to the 4,6-dinitrobenzofurazanyl acceptor moiety, and therefore to an important contribution of the resonance structure **7Z′,a–f** to the stabilization of **7Z,a–f** (Eq. 2). As a reflection of this charge transfer, similar to the one observed in the indole couplings (Scheme 1),[23] there is a strong shift to low-field of the H_1 and C_1 resonances of the pyrrole ring (δH_1=6.75, δC_1=96.16 in **5e**; δH_1=7.06, δC_1=104.66 in **7Ze**) as well as of the H_6, H_7 and H_8 resonances of the pyridine ring: δH_6=6.53, δH_7=6.69, δH_8=7.38 in **5e**; δH_6=6.91, δH_7=7.24, δH_8=7.79 in **7Ze**. Concomitantly,the C_6 and C_7 resonances move significantly to low-field e.g., δC_6=110.08, δC_7=117.78 in **5e**; δC_6=113.44; δC_7=123.89 in **7Ze**. These chemical shift variations suggest that the pyridine ring contributes to a significant delocalization of the positive charge generated on the nitrogen atom by the overall donor–acceptor interaction (see Discussion). All ^1H and ^{13}C data pertaining to the parent indolizines **5a–f** and the resulting S_NAr products **7Z,a–f** are collected in Tables 1 and 2.

Table 1
^1H NMR parameters for indolizines **5a–f** and related substitution products **7Z,a–f**, **7Fc** and **7Fe**[a,b]

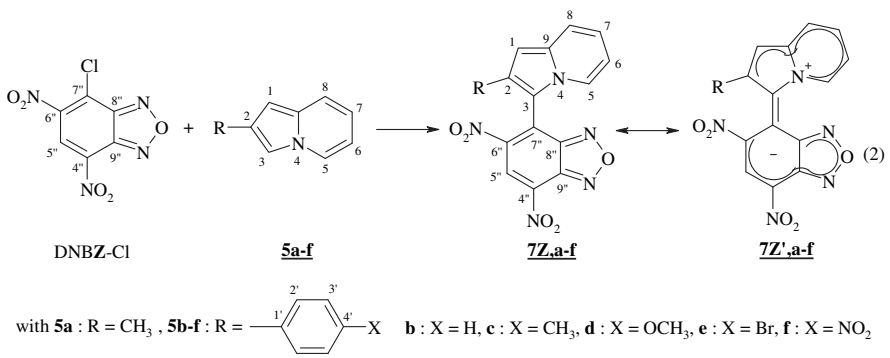
Substrate	H-5″	H-1	H-5	H-6	H-7	H-8
5a	—	6.17	8.10	6.41	6.59	7.26
7Za	9.21	6.74	8.08	6.85	7.22	7.65
5b	—	6.75	8.20	6.52	6.68	7.37
7Zb	9.12	6.97	8.12	6.85	7.24	7.73
5c	—	6.70	8.18	6.50	6.66	7.36
7Zc	9.11	6.88	8.07	6.81	7.18	7.67
7Fc	9.01	6.82	7.43	6.89	7.24	7.62
5d	—	6.66	8.18	6.49	6.65	7.35
7Zd	9.10	6.87	8.07	6.81	7.18	7.67
5e	—	6.75	8.20	6.53	6.69	7.38
7Ze	9.25	7.06	8.14	6.91	7.24	7.79
7Fe	9.02	6.84	7.43	6.92	7.25	7.65
5f	—	6.90	8.24	6.58	6.73	7.42
7Zf	9.15	7.11	8.11	6.87	7.21	7.75

[a] Solvent: Me_2SO-d_6 for **7Z,a–f** and $CDCl_3$ for **7Fc** and **7Fe**; δ in ppm, internal reference Me_4Si.
[b] See structures and numbering of atoms in Eq. 2.

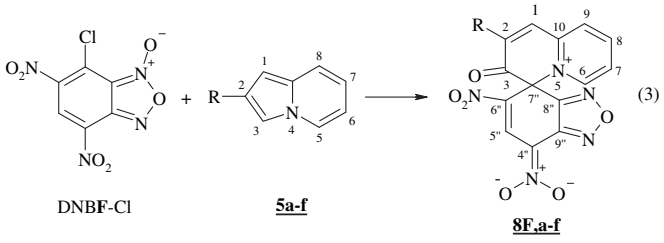
Table 2
^{13}C NMR parameters for indolizines **5a–f** and related substitution products **7Z,a–f**[a,b]

Substrate	C-4″	C-5″	C-6″	C-7″	C-8″	C-9″	C-1	C-3	C-5	C-6	C-7	C-8	C-9
DNBZ-Cl	136.75	128.18	147.34	128.01	151.76	143.77	—	—	—	—	—	—	—
5a	—	—	—	—	—	—	99.64	111.44	125.16	109.18	116.53	117.79	132.05
7Za	122.97	129.74	133.01	116.24	151.74	140.68	107.32	143.55	126.76	113.11	124.91	118.75	138.85
5b	—	—	—	—	—	—	96.15	110.43	125.71	109.84	117.55	118.63	132.92
7Zb	123.07	128.94	133.92	112.71	151.28	142.87	104.77	143.07	126.14	113.07	123.62	119.16	137.93
5c	—	—	—	—	—	—	95.97	110.28	125.64	109.54	117.43	118.52	132.86
7Zc	123.16	128.72	135.94	112.88	151.19	142.47	104.64	142.87	126.07	112.77	123.40	118.93	137.97
5d	—	—	—	—	—	—	95.82	110.16	125.59	109.15	117.36	118.41	132.87
7Zd	123.12	128.93	135.67	112.86	151.24	142.52	104.54	143.04	126.15	112.78	123.63	118.92	138.10
5e	—	—	—	—	—	—	96.16	110.65	125.75	110.08	117.78	118.68	133.02
7Ze	122.76	129.08	133.95	112.22	151.36	143.65	104.66	143.44	126.23	113.44	123.89	119.36	137.80
5f	—	—	—	—	—	—	96.95	111.71	125.97	111.36	118.37	119.06	133.39
7Zf	122.50	128.71	133.51	112.32	151.34	143.83	104.77	143.10	126.02	113.50	123.42	119.43	137.51

[a] Solvent: Me_2SO-d_6; δ in ppm, internal reference Me_4Si.
[b] See Eq. 2 for the structures and the numbering of atoms.



Again in agreement with the results obtained in using **5e** as the nucleophilic reagent, DNBF-Cl reacted with all indolizines **5a–f** to afford the orange-red zwitterionic adducts **8F,a–f** Eq. 3. In addition to the X-ray structure of **8Fe**,[29] there are several significant features supporting the proposed structures. A most important one deals with the totally different chemical shift patterns characterizing the quaternary carbons $C_{8''}$ and $C_{9''}$ in the parent DNBF-Cl substrate and the resulting adducts **8F,a–f** (Table 3). As pointed out by several authors, the electron-donating+M effect of the N-oxide group has the effect to induce the presence of a negative charge on the $C_{8''}$ carbon in a benzofuroxan structure, as depicted in the canonical form **B** see Eq. 4. This causes a large upfield shift of the resonance of this carbon, as compared with the situation in the benzofurazan series.[30–35] As a matter of fact, it has been proposed that the chemical shift pattern of $C_{8''}$ and $C_{9''}$ be used as a diagnostic feature for discriminating between benzofuroxan and benzofurazan skeletons.[30,31,33] Here, the strong downfield shift of $C_{8''}$ observed on going from DNBF-Cl to each of the spiro adducts **8F,a–f** ($\Delta\delta \approx 33$ ppm) is obviously consistent with the loss of the N-oxide functionality during the overall process.



comparison, the resonance of the related $C_{7''}$ carbons in DNBF or DNBZ σ-adducts of type **2** appears at δ=30–31 ppm.[1,19] Another argument supporting structures **8F,a–f** comes from theoretical predictions that σ-complexation of a nitroaromatic or heteroaromatic ring induces a negative charge at the *ortho*- and *para*-positions but a decrease in negative charge at the unsubstituted *meta*-positions.[13,14,36–40] As shown in Table 3, the resonances of the $C_{4''}$ and $C_{6''}$ carbons of **8F,a–f** are at much higher field than in the DNBZ-Cl and DNBF-Cl substrates or the related DNBF or DNBZ molecules. At the same time, the resonance of the $C_{5''}$ carbons moves appreciably to low-field. To be noted is that the ^{13}C resonances of the cyclohexadienyl moiety of **8F,a–f** are essentially the same as those reported for all DNBF or DNBZ adducts so far described.[2,5,6,13e,14,16,20,41] A last noteworthy feature associated with the formation of **8F,a–f** is the enormous deshielding of the H_1 resonance: δ=8.69 in **8Fe** (Table S1) versus δ=6.75 in **5e** (Table 1).

Due to the different patterns governing the reactivity of DNBZ-Cl and DNBF-Cl, there are significant differences in the physical properties of the resulting products **7Z,a–f** and **8F,a–f**. Thus the S_NAr products **7Z,a–f** have a high solubility in most organic solvents, giving rise to deeply blue-green coloured solutions, which reflect the importance of the intramolecular charge transfer mentioned above. Also worth noting is that **7Z,a–f** exhibit a satisfactory chromatographic mobility. In contrast, the dipolar spiro adducts **8F,a–f** are poorly soluble in organic solvents, including in dipolar aprotic solvents like Me_2SO. Consistent with the presence of the anionic cyclohexadienyl moiety, **8F,a–f** show UV–visible absorption spectra, which are similar to those for all DNBF and DNBZ σ-adducts previously studied, i.e., $\lambda_{max} \approx 470–480$ nm.[1–6,10,14,18,19,41]

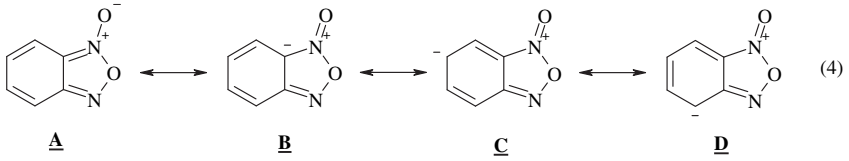


Table 3
Selected ^{13}C NMR parameters for the spiro adducts **8F** and **13F**[a–d]

Substrate	C-4″	C-5″	C-6″	C-7″ (C-4)	C-8″	C-9″	C-1	C-3
DNBZ-Cl	136.75	128.18	147.34	128.01	151.76	143.77	—	—
DNBZ	137.88	124.50	148.80	122.22	150.23	143.62	—	—
DNBF	137.96	125.83	144.85	119.53	116.12	144.65	—	—
DNBF-Cl	136.18	129.07	144.04	127.35	115.79	145.39	—	—
8Fa	111.69	135.43	122.11	71.05	149.86	143.79	111.69	135.43
8Fb	111.76	135.54	121.83	71.84	149.61	143.83	111.76	135.54
8Fc	111.72	135.52	121.87	71.78	149.62	143.83	111.72	135.52
8Fd	111.70	135.53	121.93	71.72	149.64	143.83	111.70	135.53
8Fe	111.80	135.53	121.71	71.86	149.52	143.82	111.80	135.53
8Ff	111.90	135.56	121.57	72.00	149.47	143.84	111.90	135.56
13Fa	112.84	136.52	120.99	70.53	151.12	146.21	112.84	136.52
13Fb	112.96	136.55	121.35	71.25	151.28	146.27	112.96	136.55
13Fc	112.91	136.56	121.41	71.23	151.34	146.28	112.91	136.56
13Fd	112.86	136.55	121.47	71.14	151.39	146.29	112.86	136.55
13Fe	113.00	136.52	121.26	71.25	151.23	146.27	113.00	136.52
13Ff	113.14	136.51	121.18	71.37	151.16	146.27	113.14	136.51

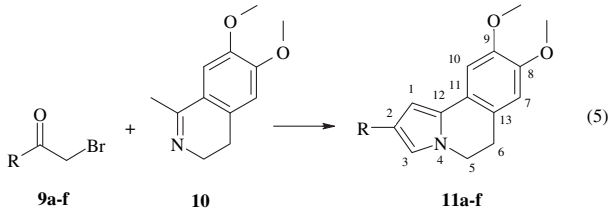
[a] Solvent: Me_2SO-d_6 for **8F,a–f** and nitrobenzene-d_5 for **13F,a–f**; δ in ppm, internal reference Me_4Si.
[b] See structures and numbering of atoms in Eq. 3 and structure **13F,a–f**.
[c] Values for DNBZ-Cl and DNBF-Cl in CD_3CN-d_3 determined in this work.
[d] Values for DNBZ and DNBF taken from Ref. 31.

Other typical data in accord with the spiro structure are the carbon chemical shifts assigned to the carbonyl group ($\delta C_3 \approx 135$ ppm) and to the sp^3-hybridized spiro centre ($\delta C_{7''} \approx 71$ ppm). Being bonded both to a carbonyl group and a positively charged nitrogen atom, this centre is characterized by a relatively low-field resonance. For

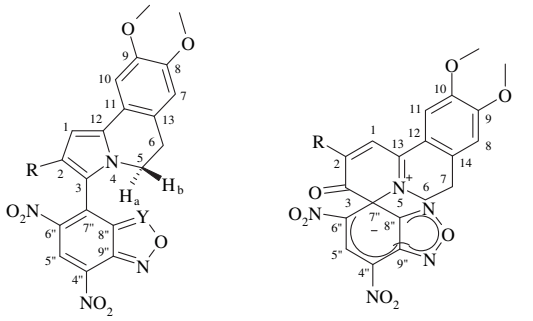
2.2. Reactions of DNBZ-Cl and DNBF-Cl with the pyrroloisoquinolines 11a–f

A major finding emerging from the indolizine reactions described above is that the formation of the spiro complexes **8F,a–f**

takes place with an expansion of the pyrrole ring. This made it of interest to look at whether this rearrangement extends to other pyrrolic structures. For this purpose, a series of 2-substituted-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolines **11a–f**, has been investigated. These compounds were obtained in good to high yields by carrying out the cyclizations in one stage, i.e., without isolating the quaternary intermediates according to the Tchichibabin protocol modified by Casagrande[42] and other authors.[43,44]



9a-f **10** **11a-f** (5)



Y= N **12Z,a-f**
Y= N+-O- **12F,a-f**

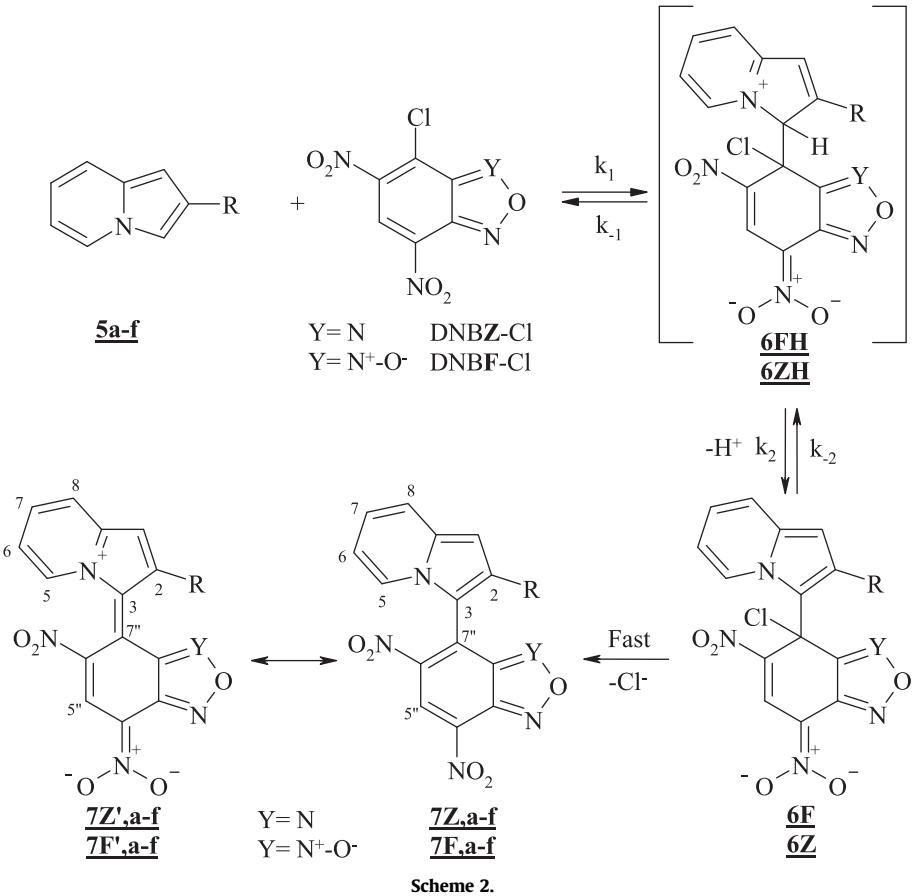
13Fa-f

As expected, the pyrroloisoquinolines **11a–f** behave similarly to the indolizines **5a–f**, reacting with DNBZ-Cl and DNBF-Cl to give the S_NAr substitution products **12Z,a–f** and the spiro adducts **13F,a–f**, respectively. The various arguments developed to account for the formation of the indolizine products **7Z** and **8F** fully apply to the recognition of structures **12Z,a–f** and **13F,a–f** so that there is no need for many additional comments. Selected ^1H and ^{13}C data are given in Tables S2 and S3 for **12Z,a–f** and Tables 3 and S4 for **13F,a–f**. Regarding compounds **12Z,a–f**, it may be further pointed out that the strong intramolecular charge transfer is evidenced by the strong shift to low-field of the H_1 and C_1 resonances, e.g., δH_1=6.90, δC_1=100.26 in **11e** as compared with δH_1=7.18, δC_1=106.70 in **12Z,e** (Tables S2 and S3). Also worth noting is that the S_NAr substitution leading to **12Z,a–f** causes a non-equivalence of the H_{5a} and H_{5b} protons of the *N*-CH_2 group with only the most deshielded one appearing at lower field than in the parent pyrrole.

3. Discussion

3.1. The S_EAr–S_NAr mechanism

As referred to in the introduction, DNBZ-Cl and DNBF-Cl have been found to readily react with indoles. Besides a thorough structural analysis, which has revealed that the resulting substitution products are subject to an intense intramolecular charge transfer, a detailed kinetic investigation of the various substitutions has been carried out.[19,23] Based on the collected data and in particular the absence of a significant dependence of the rates of coupling on the hydrogen or deuterium labelling at the reactive centre of the nucleophiles, it has been unambiguously demonstrated that the reactions take place through the S_EAr–S_NAr mechanism depicted in Scheme 1. In this scheme, the initial



5a-f

Y= N DNBZ-Cl
Y= N+-O- DNBF-Cl

6FH
6ZH

7Z',a-f
7F',a-f

Y= N **7Z,a-f**
Y= N+-O- **7F,a-f**

6F
6Z

Scheme 2.

formation of the zwitterionic Wheland–Meisenheimer intermediate **3H** takes place as the rate-limiting step of the overall interaction. This is followed by fast rearomatization of the hetarenium moiety to give the anionic Meisenheimer σ-complex **3**. This process is energetically assisted by the recovery of the aromaticity of the indole nucleophile. Facile loss of chloride anion—a good leaving group ($pK_a=-7$)—[45] from the adducts **3** then leads to the substitution products. Importantly, DNBZ-Cl and DNBF-Cl are reacting with similar rates with a given indole nucleophile, pointing out that the presence of the N-oxide functionality has very little influence on the electrophilic reactivity of mono-nitro- and dinitro-2,1,3-benzoxadiazoles in S_NAr and related σ-complexation processes.

Going to the present work, it was reasonable to anticipate that the indolizines **5a–f** and the pyrroloisoquinolines **11a–f** will behave as indoles, undergoing facile reactions with DNBZ-Cl and DNBF-Cl to afford the substitution products (**7Z,a–f**, **7F,a–f** and **12Z,a–f**, **12F,a–f**) according to the S_EAr–S_NAr mechanistic pattern outlined in Scheme 2 for the indolizine systems. As a matter of fact, there is little doubt that this scheme applies well to the DNBZ-Cl reactions. Of particular significance for the characterization of the substitution products **7Z,a–f** and **12Z,a–f** is the X-ray structure obtained for the 2-(4′-bromophenyl)indolizine compound **7Z,e**.[29] The twisting of the NO_2 group located in the *ortho* position ($C_{6''}$) to the reaction site is of only 26°, allowing an extensive conjugation between the donor and acceptor moieties of the products **7Z,a–f**. This conjugation is reflected in the notable olefinic character of the C_3–$C_{7''}$ bond (1.427 Å) and some typical NMR variations, e.g., a strong shift to low-field of the H_1 and C_1 resonances on going from **5e** or **11e** to **7Z,e** and **12Z,e** (see Tables 1, 2 and S2, S3).

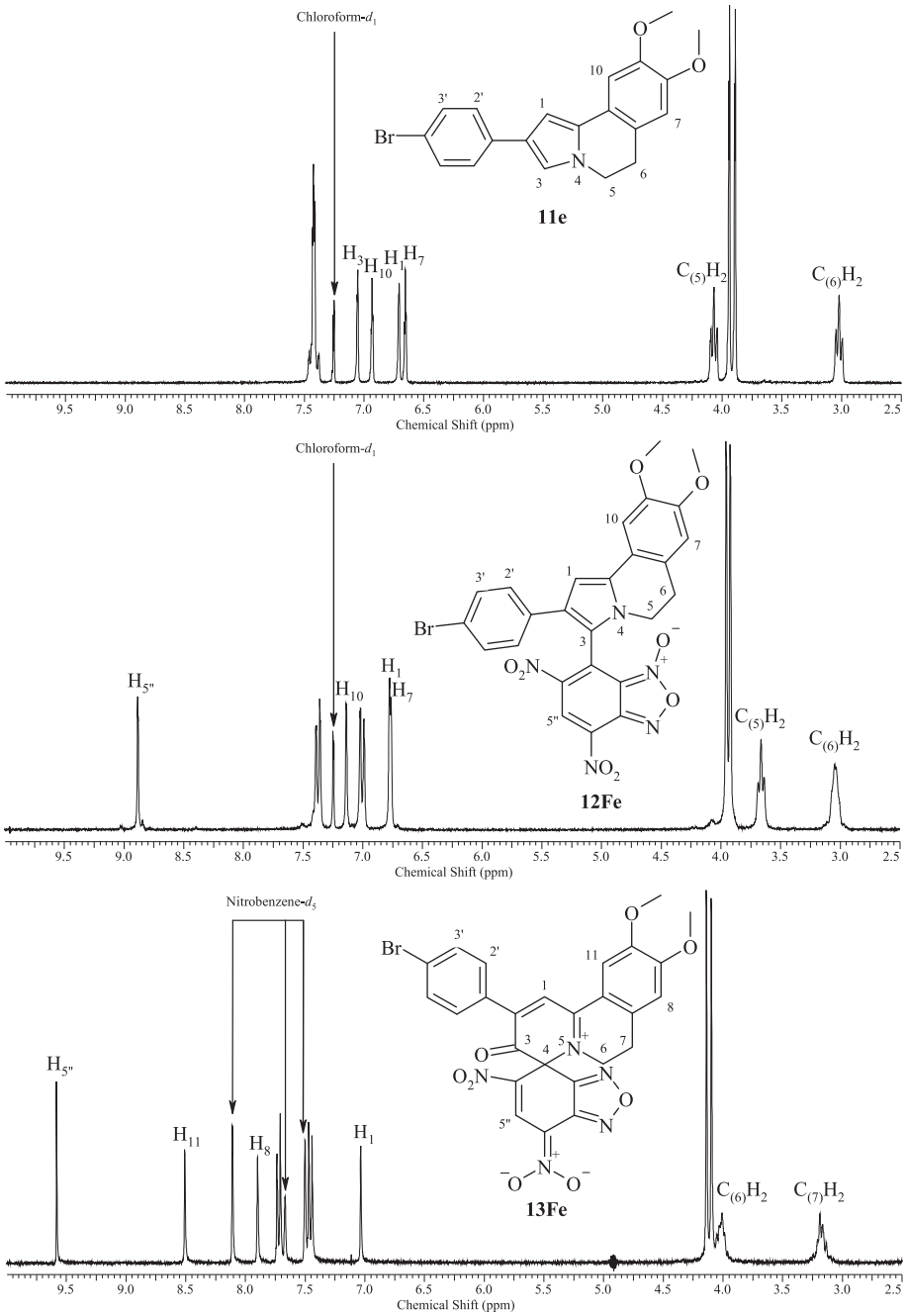
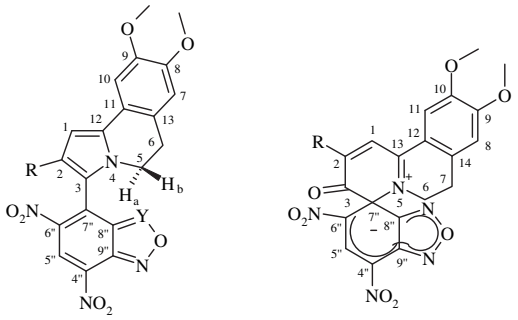


Figure 1. ^1H NMR spectra showing the formation of the transient S_NAr substitution product **12F,e** in the reaction of DNBF-Cl with **11e** to give the spiro adduct **13Fe**.

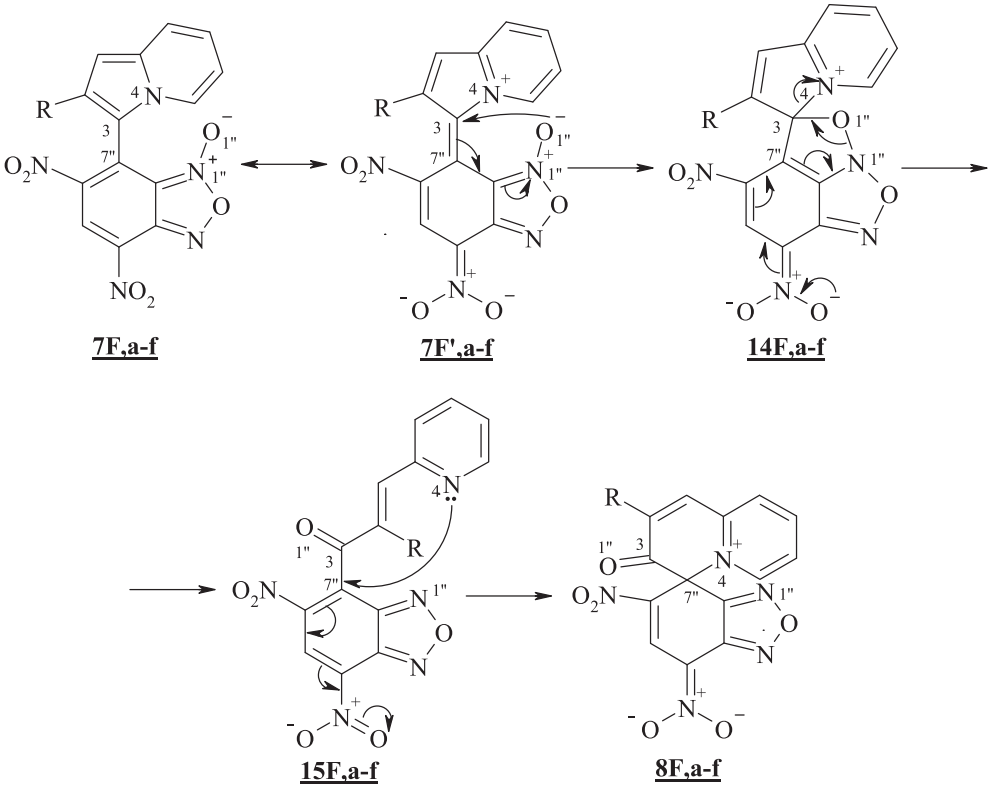
3.2. The DNBF rearrangement

Under the same experimental conditions as those used for the DNBZ-Cl reactions, the interactions of DNBF-Cl with **5a–f** and **11a–f** do not lead to the expected substitution products **7F,a–f** and **12F,a–f**. Instead, the zwitterionic spiro adducts **8F,a–f** and **13F,a–f** are isolated. These have been structurally characterized by combining the information provided by a X-ray structure of the (4′-bromophenyl)indolizine member (**8F,e**)[29] with typical NMR and UV–visible data (see comments in the Results section as well as Tables 3, S1 and S4). As the first peculiarity associated with the formation of **8F,a–f** and **13F,a–f**, there is the loss of the N-oxide functionality and the overall conversion of the starting dinitrobenzofuroxan moiety into a negatively charged dinitrobenzofurazan one. A second noteworthy feature is that this conversion goes along with a skeletal rearrangement of the pyrrole fragment of the indolizine nucleophile, resulting eventually in an enlargement of this five-membered ring and the formation of a C–N spiro adduct.

Taking into account the essentially similar reactivity of DNBZ-Cl and DNBF-Cl in the indole reactions, a reasonable mechanism accounting for the overall formation of the spiro adducts **8F,a–f** and **13F,a–f** can be proposed. The starting point is the assumption that DNBF-Cl must react initially as its DNBZ analogue to afford the S_EAr–S_NAr substitution products **7F,a–f** and **12F,a–f**. As a matter of fact, a rapid recording of the ^1H NMR spectra after mixing of the reagents has allowed the characterization of **7F** and **12F** as short-lived species in the case of the indolizines **5b** and **5e** as well as the dihydropyrroloisoquinolines **11b** and **11e**. This characterization is illustrated in Figure 1, which shows the conversion of the initially formed substitution product, here **12F,e**, into the related spiro adduct **13F,e**. Since the final spirocyclic adduct **13F,e** is poorly soluble in chloroform, it was necessary to record spectrum of the precipitated product in deuterated nitrobenzene (Fig. 1). The related NMR parameters compare well with those for the DNBZ-Cl counterparts (Tables 1 and S2). Also, the transient colour associated with the formation of these S_NAr products, namely **7F,b**, **7F,e** and **12F,b 12F,e**, is the same as that characterizing the DNBZ-Cl analogues. This implies an important contribution of the canonical structures of type **7F′** and **12F′**, thereby supporting the view that a similar intramolecular charge transfer takes place between the donor and acceptor moieties in both DNBF- and DNBZ-substitution products.

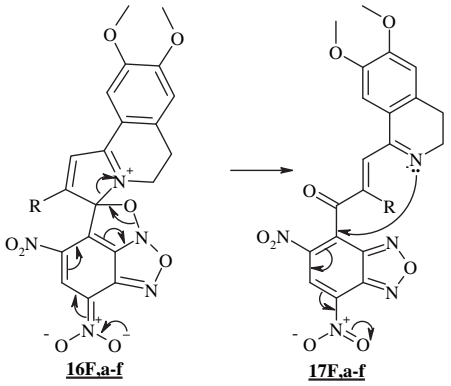


On the above grounds, we suggest that the charge transfer is the key point determining the conversion of **7F** and **12F** into the spiro adducts **8F** and **13F**. As shown in Scheme 3 with reference to the indolizine systems, this transfer has the effect of generating a positively charged indolizinium moiety, thereby promoting nucleophilic attack at the electron-deficient C_3 centre by the negatively charged oxygen atom of the N-oxide functionality. The result is the formation of a five-membered ring (structure **14**), which is prone to undergo $N_{1''}$–$O_{1''}$ and C_3–N_4 bond breakings, presumably through a concerted



Scheme 3.

process, to afford the 7-substituted-4,6-dinitrobenzofurazans **15**. In a last step, intramolecular nucleophilic addition of the basic pyridine nitrogen atom of **15**, takes place at $C_{7''}$. This process is facilitated by the superelectrophilic character of the 4,6-dinitrobenzofurazan structure, leading to the stable spiro adducts **8F**. In the case of the pyrroloisoquinolines **11a–f**, a similar mechanism will operate, the only difference with the indolizine systems being that the last step includes cyclization through nucleophilic attack by an imino nitrogen. The intermediates **16F** and **17F** involved in the rearrangement of the substitution products **12F,a–f** into the spiro adducts **13F,a–f** are shown below.



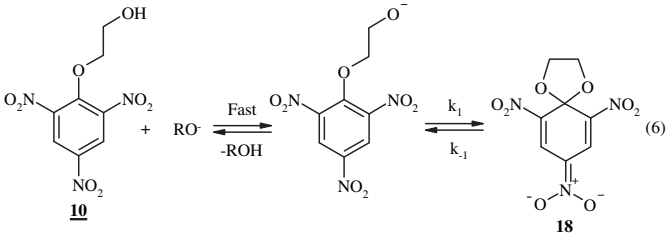
16F,a-f **17F,a-f**

3.3. Enlargement of the pyrrole ring

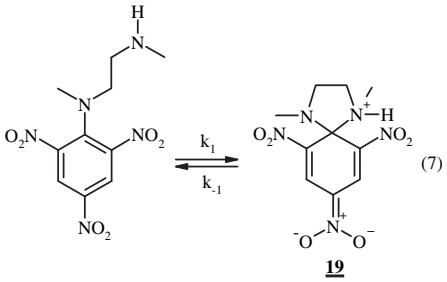
Each of the individual steps of Scheme 3 deserves further comment. Deoxygenation of a N-oxide functionality is a relatively common process in heterocyclic chemistry where it often occurs via formal elimination of a water molecule. Deoxygenative nucleophilic substitutions of hydrogen of azaactivated compounds bearing a N-oxide group are prototype examples.[14,46–50] Ring transformations induced by oxygen migration have also been reported.[51,52] The conversion of 1,2,4-triazine 4-oxides into pyridazines upon reaction with substituted acetonitriles is a representative example.[51] In this work, it is noteworthy that the oxygen transfer goes through opening of the five-membered isoxazole and pyrrole rings of the intermediates **14F** or **16F**. Thus, after cyclization, the pyrrole moiety of the starting nucleophilic reagents is replaced by a six-membered ring. While there have been many reports of pyrrole/pyridine or indole/quinoline interconversions, none of these rearrangements take place via a mechanism of the type depicted in Scheme 3. The fact that the present rearrangements are induced by the dipolar nature of the substitution products with an attack of the strongly deactivated $C_{7''}$–C_3 double bond by the oxygen atom of the N-oxide function is a further remarkable manifestation of the exceptional electrophilic character of a DNBF moiety. So far, reports of an enlargement of a pyrrole ring have derived from radical rearrangements or treatment of methylindoles and 2,5-dimethylpyrrole under strong basic conditions.[53–58]

3.4. How to account for the stability of the spiro adducts 8F and 13F? A re-examination of previously reported spiro adducts

There are several significant features to highlight regarding the formation of **8F** and **13F** as the stable products of the DNBF-Cl reactions. First, no example is known to us of a spiro σ-adduct with a sp^3 centre combining a C–C and a C–N coupling.[13,14] **8F** and **13F** are therefore original structures in the field of Meisenheimer complexes, especially because their dipolar character goes with the presence of a positively charged pyridinium or iminium moiety. In this respect, there is strong experimental evidence that a protonated amine nitrogen exhibits a very high nucleofugality in σ-complexation processes.[13,14,59–61] For example, the rate constant $k_{\&minus1}$ for spontaneous opening of the dioxolan ring of the picryl adduct **18** Eq. 6 is about 10^7 times lower than that for opening of the ethylenediamine ring of the adduct **19** Eq. 7 in aqueous solution.[59,61,62] In as much as the acidity common iminium ions ($pK_a \approx 7$)[63,64] do not differ very much from that of common ammonium ions, e.g., pK_a=8.36 for morpholine, and pK_a=5.17 for pyridine, the positive charge located on the nitrogen atom is not at all a favourable factor contributing to the thermodynamic stability of adducts **8F** and **13F**. One can therefore raise the question of whether the large delocalization of the negative charge through the dinitrobenzofurazan moiety can be the only factor contributing to this stability.

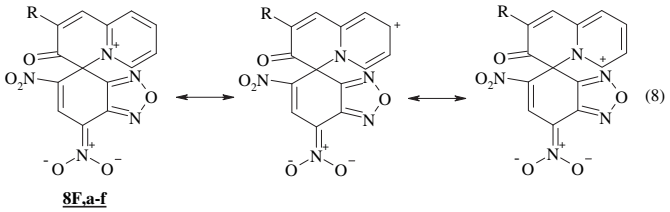


10 **18** (6)

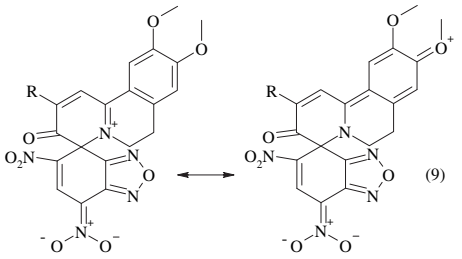


19 (7)

A possible explanation of the ease of formation and stability of **8F** and **13F** emerges when considering the canonical structures shown below in Eqs. 8 and 9. As can be seen, the positive charge of these adducts is subject to a strong delocalization through either the pyridine ring (**8F**) or the dimethoxyphenyl ring (**13F**), resulting in a favourable resonance stabilization of their positive moiety. In particular, this delocalization has the effect to remote the positive charge from the $C_{7''}$–N_5 bond, which becomes less prone to spontaneous breaking. As a matter of fact, there is experimental evidence supporting this proposal. Thus, the resonances of the H_6, H_7 and H_8 protons of the pyridine ring move strongly downfield upon formation of **8F** (see Tables 1 and S1). Similarly, the formation of **13F** is associated with a large deshielding of the H_8 and H_{11} protons of the dimethoxyphenyl ring (Table S4), while the resonance of the H1 proton, which is now remote from the positive charge is only slightly affected. These variations are clearly consistent with a dispersion of the positive charge. It is this dispersion coupled with that of the negative charge of the anionic moiety, which will account for the observed stability of **8F** and **13F**.



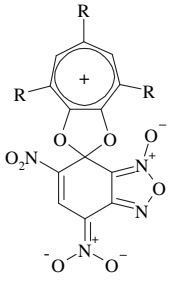
8F,a-f (8)



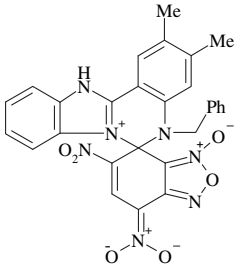
(9)

12Fa-f

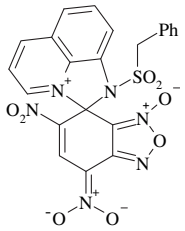
Based on the above conclusion, it is of interest to return to previously reported dipolar spiro adducts such as **20**, **21** and **22**.[65–67] In all of these species, the negative charge is delocalized through a 4,6-dinitrobenzofuroxan moiety, which is known to be as electron withdrawing as a 4,6-dinitrobenzofurazan analogue.[14,68] A most important feature is therefore that the positive charge of the three types of adducts is subject to strong dispersion through either a tropone ring, a benzimidazole ring or an isoquinoline ring. Obviously, it is the same potentiality of delocalization of both their positive and negative charges, which governs the stability of dipolar spiro adducts.



20



21



22

4. Experimental

4.1. General

Melting points were determined on a Reichert-type microscope and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DPX-250 MHz spectrometer or a Varian Unity-300 MHz spectrometer. The peaks are characterized by s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet) and t (triplet). Mass spectra were obtained using a LCQ DecaXPMAX (ESI, 1.8 kV, 180 °C) instrument. Elemental analyses were determined by the Institute of Physical and Organic Chemistry of the Southern Federal University in Rostov on Don.

4.2. Materials

7-Chloro-4,6-dinitrobenzofurazan (DNBZ-Cl) and 7-chloro-4,6-dinitrobenzofuroxan (DNBF-Cl) were prepared according to the procedures described by Sharnin et al.[69] and Norris et al.[70] Indolizines **5a–f** were long known compounds, which were synthesized following reported protocols.[71–78] Adding to the structural data so far available, a detailed ^{1}H and ^{13}C NMR characterization of **5a–f** has been made. The results are provided in pages-in the Supplementary data.

4.3. Couplings of DNBZ-Cl and DNBF-Cl with indolizines 5a–f. General procedure

To a solution of the indolizine reagent (1 mmol) in ethyl alcohol or chloroform (10–15 ml) at room temperature was added 1 equiv of DNBZ-Cl or DNBF-Cl. The resulting solution turned rapidly green, becoming either deeply blue (**7Z**,**a–f**) or brown (**8F**,**a–f**) after a few minutes. After stirring the solution for 1 h, the resulting precipitates were collected by filtration. The purification of **7Z**,**a–f** was achieved by column chromatography. Because of their low solubility, compounds **8F**,**a–f** were simply washed with copious amounts of ethyl alcohol and dried under vacuum. Analytical and spectral data for these compounds are given below. As the great majority of σ-adducts isolated so far, **8a–f** decomposed prior to melting.[1–3,15–21]

*4.3.1. Compounds **7Z**,**a–f**.* See Eq. 2 in the text for the numbering of the various atoms.

*4.3.1.1. 2-Methyl-3-(4″,6″-dinitro-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine **7Za**.* Dark-blue solid; yield 78%; mp 212–213 °C. Anal. calcd for $C_{15}H_9N_5O_5$: C, 53.10; H, 2.67; N, 20.64. Found: C, 53.28; H, 2.67; N, 20.59%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.25 (s, 3H, 2-CH_3), 6.74 (s, 1H, H-1), 6.85 (dd, J=7.0, 6.8 Hz, 1H, H-6), 7.22 (dd, J=8.6, 6.8 Hz, 1H, H-7), 7.65 (d, J=8.6 Hz, 1H, H-8), 8.08 (d, J=7.0 Hz, 1H, H-5), 9.21 (s, 1H, H-5″); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.27 (2-CH_3), 107.32 (C-1), 113.11 (C-6), 116.24 (C-7″), 118.75 (C-8), 122.97 (C-4″), 124.91 (C-7), 126.76 (C-5), 129.74 (C-5″), 131.65 (C-2), 133.01 (C-6″), 138.85 (C-9), 140.68 (C-9″), 143.55 (C-3), 151.74 (C-8″).

*4.3.1.2. 2-Phenyl-3-(4″,6″-dinitro-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine **7Zb**.* Dark-blue solid; yield 81%; mp 189–190 °C. Anal. calcd for $C_{20}H_{11}N_5O_5$: C, 59.86; H, 2.76; N, 17.45. Found: C, 60.06; H, 2.77; N, 17.41%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.85 (dd, J=6.7, 6.6 Hz, 1H, H-6), 6.97 (s, 1H, H-1), 7.24 (dd, J=8.8, 6.7 Hz, 1H, H-7), 7.24–7.28 (m, 5H, H-2′, H-3′, H-4′), 7.73 (d, J=8.8 Hz, 1H, H-8), 8.12 (d, J=6.6 Hz, 1H, H-5), 9.12 (s, 1H, H-5″); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 104.77 (C-1), 112.71 (C-7″), 113.07 (C-6), 119.16 (C-8), 123.07 (C-4″), 123.62 (C-7), 126.14 (C-5), 127.07 (C-4′), 128.49 (C-2′), 128.54 (C-3′), 128.94 (C-5″), 132.71 (C-2), 133.92 (C-6″), 135.65 (C-1′), 137.93 (C-9), 142.87 (C-9″), 143.07 (C-3), 151.28 (C-8″).

*4.3.1.3. 2-(4′-Methylphenyl)-3-(4″,6″-dinitro-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine **7Zc**.* Dark-blue solid; yield 73%; mp 233–234 °C. Anal. calcd for $C_{21}H_{13}N_5O_5$: C, 60.73; H, 3.15; N, 16.86. Found: C, 60.82; H, 3.15; N, 16.80%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.29 (s, 3H, 4′-CH_3), 6.81 (dd, J=7.0, 6.7 Hz, 1H, H-6), 6.88 (s, 1H, H-1), 7.01 (d, J=8.0 Hz, 2H, H-3′), 7.13 (d, J=8.0 Hz, 2H, H-2′), 7.18 (dd, J=8.8, 6.7 Hz, 1H, H-7), 7.67 (d, J=8.8 Hz, 1H, H-8), 8.07 (d, J=7.0 Hz, 1H, H-5), 9.11 (s, 1H, H-5″); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 20.66 (4′-CH_3), 104.64 (C-1), 112.77 (C-6), 112.88 (C-7″), 118.93 (C-8), 123.16 (C-4″), 123.40 (C-7), 126.07 (C-5), 128.36 (C-2′), 128.72 (C-5″), 129.02 (C-3′), 131.06 (C-1′), 132.46 (C-2), 135.94 (C-6″), 136.20 (C-4′), 137.97 (C-9), 142.47 (C-9″), 142.87 (C-3), 151.19 (C-8″).

*4.3.1.4. 2-(4′-Methoxyphenyl)-3-(4″,6″-dinitro-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine **7Zd**.* Dark-blue solid; yield 73%; mp 217–218 °C. Anal. calcd for $C_{21}H_{13}N_5O_6$: C, 58.47; H, 3.04; N, 16.24. Found: C, 58.64; H, 3.05; N, 16.18%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.73 (s, 3H, 4′-OCH_3), 6.74 (d, J=8.8 Hz, 2H, H-3′), 6.81 (dd, J=7.0, 6.7 Hz, 1H, H-6), 6.87 (s, 1H, H-1), 7.17 (d, J=8.8 Hz, 2H, H-2′), 7.18 (dd, J=8.8, 6.7 Hz, 1H, H-7), 7.67 (d, J=8.8 Hz, 1H, H-8), 8.07 (d, J=7.0 Hz, 1H, H-5), 9.10 (s, 1H, H-5″); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 54.71 (4′-OCH_3), 104.54 (C-1), 112.78 (C-6), 112.86 (C-7″), 113.95 (C-3′), 118.92 (C-8), 123.12 (C-4″), 123.63 (C-7), 126.15 (C-5, C-1′), 128.93 (C-5″), 129.70 (C-2′), 132.43 (C-2), 135.67 (C-6″), 138.10 (C-9), 142.52 (C-9″), 143.04 (C-3), 151.24 (C-8″), 158.47 (C-4′).

*4.3.1.5. 2-(4′-Bromophenyl)-3-(4″,6″-dinitro-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine **7Ze**.* Dark-blue solid; yield 87%; mp 244–245 °C. Anal. calcd for $C_{20}H_{10}BrN_5O_5$: C, 50.02; H, 2.10; N, 14.58.

Found: C, 49.83; H, 2.09; N, 14.63%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.91 (dd, J=7.0, 6.8 Hz, 1H, H-6), 7.06 (s, 1H, H-1), 7.24 (dd, J=8.8, 6.8 Hz, 1H, H-7), 7.28 (d, J=7.8 Hz, 2H, H-2′), 7.38 (d, J=7.8 Hz, 2H, H-3′), 7.79 (d, J=8.8 Hz, 1H, H-8), 8.14 (d, J=7.0 Hz, 1H, H-5), 9.25 (s, 1H, H-5″); ^{13}C NMR (75.43 MHz, DMSO-d_6): δ 104.66 (C-1), 112.22 (C-7″), 113.44 (C-6), 119.36 (C-8), 120.83 (C-4′), 122.76 (C-4″), 123.89 (C-7), 126.23 (C-5), 129.08 (C-5″), 130.64 (C-2′), 131.69 (C-3′), 133.21 (C-1′), 133.30 (C-2), 133.95 (C-6″), 137.80 (C-9), 143.44 (C-3), 143.65 (C-).

4.3.1.6. 2-(4′-Nitrophenyl)-3-(4″,6″-dinitro-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine ***7Zf***. Dark-blue solid; yield 80%; mp 238–239 °C. Anal. calcd for $C_{20}H_{10}N_6O_7$: C, 53.82; H, 2.26; N, 18.83. Found: C, 54.00; H, 2.26; N, 18.76%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 6.87 (dd, J=7.0, 6.8 Hz, 1H, H-6), 7.11 (s, 1H, H-1), 7.21 (dd, J=8.8, 6.8 Hz, 1H, H-7), 7.57 (d, J=8.8 Hz, 2H, H-2′), 7.75 (d, J=8.8 Hz, 1H, H-8), 8.04 (d, J=8.8 Hz, 2H, H-3′), 8.11 (d, J=7.0 Hz, 1H, H-5), 9.15 (s, 1H, H-5″); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 104.77 (C-1), 112.32 (C-7″), 113.50 (C-6), 119.43 (C-8), 122.50 (C-4″), 123.42 (C-7), 123.53 (C-3′), 126.02 (C-5), 128.71 (C-5″), 129.48 (C-2′), 132.49 (C-2), 133.51 (C-6″), 137.51 (C-9), 140.95 (C-1′), 143.10 (C-3), 143.83 (C-9″), 146.04 (C-4′), 151.34 (C-8″).

4.3.1.7. 2-(4′-Methylphenyl)-3-(4″,6″-dinitro-3″-oxido-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine ***7Fc*** *(transient species).* ^{1}H NMR (250 MHz, chloroform-d_1): δ 2.32 (s, 3H, 4′-CH$_3$), 6.82 (s, 1H, H-1), 6.89 (dd, J=7.0, 6.7 Hz, 1H, H-6), 7.05 (d, J=8.8 Hz, 2H, H-3′), 7.09 (d, J=8.8 Hz, 2H, H-2′), 7.24 (dd, J=8.8, 6.7 Hz, 1H, H-7), 7.43 (d, J=7.0 Hz, 1H, H-5), 7.62 (d, J=8.8 Hz, 1H, H-8), 9.01 (s, 1H, H-5″).

4.3.1.8. 2-(4′-Bromophenyl)-3-(4″,6″-dinitro-3″-oxido-2″,1″,3″-benzoxadiazol-7″-yl)-indolizine ***7Fe*** *(transient species).* ^{1}H NMR (250 MHz, chloroform-d_1): δ 6.84 (s, 1H, H-1), 6.92 (dd, J=6.8, 6.5 Hz, 1H, H-6), 7.06 (d, J=7.7 Hz, 2H, H-2′), 7.25 (dd, J=8.6, 6.5 Hz, 1H, H-7), 7.42 (d, J=7.7 Hz, 2H, H-3′), 7.43 (d, J=6.8 Hz, 1H, H-5), 7.65 (d, J=8.6 Hz, 1H, H-8), 9.02 (s, 1H, H-5″).

4.3.2. Compounds ***8F,a–f***. See Eq. 3 in the text for the numbering of the various atoms.

4.3.2.1. 2-Methyl-4″,6″-dinitro-3-oxo-3H-spiro(2″,1″,3″-benzoxadiazole-7″,4-quinolizine) ***8Fa***. Brown solid; yield 85%; mp 234–235 °C (dec). Anal. calcd for $C_{15}H_9N_5O_6$: C, 50.71; H, 2.55; N, 19.71. Found: C, 50.80; H, 2.55; N, 19.65%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.18 (s, 3H, 2-CH$_3$), 7.97 (dd, J=7.4, 6.7 Hz, 1H, H-7), 8.28 (s, 1H, H-1), 8.39 (d, J=7.7 Hz, 1H, H-9), 8.71 (dd, J=7.7, 7.4 Hz, 1H, H-8), 9.09 (s, 1H, H-5″), 9.10 (d, J=6.7 Hz, 1H, H-6); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 15.11 (2-CH$_3$), 71.05 (C-7″), 111.69 (C-4″), 122.11 (C-6″), 128.68 (C-7), 129.61 (C-9), 134.32 (C-1), 135.43 (C-5″), 138.05 (C-2), 142.69 (C-10), 143.79 (C-9″), 145.89 (C-6), 148.43 (C-8), 149.86 (C-8″), 187.09 (C-3).

4.3.2.2. 2-Phenyl-4″,6″-dinitro-3-oxo-3H-spiro(2″,1″,3″-benzoxadiazole-7″,4-quinolizine) ***8Fb***. Brown solid; yield 88%; mp 176–177 °C (dec). Anal. calcd for $C_{20}H_{11}N_5O_6$: C, 57.56; H, 2.66; N, 16.78. Found: C, 57.75; H, 2.66; N, 16.72%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.53 (t, J=4.2 Hz, 1H, H-4′), 7.54 (d, J=4.2 Hz, 2H, H-2′), 7.68 (t, J=4.2 Hz, 2H, H-3′), 8.03 (dd, J=7.4, 6.3 Hz, 1H, H-7), 8.54 (d, J=7.7 Hz, 1H, H-9), 8.66 (s, 1H, H-1), 8.76 (dd, J=7.7, 7.4 Hz, 1H, H-8), 9.14 (s, 1H, H-5″), 9.17 (d, J=6.3 Hz, 1H, H-6); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 71.84 (C-7″), 111.76 (C-4″), 121.83 (C-6″), 128.89 (C-2′), 129.00 (C-3′, C-7), 130.82 (C-9), 130.90 (C-2), 131.12 (C-4′), 134.20 (C-1), 135.54 (C-5″), 137.43 (C-1′), 142.86 (C-10), 143.83 (C-9″), 145.94 (C-6), 148.26 (C-8), 149.61 (C-8″), 185.55 (C-3).

4.3.2.3. 2-(4′-Methylphenyl)-4″,6″-dinitro-3-oxo-3H-spiro(2″,1″,3″-benzoxadiazole-7″,4-quinolizine) ***8Fc***. Dark-brown solid; yield 80%; mp 178–179 °C (dec). Anal. calcd for $C_{21}H_{13}N_5O_6$: C, 58.47; H, 3.04; N, 16.24. Found: C, 58.57; H, 3.05; N, 16.18%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.37 (s, 3H, 4′-CH$_3$), 7.35 (d, J=7.7 Hz, 2H, H-3′), 7.61 (d, J=7.7 Hz, 2H, H-2′), 8.00 (dd, J=7.0, 6.7 Hz, 1H, H-7), 8.51 (d, J=7.7 Hz, 1H, H-9), 8.62 (s, 1H, H-1), 8.74 (dd, J=7.7, 7.0 Hz, 1H, H-8), 9.13 (s, 1H, H-5″), 9.15 (d, J=6.7 Hz, 1H, H-6); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 21.02 (4′-CH$_3$), 71.78 (C-7″), 111.72 (C-4″), 121.87 (C-6″), 128.24 (C-2), 128.77 (C-7), 128.92 (C-2′), 129.48 (C-3′), 130.63 (C-9), 133.19 (C-1), 135.52 (C-5″), 137.34 (C-4′), 141.10 (C-1′), 143.08 (C-10), 143.83 (C-9″), 145.75 (C-6), 148.16 (C-8), 149.62 (C-8″), 185.65 (C-3).

4.3.2.4. 2-(4′-Methoxyphenyl)-4″,6″-dinitro-3-oxo-3H-spiro(2″,1″,3″-benzoxadiazole-7″,4-quinolizine) ***8Fd***. Dark-brown solid; yield 83%; mp 230–231 °C (dec). Anal. calcd for $C_{21}H_{13}N_5O_7$: C, 56.38; H, 2.93; N, 15.65. Found: C, 56.45; H, 2.94; N, 15.59%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.83 (s, 3H, 4′-OCH$_3$), 7.10 (d, J=8.4 Hz, 2H, H-3′), 7.72 (d, J=8.4 Hz, 2H, H-2′), 7.97 (dd, J=7.0, 6.3 Hz, 1H, H-7), 8.49 (d, J=7.7 Hz, 1H, H-9), 8.58 (s, 1H, H-1), 8.72 (dd, J=7.7, 7.0 Hz, 1H, H-8), 9.12 (d, J=6.3 Hz, 1H, H-6), 9.13 (s, 1H, H-5″); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 55.52 (4′-OCH$_3$), 71.72 (C-7″), 111.70 (C-4″), 114.47 (C-3′), 121.93 (C-6″), 123.19 (C-2), 128.41 (C-7), 130.41 (C-9), 130.78 (C-2′), 131.87 (C-1), 135.53 (C-5″), 136.84 (C-1′), 143.38 (C-10), 143.83 (C-9″), 145.48 (C-6), 148.01 (C-8), 149.64 (C-8″), 161.59 (C-4′), 185.85 (C-3).

4.3.2.5. 2-(4′-Bromophenyl)-4″,6″-dinitro-3-oxo-3H-spiro(2″,1″,3″-benzoxadiazole-7″,4-quinolizine) ***8Fe***. Dark-purple solid; yield 78%; mp 204–205 °C (dec). Anal. calcd for $C_{20}H_{10}BrN_5O_6$: C, 48.41; H, 2.03; N, 14.11. Found: C, 48.27; H, 2.03; N, 14.13%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.64 (d, J=7.8 Hz, 2H, H-3′), 7.74 (d, J=7.8 Hz, 2H, H-2′), 8.03 (dd, J=6.8, 6.6 Hz, 1H, H-7), 8.53 (d, J=8.8 Hz, 1H, H-9), 8.69 (s, 1H, H-1), 8.76 (dd, J=8.8, 6.8 Hz, 1H, H-8), 9.13 (s, 1H, H-5″), 9.17 (d, J=6.6 Hz, 1H, H-6); ^{13}C NMR (62.9 MHz, DMSO-d_6): 71.86 (C-7″), 111.80 (C-4″), 121.71 (C-6″), 124.66 (C-4′), 129.18 (C-7), 130.24 (C-2), 130.98 (C-9, C-2′), 131.92 (C-3′), 134.56 (C-1), 135.53 (C-5″), 136.17 (C-1′), 142.63 (C-10), 143.82 (C-9″), 146.07 (C-6), 148.30 (C-8), 149.52 (C-8″), 185.31 (C-3).

4.3.2.6. 2-(4′-Nitrophenyl)-4″,6″-dinitro-3-oxo-3H-spiro(2″,1″,3″-benzoxadiazole-7″,4-quinolizine) ***8Ff***. Brown solid; yield 75%; mp 186–187 °C (dec). Anal. calcd for $C_{20}H_{10}N_6O_8$: C, 51.96; H, 2.18; N, 18.18. Found: C, 52.11; H, 2.18; N, 18.11%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 7.96 (d, J=8.9 Hz, 2H, H-2′), 8.08 (dd, J=7.0, 6.7 Hz, 1H, H-7), 8.37 (d, J=8.9 Hz, 2H, H-3′), 8.58 (d, J=7.7 Hz, 1H, H-9), 8.80 (dd, J=7.7, 7.0 Hz, 1H, H-8), 8.84 (s, 1H, H-1), 9.13 (s, 1H, H-5″), 9.22 (d, J=6.7 Hz, 1H, H-6); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 72.00 (C-7″), 111.90 (C-4″), 121.57 (C-6″), 123.90 (C-3′), 129.76 (C-7), 130.48 (C-2′), 131.49 (C-9), 135.26 (C-1), 135.56 (C-5″), 136.63 (C-1′), 137.30 (C-2), 142.09 (C-10), 143.84 (C-9″), 146.48 (C-6), 148.48 (C-8, C-4′), 149.47 (C-8″), 185.07 (C-3).

4.3.3. 2-Substituted 5,6-dihydropyrrolo[2,1-a]isoquinolines ***11a–f***. Numbering of the various atoms is shown in the structures drawn in the main text.

The dihydropyrroloisoquinolines **11a–f** were obtained following the Tchichibabin procedure modified by Casagrande[42] and other authors.[43,44] Equimolar amounts of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**10**)[44] and of the appropriate bromide (**9a–f**) were mixed in the presence of 3 equiv $NaHCO_3$. After addition of a minimal amount of *n*-butanol—Casagrande et al. used ethanol–to achieve a complete dissolution of the reagents[42]—the resulting mixture was refluxed for about 30 min. All cyclizations were thus carried out in one stage without isolating the quaternary intermediates. A TLC control showed that the reactions proceeded satisfactorily, affording the requested pyrroloisoquinolines **11a–f** in

good yields after cooling of the reaction mixture at 0 °C. Compounds **11b–e** were recrystalized in butanol while **11a** and **11f** were purified by column chromatography (silica, $CHCl_3$). Analytical and spectral data for the six compounds are given in pages S8–S9 in Supplementary data. To be noted is that only **11a** and **11e** were previously reported.[44]

*4.3.4. Couplings of DNBZ-Cl and DNBF-Cl with **11a–f**.* Numbering of the various atoms is shown in the structures drawn in the main text.

The synthesis of the coupling products **12Z,a–f** and **13F,a–f** has been completed, including the purification, under the same experimental conditions as those used for that of the indolizine products **7Z,a–f** and **8F,a–f**. Analytical data for compounds **12Z,a–f** and **13F,a–f** are given in pages S9–S15 in Supplementary data.

Acknowledgements

The authors are grateful for the support to this research by RFBR (Russian Foundation of Basic Researches, project 07-03-92173-CNRS_a) and RNP 2.2.1.1/2348, and the CNRS (Centre National pour la Recherche Scientifique) France.

Supplementary data

^1H and ^{13}C NMR data pertaining to compounds **8F,a–f**, **11a–f**, **12Z,a–f** and **13F,a–f** are collected in Tables S1–S4 in pages S2-S5. Analytical data for compounds **5a–f**, **11a–f** and related adducts **12Z,a–f** and **13F,a–f** are given in pages S6–S15. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.11.071.

References and notes

1. (a) Terrier, F.; Kizilian, E.; Halle, J. C.; Buncel, E. *J. Am. Chem. Soc.* **1992**, *114*, 1740; (b) Terrier, F.; Pouet, M. J.; Halle, J. C.; Hunt, S.; Jones, J. R.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1665.
2. (a) Buncel, E.; Renfrow, R. A.; Strauss, M. J. *J. Org. Chem.* **1987**, *52*, 488; (b) Buncel, E.; Manderville, R. A.; Dust, J. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1019.
3. (a) Crampton, M. R.; Rabbitt, L. C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1669; (b) Crampton, M. R.; Rabbitt, L. C.; Terrier, F. *Can. J. Chem.* **1999**, *77*, 639; (c) Crampton, M. R.; Lunn, R. E. A.; Lucas, D. *Org. Biomol. Chem.* **2003**, *1*, 3438.
4. (a) Asghar, B. H. M.; Crampton, M. R. *Org. Biomol. Chem.* **2007**, *5*, 1646; (b) Asghar, B. H. M.; Crampton, M. R. *J. Phys. Org. Chem.* **2007**, *20*, 702; (c) Asghar, B. H. M.; Crampton, M. R.; Isanbor, C. *Can. J. Chem.* **2008**, *86*, 225.
5. (a) Boga, C.; Forlani, L. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1408; (b) Boga, C.; Del Vecchio, E.; Forlani, L.; Mazzanti, A.; Todesco, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3285.
6. (a) Forlani, L.; Tocke, A. L.; Del Vecchio, E.; Lakhdar, S.; Goumont, R.; Terrier, F. *J. Org. Chem.* **2006**, *71*, 5527.
7. Remennikov, G. Y.; Kempf, B.; Ofial, A. R.; Polborn, K.; Mayr, H. *J. Phys. Org. Chem.* **2003**, *16*, 431.
8. (a) Evgen'yev, M. I.; Garmonov, S. Y.; Shakirova, L. S.; Brysaev, A. S. *J. Anal. Chem.* **2002**, *57*, 1103; (b) Evgen'ev, M. I.; Evgen'eva, I. I.; Levinson, F. S.; Ermolaeva, E. A.; Valitova, Y. R. *J. Anal. Chem.* **2006**, *61*, 133.
9. (a) Kurbatov, S. V.; Budarina, Z. N.; Vaslyaeva, G. S.; Borisenko, N. I.; Knyazev, A. P.; Minkin, V. I.; Zhdanov, Y. A.; Olekhnovich, L. P. *Izv. Acad. Nauk, Ser. Khim.* **1997**, 1509; (b) Olekhnovich, L. P.; Budarina, Z. N.; Lesin, A. V.; Kurbatov, S. V.; Borodkin, G. S.; Minkin, V. I. *Mendeleev Commun.* **1997**, 162.
10. (a) Terrier, F.; Millot, F.; Norris, W. P. *J. Am. Chem. Soc.* **1976**, *98*, 5883; (b) Terrier, F.; Chatrousse, A. P.; Soudais, Y.; Hlaibi, M. *J. Org. Chem.* **1984**, *49*, 4176.
11. Lakhdar, S.; Goumont, R.; Boubaker, T.; Mokhtari, M.; Terrier, F. *Org. Biomol. Chem.* **2006**, *4*, 1910.
12. Bernasconi, C. F. *J. Am. Chem. Soc.* **1972**, *93*, 6975.
13. (a) Crampton, M. R. *Adv. Phys. Org. Chem.* **1969**, *7*, 211; (b) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667; (c) Terrier, F. *Chem. Rev.* **1982**, *82*, 77; (d) Buncel, E. In *The Chemistry of Amino, Nitro and Nitroso Compounds*; Patai, S., Ed.; Wiley: London, 1982; (e) Buncel, E.; Crampton, M. R.; Strauss, M. J.; Terrier, F. *Electron-Deficient Aromatic– and Heteroaromatic–Base Interactions*; Elsevier: Amsterdam, 1984; (f) Part 2 Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4.
14. Terrier, F. In *Nucleophilic Aromatic Displacement*; Feuer, H., Ed.; VCH: New York, NY, 1991.
15. Terrier, F.; Pouet, M. J.; Halle, J. C.; Kizilian, E.; Buncel, E. *J. Phys. Org. Chem.* **1998**, *11*, 707.
16. (a) Read, R. W.; Spear, R. J.; Norris, W. P. *Aust. J. Chem.* **1983**, *36*, 1227; (b) Read, R. W.; Norris, W. P. *Aust. J. Chem.* **1985**, *38*, 297.
17. (a) Kizilian, E.; Terrier, F.; Chatrousse, A. P.; Gzouli, K.; Halle, J. C. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2667; (b) Terrier, F.; Halle, J. C.; Simonnin, M. P.; Pouet, M. J. *J. Org. Chem.* **1984**, *49*, 4363.
18. Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. *J. Org. Chem.* **2006**, *71*, 9088.
19. Terrier, F.; Lakhdar, S.; Boubaker, T.; Goumont, R. *J. Org. Chem.* **2005**, *70*, 6242.
20. (a) Moutiers, G.; Goumont, R.; Pinson, J.; Terrier, F. *Chem.—Eur. J.* **2001**, *7*, 1712; (b) Goumont, R.; Jan, E.; Makosza, M.; Terrier, F. *Org. Biomol. Chem.* **2003**, *1*, 2192.
21. Sikder, M. A. K.; Salunke, R. B.; Sikder, N. *New J. Chem.* **2001**, *25*, 1549.
22. Bemi, M.; Vasilescu, M.; Caproiu, M. T.; Draghici, C.; Beteringhe, A.; Constantinescu, T.; Banciu, M. D.; Balaban, A. T. *Cent. Eur. J. Chem.* **2004**, 672.
23. Kurbatov, S.; Rodriguez Da Fonte, P.; Goumont, R.; Marrot, J.; Terrier, F. *Chem. Commun.* **2003**, 2150.
24. Vogel, S.; Kmoche, W.; Schoeller, W. W. *J. Chem. Soc., Perkin Trans. 2* **1986**, 769.
25. (a) Effenberger, F. *Acc. Chem. Res.* **1989**, *22*, 27; (b) Effenberger, F.; Agster, W.; Fischer, P.; Jogun, K. H.; Stezowski, J. J.; Daltrozzo, E.; Kohlmannsberger-von Nell, G. J. *Org. Chem.* **1983**, *48*, 4649.
26. Shipman, M. In *Science of Synthesis*; Thomas, J., Ed.; Georg Thieme: Stuttgart, New York, NY, 2000; Vol. 10, pp 745–787.
27. (a) Fraser, M.; McKenzie, S.; Reid, D. H. *J. Chem. Soc. B* **1966**, 44; (b) Armarego, W. L. F. *J. Chem. Soc.* **1964**, 4226; (c) Tietzer, L. F.; Eicher, T. *Reaktionen und Synthesen im organisch-chemischen: Praktikum und Forschungslaboratorium*; Georg Thieme: Stuttgart, New York, NY, 1991, pp 359–360.
28. (a) Terrier, F.; Debleds, F. L.; Verchere, J. F.; Chatrousse, A. P. *J. Am. Chem. Soc.* **1985**, *107*, 307; (b) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic: London, New York, NY, 1977, pp 446–451.
29. Kurbatov, S. V.; Tatarov, A. V.; Minkin, V. I.; Goumont, R.; Terrier, F. *Chem. Commun.* **2006**, 4279.
30. Lowe-Ma, C. K.; Nissan, R. A.; Wilson, S. *J. Org. Chem.* **1990**, *55*, 3755.
31. Terrier, F.; Halle, J. C.; MacCormack, P.; Pouet, M. J. *Can. J. Chem.* **1989**, *67*, 503.
32. Cmoch, P.; Stefaniak, L.; Webb, G. A. *Magn. Reson. Chem.* **1997**, *35*, 483.
33. Anet, F. A. L.; Yavari, I. *Org. Magn. Reson.* **1976**, *8*, 158.
34. Witanowski, M.; Stefaniak, L.; Biernat, S.; Webb, G. A. *Org. Magn. Reson.* **1980**, *14*, 356.
35. Katritzky, A. R.; Gordeev, M. F. *Heterocycles* **1993**, *35*, 483.
36. Wennerström, H.; Wennerström, O. *Acta Chem. Scand.* **1972**, *96*, 2883.
37. Hosoya, H.; Hosoya, S.; Nagakura, S. *Theor. Chim. Acta* **1968**, *12*, 117.
38. Strauss, M. J.; Fleischmann, S.; Buncel, E. *J. Mol. Struct.* **1985**, *121*, 37.
39. Olah, G.; Mayr, H. *J. Org. Chem.* **1976**, *41*, 3448.
40. Terrier, F.; Millot, F.; Chatrousse, A. P.; Pouet, M. J.; Simonnin, M. P. *Org. Magn. Reson.* **1976**, *8*, 56.
41. Terrier, F.; Goumont, R.; Pouet, M. J.; Halle, J. C. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1629.
42. Casagrande, C.; Invernizzi, A.; Ferrini, R.; Ferrari, G. G. *J. Med. Chem.* **1968**, *11*, 765.
43. Shevchuk, M. I.; Dombrovskii, A. V. *Zh. Obshch. Khim.* **1963**, *33*, 1135.
44. Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955.
45. (a) Perrin, D. D. *Pure Appl. Chem.* **1969**, *20*, 133; (b) Perrin, D. D. *Dissociation Constants of Inorganic Acids and Bases in Aqueous Solution*; Butterworths: London, 1969.
46. (a) Makosza, M. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: New York, NY, 1993; p 401; (b) Makosza, M.; Woniarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.
47. Makosza, M.; Wojciechowski, K. *Chem. Rev.* **2004**, *104*, 2631.
48. Chupakhin, O. N.; Charushin, V. N.; Van der Plas, H. C. *Nucleophilic Aromatic Substitution of Hydrogen*; Academic: San Diego, CA, 1994.
49. Kozhevnikov, D. N.; Rusinov, V. L.; Chupakhin, O. N.; Makosza, M.; Rykiwski, A.; Wolinska, E. *Eur. J. Org. Chem.* **2002**, 1412.
50. Prokhorov, A. M.; Kozhevnikov, D. N.; Rusinov, V. L.; Chupakhin, O. N. *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 1195.
51. Kozhevnikov, D. N.; Kataeva, N. N.; Rusinov, V. L.; Chupakhin, O. N.; Alexandrov, G. G. *Mendeleev Commun.* **2005**, 31.
52. Terrier, F.; Beaufour, M.; Halle, J. C.; Cherton, J. C.; Buncel, E. *Tetrahedron Lett.* **2001**, *42*, 4499.
53. Jones, R. L.; Rees, C. W. *J. Chem. Soc. C* **1969**, 2255.
54. Landor, S. R.; Rogers, V.; Sood, H. R. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2103.
55. Gabbut, P. D.; Hepworth, J. D.; Heron, B. M.; Elsegood, M. R. J.; Clegg, W. *Chem. Commun.* **1999**, 289.
56. Gambarcorta, A.; Nicoletti, R.; Forcellese, M. L. *Tetrahedron* **1971**, *27*, 985.
57. Elliot, A. R.; Herrick, A. B.; Roder, T. M. *J. Am. Chem. Soc.* **1950**, *72*, 2760.
58. Turner, P. G.; Donokse, T. J.; Cousins, R. P. C. *Chem. Commun.* **2004**, 1422.
59. (a) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147; (b) Bernasconi, C. F.; Gehriger, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 1092; (c) Bernasconi, C. F.; Gehriger, C. L.; De Rossi, R. D. *J. Am. Chem. Soc.* **1976**, *98*, 8451.
60. Bernasconi, C. F.; Terrier, F. *J. Am. Chem. Soc.* **1975**, *97*, 7458.
61. (a) Bernasconi, C. F.; Howard, K. *J. Am. Chem. Soc.* **1982**, *104*, 7248; (b) Bernasconi, C. F.; Gemdler, J. R. *J. Org. Chem.* **1977**, *42*, 3387.
62. Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1681.
63. Jenks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, NY, 1969, Chapter 3.
64. Kirby, A. J.; Jenks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3217.
65. Kurbatov, S. V.; Budarina, Z. N.; Vaslyaeva, G. S.; Borisenko, N. I.; Knyazev, A. P.; Minkin, V. I.; Zhdanov, Y. A.; Olekhnovich, L. P. *Russ. Chem. Bull. Int. Ed.* **1997**, *46*, 1445.

66. (a) Morozov, P. G.; Kurbatov, S. V.; Olekhnovich, L. P. *Chem. Heterocycl. Comp.* **2001**, *38*, 1428; (b) Morozov, P. G.; Kurbatov, S. V.; Dolgushin, F. M.; Antipin, M. Y.; Olekhnovich, L. P. *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 2075.
67. Voronina, V. A.; Kurbatov, S. V.; Olekhnovich, L. P. *Russ. J. Org. Chem.* **2004**, *40*, 1384.
68. Terrier, F.; Xiao, L.; Hlaibi, M.; Halle, J. C. *J. Chem. Soc., Perkin Trans. 2* **1993**, 337.
69. Sharnin, G. I.; Levinson, S. A.; Akimova, S. A.; Kasamov, R. K. USSR Patent 657,025, 1979. *Chem. Abstr.* **1979**, *91*, P20519h.
70. Norris, W. P.; Chafin, A.; Spear, R. J.; Read, R. W. *Heterocycles* **1984**, *22*, 271.
71. Tchichibabin, A. E. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1607.
72. Posseels, G.; Peiven, M.; Cornil, R.; Prost, M.; Descamps, M. *Ing. Chem. (Brussels)* **1981**, *63*, 3.
73. Anitha, I.; Rajan, P. K. *J. Indian Chem. Soc.* **1989**, *66*, 460.
74. Borrows, E. T.; Holland, D. O.; Kenyon, J. *J. Chem. Soc.* **1946**, 1077.
75. Lins, C. L. K.; Block, J. H.; Ooerge, R. F. *J. Pharm. Sci.* **1982**, *71*, 556.
76. Kochetkova, E. A. *Zh. Obshch. Khim.* **1963**, *73*, 1201.
77. Buu-Hoï, N. P.; Jacquignon, P.; Xuong, N. D.; Lavit, D. *J. Org. Chem.* **1954**, *19*, 1370.
78. Cliff, G. R.; Jones, G.; Stanyer, J. *J. Chem. Soc. C* **1971**, 3426.