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SELECTIVE (^{15}N) NITRATION OF 2,2-DIPHENYL-1-(2,4- OR 2,6-DINITROPHENYL)-HYDRAZINES OR -HYDRAZYLS

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SUMMARY

Treatment of the title compounds with sodium [^{15}N]nitrite in the presence of crown ether 15-crown-5 led to selective nitration yielding 2-(*para*-[^{15}N]nitrophenyl)-2-phenyl-1-(2,4- or 2,6-dinitrophenyl) hydrazines. When starting from the 2,6-dinitro-derivative under the same reaction conditions, a di-[^{15}N]nitro-derivative in the *para*-phenyl and 4-positions (picryl) was also obtained. The same reaction carried out with [^{15}N]nitrous acid afforded the same products mentioned above and, in addition when using the 2,6-disubstituted compound, a tri-[^{15}N]nitro-hydrazine in the *p,p'*, and 4-positions. The electronic, ESR and NMR spectra of the newly obtained products are presented, and the reaction mechanisms for these unconventional nitrations are discussed.

Keywords: DPPH, hydrazyl, crown ether, synthesis, regioselective nitration, ^{15}N-labeling

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INTRODUCTION

For the regioselective *para*-phenyl nitration of the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH), previous papers presented two approaches:[1] (I) in a solid-liquid (s-l) biphasic system, nitration of DPPH with sodium nitrite and crown ether (CE) 15-C-5 yields the mono-*para*-nitrophenyl-hydrazine derivative *p*-NO_2-$DPPH_2$; (ii) in a liquid-liquid (l-l) biphasic system, nitration of DPPH leads both to mono-*para*-nitrophenyl-hydrazine, and further nitration of this product to 2,2-di-(*p*-nitrophenyl)-1-picrylhydrazine (eqs. 1,2).

$$\text{DPPH} \xrightarrow[\text{CE}]{\text{NaNO}_2} p\text{-NO}_2\text{-DPPH} \underset{\text{ox.}}{\overset{\text{red.}}{\rightleftharpoons}} p\text{-NO}_2\text{-DPPH}_2 \qquad (1)$$

$$\text{DPPH} \xrightarrow{\text{HNO}_2} p\text{-NO}_2\text{-DPPH} \xrightarrow{\text{HNO}_2} p,p'\text{-(NO}_2)_2\text{-DPPH}_2 \qquad (2)$$

These procedures afford better selectivity and yields than the previously described nitration of DPPH with gaseous nitrogen dioxide in benzene solution.[2]

In the present paper we describe the analogous regioselective formation of *para*-nitrophenyl derivatives starting from dinitro congeners of DPPH, namely 2,4- and 2,6-disubstituted derivatives (Fig. 1).

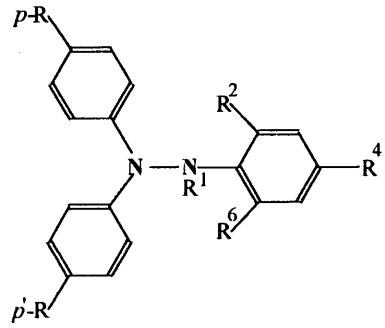


Fig. 1. The compounds involved in this study.

Fig. 1 (continued)

Compound	R^1	R^2	R^4	R^6	*p*-R	*p'*-R
1a/b 2,4-ine/yl	H / ·	H	NO_2	NO_2	H	H
2a/b 2,6-ine/yl	H / ·	NO_2	H	NO_2	H	H
3a/b* *p*-$^{15}NO_2$-2,4-ine/yl	H / ·	H	NO_2	NO_2	$^{15}NO_2$	H
3a/b** *p*-$^{15}NO_2$-^{15}2,4-ine/yl	H / ·	H	NO_2	$^{15}NO_2$	$^{15}NO_2$	H
4a/b* *p*-$^{15}NO_2$-2,6-ine/yl	H / ·	NO_2	H	NO_2	$^{15}NO_2$	H
5a/b** *p*-$^{15}NO_2$-2, ^{15}4,6-ine/yl	H / ·	NO_2	$^{15}NO_2$	NO_2	$^{15}NO_2$	H
6a/b*** *p,p'*-($^{15}NO_2$)$_2$-2, ^{15}4,6-ine/yl	H / ·	NO_2	$^{15}NO_2$	NO_2	$^{15}NO_2$	$^{15}NO_2$

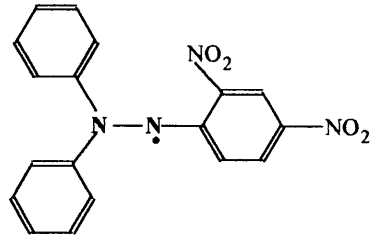
Letter **a** denotes hydrazines (R^1=H) and **b** (R^1 = ·) denotes hydrazyls; each asterisk indicates one ^{15}N

RESULTS AND DISCUSSION

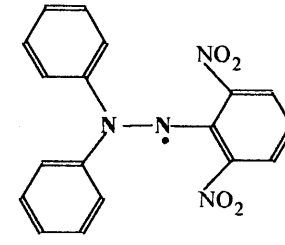
For discriminating between substitution of hydrogen atoms at phenyl groups, and *ipso*-substitution of pre-existing nitro groups, we used as nitrating agents ^{15}N-labelled precursors (sodium [^{15}N]nitrite and the corresponding [^{15}N]nitrous acid).

Literature procedures were employed for preparing the starting materials **1** and **2**, either as hydrazines or as hydrazyls (abbreviated as indicated in Fig.1).[3] The free radicals were prepared from the corresponding hydrazines by oxidation with lead dioxide or with potassium permanganate. Unlike the 2,6-yl which is stable both as solid and in solution, the 2,4-yl decomposes slowly in solution.[4]

1a (2,4-ine) $\xrightarrow{\text{oxid.}}$ **1b** (2,4-yl) ; **2a** (2,6-ine) $\xrightarrow{\text{oxid.}}$ **2b** (2,6-yl) (3)



1b

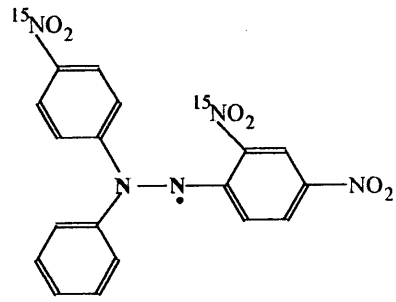


2b

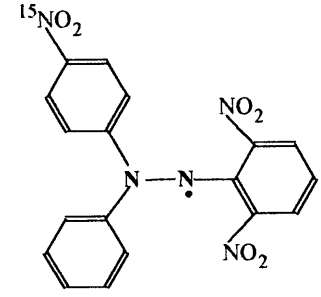
Reaction with sodium [^{15}N]nitrite and CE in a s-l biphasic system. Reaction products are described by eqs. 4 and 5.

1b (2,4-yl) $\longrightarrow$ **3a**$^{\bullet}$ + **3a**$^{\bullet\bullet}$ + Ph-NH-C_6H_4-$^{15}NO_2$ + side-products (4)

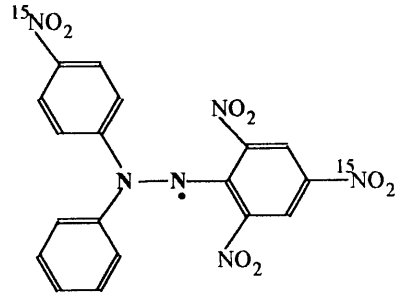
2b (2,6-yl) $\longrightarrow$ **4a**$^{\bullet}$ + **5a**$^{\bullet\bullet}$ (5)



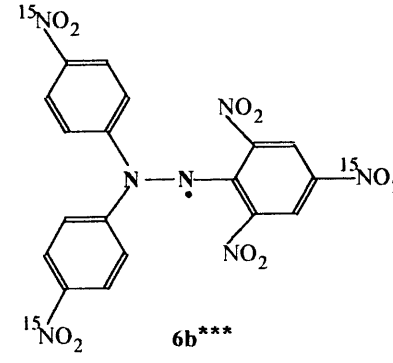
3b**



4b*



5b**



6b***

The proposed mechanism for these reactions involves[1] a CE-mediated transfer of $Na^{15}NO_2$ from the solid to the organic phase yielding a supramolecular complex according to eq. 6. Then the nitrite anion generates [^{15}N]nitrogen dioxide by electron transfer (ET) involving a hydrazyl radical (eq. 7). Finally, another hydrazyl molecule traps $^{15}NO_2^{\bullet}$ yielding the observed products (eqs. 8-10) after the corresponding tautomerization (hydrogen atom migration from phenyl to the hydrazinic nitrogen atom, Fig.2).

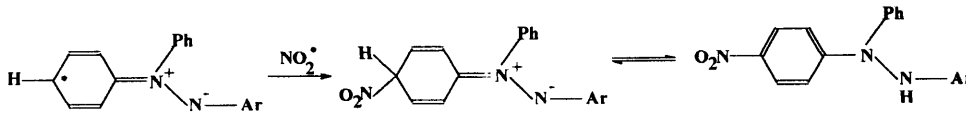


Fig.2. Nitration followed by hydrogen atom migration from phenyl to the hydrazinic nitrogen atom

$$CE + Na^{+}\ {}^{15}NO_2^{-} \longrightarrow (CE..Na)^{+}\ {}^{15}NO_2^{-} \quad (6)$$

$$(CE..Na)^{+}\ {}^{15}NO_2^{-} + 2,4\text{-yl (\mathbf{1b})} \longrightarrow (CE..Na)^{+}\ 2,4\text{-ine}^{-} + {}^{15}NO_2^{\bullet} \quad (7)$$

$$2,4\text{-yl (\mathbf{1b})} + {}^{15}NO_2^{\bullet} \longrightarrow p\text{-}{}^{15}NO_2\text{-}{}^{15}2,4\text{-ine (\mathbf{3a^{\bullet}})} \quad (8)$$

$$\mathbf{3b^{\bullet}} + {}^{15}NO_2^{\bullet} \longrightarrow p\text{-}{}^{15}NO_2\text{-}{}^{15}2,4\text{-ine (\mathbf{3a^{\bullet\bullet}})} \quad (9)$$

$$(CE..Na)^{+}\ {}^{15}NO_2^{-} + 2,6\text{-yl (\mathbf{2b})} \longrightarrow (CE..Na)^{+}\ 2,6\text{-ine}^{-} + {}^{15}NO_2^{\bullet} \quad (10)$$

$$2,6\text{-yl (\mathbf{2b})} + {}^{15}NO_2^{\bullet} \longrightarrow p\text{-}{}^{15}NO_2\text{-}{}^{15}2,6\text{-ine (\mathbf{4a^{\bullet}})} \quad (11)$$

$$p\text{-}{}^{15}NO_2\text{-}2,6\text{-ine (\mathbf{4a^{\bullet}})} + {}^{15}NO_2^{\bullet} \longrightarrow p\text{-}{}^{15}NO_2\text{-}2,6\text{-yl (\mathbf{4a^{\bullet}})} + H{}^{15}NO_2 \quad (12)$$

$$p\text{-}{}^{15}NO_2\text{-}2,6\text{-yl (\mathbf{4b^{\bullet}})} + {}^{15}NO_2^{\bullet} \longrightarrow p\text{-}{}^{15}NO_2\text{-}2,{}^{15}4,6\text{-ine (\mathbf{5b^{\bullet\bullet}})} \quad (13)$$

$$p\text{-}{}^{15}NO_2\text{-}2,{}^{15}4,6\text{-ine (\mathbf{5b^{\bullet\bullet}})} + {}^{15}NO_2^{\bullet} \longrightarrow p,p'\text{-}{}^{15}NO_2\text{-}2,{}^{15}4,6\text{-yl (\mathbf{6b^{\bullet\bullet\bullet}})} + H{}^{15}NO_2 \quad (14)$$

The formation of *p*-nitro-diphenylamine (eq. 4) is apparently due to the decomposition of 2,4-yl by fission of the N-N bond. By ^{1}H-NMR and ^{13}C-NMR it was found that no *ipso*-substitution of pre-existing nitro groups occurred, unlike cases described in the literature;[5] an exception is compound **3a**$^{\bullet}$ which shows *ipso*-substitution on its *ortho*-nitro group. The reaction products **3a**$^{\bullet\bullet}$ and **5a**$^{\bullet\bullet}$ do not afford further nitration under the same reaction conditions, but **4a** yields **5a** under these conditions (eq. 15).

$$\mathbf{4a^{\bullet}} \longrightarrow \mathbf{5a^{\bullet\bullet}} \quad (15)$$

Reaction with [^{15}N]nitrous acid . The tri-[^{15}N]nitroderivative **6a***** can be prepared in 90% yield from 2,6-yl (**2b**) and [^{15}N]nitrous acid in 24 hrs. If the starting material is the corresponding hydrazine (**2a**), the duration of the reaction is much longer (two weeks) but the product is the same. The 2,4-dinitro congeners do not afford under these reaction conditions different products from those obtained with sodium nitrite and CE. The reaction mechanism[1] involves disproportionation of [^{15}N]nitrous acid affording [^{15}N]nitrogen dioxide. By ET reactions, hydrazines are oxidized to hydrazyls, and these free radicals trap nitrogen dioxide (eqs. 16, 17).

1a $\longrightarrow$ **3a**** + side-products (16)

2a $\longrightarrow$ **6a***** (17)

NMR spectra provide evidence for the structure of the reaction products, as seen in the Experimental Part. The new radicals **3b**$^{\bullet}$ and **4b**$^{\bullet}$ have ESR spectra (Fig. 3) with seven and five broad peaks, respectively.

CONCLUSIONS

Under the above non-conventional nitration procedures, good yields and high selectivity of products can be attained. The reaction mechanism involves odd-electron species (hydrazyls, nitrogen dioxide). A difference was observed between reactions carried out with or without acids in the reaction medium (in the former case, a third nitro group was introduced into 2,6-yl, but not into 2,4-yl, converting the dinitrophenyl group into picryl).

EXPERIMENTAL PART

UV spectral determinations were performed with a Specord UV-VIS spectrophotometer.

The ESR spectra were recorded in toluene at room temperature on a JES-3B (JEOL) spectrometer with 100 kHz field modulation using X-band frequency. The parameters of the ESR spectra were measured in comparison with those of Fremy's salt (a_N=13.0 Gauss).

The NMR spectra were recorded at ambient temperature (ca. 295K) with a Varian Gemini 300BB instrument; the solvent was deuterated chloroform; internal TMS was used as reference both for ^{1}H-NMR and ^{13}C-NMR spectra. All the carbon spectra were measured in quantitative conditions: pw(π/4)= 4.4 μs, 20 s delay between pulses, the decoupler switched on only in the aquisition period, and 2048 transients in every FID. Besides, COSY(^{1}H-^{13}C) experiments were performed in order to assign the chemical shifts.

The starting materials (**1a,b** and **2a,b**) were obtained as described earlier.[3] All other reagents were commercial materials, of analytical purity. The sodium [^{15}N]nitrite used in this paper was enriched to 98.3% of isotopic purity, and was delivered by the Institute of Stable Isotopes Cluj, Roumania.

UV-Vis: **3a** *p*-$^{15}NO_2$-2,4-ine: λ_{max}= 360 nm; corresponding free radical **3b** *p*-$^{15}NO_2$-2,4-yl: λ_{max}= 490 nm; the compound **3a** in basic media give the corresponding anion, λ_{max}= 470 nm.
4a *p*-$^{15}NO_2$-2,6-ine: λ_{max}= 355 nm; corresponding free radical **4b** *p*-$^{15}NO_2$-2,6-yl: λ_{max}= 495 nm; the compound **4a** in basic media give the corresponding anion, λ_{max}= 465 nm.

NMR

3a ^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): **10.19**(bs, 1H, N-H, deuterable); **9.15**(dt, 1H, H-3, 1.2, 2.5, ^3J(H-^{15}N)=1.2); **8.32**(dd, 1H, H-5, 2.6, 9.3); **8.12**(dd, 2H, H-9-11, 9.2, ^3J(H-^{15}N)=1.6); **7.47**(t, 2H, H-15-17, 7.2); **7.39**(dd, 1H, H-6, 9.3, 1.2); **7.33**(tt, 1H, H-16, 7.2, 1.3); **7.16**(dd, 2H, H-14-18, 7.2, 1.3); **7.08**(d, 2H, H-8-12, 9.2).
^{13}C-NMR($CDCl_3$, δ ppm): **151.03**(C-q, C-7); **147.70**(C-q, C-13); **142.42**(C-q, C-1); **141.98**(d, C-q, C-10, J(C-^{15}N)=16.1 Hz); **139.06**(d, C-q, C-2, J(C-^{15}N)=17.4 Hz); **131.16**(C-q, C-4); **130.97**(CH, C-5); **130.40**(CH, C-15-17); **127.56**(CH, C-16); **125.81**(CH, C-9-11); **123.79**(CH, C-3); **123.39**(CH, H-14-18); **114.83**(CH, C-8-12); **114.72**(CH, C-6); **139.08**(C-q);

4a ^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): **9.72**(bs, 1H, NH, deuterable); **8.13**(dd, 2H, H-9-11, 9.2, ^3J(N-H)=1.8 Hz); **8.16÷7.96**(vbs, 2H, H-3 and H-5); **7.41**(t, 2H, H-15-17, 7.2); **7.31**(t, 1H, H-16, 7.2); **7.20**(d, 2H, H-14-18, 7.2); **7.15**(d, 2H, H-8-12, 9.2); **7.03**(t, 1H, H-4, 8.2).
^{13}C-NMR($CDCl_3$, δ ppm): **152.48**(C-q, C-7); **144.34**(C-q, C-13); **142.51**(d, C-q, C-10, J(^{15}N-C)=16.0 Hz); **137.56**(C-q); **130.39**(CH, C-15-17); **128.32**(CH, C-16); **124.91**(CH); **124.83**(CH); **119.43**(CH); **115.59**(CH).

5a ^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): **10.23**(bs, 1H, NH, deuterable); **9.22**(bs, 1H, H-3 or H-5); **8.58**(bs, 1H, H-5 or H-3); **8.15**(dd, 2H, H-9-11, 9.3, ^3J(N-H)=1.8 Hz); **7.46**(t, 2H, H-15-17, 7.3); **7.37**(t, 1H, H-16, 7.3); **7.23**(d, 2H, H-14-18, 7.3); **7.12**(d, 2H, H-8-12, 9.3).
^{13}C-NMR($CDCl_3$, δ ppm): **151.32**(C-q, C-7); **144.14**(C-q, C-13); **143.27**(d, C-q, C-10, J(^{15}N-C)=16.0 Hz); **141.49**(C-q, C-1); **137.71**(d, C-q, C-4, J(^{15}N-C)=18.1 Hz); **130.67**(CH, C-15-17); **128.86**(CH, C-16); **125.04**(CH, C-9-11); **124.52**(CH, C-14-18); **116.14**(CH, C-8-12).

140.61(bs, C-q, C-2 or C-6); **134.58**(bs, C-q, C-6 or C-2); **126.35**(bs, CH, C-3 and C-5).

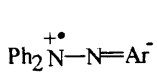
6a ^{1}H-NMR(acetone-d6, δ ppm, *J* Hz): **11.41**(bs, 1H, NH, deuterable); **9.20**(bs, 1H, H-3 or H-5); **8.84**(bs, 1H, H-5 or H-3); **8.28**(dd, 4H, H-9-11-15-17, 9.2, ^{3}J(N-H)=1.8 Hz); **7.61**(d, 4H, H-8-12-14-18, 9.2).
^{13}C-NMR(acetone-d6, δ ppm): **150.27**(C-q, C-7-13); **145.33**(d, C-10-16, $J(^{15}$N-C)=15.6 Hz); **125.64**(d, CH, C-9-11-15-17, $^{2}J(^{15}$N-C)=1.8 Hz); **121.42**(d, CH, C-8-12-14-18, $^{3}J(^{15}$N-C)=2.4 Hz); **143.17** (vbs, C-q); **141.64**(bs, C-q); **138.18**(bbs, C-q); **136.08**(bbs, C-q); **127.32**(bbs, CH); 125.84(bbs, CH).
^{1}H-NMR($CDCl_3$, δ ppm, *J* Hz): **10.38**(bs, 1H, NH, deuterable); **9.30**(bs, 1H, H-3 or H-5); **8.55**(bs, 1H, H-5 or H-3); **8.28**(dd, 4H, H-9-11-15-17, 9.1, ^{3}J(N-H)=1.7 Hz); **7.31**(d, 4H, H-8-12-14-18, 9.2).
^{13}C-NMR($CDCl_3$, δ ppm): **148.72**(C-q, C-7-13); **140.41**(C-q); 138.16(C-q); **125.73**(d, CH, C-9-11-15-17, $^{2}J(^{15}$N-C)=2.0 Hz); **120.33**(d, CH, C-8-12-14-18, $^{3}J(^{15}$N-C)=2.5 Hz).

ESR The ESR spectra of **1b** and **3b**$^{\bullet}$ in toluene show similar features with some of those obtained by Weil *et al.* for DPPH substituted with electron acceptors such as -NO_2 or -$COOCH_3$ in phenyl rings, while the hydrazyl radical **4b**$^{\bullet}$ shows similar features with that obtained from N-picryl-9-amino-carbazyl.[6] The nitrogen hyperfine coupling constants resulted after the simulation of the experimental spectra are given in Table 1. The radical **1b** has been previously obtained and its ESR spectrum was measured in benzene by Balaban *et al.*[4] The hfc coupling ratio (0.72) in this radical, measured by a method similar with that employed by Deal and Koski,[7] is almost identical with that resulting from our simulation of the spectra, a fact which increases the confidence in the simulation results. The larger coupling constant *a* in Table 1 has been assigned to the nitrogen atom N(1), by similarity with the assignment in the corresponding picryl-hydrazyls.

Table 1. ESR parameters of hydrazyl radicals in toluene

Radical	a_N (G)	a'_N (G)	Δ H (G)
1b	9.1	6.4	6.4
3b$^{\bullet}$	11.2	5.9	4.5
4b$^{\bullet}$	10.6	6.0	6.3

The data in Table 1 lead to the following observations: (i) compared to the hyperfine coupling constants of DPPH (a= 9.9 G and a'=7.6 G)[5] in a solvent (benzene) similar to that used in our measurements, both constants of the radical **1b** are smaller (a= 9.1 G and a'=6.4 G). According to ref. 7 a smaller a' could be explained by a lower contribution of structure like I in the latter radical. Some changes in the geometrical configuration around the radical center (with consequences on the spin density map) in the latter radical, as well as the lower electron attracting ability of the Ar group due to the lack of a nitro group in the 6-position of the benzene ring, might also be responsible for the changes in the coupling constants; (ii) compared to the hyperfine coupling constants of radical **1b**, a substantial increase of a value and a decrease of a' value in radical **3b*** is similar to that observed for the same coupling constants in DPPH radical, when substituted with the electron acceptor group, -NO_2, in the *para*-position of the phenyl group(s). This behaviour places the radical **3b*** in the class *O* given by Walter[8] and has been explained[6,8] by the contribution of valence-bond structures II and III, which are "allowed" only in the case of substitution with electron acceptor group(s); (iii) in the assumption that both radicals **1b** and **3b*** have the same geometrical configuration, the higher line-width (ΔH) in the former indicates higher spin densities at atoms other than the two hydrazinic nitrogen atoms.



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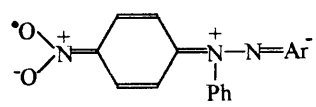
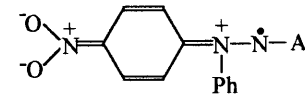


II



III

Reaction with $Na^{15}NO_2$ in the presence of 15-C-5

The hydrazine **1a** or **2a** (1 mmole, 350 mg) was oxidized in methylene chloride with an excess of powdered $KMnO_4$ or PbO_2.[3] Then the crown ether 15-C-5 (3 mmole, 660 mg) and [^{15}N]sodium nitrite (5 mmole, 350 mg) were added, and the mixture was stirred at room temperature for 24 hrs. After filtration, the organic phase was washed with 1 M hydrochloric acid three times and twice with water. After drying over sodium sulfate and chromatography on silica gel (GF-254 Merck), the following products were obtained. From **1a**: *p*-nitrodiphenylamine (10 mg, 50 μmole) and **3a**$^{\bullet}$ (195 mg, 0.5 mmole). From **2a** : **4a**$^{\bullet}$ (135 mg, 0.35 mmole) and **5a**$^{\bullet\bullet}$ (150 mg, 0.35 mmole).

Reaction with [^{15}N]nitrous acid

The reaction was carried out in a biphasic l-l system (water : methylene chloride 1 : 1, total volume 50 mL, at room temperature (no crown ether was added). The reagents were **1a** or **2a** (350 mg, 1 mmole), an excess of 1 M hydrochloric acid, and sodium [^{15}N]nitrite (350 mg, 5 mmole). After stirring for 24 hrs, the mixture was worked up as in the preceding case. From **1a** the product was **3a**$^{\bullet\bullet}$ (270 mg, 0.7 mmole). From **2a**, the product was **6a**$^{\bullet\bullet\bullet}$ (430 mg, 0.9 mmole).

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