Radical Reactions of N-Heterocyclic Compounds, XV [1]. Radical Intermediates and End Products of the Oxidation of 3-Anilino-1,5-diphenylpyrazoles with Pb(OAc)$_4$

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Summary. Substituted 3-anilino-1,5-diphenylpyrazoles **1a–i** were oxidized with Pb(OAc)$_4$ in benzene or CH$_2$Cl$_2$ solution. The ESR measurements confirmed the formation of aminyl radicals **3f–i** from *para*-CH$_3$ substituted pyrazoles **1f–i**. The radical intermediates from unsubstituted pyrazoles **1a–e** were assigned to triarylaminium cation radicals **6a–e**. These were generated by consecutive oxidation of the dimeric products **4a–e** whose structure was proven by NMR spectroscopy and ^{15}N labeling.

Keywords. Aminyl radicals; ESR; NMR; Pyrazoles; Triarylaminium cation radicals.

Radikalreaktionen von N-Heterocyclen, 15. Mitt. [1]. Intermediäre Radikale und Endprodukte der Oxidation von 3-Anilino-1,5-diphenylpyrazolen mit Pb(OAc)$_4$

Zusammenfassung. Die substituierten 3-Anilino-1,5-diphenylpyrazole **1a–i** wurden mit Pb(OAc)$_4$ in Benzol oder CH$_2$Cl$_2$ oxidiert. Die intermediären Aminylradikale **3f–i** wurden ESR-spektroskopisch bei der Oxidation der im Anilinrest methylsubstituierten Pyrazole **1f–i** nachgewiesen. Die ESR-spektroskopisch nach Oxidation der Pyrazole **1a–e** beobachteten Radikalintermediate interpretieren wir als Kationradikale **6a–e**. Diese werden durch Weiteroxidation der Dimeren **4a–e** gebildet, deren Struktur durch NMR-Untersuchungen und ^{15}N-Markierung bewiesen wurde.

Introduction

About a decade ago, the antioxidative properties of substituted 3-anilino-1,5-diphenylpyrazoles have been investigated [2]. The oxidation of **1a–i** with *t*-BuO$_2^{\bullet}$ radicals studied by ESR spectroscopy proved the generation of stable nitroxyl radicals [3]. The same reaction pathway was also confirmed by *t*-BuO$_2^{\bullet}$ oxidation of other secondary amines of the general formula *Y*-NH-Ph (*Y* = phthalimide, triazole, tetrazole, or benzimidazole; [4, 5]). In accordance with the mechanism proposed by

Thomas [6], aminyl radicals were supposed to be formed in the primary step of the reaction. The rapid consecutive rearrangement, however, did not permit their identification by ESR spectroscopy. In our study we attempted to characterize for the first time aminyl radicals from secondary amines containing both phenyl and N-heterocyclic rings. 3-Anilino-1,5-diphenylpyrazoles **1a–i** were oxidized with Pb(OAc)$_4$, which was found to be an effective agent for the dehydrogenation of $-$NH$-$ groups in substituted diphenylamines [7] and N-alkoxyamides [8]. Preliminary experiments showed that primary aminyl radicals were not the only radical intermediates observed: the formation of additional radical species was evident. Their structural assignment could be performed after analysis of the reaction mixture, where the products of N–N, N–C, or C–C dimerization of primary aminyls were presumed [9]. In this respect, the present work follows recent end product studies dealing with the oxidation of other types of 3-anilinopyrazoles where the formation of N–N dimeric products and pyrazolobenzimidazoles has been demonstrated [1].

Results and Discussion

Within the scope of this paper, a series of substituted 3-anilino-1,5-diphenylpyrazoles (**1a–i**) was investigated. For the comparative ESR measurements, 5-anilinopyrazole (**2**) was subjected to Pb(OAc)$_4$ oxidation under analogous experimental conditions.


1a–i   **2**
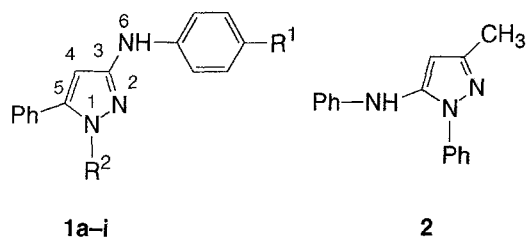
a: R^1 = H, R^2 = C$_6$H$_5$
b: R^1 = H, R^2 = C$_6$H$_5$ (N^1,N^2 = ^{15}N)
c: R^1 = H, R^2 = 4–Br–C$_6$H$_4$
d: R^1 = H, R^2 = 4–CH$_3$O–C$_6$H$_4$
e: R^1 = H, R^2 = 4–NO$_2$–C$_6$H$_4$
f: R^1 = CH$_3$, R^2 = C$_6$H$_5$
g: R^1 = CH$_3$, R^2 = 4–Br–C$_6$H$_4$
h: R^1 = CH$_3$, R^2 = 4–CH$_3$O–C$_6$H$_4$
i: R^1 = CH$_3$, R^2 = 4–NO$_2$–C$_6$H$_4$

Although our efforts were directed preferentially at the detection of radical intermediates, we also paid attention to the analysis of reaction products. This approach was found to be necessary because, as mentioned below, two types of radical products were identified from **1a–i** depending on the substituent R^1 (R^1 = H or CH$_3$). Consequently, the analysis of reaction products was performed with compounds **1a**, **1b**, and **1f** containing both substituents in the starting 3-anilino-1,5-diphenylpyrazoles.

Characterization of reaction products from 1a, 1b, and 1f

The preparative oxidations of **1a**, **1b**, and **1f** were carried out with Pb(OAc)$_4$ in benzene solution at room temperature in an argon atmosphere. Analysis of the reaction mixture showed that the oxidation reaction did not proceed completely, even when employing an excess amount of Pb(OAc)$_4$. As the main reaction products, the dimers **4a**, **4b**, and **4f** were isolated (yield: 20% of pure products after multiple recrystallization). No other dimeric products or dihydrophenazines could be detected in appreciable amounts. The formation of intermediate aminyl radicals **3a**, **3b**, and **3f** is assumed to proceed in the first step of the oxidation. The reaction pathway for the whole series of starting compounds **1a–i** is outlined in Scheme 1. However, the formation of dimers **4** via intermediate cation radicals or nitrenium ions cannot be excluded.
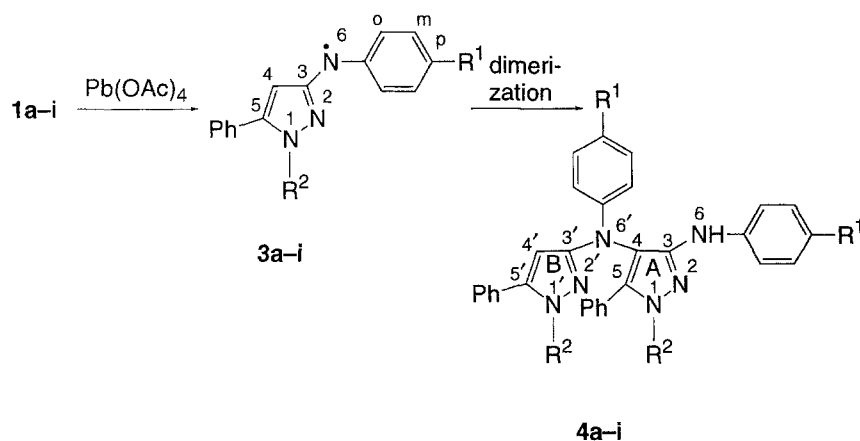
Scheme 1

The constitutions of **4a** and **4f** were determined by means of elemental analysis, mass, IR and ^{1}H NMR spectroscopy. ^{13}C NMR spectroscopy, using the APT technique, allowed the differentiation between C and CH signals [10]. ^{15}N labeling of the pyrazole N atoms (oxidation of doubly ^{15}N labeled pyrazole **1b** to **4b**) was useful for the assignment of the different carbon atoms of the pyrazole rings and the *ipso* C atoms of the phenyl rings via their ^{13}C –^{15}N coupling constants. The ^{13}C NMR data (Table 1) are in agreement with the unsymmetrical dimeric constitution of **4a**, **4b**, and **4f**. The spectra of **4a** and **4f** exhibited two sets of signals with similar chemical shifts compared to the starting compounds **1a** and **1f**. The ^{13}C–^{15}N coupling constants of C-4 and C-4$'$ did not differ markedly and were comparable with the analogous parameters in starting pyrazole **1b**. The only significant differences were found with the signals of the C-4 atoms of the pyrazole rings, showing typical downfield shifts of more than 25 ppm caused by the amino substituent at C-4 in the dimers **4a**, **4b**, and **4f** (compare Ref. [11]). Simultaneously, the modification of a CH-signal (C-4 in **1a**, **1f**) to a quarternary C-signal occured. However, the ^{13}C–^{15}N coupling constant of the C-4 atom in **4b** was comparable to those of the C-4$'$ atom in **4b** and the C-4 atom in **1b**. Additionally, the ^{15}N NMR spectrum of **4b** was recorded showing four doubletts at $\delta = -90.39$ ppm and $\delta = -91.0$ ppm (N-2 and

N-2$'$) and at $\delta = -173.2$ ppm and $\delta = -179.3$ ppm (N-1 and N-1$'$) with typical ^{15}N$-^{15}$N coupling constants of $^1J = 13$Hz (for **1b**, see experimental part).

All observed ^{13}C and ^{15}N NMR data were in good agreement with data of a large number of other pyrazole derivatives [10–12].

Table 1. ^{13}C NMR chemical shifts of pyrazole derivatives **4a**, **4b**, and **4f** as compared to the corresponding pyrazoles **1a**, **1b**, and **4f**

	1a	1b[a]	4a	4b[a]	1f	4f
			(δ in ppm, $J(^{15}$N$-^{13}$C) in parentheses in Hz)			
C-3/C-3$'$[b]	151.62		151.33		151.60	151.24
			147.60			147.65
C-4/C-4$'$	96.48	(8.3)	122.14	(10.0)	95.50	122.00
			99.39	(8.3)		99.26
C-5/C-5$'$[b]	143.41	(15.7)	145.95	(14.0)	144.15	144.85
			138.70	(16.0)		139.09
N-1/N-1$'$-Phenyl[b]						
i-C	140.16	(19.0/5.0)	140.40	(18.8/4.5)	140.20	140.60
			140.60	(18.8/4.5)		140.44
o-C	124.45		124.58		124.47	124.65
			123.82			123.65
m-C	129.75		129.80		129.76	129.66
			129.70			128.79
p-C[c]	128.52		128.67		128.50	128.47
			128.54			128.61
C-5/C-5$'$-Phenyl[b]						
i-C	134.52	(7.5/2.8)	134.44	(7.5/2.5)	134.58	134.47
			133.21	(7.5/2.5)		133.29
o-C	126.09		126.06		126.11	126.02
			128.80			127.92
m-C	129.26		129.26		129.27	129.21
			129.07			129.06
p-C[c]	127.74		127.99		127.70	127.84
			127.54			127.52
N-6/N-6$'$-Phenyl[b]						
i-C	145.50		146.90		142.90	146.37
			145.90			143.47
o-C	115.96		118.47		116.48	118.59
			114.78			114.90
m-C	130.00		129.50		130.48	130.30
			129.10			130.07
p-C[c]	120.57		119.90		129.83	130.98
			121.86			130.90

[a] Chemical shifts are identical with those of **1a** or **4a**, respectively; [b] signals could not be assigned unequivocally to the pyrazole rings A or B of the dimers **4a**, **4b**, or **4f**, although one set of the signals is nearly identical with **1a**, **1b**, and **1f**, strongly indicating an assignment to ring B; [c] signals of p-C atoms are about half as intense as those of the corresponding o- and m-C atoms

ESR investigation of radical intermediates

The oxidation of 3-anilino-1,5-diphenylpyrazoles **1a–i** using $Pb(OAc)_4$ in benzene or CH_2Cl_2 solution afforded radical products which exhibited high-resolved ESR spectra. Their analysis revealed the generation of two different radical types depending on the substituent R^1. The first group was represented by the radicals derived from *para*-CH_3 substituted compounds **1f–i**. In the ESR spectra, the interaction of an unpaired electron with all atoms of the phenyl and pyrazole ring was manifested (Fig. 1a). This fact, together with the g-value $(g = 2.0035)$, documented unambigously the formation of aminyl radicals **3f–i** (Table 2). A comparison of ESR parameters of **3f–i** with analogous data for corresponding nitroxyl radicals [3] indicated that except for the splitting constant of the exocyclic nitrogen atom in position 6 all other splitting constants were substantially higher (*e.g.* a_H values for *ortho* protons are about 50%, those for *para* methyl protons about 70% higher). It can be concluded that the spin density (partially delocalized in nitroxyl radicals between the nitrogen and oxygen atom in the $-NO^{•}$ – fragment) is more delocalized in both phenyl and pyrazole rings. A similar tendency was observed when proceeding from the diphenylnitroxyl to the diphenylaminyl radical [13, 14]. When the dimer **4f** was oxidized using the same method in benzene solution, the ESR parameters of the generated radical did not significantly differ from the ESR data of **3f** and could be ascribed to the aminyl radical **5f** (Table 2).
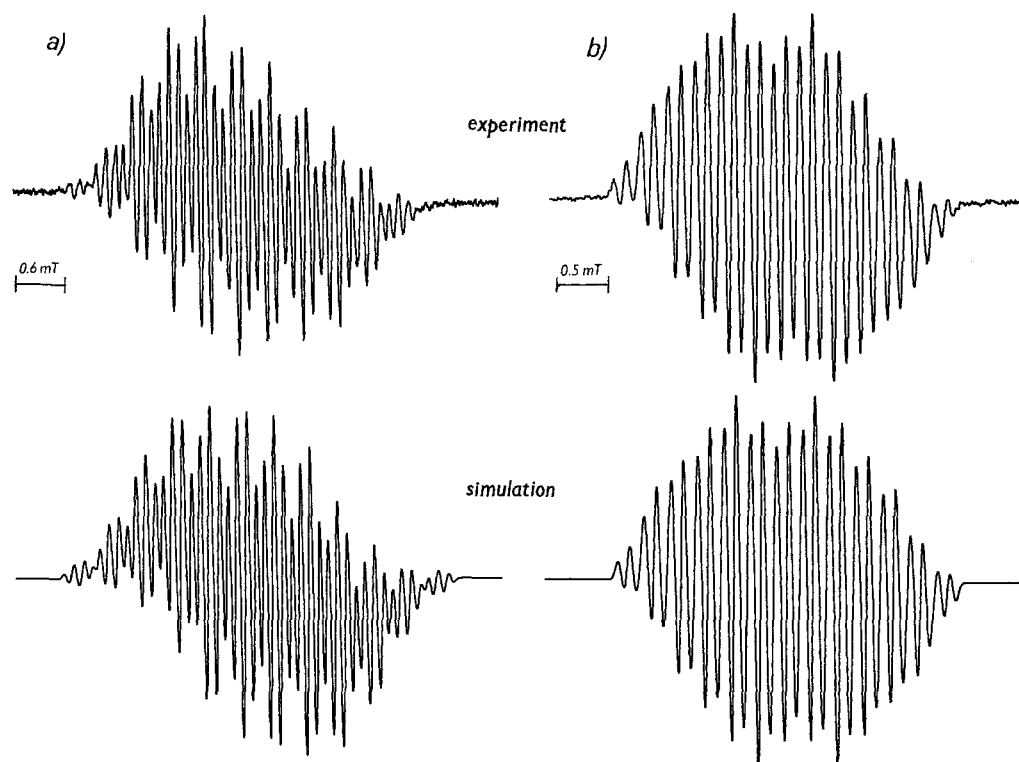

Fig. 1. Experimental and simulated ESR spectrum of the aminyl radical **3g** (*a*) and the cation radical **6b** (*b*)

Table 2. ESR parameters of aminyl radicals 3f–i and 5f in CH_2Cl_2

	$a_N(6)$	$a_N(1)$	$a_N(2)$	$a_H(4)$	a_H^o	a_H^m	a_H^p
3f	0.805	0.131	0.225	0.178	0.340	0.124	0.435[a]
3g	0.800	0.132	0.235	0.179	0.335	0.117	0.431[a]
3h	0.808	0.137	0.236	0.189	0.319	0.127	0.429[a]
3i	0.788	0.129	0.222	0.195	0.352	0.127	0.442[a]
5f[b]	0.730	0.120	0.370	–	0.360	0.120	0.390[a]

[a] splitting from protons of the methyl group; [b] splitting constants in benzene solution

5f
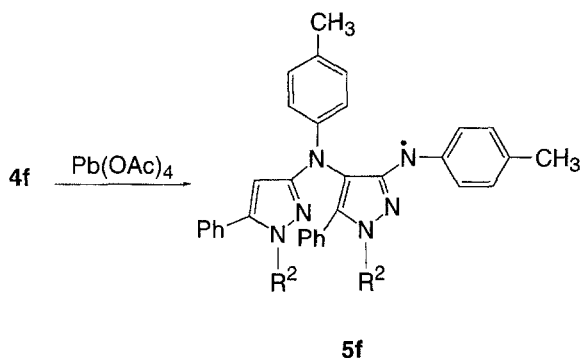
The small differences could be explained by the steric influence of the bulky substituent in position 4 of the pyrazole ring in 5f. Generalizing from this result, we presume that the formation of aminyl radicals 5f–i is a common characteristic of all *para*-CH_3 substituted dimers 4f–i when oxidized with $Pb(OAc)_4$ (Scheme 2).

The second group of intermediate products was represented by the radicals generated from 3-anilino-1,5-diphenylpyrazoles 1a–e. In this case, the splitting constants (Table 3) were not comparable with those observed with aminyl radicals 3f–i. For example, no a_H^o and a_H^p values, generally characterizing diarylaminyl radicals ($a_H > 0.3$ mT) were observed in the ESR spectra. Moreover, the splitting constant for one proton was lacking in the ESR spectra (Fig. 1b). From the spectroscopic point of view, no remarkable differences in spin density distribution could be detected between the aminyl radicals 3f–i and 3a–e. Therefore, we assumed that in the course of the oxidation of 1a–e the secondary radicals were detected. This assumption was further supported by additional experiments. These showed that the oxidation of 1a and 4a (or ^{15}N labeled compounds 1b and 4b) led, in contrast to 1f and 4f, to identical ESR spectra. The mentioned facts suggest that in intermediate products derived from 1a–e the radical centre is not situated at the nitrogen atom N^6. Considerng the structure of the dimeric compounds 4a–e, the transfer of the radical centre to the tertiary amino group in position 4 appears to be a possible alternative for the interpretation of experimental results. Consequently, the corresponding triarylaminium cation radicals 6a–e are supposed to be the final radical products (Scheme 2). Triarylaminium cation radicals containing N-heterocyclic rings have not been described in the literature so far, and only ESR data of

triphenylaminium cation radicals are available. In the work of *Neugebauer et al.* [15], the following slitting constants of the planar unsubstituted cation radical (Ph)$_3$N$^{+\bullet}$ are given: $a_N = 1.019\,\mathrm{mT}$, $a_H^o = 0.226\,\mathrm{mT}$, $a_H^m = 0.122\,\mathrm{mT}$, $a_H^p = 0.327$ mT. In comparison with the ESR data for aminyl radicals, these values demonstrate a decrease of the spin density in the phenyl ring. Therefore, the splitting constants for phenyl protons in radical products from **1a–e** ($a_H < 0.3\,\mathrm{mT}$) can be accepted as an argument in favour of the assignment to cation radicals **6a–e**. Nevertheless, the steric effects of phenyl substituents in positions 1 and 5 of the pyrazole ring have to be taken into account, since in addition to the splitting constants of the phenyl protons only three a_N coupling constants were observed (Table 3). These facts suggest that a deviation from planarity leading to a decrease of conjugation probably occurs in radicals **6a–e**.

Table 3. ESR parameters of triarylaminium cation radicals **6a–e** in benzene

	a_H^o	a_H^m	a_H^p	a_{other}		
6a	0.267	0.115	0.280	0.818(1N),	0.388(1N),	0.127(1N)
6b	0.267	0.115	0.280	0.818(1N),	0.540(1N)^a,	0.177(1N)^a
6c	0.275	0.126	0.300	0.800(1N),	0.395(1N),	0.117(1N)
6d	0.270	0.138	0.275	0.808(1N),	0.395(1N),	0.123(1N)
6e	0.275	0.110	0.295	0.800(1N),	0.397(1N),	0.100(1N)

^{a} splitting constant of ^{15}N labeled atom
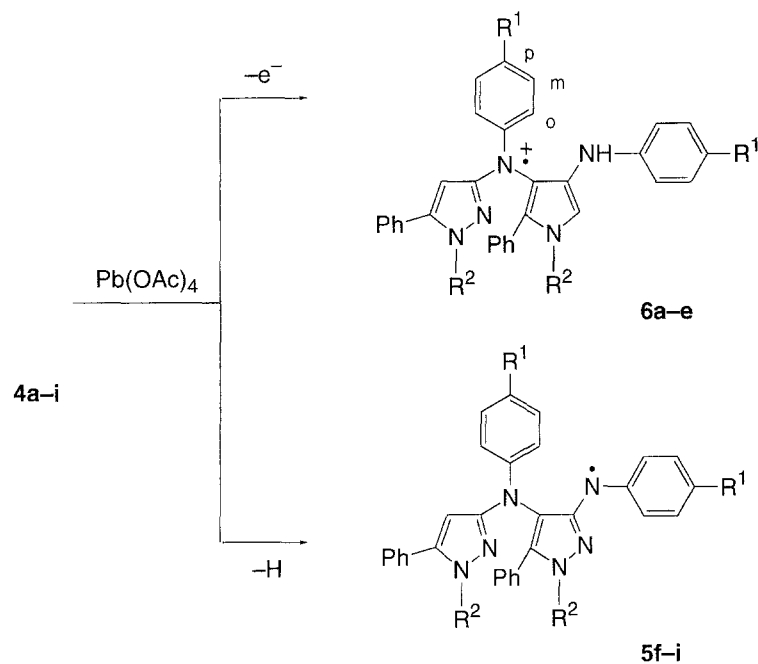
Scheme 2

Although the isolation of the end products **4a**, **4b** and **4f** indicated that dimerization proceeded in the second step of the oxidation, the ESR measurements pointed at differences in the stability of aminyl radicals **3a–e** and **3f–i**. Owing to the stabilizing influence of a CH_3 substituent in *para* position of the anilino group, the aminyl radicals **3f–i** could be observed. On the other hand, the more reactive aminyls **3a–e** derived from pyrazoles with an unsubstituted anilino group underwent a rapid consecutive rearrangement, and only secondary radicals could be detected by ESR spectroscopy. Additional ESR experiments showed that the enhanced reactivity was typical of aminyl radicals with an unsubstituted anilino group in position 3 of the pyrazole ring. When compound **2** was subjected to $Pb(OAc)_4$ oxidation a stable radical was produced. Its ESR parameters $(a_H^m =$ 0.111 mT (2H), $a_H^o = 0.380$ mT (2H), $a_H^p = 0.405$ mT (1H), $a_H = 0.122$ (3H), $a_H = 0.183$ mT (1H), $a_N = 0.155$ mT (1N), $a_N = 0.148$ mT (1N), $a_N = 0.810$ mT (1N)) unambiguously documented the formation of the aminyl radical **7** in this case. The attribution to the cation radicals **6a–e** did not exclude the preferential oxidation of the exocyclic –NH– group in the dimeric products **4a–e** and the subsequent stabilization of the corresponding cation radical $(pyr - NH^{+\bullet} - Ph)$ by charge transfer to the tertiary nitrogen atom.

2 $\xrightarrow{\text{Pb(OAc)}_4}$

7
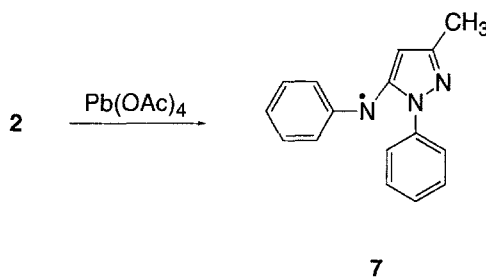
Experimental

Melting points were measured on a Boetius Hot stage apparatus and are uncorrected. NMR spectra were recorded on Varian Unity 500 NMR spectrometer (500 MHz). For ^1H and ^{13}C NMR spectra, hexamethyldisiloxane was used as an internal standard. ^{15}N NMR chemical shifts are given relative to external ^{15}N-formamide $(\delta = -270 \text{ ppm})$. Mass spectra were recorded using an AMD 402 mass spectrometer (AMD) Intectra GmbH) at 70 eV. Infrared spectra were registered with a Philips FT-IR spectrometer PU 9624. The ESR spectra were recorded with a Bruker EP 200E-SRC spectrometer equipped with an Aspect 2000 computer. HPLC analysis was carried out with a Merck-Hitachi apparatus (D 6000, L-6250, L-3000) on a Merck Li-Chrospher 100 RP-18 250 ×4 mm column. The elemental analyses were performed using a Leco CHNS-932 analyzer. They agreed satisfactorily with the calculated values (C, H, N). Anilinopyrazoles **1a–i** and **2** were prepared according to the procedure of *Hünig* and coworkers [16]. The purity of **1a–i** was determined by HPLC analysis and elemental analysis prior to use.

3-Anilino-[1,2-$^{15}N_2$]-1,5-diphenylpyrazole (**1b**)

1b was prepared in analogy to **1a** using [$^{15}N_2$]-phenylhydrazine (Berlin-Chemie, amount of ^{15}N > 95%).

Yield: 69%; m.p. 153–155°C; MS(EI): $m/z = 313$ (M⁺); ¹⁵N NMR (50.6 MHz, acetone-d₆): $\delta = -93.51$ (d, $J = 13$ Hz), -176.31 (d, $J = 13$ Hz) ppm.

3-Anilino-1,5-diphenyl-4-(1,5-diphenylpyrazole-3-yl)-phenyl)amino-pyrazole (4a, C₄₂H₃₂N₆)

0.311 g (1 mmol) **1a** were dissolved at room temperature in 10 ml of abs. benzene. Under vigorous stirring, 0.443 g lead(IV) acetate were added in an argon atmosphere. The resulting green solution was stirred for further 48 h at room temperature. The benzene solution was filtered, and the solvent was removed under reduced pressure. The resulting greenish brown residue was taken up in acetone, and the product was precipitated by treatment with water. The solid was filtered off and crystallized several times from acetone/water. 0.063 g (20%) pure **3a** were obtained as greenish-white crystals.

M.p.: 167–171°C (decomp.); purity > 97% (HPLC); MS(EI): $m/z = 620$ (M⁺); ¹H NMR (500 MHz *DMSO*-d₆): $\delta = 6.14 - 7.95$ (m, 31 H), 8.15 (s, 1H, NH) ppm; IR (KBr): 3359 (NH), 1513, 1498 cm⁻¹.

3-Anilino-1,5-diphenyl-4-(1,5-diphenyl-1,2-[¹⁵N₂]pyrazole-3-yl)-phenyl)amino-1,2-[¹⁵N₂]-pyrazole (4b, C₄₂H₃₂N₆)

1b was oxidized as described for **1a**. The product **4b** was isolated and purified as mentioned above.

Yield: 20%; m.p.: 167–171°C (decomp); MS(EI): $m/z = 624$ (M⁺); ¹⁵N NMR (50.6 MHz, acetone-d₆): $\delta - 90.39$ (d, $J = 13$ Hz), -91.0 (d, $J = 13$ Hz), -173.0 (d, $J = 13$ Hz), -179.3 (d, $J = 13$ Hz) ppm.

3-(4-Methylphenyl)amino-1,5-diphenyl-4-(1,5-diphenylpyrazole-3-yl)-4-methylphenyl)amino-pyrazole (4f, C₄₄H₃₆N₆)

0.325 g (1 mmol) **1f** were oxidized with 0.443 g (1 mmol) lead(IV) acetate in benzene solution as described for **1a**. Subsequently, the obtained crude material was purified by crystallization from acetone/water. 0.065 g (20%) **3f** were isolated as greenish-white crystals.

M.p.: 188–191°C (decomp); purity > 98% (HPLC); MS(EI): *m/z* 648 (M⁺); IR (KBr): 3359 (NH), 1596, 1548, 1513, 1498 cm⁻¹.

Preparation of EPR samples

The similar procedure was applied as described for the synthesis of **4a**. 0.4 ml of the reaction mixture prepared by the addition of lead (IV) acetate to the benzene or CH₂Cl₂ solution of the corresponding 3-anilino-1,5-diphenylpyrazole (**1**) was transferred into the EPR cell and measured in an argon atmosphere.

Acknowledgements

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