Synthesis of new spin probes based on aminoaryl-substituted imidazoline nitroxides

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A series of new spin probes, azides and isothiocyanates, were synthesized starting from aminoaryl-substituted nitroxides which are derivatives of 3-imidazoline and 3-imidazoline-3-oxide. The new compounds were transformed to complexones, derivatives of iminodiacetic acid.

Key words: nitroxyl radical; azides; isothiocyanates; spin probes; diazonium salts.

4-(Aminoaryl)-substituted nitroxyl radicals of the 3-imidazoline and 3-imidazoline-3-oxide series can easily be obtained by reduction of the respective nitro derivatives.[1,2] We thought that amines of this kind might be useful in the syntheses of spin probes and paramagnetic chelating reagents. In view of this, several reactions involving these compounds were studied in the present work.

The diazotization of amines **1c,d** affords diazonium salts (**2c,d**) which, as was shown previously, react with active arenes (β-naphthol, phenol, 8-hydroxyquinoline) to give the respective azo compounds.[1] However, attempts to conduct similar transformations starting from amines **1a,b** under analogous conditions or in 10 *N* HCl resulted in cleavage of the heterocycle and formation of acetyl-substituted diarylazo compounds (**3**) (Scheme 1). It should be noted that cleavage of the heterocycle in 3-imidazoline can either follow the formation of a diazonium salt or precede it. Diazotization of amines **1a,b** followed by a reaction with 3-imidazolinium methylsulfate (**4**) and neutralization results in asymmetric azobiradicals (**5a,b**) (*cf.* Ref. 3). Thus, diazotization of amines **1a,b** gives diazonium salts **2a,b**, whose stability turns out to be somewhat lower than that of salts **2c,d**. The latter react with methylsulfate **4** to give, similarly, the respective biradicals **5c,d**.

The reaction of diazonium salts **2a—e,g** with sodium azide gives paramagnetic azides (**6a—e,g**), which are potential photo-sensitive spin probes.[4] It is noteworthy that the molecule of azide **6e** also contains an amidine group, which enables the use of this compound as a spin probe with a pH-sensitive ESR spectrum (*cf.* Ref. 5).

Amines **1a,e** smoothly react with thiophosgene to give paramagnetic isothiocyanates (**7a,e**), spin probes that acylate protein molecules at NH groups. One more spin-probe isothiocyanate (**7f**) was obtained from a bromomethyl derivative of imidazoline (**8f**). The latter was first transformed to azide **6f** by treatment with sodium azide. Subsequent reaction with carbon disulfide[4] gives isothiocyanate **7f** which is also of interest as an acylating spin probe with a pH-dependent ESR spectrum (*cf.* Ref. 6).

The reaction of isothiocyanates **7a,f** with dimethyl iminodiacetate followed by hydrolysis affords diacids (**9a,f**), spin-probe complexones useful as paramagnetic ligands in the syntheses of relaxants for NMR tomography.[7]

Experimental

IR spectra were recorded for KBr pellets (C = 0.25 %, pellet thickness 1 mm) and solutions in CCl_4 (C = 5 %) on Specord M-80 and UR-20 spectrometers. UV spectra were obtained on a Specord UV-VIS spectrophotometer (EtOH). Elemental analysis data, IR and UV spectra, melting points and yields of the compounds synthesized are given in Table 1. Amine **1e** was synthesized by the known procedure.[5] Amine **1b** was obtained by a procedure analogous to that reported[2] for amine **1a**.

1-Hydroxy-2,4,5,5-tetramethyl-2-(3′-nitrophenyl)-3-imidazoline (10). A mixture of *N*-(2-methyl-3-oxo-2-butyl)-hydroxylamine hydrochloride (4.44 g, 29 mmol), $MeCOONH_4$ (7.76 g, 97 mmol), and *m*-nitrophenylacetophenone (4 g, 24 mmol) in MeOH (100 mL) was boiled for 6 h and concentrated. The residue was diluted with water (100 mL), and the precipitate of compound **10** was filtered off, washed with water, dried, and purified by recrystallization from an ethyl acetate—ethanol mixture (3 : 1).

2-(3′-Aminophenyl)-1-hydroxy-2,4,5,5-tetramethyl-3-imidazoline (11) was obtained by hydrogenation of nitro derivative **10** (2 g) at 20 °C under atmospheric pressure in the

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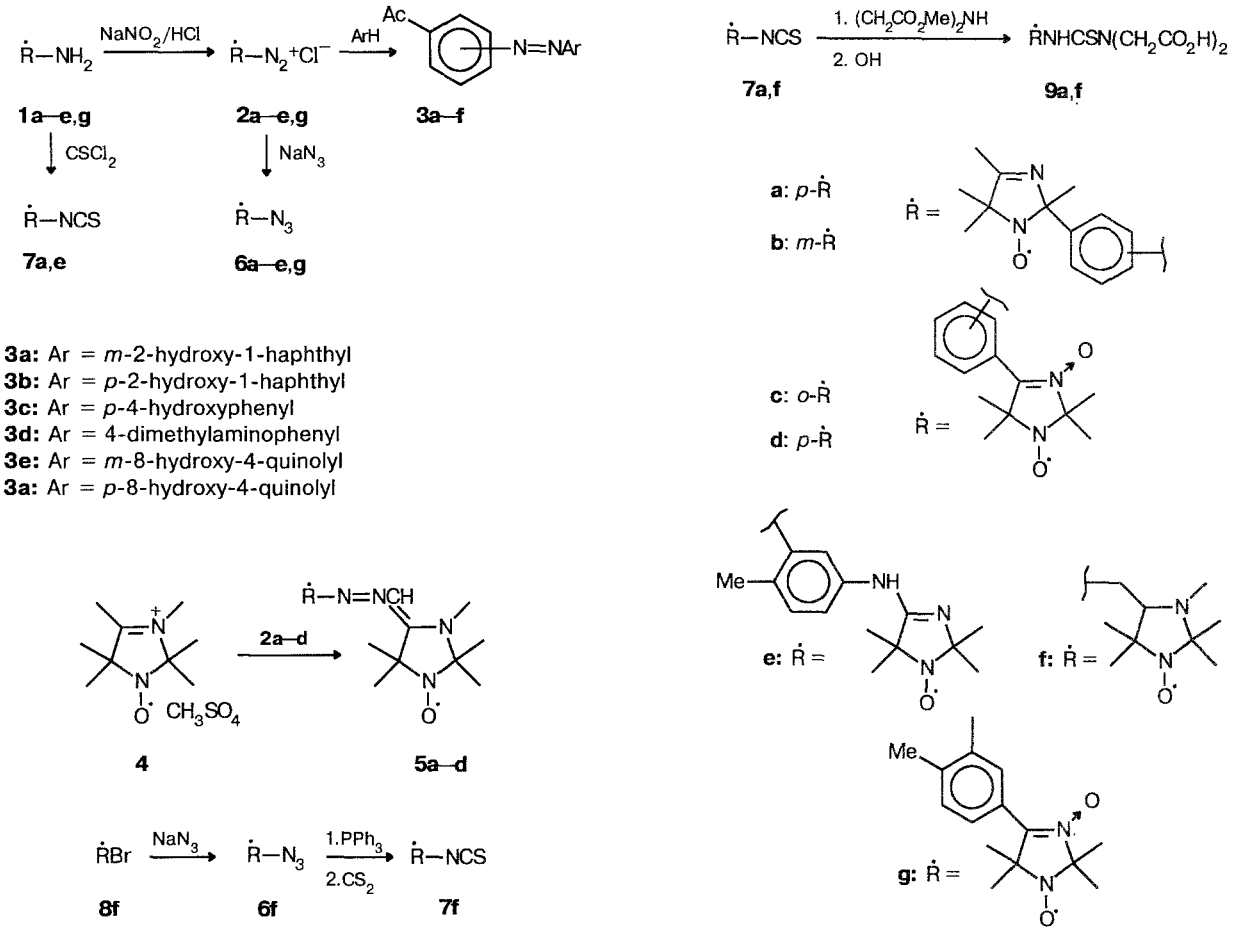
Scheme 1



presence of a catalyst (0.3 g of 5 % Pd/C) in EtOH for 10 h. The catalyst was filtered off, the solution was concentrated, and the precipitate was dissolved in dry Et_2O (10 mL). Amine **11**, which precipitated on storage in the cold, was filtered off. Oxidation of the filtrate with MnO_2 under the conditions described below can be used for obtaining radical **1b**. The latter was isolated by chromatography on a column with silica gel using $CHCl_3$ as the eluent.

2-(3′-Aminophenyl)-2,4,5,5-tetramethyl-3-imidazoline-1-oxyl (1b). A suspension of hydroxy derivative **11** (1 g) in $CHCl_3$ (20 mL) was stirred for 15 min at 20 °C with MnO_2 (3 g). The excess oxidant was filtered off, and the solution was concentrated. Crystallization occured when several mL of dry Et_2O were added. The residue of amine **1b** was filtered off.

Reaction of diazonium salts 2 with 2,2,3,4,5,5-hexamethyl-3-imidazolinium-1-oxyl methylsulfate 4 (general procedure). A solution of $NaNO_2$ (0.07 g, 1.05 mmol) in water (1 mL) was added dropwise with stirring and cooling to 0 °C to a solution of amine **1a—d** (0.8 mmol) in 10 % HCl (5 mL). Stirring was continued for 5 min at 0 °C, and then a solution of compound **4** (0.3 g, 1.05 mmol) in water (2 mL) was added dropwise with stirring to the solution of diazonium salt **2** obtained. Stirring was continued for 20 min at 0 °C, then $CHCl_3$ (20 mL) was added, and the stirred reaction mixture was alkalized to pH 9 with 10 % aqueous Na_2CO_3. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×20 mL). The combined extract was dried with $MgSO_4$, and the solution was concentrated. Crystallization occured when dry Et_2O (3 mL) was added. The precipitates of compounds **5a—d** were filtered off and washed with hexane.

Reaction of diazonium salts 2 with activated arenes. The reactions of diazonium salts **2a,b** with β-naphthol, phenol, dimethylaniline, and 8-hydroxyquinoline were performed under the conditions described above for the reactions with compound **4** and gave *p*- and *m*-acetylphenylazoarenes **3** in 10—60 % yields. The structures of compounds **3** were established based on IR and UV spectra and elemental analysis data. The compounds synthesized had m.p./°C: **3a**, 157—158 (from a hexane—ethyl acetate mixture); **3b**, 186—187 (from a hexane—ethyl acetate mixture); **3c**, 198—199 (from ethanol); **3d**, 208—209 (from a hexane—ethyl acetate—CH_2Cl_2 mixture, 1 : 3 : 1); **3e**, 218—220 (from a $CHCl_3$—ethanol mixture); **3f**, 237—238 (from a $CHCl_3$—MeOH mixture).

Synthesis of phenylazides 6a—g (general procedure). A solution of NaN_3 (0.23 g, 3.5 mmol) in water (3 mL) was added dropwise with stirring and cooling to 0 °C to a solution of aryldiazonium salt **2a—g** obtained from 1.7 mmol of the respective arylamine **1a—g** under the conditions described above. Stirring was continued for 10 min at 0 °C, the solution was extracted with $CHCl_3$ (2×15 mL), the extract was dried with $MgSO_4$, and the solution was concentrated. Compounds **6a,b,e** were isolated by chromatography on a column with silica gel using $CHCl_3$ as the eluent.

4-Azidomethyl-2,2,3,5,5-pentamethylimidazoline-1-oxyl (6f). A solution of bromo derivative **8f** (0.5 g, 2 mmol) and NaN_3 (0.52 g, 8 mmol) in a mixture of DMF (10 mL) and

Table 1. Parameters of the compounds synthesized

Compound	Yield (%)	M.p.* /°C	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (lg ε)	Found / Calculated (%) C	H	N	Molecular formula**
1b	85	103—106	1645(C=N); 3225, 3330, 3415(NH_2)	237 (3.99)	67.4 / 67.2	8.1 / 7.8	18.1 / 18.1	$C_{13}H_{18}N_3O$
5a	45	191—194	1590, 1605(C=C—N=N); 1665(C=N)	256 (4.14) 4.17 (4.62)	64.0 / 64.1	7.6 / 7.8	20.2 / 20.4	$C_{22}H_{32}N_6O_2$
5b	40	147—149	1605(C=C—N=N); 1670(C=N)	230 (4.18) 400 (4.49)	63.9 / 64.1	7.5 / 7.8	20.2 / 20.4	$C_{22}H_{32}N_6O_2$
5c	40	153—154	1600(C=C—N=N, C=N)	243 (4.31) 390 (4.52)	61.4 / 61.7	7.5 / 7.5	19.4 / 19.6	$C_{22}H_{32}N_6O_3$
5d	65	199—201	1545(C=N); 1590, 1605(C=C—N=N)	247 (4.16) 298 (3.87) 417 (4.60)	61.4 / 61.7	7.3 / 7.5	19.2 / 19.6	$C_{22}H_{32}N_6O_3$
6a	70	82—84	1645(C=N); 1605(C=C); 2080—2140(N_3)	254 (4.14) 285 sh (3.6)	60.3 / 60.4	6.2 / 6.3	27.1 / 27.1	$C_{13}H_{16}N_5O$
6b	40	Oil	1645(C=N); 1605(C=C); 2090—2150(N_3)	247 (4.02)	60.2 / 60.4	6.2 / 6.3	26.8 / 27.1	$C_{13}H_{16}N_5O$
6c	95	134—135	1570(C=N); 2130 s, 2100 w (N_3); 1600(C=N)	248 (4.23)	56.7 / 56.9	5.7 / 5.9	25.5 / 25.5	$C_{13}H_{16}N_5O_2$
6d	95	134—136	1540(C=N); 1600(C=C); 2090 s, 2120 w (N_3)	232 (4.04) 312 (4.27)	57.1 / 56.9	5.6 / 5.9	25.2 / 25.5	$C_{13}H_{16}N_5O_2$
6e	95	175—177	2120(N_3); 3365(NH); 1540, 1600, 1630 (PhNH—C=N)	256 (4.42) 306 (3.60)	58.9 / 58.5	6.4 / 6.6	29.0 / 29.3	$C_{14}H_{19}N_6O$
6f	75	Oil	2110(N_3)	—	50.7 / 50.9	8.5 / 8.5	32.7 / 33.0	$C_9H_{18}N_5O$
6g	95	145—147	1565(C=N); 2160 w; 2120 s (N_3)	254 (4.23) 292 (4.12)	58.1 / 58.3	6.1 / 6.3	24.0 / 24.3	$C_{14}H_{18}N_5O_2$
7a	60	Oil	1640(C=N); 2000—2150, 2200(NCS)	—	61.0 / 61.3	5.8 / 5.8	15.0 / 15.3	$C_{14}H_{16}N_3OS$
7e	70	170—171	1545, 1600, 1635 (PhNH—C=N); 2050—2180(NCS)	258 (4.55) 303 (3.56)	59.1 / 59.4	6.3 / 6.3	18.2 / 18.5	$C_{15}H_{19}N_4OS$
7f	65	Oil	2080—2160(NCS)	—	52.3 / 52.7	7.7 / 7.9	18.2 / 18.4	$C_{10}H_{18}N_3OS$
9a	70	188—189	1760(C=O); 1645(C=N)	243 (4.26) 268 (4.24)	53.5 / 53.2	5.6 / 5.7	13.5 / 13.8	$C_{18}H_{23}N_4O_5S$
9f	80	80 (dec.)	1760(C=O)	—	46.6 / 46.6	6.9 / 6.9	15.2 / 15.6	$C_{14}H_{25}N_4O_5S$
10	75	181—183	1645(C=N); 1600(C=C); 1515, 1350(NO_2)	243 (4.16)	59.1 / 59.3	6.7 / 6.5	15.9 / 16.0	$C_{13}H_{17}N_3O_3$
11	70	157—159	1630(C=N); 1605(NH_2, C=C); 3215, 3370(NH_2)	238 (3.95)	66.8 / 67.0	8.0 / 8.2	17.7 / 18.0	$C_{13}H_{19}N_3O$

*Compounds **1b**, **5b**, **6c—e,g**, and **7e** were purified by recrystallization from an ethyl acetate—hexane mixture, compounds **5a** and **11** from ethyl acetate, **6b** from hexane, **9a** from ethanol, **10** from an ethyl acetate—ethanol mixture. Compounds **5c,d**, **6b,f**, and **7a,f** were purified by chromatography. ** S. Found/calculated (%): 11.6/11.7 (**7a**); 10.2/10.6 (**7e**); 13.6/14.0 (**7f**); 8.1/7.9 (**9a**); 8.7/8.9 (**9f**).

water (2 mL) was heated for 1 h in a water bath, diluted with water (50 mL), and extracted with ether (4×20 mL). The extract was washed with water (5×20 mL) and dried with $MgSO_4$. The solution was concentrated to give azide **6f**.

2-(4'-Isothiocyanatophenyl)-2,4,5,5-tetramethyl-3-imidazoline-1-oxyl (7a). Thiophosgene (0.2 mL, 2.64 mmol) was added to a solution of amine **1a** (0.4 g, 1.72 mmol) and triethylamine (0.6 mL, 4.3 mmol) in 20 mL of $CHCl_3$ dried with $CaCl_2$, and the solution was concentrated. Isothiocyanate **7a** was isolated by chromatography on a column with silica gel, using $CHCl_3$ dried with $CaCl_2$ as the eluent.

Isothiocyanate **7e** was obtained under similar conditions by treatment of amine **1e** with thiophosgene.

4-Isothiocyanatomethyl-2,2,3,5,5-pentamethylimidazolidine-1-oxyl (7f). A mixture of azide **6f** (0.3 g, 1.41 mmol) and PPh_3 (0.74 g, 2.82 mmol) in Et_2O (20 mL) was boiled for 3 h, then the ether was evaporated. The residue was dissolved in carbon disulfide (5 mL), then PPh_3 (0.37 g, 1.41 mmol) was added, and the reaction mixture was boiled for 1 h. The solution was concentrated, the residue was suspended in dry Et_2O, and the precipitate was filtered off and washed with dry Et_2O. The solution was concentrated, and isothiocyanate **7f** was isolated by chromatography on a column with silica gel using $CHCl_3$ dried with $CaCl_2$ as the eluent.

4-*N',N'*-Biscarboxymethylthioureidomethyl-2,2,3,5,5-pentamethylimidazoline-1-oxyl (9f). A solution of isothiocyanate **7f** (0.2 g, 0.88 mmol) and dimethyl iminodiacetate (0.17 g, 1.05 mmol) in 10 mL of $CHCl_3$ dried with $CaCl_2$ was kept for 12 h at 20 °C and then concentrated. The residue was chromatographed on a column with silica gel ($CHCl_3$ as the eluent), and the colored zone was collected. The eluate was concentrated, and the residue was dissolved in a mixture of 5 % aqueous NaOH (3 mL) and MeOH (10 mL). The solution was kept for 10 min at 20 °C, the MeOH was evaporated, and the solution was acidified with 5 % HCl to pH 4, saturated with NaCl, and extracted with $CHCl_3$ (5×10 mL). The extract was dried with $MgSO_4$, the solution was concentrated, and the residue was mixed with dry ether (20 mL). The solution was decanted, diluted with hexane (10 mL), and concentrated by 2/3. The precipitate of diacid **9f** was filtered off, washed with hexane, and dried.

Diacid **9a** was obtained under similar conditions by treatment of isothiocyanate **7a** with dimethyl iminodiacetate followed by hydrolysis.

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