Reactions of metallated 1-hydroxy-2,2,4,5,5-pentamethyl-3-imidazoline with electrophiles

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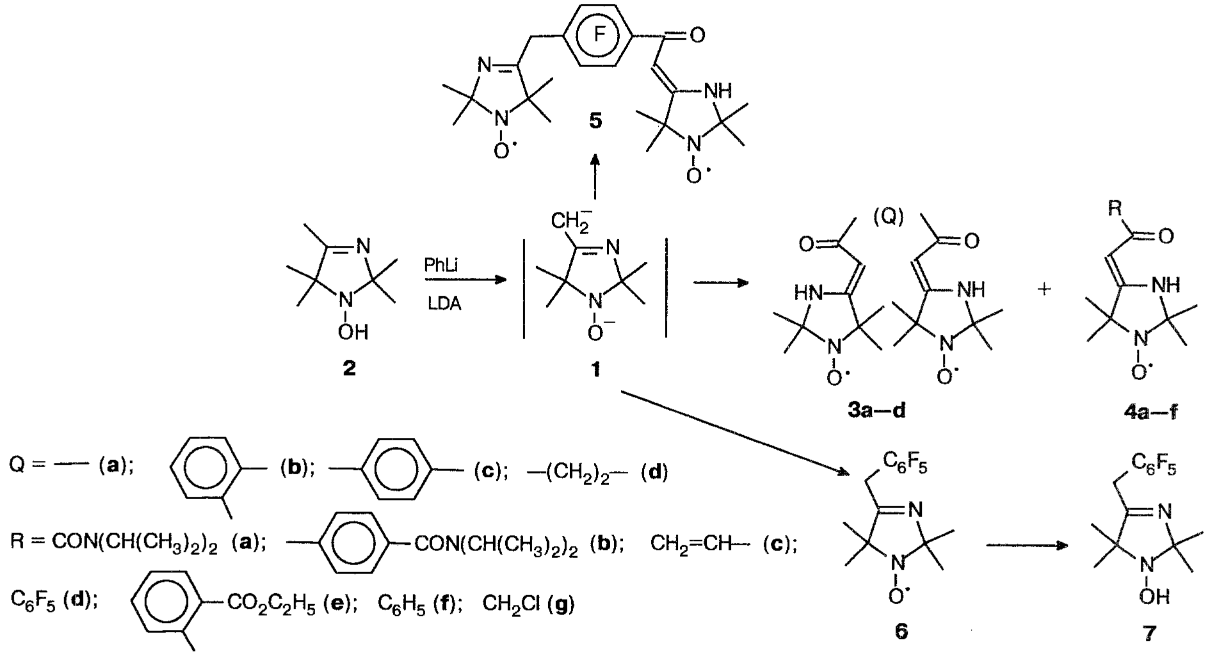
Reactions of metallated 1-hydroxy-2,2,4,5,5-pentamethyl-3-imidazoline with electrophilic reagents followed by oxidation result in mono- and bifunctional substituted nitroxides of 3-imidazoline and an imidazolidine series including enaminocarbonyl and -thiocarbonyl derivatives and enaminoimines, the spin-labeled chelating reagents.

Key words: nitroxyl radical, 3-imidazoline, enaminoketone, enaminoimine, enaminoamide, enaminothioamide, imine, metallation.

We have shown previously that reactions of metallated derivative **1**, formed by the action of PhLi or lithium diisopropylamide (LDA) on imidazoline **2**, with esters of carboxylic or thiocarboxylic acids and methyl nitrate result in conjugated heterocyclic enamines of the imidazolidin oxyl series.[1—3] It was proposed that some of the compounds prepared might be useful as spin-labeled analytical reagents[4] and as paramagnetic ligands in coordination chemistry.[5] The complexes of these compounds were found to undergo low-temperature phase transition to the ferromagnetic state.[6] The present work continues the study of reactions of metallated derivative **1** with electrophilic reagents. The structures of the products formed on oxidation of the reaction mixture with MnO_2 are discussed in all of the cases.

Depending on the conditions, reactions of compound **1** with diesters of dicarboxylic acids can result in products of condensation involving either one or both ester groups.[1] If LDA is used as the metallating reagent, the reaction selectivity can be improved. In particular, biradical **3a** was obtained in a low yield in the reaction of **1** with diethyl oxalate (Scheme 1) (*cf.* ref. 1). In addition, the formation of diisopropylamide **4a** is observed in this case. Taking into account the interest in

Scheme 1



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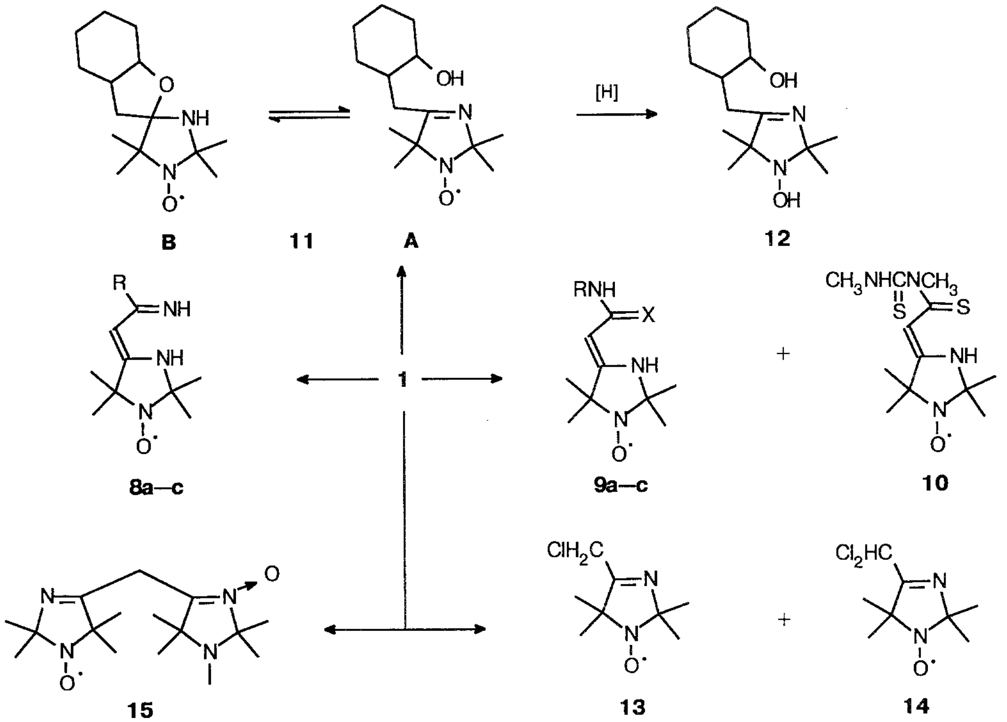
Scheme 2



8a, 9a, 9d: R = C_6H_5
8b: R = CH_2Cl
8c: R = CH_2I
9b: R = cyclohexyl
9c: R = CH_3
9a,b: X = O;
9c,d: X = S

biradicals that incorporate an enaminoketone unit, as tetradentate ligands, we also synthesized other analogous compounds. Reactions of **1** with diesters of phthalic, terephthalic, or succinic acid afford biradicals **3b—d**, respectively. The reaction with dimethyl terephthalate gave amide **4b** along with biradical **3c**, while the reaction with diethyl phthalate yielded monoradical **4b** along with biradical **3b**.

The reaction of metallated derivative **1** with methyl acrylate proceeds in a complicated way to give enaminoketone **4c** in a low yield.

The reaction of compound **1** with methyl pentafluorophenylbenzoate gave compound **5** along with enaminoketone **4d**. The structure of compound **5** was established on the basis of IR and UV spectroscopic data. Compound **5** is formed by nucleophilic substitution of a fluorine atom in the aromatic ring. The product of nucleophilic substitution of a fluorine atom by anion **1** with the retention of the ester group could not be detected, which agrees with the literature data on the reactions of esters of perfluorobenzoic acid with organometallic compounds (*cf.* ref. 7). The possibility of such a reaction was demonstrated in the treatment of metallated derivative **1** with hexafluorobenzene, which resulted in the pentafluorobenzyl derivative **6**. It should be noted that compound **6** exists in the unconjugated imine form, according to IR and UV spectral data, as well as ^1H NMR data for the diamagnetic reduction product **7**.

Compounds having a strongly basic moiety in the vicinity of the nitroxyl group can be used as indicators for the microvolume ESR-spectroscopic determination of acidity. Paramagnetic amidines are among the compounds that are the most interesting in this respect, since their p*K* values are within the range typical of biological systems.[8] Enaminoimines, the vinylogs of amidines, are also very strong bases.[9] With this in mind, an attempt was undertaken to synthesize similar compounds belonging to the series of imidazolidine nitroxyl radicals.

Metallated derivative **1** reacted with benzonitrile or chloroacetonitrile to give enaminoimines **8a,b** (Scheme 2). The reaction of compound **8b** with NaI resulted in the iodo derivative **8c**, which may be regarded as an alkylating spin label having a pH-dependent ESR spectrum. Compounds **8**, like enaminocarbonyl derivatives, exist in the conjugated enaminoimine form (*cf.* ref. 9), which is corroborated by their spectral characteristics, particularly the similarity of their UV spectra to those for enaminoketones **4**. It was difficult to determine the p*K* values for compounds **8a,b**, and even more difficult to use them as indicators, due to their exceedingly high susceptibility to hydrolysis into the corresponding enaminoketones **4f,g**.

The reactions of metallated derivative **1** with phenyl- or cyclohexylisocyanates proceeded by addition of the isocyanate group to the C=N bond to give enaminoamides **9a,b**. Similarly, enaminothioamides **9c,d** were obtained by reactions involving methyl- or phenylisothiocyanates. It should be noted that the reaction of **1** with methylisothiocyanate gave not only enaminothioamide **9c**, but also compound **10**, whose IR and UV spectra were similar to those for **9**, and which, according to the elemental analysis data, resulted from the reaction of compound **1** with two molecules of methylisothiocyanate. Compound **10** may be formed by electrophilic attack on the NH moiety in the thioamide grouping in **9c** by the CH_3NCS molecule.

It may be assumed that alcohol **11**, which is isolated after the interaction of metallated derivative **1** with cyclohexene oxide, exists as a mixture of the imine (A) and spiran (B) tautomeric forms (*cf.* refs. 10, 11). The IR spectrum of compound **11** (in CCl_4) contains an absorption band of the C=N bond at 1640 cm^{-1} and bands at 3620 cm^{-1} and 3200—3500 cm^{-1} for the OH group. The pattern of the spectrum did not change when the solution was diluted to 0.05 %, which suggests the presence of an intramolecular hydrogen bond. The far region of the IR spectrum (KBr) contains absorption bands at 3410 cm^{-1} and 3490 cm^{-1}, which may be attributed to vibrations of the N—H bond in tautomeric form B and vibrations of the O—H bond in form A, as well as an absorption band of the C=N bond at 1640 cm^{-1}. The IR spectrum for diamagnetic derivative **12**, both in the solid phase and as solutions in CCl_4 and $CHCl_3$, is similar to that for compound **11** in the 700—800 cm^{-1} region. This suggests that for compounds **11** and **12** the compositions of the tautomeric mixtures are similar, provided that a tautomeric equilibrium really exists. The ^{13}C NMR spectrum for the diamagnetic analog of **12** in DMSO-d_6 and $CDCl_3$ contains only signals relating to form A.

The reaction of metallated derivative **1** with *p*-toluenesulfonyl chloride unexpectedly resulted in mono- (**13**) and dichloromethyl derivatives (**14**), *i.e.*, *p*-toluenesulfonyl chloride acts as a donor of an electrophilic chlorine atom in this reaction.

Metallated derivative **1** underwent nucleophilic addition to such a sterically hindered aldonitrone as 1,2,2,5,5-pentamethyl-3-imidazoline 3-oxide. Subsequent oxidation with MnO_2 afforded the nitroxyl monoradical **15**, which, according to UV spectral data (λ_{max} 236 nm (log ε 4.02), λ_{max} 318 nm (log ε 4.34)), exists in solution in the enaminonitrone or enhydroxylaminoimine tautomeric forms (*cf.* ref. 14).

Experimental

IR spectra were recorded on Specord M-80 and UR-20 spectrophotometers in KBr pellets (at a concentration of 0.25 %) and in CCl_4 and $CDCl_3$ solutions (at a concentration of 5 %). UV spectra were recorded on a Specord UV-VIS spectrophotometer in ethanol. ^1H and ^{13}C NMR spectra were obtained on a Bruker AC-200 spectrometer in the pulse mode at 300 K in DMSO-d_6 solutions (at a concentration of 5 %). Chemical shifts were measured relative to the signals for the solvents. The properties of the compounds synthesized are given in Table 1.

Reaction of metallated derivative 1 with electrophilic reagents (general procedure). Diisopropylamine (7.4 mL, 52.5 mmol) was added dropwise at 20 °C under argon to a stirred solution of phenyllithium prepared from bromobenzene (6.4 mL, 60 mmol) and lithium (0.84 g, 120 mmol) in abs.

Table 1. Properties of compounds **3—15**

Compound	Yield (%)	M.p./°C (solvent)	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (log ε)	Found/Calculated (%)			Molecular formula
					C	H	N	
3a	35 40	239—240 (MeOH)	1560,1610 (C=C—C=O), 3270 (N—H)	247 (3.97) 357 (4.44)	59.1 59.3	7.8 7.7	15.4 15.4	$C_{18}H_{28}N_4O_4$
3b		210—211 ($CHCl_3$—MeOH)	1515,1545,1560,1595,1615, 1620,1640 (C=C—C=O), 3245 (N—H)	253 (4.27) 294 (4.20) 311 (4.16) 327 (4.23) 345 (4.20) 470 (3.52)	65.2 65.4	7.4 7.3	12.5 12.7	$C_{24}H_{32}N_4O_4$
3c	45	248—250	1550,1585,1610 (C=C—C=O)	254, 360*	65.2 65.4	7.3 7.3	12.6 12.7	$C_{24}H_{32}N_4O_4$
3d	55	219—221 (hexane—ethyl acetate)	1565,1620 (C=C—C=O) 3275 (N—H)	304 (4.56)	61.2 61.2	8.4 8.2	14.1 14.3	$C_{20}H_{32}N_4O_4$
4a	10	247—249 (MeOH)	1565,1595,1630 (C=C—C=O) 3245 (N—H)	310 (4.38)	61.7 61.9	9.8 9.1	13.6 13.5	$C_{16}H_{28}N_3O_3$
4b	10	190—192 (EtOH—H_2O)	1545,1570,1610,1640 (C=C, C=O)	247 (3.96) 336 (4.20)	68.5 68.4	8.4 8.4	10.6 10.9	$C_{22}H_{32}N_3O_3$

Table 1. Continued

Compound	Yield (%)	M.p./°C (solvent)	IR (KBr), ν/cm^{-1}	UV, λ_{max}/nm (log ε)	Found/Calculated (%)			Molecular formula
					C	H	N	
4c	15	135—137 (hexane)	1560,1610,1640 (C=C—C=O) 3090 (=CH_2), 3285 (N-H)	235 (4.0) 333 (4.33)	63.3 63.1	8.4 8.2	13.2 13.4	$C_{11}H_{17}N_2O_2$
4d	50	195—196 (hexane—ethyl acetate)	1555,1570,1615 (C=C—C=O) 3270 (N—H)	320 (4.05)	51.4 51.6	4.0 4.1	7.8 8.0	$C_{15}H_{14}F_5N_2O_2$**
4e	20	137—138 (hexane—ethyl acetate)	1555,1585,1615 (C=C—C=O) 1765 (C=O), 3250 (N-H)	236 (4.02) 318 (4.34)	65.0 65.3	7.0 7.0	8.5 8.5	$C_{18}H_{23}N_2O_4$
5	25	226—228 (methanol—ethyl acetate)	1570,1620 (C=C—C=O), 1640 (C=N), 3270 (N—H)	238 (3.73) 326 (3.98)	56.8 57.0	5.8 5.8	11.4 11.6	$C_{23}H_{28}F_4N_4O_3$**
6	40	125—127 (hexane)	1660 (C=C, C=N)	242 (3.74)	52.3 52.3	4.4 4.4	8.5 8.7	$C_{14}H_{14}F_5N_2O$**
7	95	132—134 (hexane)	1660 (C=C, C=N)	—	52.5 52.2	4.8 4.7	8.6 8.7	$C_{14}H_{15}F_5N_2O$**
8a	45	149—150 (hexane—ethyl acetate)	1550,1625 (C=C—C=N), 3180,3360 (N—H)	236 (3.91) 330 (4.09)	69.8 69.7	7.9 7.8	16.0 16.3	$C_{15}H_{20}N_3O$
8b	30	133—135 (hexane—ethyl acetate)	1560,1640 (C=C—C=N), 3180,3215,3250,3290, 3390 (N—H)	305 (4.25)	51.8 52.1	7.4 7.4	17.9 18.2	$C_{10}H_{17}ClN_3O$**
8c	80	106—108	1555,1630 (C=C—C=N) 3390 (N—H)	259 (3.70) 313 (4.05)	37.6 37.3	5.4 5.3	13.3 13.1	$C_{10}H_{17}IN_3O$**
9a	30	176—178 (methanol—ethyl acetate)	1510,1535,1565,1600,1620 1670 (C=C—C=O), 3315 (N—H)	250 (4.26) 302 (3.99)	65.6 65.7	7.4 7.4	15.3 15.3	$C_{15}H_{20}N_3O_2$
9b	15	195—196 (hexane—ethyl acetate)	1550,1610,1665 (C=C—C=O)	244 (3.61) 287 (3.72)	64.6 64.2	9.6 9.4	14.9 15.0	$C_{15}H_{26}N_3O_2$
9c	25	140—142 (hexane—ethyl acetate)	1520,1615 (C=C—C=S), 3130,3220 (N—H)	283 (4.16) 323 (4.31)	52.4 52.6	8.1 8.0	18.4 18.4	$C_{10}H_{18}N_3OS$**
9d	45	197—198 (EtOH)	1500,1525,1595,1625 (C=C—C=S), 3285 (N—H)	337 (4.12)	61.8 62.0	7.6 7.0	14.4 14.5	$C_{12}H_{21}N_4OS_2$**
10	10	154—156 (hexane—ethyl acetate)	1520,1565,1625 (C=C—C=S)	243 (3.83) 263 (3.94) 285 (3.75) 328 (3.83)	48.1 47.8	6.9 7.0	18.8 18.6	$C_{12}H_{21}N_4OS_2$**
11	50	115—117 (hexane—ethyl acetate)	1645 (C=N), 3200—3500, 3620 (O—H)	—	66.6 66.4	10.2 10.0	11.1 11.1	$C_{14}H_{25}N_2O_2$
12	95	124—126 (hexane—ethyl acetate)	1640 (C=N), 3100—3500, 3590 (O—H)	—	66.3 66.1	10.4 10.3	11.0 11.0	$C_{14}H_{26}N_2O_2$
15	30	203—204 (EtOH)	1550,1650 (C=N)	234 (3.78) 329 (4.03)	61.9 62.2	9.8 9.4	18.0 18.1	$C_{16}H_{29}N_4O_2$

* The spectrum was recorded in KBr. ** **4d**, found (%): F, 26.9; calculated (%): F, 27.2; **5**, found (%): F, 15.79; calculated (%): F, 15.7; **6**, found (%): F, 30.0, calculated (%): F, 29.6; **7**, found (%): F, 30.0, calculated (%): F, 29.5; **8b**, found (%): Cl, 15.7, calculated (%): Cl, 15.4; **8c**, found (%): I, 39.1, calculated (%): I, 39.5; **9c**, found (%): S, 14.4, calculated (%): S, 14.0; **9d**, found (%): S, 11.4, calculated (%): S, 11.0; **10**, found (%): S, 21.6, calculated (%): S, 21.3.

ether (80 mL). After 15 min a solution of imidazoline **2** (2.34 g, 15 mmol) in abs. ether was added, and the mixture was stirred for 20 min at 20 °C. Then a solution of the respective electrophilic reagent (36 mmol) in abs. ether was added dropwise over 10—15 min to the resulting suspension of metallated derivative **1** with stirring and cooling to 0 °C. When dimethyl terephthalate was used, it was added portionwise. The reaction with 1,2,2,5,5-tetramethyl-3-imidazoline 3-oxide was carried out at the equimolar ratio of the reagents. Stirring was continued for 20 min at 0 °C and then for 1 h at 20 °C. The reaction mixture was treated with water (20 mL), the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4×30 mL). In the case of diethyl succinate, the precipitate was filtered off, the solution was concentrated, the residue was washed with hexane, and the precipitate of biradical **3d** was filtered off. In the case of the remaining reagents, the combined extract was dried with $MgSO_4$, and the solution was concentrated. The residue was dissolved in $CHCl_3$ (50 mL), and the solution was stirred for 30 min with MnO_2 at 20 °C. The excess oxidant was filtered off, the solution was concentrated, and the reaction products were isolated by column chromatography using silica gel and the following eluents: $CHCl_3$ (**3a—c**, **4a,b,d,e**, **5**, **6**, **8a,b**, **9a**, **11**, **13—15**), ether — hexane, 1:1 (**4c**), ethyl acetate — hexane, 1:3 (**9c,d**, **10**), or ether (**9b**). Mono-(**13**) and dichloromethyl (**14**) derivatives identified by comparison with authentic samples[12,13] were obtained in yields of 25 % and 30 %, respectively.

1-Hydroxy-4-pentafluorophenylmethyl-2,2,5,5-tetramethyl-3-imidazoline (7). A mixture of radical **6** (0.5 g), Zn powder (2 g), and NH_4Cl (0.1 g) in MeOH (20 mL) was stirred for 10 min at 20 °C. Then the excess zinc was filtered off, and the solution was concentrated. Water (10 mL) was added to the residue, and the product was extracted with $CHCl_3$ (3×20 mL). The extract was dried with $MgSO_4$, and the solution was concentrated. The residue was washed with hexane (5 mL), and the precipitate of hydroxy derivative **7** was filtered off. ^{1}H NMR (DMSO-d_6), δ: 1.11 (s, 6 H, 5-$(CH_3)_2$); 1.22 (s, 6 H, 2-$(CH_3)_2$); 3.64 (s, 2 H, CH_2).

Reduction of compound **11** under similar conditions afforded **1-hydroxy-4-(2-hydroxycyclohexyl)methyl-2,2,5,5-tetramethyl-3-imidazoline (12).** ^{13}C NMR (DMSO-d_6), δ: 22.55, 23.66, 25.85, 26.87 (CH_3); 24.72, 25.21, 30.28, 32.15, 35.57 (CH_2); 41.46 (C—H (cyclohexyl)); 70.76 (C(5)); 72.78 (CHOH); 88.62 (C(2)); 176.19 (C(4)).

4-(3-Iodo-2-iminopropylidene)-2,2,5,5-tetramethylimidazolin-1-oxyl (8c). A solution of compound **8b** (0.15 g) and NaI (0.5 g) in acetone (20 mL) was refluxed for 30 min and concentrated. Compound **8c** was isolated by column chromatography on silica gel using $CHCl_3$ as the eluent.

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