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Diastereoselective Reaction of a 2-Nitroenamine with an Excess of Grignard Reagent

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Nitroenamine 1 reacts with four equivalents of Grignard reagents to yield hydroxylamines 8–10 after hydrolysis. In the case of 8 and 10 this reaction is highly diastereoselective (Scheme). ^{1}H-NMR signal assignments of imidazolidine 3 by NOE result in the relative configurations (Scheme) for the preferred diastereomers of 2 and 4.

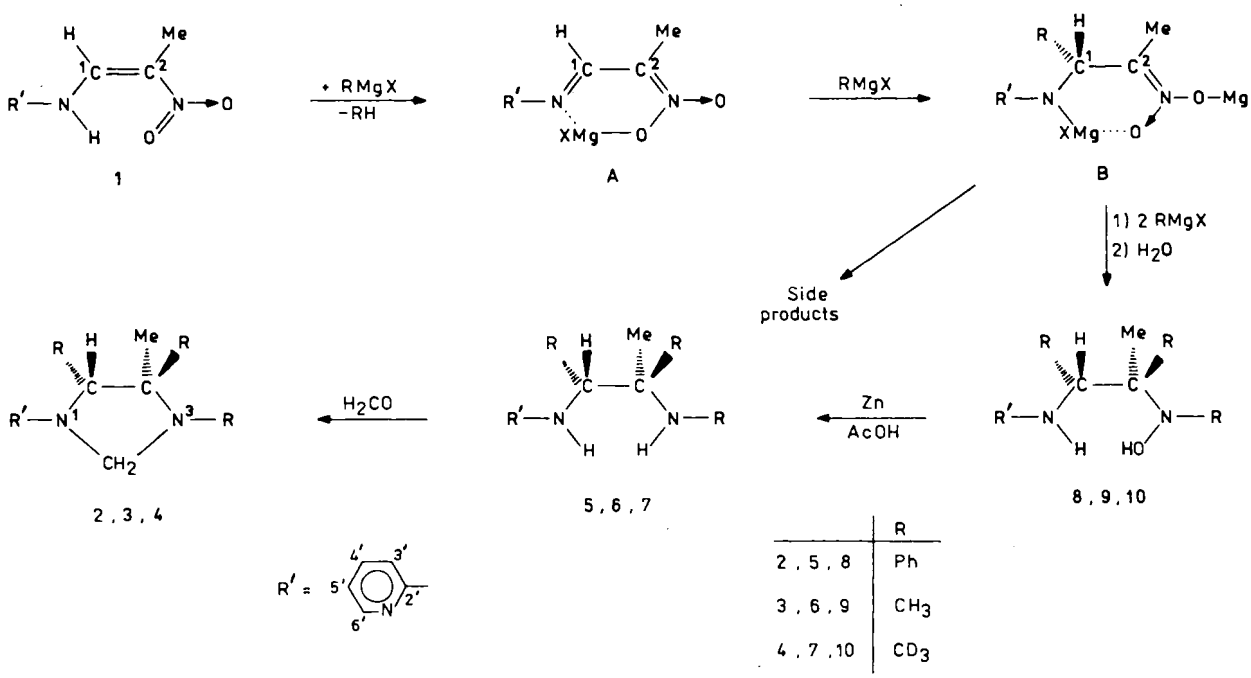
Reactions of nitroalkanes[1] or nitroenamines[2] with organometallic reagents have not been studied intensely. In the case of secondary 2-nitroenamines investigated by NMR[3] under anionic activation conditions, we anticipated C^1 in the anionic synthon to be a centre for nucleophilic attack. To check this hypothesis we have chosen an excess of Grignard reagent for generating the nitroenamine anion in situ. The suggested course of the reaction is shown in the Scheme.

Examination of the reaction mixtures with limited work-up of **8** and **10** revealed the presence of only one diastereomer of **8** and a 85% preference of one diastereomer of **10**. Hence the reaction is highly diastereoselective. In order to help in assigning the relative configurations a sequence of reactions (Scheme) was planned which transforms the open-chain hydroxylamines **8**–**10** into the cyclic imidazolidines **2**–**4**.

The NOE experiments performed on **3** (Figure 1) showed that the methyl group at $\delta = 0.67$ eclipses the C–H^5 hydrogen atom. The ^{1}H NMR of **4** (see Exp.) shows that this methyl group originates from the Grignard reagent. Irradiation of the other methyl signal ($\delta = 0.86$) of **3** showed no appreciable enhancement of the C–H^5 absorption but did so for the Me^5 resonance. The above experiments, giving the ^{1}H signal assignments of **3** shown in Figure 1, also resulted in the relative configurations (Scheme) for the preferred diastereomers of imidazolidines **2** and **4**.

These results are in agreement with a steric course of the reaction determined by the intermediate **B** in the Scheme. Its rigidity, due

Scheme[4]



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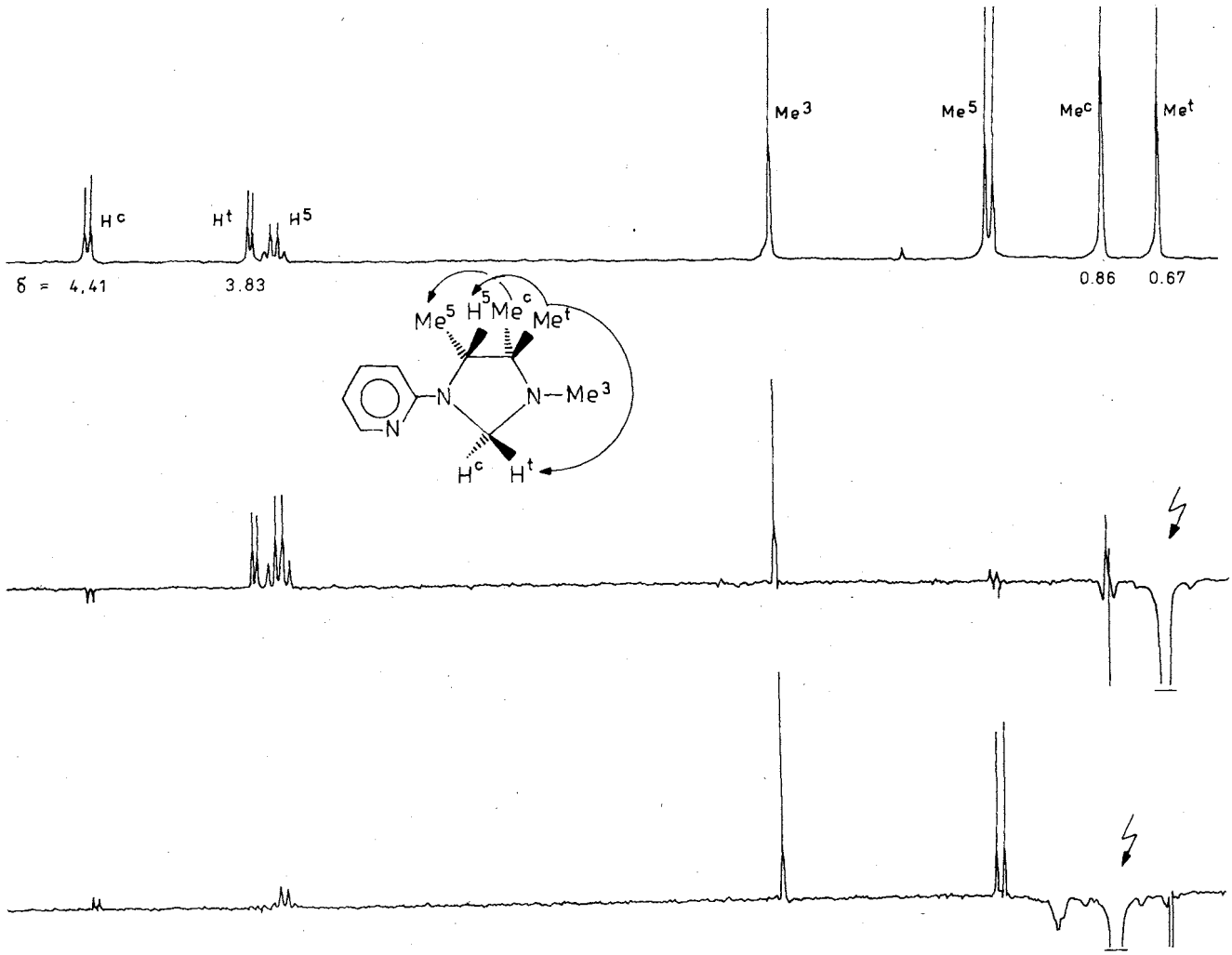

Figure 1. ^{1}H NMR, aliphatic protons of imidazolidine **3**[4] in C_6D_6 at 24°C and 250 MHz. Top: Normal spectrum, the irradiation frequency being offset. Center: NOE difference spectrum upon irradiation at δ = 0.67. Bottom: NOE difference spectrum upon irradiation at δ = 0.86. The relative intensities of the two difference spectra are the same. The arrows on the formula indicate NOE enhancements which result in the assignments given for the normal spectrum (top)

to metal coordination, apparently creates a steric situation favourable to a stereospecific attack at C^2 of **B** from the side *trans* to the substituent R on C^1. Interestingly, the entering substituent CD_3, which is sterically less demanding than phenyl, results in **4** with a diastereomeric preference of 85% only. This result indicates that intermediate **A** is primarily attacked at C^1 to yield **B**. If **A** were attacked at C^2 first, it seemed highly improbable that the moiety $CD_3-C^2-CH_3$ would create such a high diastereoselectivity of C^1 trideuteriomethylation as observed in the case of **10**.

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Experimental

^{1}H-NMR spectra: Varian T-60, Bruker WP-100, and Bruker WM-250. – Mass spectra: MAT CH-5 at 70 eV. – Liquid chromatography (LC) on triacetylcellulose: Low-pressure equipment as described[5]: capacity factors[5] *k* are given.

1-(2-Pyridinylamino)-2-nitropropene (**1**)[6]

Reaction of **1** *with Organomagnesium Halides:* 1.79 g (10 mmol) of **1** was added to 60 mmol of PhMgBr (10.87 g), MeMgI (9.97 g) or CD_3MgI (10.15 g) in 50 ml of Et_2O at 0–5°C. After 12 h at room temperature the mixture was hydrolyzed with ice and NH_4Cl and extracted with Et_2O. After evaporation 15 ml of Et_2O/*i*-PrOH (1:1) was added and the product left in the refrigerator for 12 h. **8**, **9**, or **10** was filtered off and recrystallized from *i*-PrOH. Yields were 0.59 g (15%), 0.27 g (13%), and 0.28 g (13%) for **8**, **9** and **10**, respectively.

1,2-Diphenyl-2-(N-phenylhydroxylamino)-1-(2-pyridinylamino)-propane (**8**): M.p. 122–124°C. – ^{1}H NMR ($CDCl_3$): δ = 1.4 (s, 3H, CH_3), 5.64 (d, *J* = 4 Hz, 1H, NH–C*H*), 5.0 (d, *J* = 8 Hz, 1H, $H^{3'}$), 6.2–6.55 (m, 2H, NH and $H^{5'}$), 6.8–7.6 (m, 16H, aromat. H), 7.76 (d, *J* = 6 Hz, 1H, $H^{6'}$), 9.7 (s, 1H, HO). – LC on triacetylcellulose (EtOH): Two enantiomers, *k* = 0.38.

$C_{26}H_{25}N_3O \cdot H_2O$ (413.5) Calcd. C 75.52 H 6.58 N 10.16
Found C 75.21 H 6.68 N 10.04

3-Methyl-3-(N-methylhydroxylamino)-2-(2-pyridinylamino)butane (**9**): M.p. 136–137°C. – ^{1}H NMR ($CDCl_3$): δ = 0.98 and 1.07 [two s, 6H, $C(CH_3)_2$], 1.20 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 2.56

(s, 3H, NCH_3), 4.25 (q, J = 6.2 Hz, 1H, $CH-CH_3$), 6.3–6.6 (m, 2H, $H^{3'}$ and $H^{5'}$), 7.2–7.5 (m, 1H, $H^{4'}$), 7.9–8.0 (m, 1H, $H^{6'}$). – LC on triacetylcellulose (EtOH): Two enantiomers, k = 0.25.

$C_{11}H_{19}N_3O$ (209.3) Calcd. C 63.13 H 9.15 N 20.08
Found C 63.07 H 9.05 N 20.09

1,1,1,4,4,4-Hexadeuterio-3-methyl-2-(pyridinylamino)-3-[N-(trideuteriomethyl)hydroxylamino]butane (**10**): M.p. 136 to 137°C. – ^{1}H NMR ($CDCl_3$): δ = 0.98 and 1.07 (two s, 0.85 · 3H and 0.15 · 3H, resp., $D_3C-C^2-CH_3$), 4.25 (s, 1H, $CH-CD_3$), 6.3–6.6 (m, 2H, $H^{3'}$ and $H^{5'}$), 7.2–7.5 (m, 1H, $H^{4'}$), 7.9–8.0 (m, 1H, $H^{6'}$).

$C_{11}H_{10}D_9N_3O$ (218.2) Calcd. C 60.51 H + D 8.78[7] N 19.24
Found C 60.56 H + D 8.77 N 19.30

Reduction of Hydroxylamines **8**–**10** *to Amines* **5**–**7**: 1.0 mmol of **8** (0.40 g), **9** (0.21 g), or **10** (0.22 g) was boiled with 0.27 g (4.0 mmol) of zinc in 12 ml (100 mmol) of 50% acetic acid for 15 min. After removal of the excess of zinc the solution was diluted with water. Aq. NH_3 was added until the solution was alkaline. It was extracted with CH_2Cl_2, which was then evaporated. The yield of crude product was almost theoretical. **5** was crystallized from Et_2O/*n*-hexane.

1,2-Diphenyl-2-(phenylamino)-1-(2-pyridinylamino)propane (**5**): M. p. 143–145°C. – ^{1}H NMR ($CDCl_3$): δ = 1.75 (s, 3H, CH_3), 4.8–5.8 (m, 3H, $CH-NH$, HNPh), 6.1–7.6 (m, 18H, aromat. H), 8.0–8.3 (m, 1H, $H^{6'}$).

$C_{26}H_{25}N_3$ (379.5) Calcd. C 82.29 H 6.64 N 11.07
Found C 82.12 H 6.82 N 11.14

3-Methyl-3-(methylamino)-2-(2-pyridinylamino)butane (**6**): Crude; the liquid was not characterized.

1,1,1,4,4,4-Hexadeuterio-3-methyl-2-(2-pyridinylamino)-3-[(trideuteriomethyl)amino]butane (**7**): Crude; the liquid was not characterized.

Condensation of Amines **5**–**7** *with Formaldehyde to yield Imidazolidines* **2**–**4**: 1.0 mmol of crude **5** (0.38 g), **6** (0.19 g), or **7** (0.20 g) was refluxed in 5 ml of MeOH with 0.1 ml (1.3 mmol) of 40% H_2CO/H_2O and 2 drops of acetic acid. MeOH was evaporated, the mixture was diluted with 10 ml of H_2O and extracted with CH_2Cl_2. After removal of the solvent the crude product was obtained in nearly theoretical yield. **2** was recrystallized from MeOH. **3** and **4**, colourless oils, were purified by chromatography on silica gel with CH_2Cl_2/Me_2CO (4:1).

4-Methyl-3,4,5-triphenyl-1-(2-pyridinyl)imidazolidine (**2**): M. p. 95–98°C. – ^{1}H NMR ($CDCl_3$): δ = 1.31 (s, 3H, CH_3), 4.86 (s, 1H, CHN), 5.78 (AB, J = 5.8 Hz, 2H, NCH_2N), 5.99 (d, J = 8.6 Hz, 1H, $H^{3'}$), 6.5–6.7 (m, 4H, $H^{5'}$, H^2, H^4, and H^6 of *N*-phenyl group), 7.0–7.4 (m, 13H, aromat. H), 8.25–8.28 (m, 1H, $H^{6'}$). – LC on triacetylcellulose (EtOH): One peak without α-detection, k = 0.28.

$C_{27}H_{25}N_3 \cdot 0.5\ H_2O$ (400.5) Calcd. C 80.97 H 6.54 N 10.41
Found C 80.85 H 7.03 N 10.31

3,4,4,5-Tetramethyl-1-(2-pyridinyl)imidazolidine (**3**): ^{1}H NMR (C_6D_6): δ = 0.67 and 0.86 [two s, 6H, $C(CH_3)_2$], 1.25 (d, J = 6.3 Hz, 3H, $HC-CH_3$), 2.01 (s, 3H, NCH_3), 3.74 (q, J = 6.3 Hz, 1H, $HC-CH_3$), 3.83 and 4.41 (AB, J = 4.7 Hz, 2H, NCH_2N), 6.02 (m, 1H, $H^{3'}$), 6.37 (m, 1H, $H^{5'}$), 7.15 (m, 1H, $H^{4'}$), 8.32 (m, 1H, $H^{6'}$), (Figure 1, top). – MS, molecular ion: Calcd. and found 205.

4-Methyl-1-(2-pyridinyl)-3,4,5-tris(trideuteriomethyl)imidazolidine (**4**): ^{1}H NMR (C_6D_6): δ = 0.67 and 0.86 (two s, 0.15 · 3H and 0.85 · 3H, resp., CD_3-C-CH_3), 3.72 (s, 1H, $HC-CD_3$), 3.83 and 4.41 (AB, J = 4.7 Hz, 2H, NCH_2N), 6.02 (m, 1H, $H^{3'}$), 6.37 (m, 1H, $H^{5'}$), 7.16 (m, 1H, $H^{4'}$), 8.32 (m, 1H, $H^{6'}$). – MS, molecular ion: Calcd. and found 214.

CAS Registry Numbers

1: 86602-43-9 / **2**: 112151-99-2 / **3**: 112152-00-8 / **4**: 112152-01-9 / **5**: 112151-96-9 / **6**: 112151-97-0 / **7**: 112151-98-1 / **8**: 112151-93-6 / **9**: 112151-94-7 / **10**: 112151-95-8

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[7] For a certain amount of a compound (expressed in mol) the content of deuterium has an influence upon the mass of that amount, i.e. its weight, but has no influence upon the amount (expressed in mol) of hydrogen and deuterium together. The latter was measured by chromatographic detection which does not differentiate H_2O, HDO, and D_2O. Therefore, the whole amount of hydrogen and deuterium is given by the following expression which was adopted to the above type of analysis.

$$\frac{M_H\,(n_H + n_D)\,100\%}{M} = \frac{1.008 \cdot 19 \cdot 100\%}{218.21} = 8.78\%$$

n_H: Number of hydrogen atoms in the molecule
n_D: Number of deuterium atoms in the molecule
M: Mass of the molecule
M_H: Mass of the hydrogen atom.

[288/87]