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One-Pot Synthesis of 1,4-Diamines from Allyl Halides and Amines via a Rhodium-Catalysed Multistep Reaction Sequence under Hydroformylation Conditions

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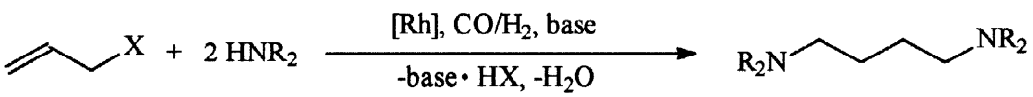
Abstract

1,4-Diamines **8** are prepared with good yields and selectivities by the reaction of methallyl chloride **(6)**, secondary amines **7**, carbon monoxide and hydrogen in presence of $[Rh(cod)Cl]_2$ as catalyst via a one-pot nucleophilic substitution - hydroformylation - amine condensation - reduction sequence. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Rhodium catalysis, 1,4-Diamines, Multistep reaction sequence, Hydroformylation, Carbonylation.

Due to their biological activity 1,4-diamines play an important role as cytotoxics[1], antiestrogenics[2], as antipsychotics[3] and as substances with antitumor[4] activity. Various methodologies towards their synthesis have been developed, usually starting from 1,4-difunctionalised precursors.[1-5] Here we report an easy and convenient one-pot synthesis of 1,4-diamines **5** starting from allyl halides **1** and secondary amines.



1 **5**

Scheme 1. One-pot conversion of allyl halides **1** and secondary amines to the 1,4-diamines **5**

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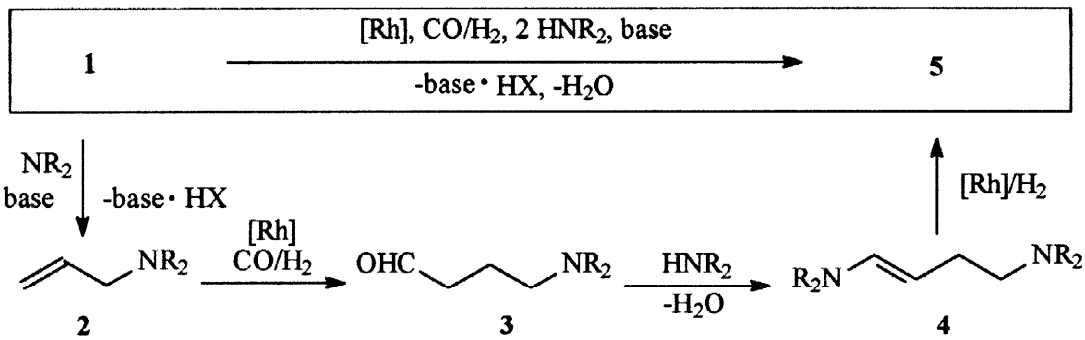
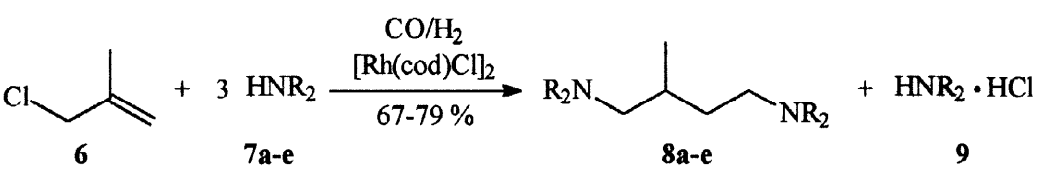
Following our interests in tandem hydroformylations[6] we recently reported[6e] that 1,4-diamines are easily accessible via a hydroformylation - reductive amination (hydroamino-methylation) sequence starting from *N*-allylic compounds. Furthermore it is well established that allylic amines are easily prepared from allyl halides and the corresponding amines via nucleophilic substitution.[7] A combination of all steps in a one-pot procedure would be even more convenient.



Scheme 2. Synthesis of 1,4-diamines **5** starting from allyl halides **1** and secondary amines

We here report conditions for such a multistep reaction sequence starting with an *in-situ* generation of an allylic amine **2** which undergoes selective hydroaminomethylation to form the corresponding 1,4-diamine **5** in a following step (scheme 2).

If using methallyl chloride **(6)** as allyl halide under typical hydroaminomethylation conditions with $[Rh(cod)Cl]_2$ as catalyst 1,4-diamines **8** are selectively formed if three equivalents of secondary amine are applied (scheme 3). One equivalent of the amine acts as a base forming the hydrochloride **9**. The two others are introduced into the substrate as discussed above. As summarised in table 1 acyclic as well as cyclic aliphatic secondary amines **7a-e** lead to the corresponding 1,4-diamines **8a-e** in good yields and selectivities (scheme 3, table 1).[8] Due to the sterical hindrance of the α-C carbonylation side products such as 1,3-diamines resulting from *iso*-hydroaminomethylation are not observed.

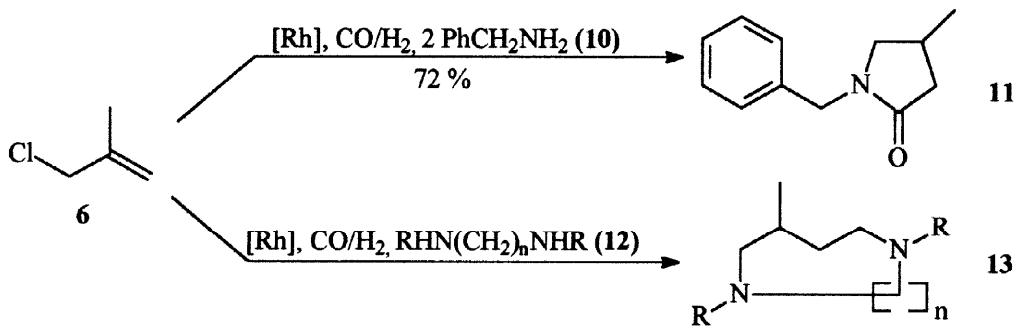


Scheme 3. Conversion of methallyl chloride **(6)** with various secondary amines **7a-e**

Table 1. Conversion of methallyl chloride **(1)** with various secondary amines **7a-e**[8]

Entry	Olefin	Amine	Product	Yield [%]
1	6	Diethylamine (7a)	8a	67
2	6	Pyrrolidine (7b)	8b	79
3	6	Piperidine (7c)	8c	73
4	6	Hexamethylenimine (7d)	8d	71
5	6	Morpholine (7e)	8e	70

With primary amines or diamines this method can also be used in the synthesis of heterocyclic systems. Thus, according to preliminary results, γ-lactam **11** is obtained in good yields from methallyl chloride **(6)** and benzyl amine **(10)**, whereas in presence of secondary diamines **12** cyclisation to heterocyclic ring systems **13** is observed (scheme 4). Further investigations towards an extension of the synthetic potential of this reaction are in current progress.



Scheme 4. Synthesis of γ-lactams and heterocyclic ring systems via a one-pot multistep conversion of **6**

EXPERIMENTAL

NMR spectra were recorded on Bruker spectrometers DPX 300 and DRX 400 using TMS as internal standard. IR spectra were obtained with a Nicolet Impact 400D, mass spectra on a Finnigan CA 5 and elementary analysis with a Leco CHNS-932. Column chromatography was carried out with aluminum oxide N (act. I) from ICN Biomedicals, Eschwege, by using MTBE (methyl *tert*-butyl ether)/PE (petroleum ether, bp 30-60 °C) mixtures as eluent. Gas chromatography was carried out on a Carlo Erba GC-4160 with 25 m or on a Fisons GC-8130 with 30 m CP sil-5 capillaries. GC-MS and GC-IR spectra were obtained by using comparable capillaries and a Finnigan MAT 8320 (MS) or a Bruker IFS 48 (IR), respectively. The $[Rh(cod)Cl]_2$ catalyst was prepared according to literature procedures.[8] Pressure reactions have been carried out in autoclaves (type A, 250 ml, PTFE-insert) from Berghof, Eningen, Germany.

General procedure for the preparation of the 1,4-diamines 8a-e and the γ-lactam 11

A mixture of methallyl chloride (**6**) (14.4 mmol), the corresponding amine (43.2 mmol) and $[Rh(cod)Cl]_2$ (1 mol % Rh) in 10 ml anhydrous dioxane was heated for 2 d, at 110°C in an autoclave under 90 bar carbon monoxide and 20 bar hydrogen (p_{total} = 110 bar) pressure. The residue was dissolved in Et_2O and filtered through neutral alumina. Product mixtures were separated by column chromatography on neutral alumina using a mixture of MTBE/PE as eluent or by Kugelrohr distillation.

N1,N1N4,N4-Tetraethyl-2-methylbutyl-1,4-butanediamine (8a). Obtained from diethylamine (**7a**) and methylallyl chloride (**6**) as a colourless oil in 67 % yield. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 0.90 (d, ^{3}J = 5.9 Hz, 3 H, CH_3), 1.00 (m, 12 H, 4 x CH_3), 1.16 (m, 1 H, C<u>H</u>H-CHR_2), 1.61 (m, 2 H, CH<u>H</u>-CHR_2, CH), 2.10 (dd, ^{2}J = 12.4 Hz, ^{3}J = 7.5 Hz, 1 H, NC<u>H</u>H-CHR_2), 2.20 (dd, ^{2}J = 12.4 Hz, ^{3}J = 6.0 Hz, 1 H, NCH<u>H</u>-CHR_2), 2.48 (m, 10 H, 5 x NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 11.6 (2 x CH_3), 11.7 (2 x CH_3), 18.5 (CH_3), 30.0 (CH), 32.0 (CH_2), 46.7 (2 x NCH_2), 47.4 (2 x NCH_2), 50.6 (NCH_2), 60.5 (NCH_2). GC-MS (EI, 70 eV): m/z (%) = 215 (M^++1, 6), 185 (9), 142 (15), 112 (7), 98 (4), 86 (100), 58 (10). IR (NaCl/film) $\tilde{\nu}$ = 2969 s, 2933 s, 2873 m, 2798 s, 1464 m, 1382 m, 1292 m, 1204 m, 1084 m, 1069 cm^{-1} m.

1-(2-Methyl-4-tetrahydro-1H-1-pyrrolylbutyl)pyrrolidine (8b). Obtained from pyrrolidine (**7b**) and methylallyl chloride (**6**) as a yellow oil in 79 % yield. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 0.94 (d, ^{3}J = 6.5 Hz, 3 H, CH_3), 1.29 (m, 1 H, C<u>H</u>H-CHR_2), 1.66 (m, 2 H, CH<u>H</u>-CHR_2, CH), 1.76 (m, 8 H, 4 x CH_2), 2.26 (m, 2 H, NCH_2), 2.45 (m, 10 H, 5 x NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 18.5 (CH_3), 23.27 (2 x CH_2), 23.31 (2 x CH_2), 31.0 (CH), 34.5 (CH_2), 54.2 (2 x NCH_2), 54.3 (2 x NCH_2), 54.4 (NCH_2), 63.8 (NCH_2). GC-MS (EI, 70 eV): m/z (%) = 211 (M^++1, 8), 140 (10), 84 (100), 70 (8), 55 (8). IR (NaCl/film) $\tilde{\nu}$ = 2962 vs, 2927 s, 2874 s, 2782 vs, 1459 m, 1447 m, 1386 m, 1351 m, 1140 m, 1120 cm^{-1} m. $C_{13}H_{26}N_2$ (210.4): Calc. C, 74.2; H, 12.5; N, 13.3. Found C, 73.8; H, 12.3; N, 13.0.

1-(2-Methyl-4-piperidinobutyl)piperidine (8c). Obtained from piperidine (**7c**) and methylallyl chloride (**6**) as a colourless oil in 73 % yield. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 0.89 (d, ^{3}J = 6.5 Hz, 3 H, CH_3), 1.23 (m, 1 H, C<u>H</u>H-CHR_2), 1.41 (m, 4 H, 2 x CH_2), 1.55 (m, 8 H, 4 x CH_2), 1.65 (m, 2 H, CH<u>H</u>-CHR_2, CH), 2.02 (dd, ^{2}J = 12.1 Hz, ^{3}J = 7.3 Hz, 1 H, NC<u>H</u>H-CHR_2), 2.08 (dd, ^{2}J = 12.1 Hz, ^{3}J = 6.7 Hz, 1 H, NCH<u>H</u>-CHR_2), 2.31 (m, 10 H, 5 x NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 18.6 (CH_3), 24.5 (CH_2), 24.6 (CH_2), 25.96 (2 x CH_2), 25.99 (2 x CH_2), 29.1 (CH), 32.4 (CH_2), 54.6 (2 x NCH_2), 55.0 (2 x NCH_2), 57.5 (NCH_2), 66.5 (NCH_2). GC-MS (EI, 70 eV): m/z (%) = 239 (M^++1, 40), 154 (33), 98 (100), 70 (7). IR (NaCl/film) $\tilde{\nu}$ =

2933 s, 2853 m, 2799 m, 2760 m, 1442 m, 1155 m, 1116 cm^{-1} m. $C_{15}H_{30}N_2$ (238.4): Calc. C, 75.6; H, 12.7; N, 11.8. Found C, 75.4; H, 12.6; N, 11.4.

1-[4-(1-Azepanyl)-2-methylbutyl]azepane (8d). Obtained from hexamethylenimine **(7d)** and methylallyl chloride **(6)** as a colourless oil in 71 % yield. ^1H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 0.82 (d, ^3J = 6.6 Hz, 3 H, CH_3), 1.15 (m, 1 H, C<u>H</u>H-CHR_2), 1.55 (m, 18 H, 8 x CH_2, CH, CH<u>H</u>-CHR_2), 2.11 (dd, ^2J = 12.2 Hz, ^3J = 7.4 Hz, 1 H, NC<u>H</u>H-CHR_2), 2.24 (dd, ^2J = 12.2 Hz, ^3J = 6.6 Hz, 1 H, NCH<u>H</u>-CHR_2), 2.48 (m, 10 H, 5 x NCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 18.4 (CH_3), 26.9 (2 x CH_2), 27.1 (2 x CH_2), 28.0 (2 x CH_2), 28.3 (2 x CH_2), 30.2 (CH), 32.6 (CH_2), 56.2 (NCH_2), 55.5 (2 x NCH_2), 55.8 (2 x NCH_2), 65.2 (NCH_2). GC-MS (EI, 70 eV): m/z (%) = 267 (M^++1, 11), 168 (21), 152 (4), 112 (100), 58 (25). IR (NaCl/film) $\tilde{\nu}$ = 2924 vs, 2848 vs, 2807 vs, 1456 vs, 1371 vs, 1358 vs, 1312 s, 1300 s, 1284 s, 1240 s, 1228 s, 1182 s, 1157 s, 1130 vs, 1103 s, 1083 vs, 1042 m, 1010 m, 965 s, 943 cm^{-1} m. $C_{17}H_{34}N_2$ (266.5): Calc. C, 76.6; H, 12.9; N, 10.5. Found C, 76.4; H, 12.7; N, 10.5.

4-(2-Methyl-4-morpholinobutyl)morpholine (8e). Obtained from morpholine **(7e)** and methylallyl chloride **(6)** as a yellow oil in 70 % yield. ^1H NMR (400 MHz, $CDCl_3$, 20 °C): δ =0.91 (d, ^3J = 6.3 Hz, 3 H, CH_3), 1.22 (m, 1 H, C<u>H</u>H-CHR_2), 1.69 (m, 2 H, CH<u>H</u>-CHR_2, CH), 2.12 (m, 2 H, NCH_2), 2.38 (br s, 8 H, 4 x NCH_2), 2.43 (br s, 2 H, NCH_2), 3.69 (t, ^3J = 5.1 Hz, 8 H, 4 x OCH_2). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 18.2 (CH_3), 28.0 (CH), 31.5 (CH_2), 53.6 (2 x NCH_2), 53.8 (2 x NCH_2), 56.7 (NCH_2), 65.8 (NCH_2), 66.71 (2 x OCH_2), 66.73 (2 x OCH_2). GC-MS (EI, 70 eV): m/z (%) = 243 (M^++1, 16), 224 (5), 156 (39), 140 (13), 112 (5), 100 (100), 70 (16), 56 (10). IR (NaCl/film) $\tilde{\nu}$ = 2955 s, 2927 s, 2853 s, 2806 s, 1457 m, 1299 m, 1273 m, 1119 vs, 1070 m, 1015 m, 865 m, 631 m, 611 cm^{-1} m. $C_{13}H_{26}N_2O_2$ (242.4): Calc. C, 64.4; H, 10.8; N, 11.6. Found C, 63.9; H, 10.7; N, 11.4.

Benzyl-4-methyl-2-pyrrolidinone (11).[9-11] Obtained from benzylamine **(10)** and methallyl chloride **(6)** as a yellow oil in 72 % yield. ^1H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 0.99 (d, ^3J = 6.8 Hz, 3 H, CH_3), 1.97 (dd, ^2J = 16.5 Hz, ^3J = 6.8 Hz, 1 H, C<u>H</u>H-CHR_2), 2.29 (sextet*, J = 7.1 Hz, 1 H, CH), 2.49 (dd, ^2J = 16.5 Hz, ^3J = 8.5 Hz, 1 H, CH<u>H</u>-CHR_2), 2.74 (dd, ^2J = 9.5 Hz, ^3J = 5.9 Hz, 1 H, NC<u>H</u>H-CHR_2), 3.27 (dd, ^2J = 9.5 Hz, ^3J = 7.8 Hz, 1 H, NCH<u>H</u>-CHR_2), 4.36 (s, 2 H, NCH_2Ph), 7.24 (m, 5 H, 5 x PhH). ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 19.2 (CH_3), 25.7 (CH), 38.7 (CH_2), 45.8 (NCH_2), 53.2 (NCH_2Ph), 126.9 (PhH), 127.4 (2 x PhH), 128.1 (2 x PhH), 136.0 (Cq), 173.8 (Cq, C=O). GC-MS (EI, 70 eV): m/z (%) = 190 (M^+, 100), 146 (5),

118 (5), 112 (14), 91 (5). IR (NaCl/film): $\tilde{\nu}$ = 3086 w, 3062 w, 3028 m, 2959 s, 2927 s, 2871 m, 1688 vs, 1495 s, 1454 s, 1441 s, 1427 s, 1381 m, 1356 m, 1297 m, 1267 s, 741 s, 665 cm^{-1} s.

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