# One-pot Preparation of 1,2-Aminoalcohols or Pyrroles by $CeCl_3 \cdot 7\ H_2O$-mediated Barbier Reactions of *N,N'*-Bis[(S)-1-phenylethyl]ethanediimine

Gianluca Martelli, Stefano Morri, Diego Savoia*

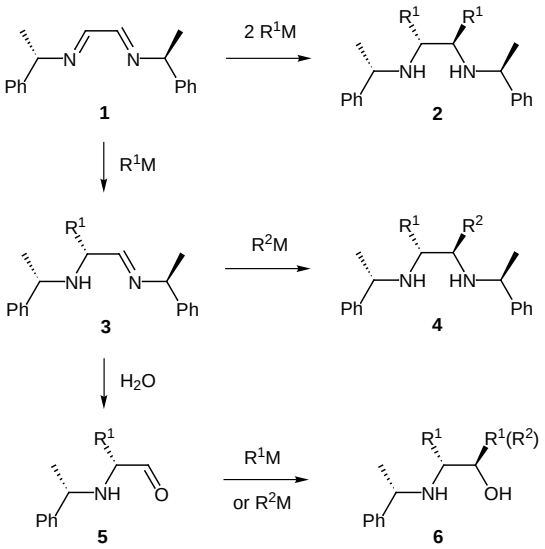
Dipartimento di Chimica "G. Ciamician", via Selmi 2, 40126 Bologna, Italy
Fax +39(051)2099456; E-mail: savoia@ciam.unibo.it

*Received 31 October 2001*

**Abstract:** 1,2-Aminoalcohols or pyrroles were obtained from *N,N'*-bis[(*S*)-1-phenylethyl]ethanediimine by a one-pot procedure involving two Barbier additions of allylic and/or propargyl zinc reagents alternated with the hydrolysis of the unreacted imine function, followed by a cyclisation/dehydration sequence when a 1-amino-5-pentyne moiety was involved, all these steps being promoted by $CeCl_3 \cdot 7\ H_2O$.

**Key words:** 1,2-aminoalcohols, cerium trichloride, 1,2-diamines, pyrroles, stereoselective synthesis

The one-pot syntheses of $C_2$-symmetric 1,2-diamines **2**[1] and some unsymmetrically disubstituted 1,2-diamines **4**[2] by organometallic additions to the glyoxal diimine **1** have been reported. The corresponding preparation of 1,2-aminoalcohols **6** would be possible in principle by a three step sequence involving the hydrolysis of the intermediate imine **3** to give the α-aminoaldehyde **5**, but has not been yet described (Scheme 1). The successful synthesis of **4** and **6** requires the control of the organometallic addition to the diimine **1**, as the second addition of the same reagent $R^1M$ to the second imine function must be avoided. This has been achieved using of a poorly reactive organometallic reagent and exploiting the different reactivity of the 1,2-diimine and α-amidoimine moieties. In fact, we have reported that the addition of an excess of prenylzinc bromide to the diimine **1** at low temperature gave almost exclusively the branched mono-adduct **3** (R = 1,1-dimethyl-2-propenyl, 90% yield, dr 90:10), then the corresponding aldehyde was obtained by hydrolysis (50% yield).[1e] We have successively observed that almost the same result can be obtained by applying a previously described[3] Barbier procedure in which the zinc reagent was formed in situ from prenyl bromide and zinc powder in the presence of a catalytic amount of $CeCl_3 \cdot 7\ H_2O$ in THF at 25 °C. In the attempt to prepare the corresponding $C_2$-symmetric 1,2-diamine **2** using more drastic conditions, we added an excess of reagents (prenyl bromide, Zn and salt) to the intermediate mono-adduct **3** avoiding quenching, so triggering an exothermic reaction. Unexpectedly, the isolated product was the 1,2-disubstituted 1,2-aminoalcohol **7** rather than the expected 1,2-diamine **2** (Scheme 2).

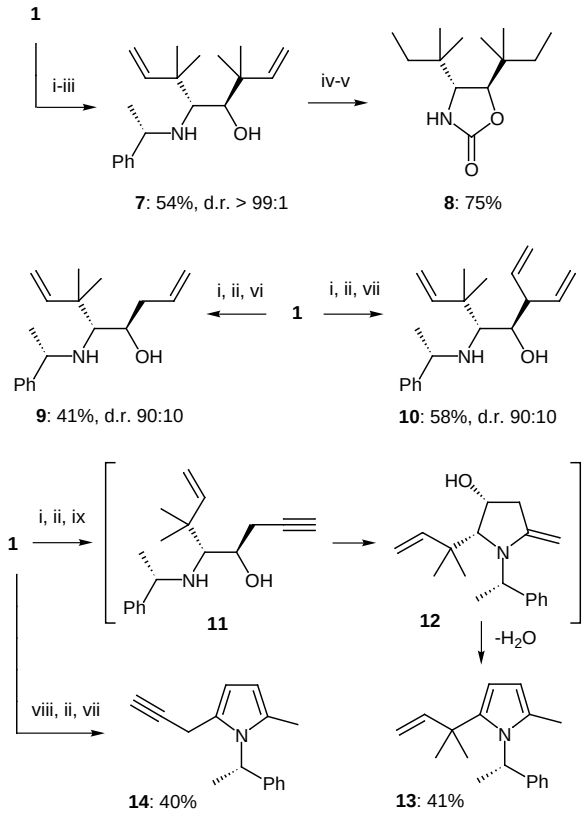



**Scheme 1**

We reasoned that the product **7** was formed through the reaction sequence depicted in Scheme 1 (**1**, **3**, **5**, **6**) and the hydrolysis of the intermediate imine **3** was due to the water released by the hydrated cerium salt.[4] By performing the reaction by stepwise addition of controlled amounts of reagents and monitoring its course by GC-MS analysis of quenched samples, we identified the intermediates, particularly the aldehyde, and optimised the protocol. The first organometallic addition is preferably performed using prenyl bromide, Zn and $CeCl_3 \cdot 7\ H_2O$ (1.5, 4 and 1 molar equivalents, respectively, with respect to the diimine **1**), so obtaining the mono-adduct **3** with satisfactory selectivity. Then the hydrolysis of the preserved imine function was carried out by adding 2 equivalents of the hydrated salt and heating at reflux temperature for 1 hour (in the original experiment heat was provided by the exothermic reaction that was established after the addition of neat prenyl bromide to the reaction mixture containing Zn). The addition of further prenyl bromide (1.5 equiv) to the so formed aldehyde **5** at room temperature gave the 1,2-aminoalcohol **7** with high yield and stereocontrol. The pure main diastereomer was obtained after chromatography and crystallisation with 54% yield. The configuration of **7**, presumably controlled by chelation in the second organometallic step, was determined after routine conversion to the 1,3-oxazolidin-2-one **8**, involving hydrogenolysis of the N-substituents and concomitant hydrogenation of the double bonds, followed by reaction with 1,1'-carbonyldi-

Synlett 2002, No. 1, 28 12 2001. Article Identifier:
1437-2096,E;2002,0,01,0158,0160,ftx,en;G32001ST.pdf.

ISSN 0936-5214




**Scheme 2** *Reagents and conditions*: (i) Zn (4 equiv), prenyl bromide (1.5 equiv), $CeCl_3 \cdot 7\ H_2O$ (1 equiv), THF, 25 °C, 0.5 h; (ii) $CeCl_3 \cdot 7\ H_2O$ (2 equiv), 65 °C, 1 h; (iii) prenyl bromide (1.5 equiv), 25 °C, 1 h; (iv) $H_2$/Pd/C, MeOH, 6 h; (v) 1,1'-carbonyldiimidazole, $CH_2Cl_2$, 2 h; (vi) allyl bromide (1.5 equiv), 25 °C, 1 h; (vii) pentadienyl bromide (1.5 equiv), 25 °C, 1 h (viii) Zn (4 equiv), propargyl bromide (1.5 equiv), $CeCl_3 \cdot 7\ H_2O$ (1 equiv), THF, 25 °C, 1 h; (ix) propargyl bromide (1.5 equiv), THF, 25 °C, 1h.

imidazole. While the configuration of the stereocentre created in the first addition step was known from previous studies,[1] the relative *trans*-configuration of the ring substituents at C4 and C5 was indicated by the coupling constant of the corresponding protons ($J$ = 2.1 Hz) and NOE studies, as no response at H4 was observed by irradiating H5, and vice versa. The optimised protocol was then exploited to prepare two new aminoalcohols by varying the allylic bromide used in the second Barbier step: by using allyl bromide and pentadienyl bromide the corresponding products **9** and **10** were isolated as oils with moderate yields after chromatography, but the diastereomers (dr 90:10) were not separated.

In a further experiment we used first prenyl bromide, then propargyl bromide after the hydrolysis step and were surprised to find that the final product was the 1,2,5-trisubstituted pyrrole **13**, which was isolated with 41% yield by column chromatography and identified by GC-MS, IR and $^1$H NMR analysis. The pyrrole **13** can be formed from the intermediate bis-adduct **11** through $CeCl_3$-promoted 5-*exo*-cyclisation of the 1-amino-5-pentyne moiety and dehydration steps. As a fact, the additions of propargylic/allenic zinc bromides to both imines[5] and aldehydes[6] to give prevalently homopropargylic derivatives have been reported. Moreover, cyclisations of 1-amino-5-alkynes catalysed by organolanthanide complexes, apart cerium, have been reported.[7,8] By using propargyl bromide in both Barbier steps the pyrrole **14** was similarly obtained with moderate yield. Instead, the reaction performed by using propargyl bromide and allyl bromide, in the order, gave the corresponding 1,2-aminoalcohol with 33% yield, but impure owing to its difficult separation from byproducts.

In summary, we have described two convenient protocols for the one-pot conversion of a glyoxal diimine to 1,2-aminoalcohols and 1,2,5-trisubstituted pyrroles, both transformations being promoted by $CeCl_3 \cdot 7\ H_2O$. The noteworthy feature of the first reaction is that an imine group can be hydrolysed to the aldehyde in an anhydrous solvent and in neutral conditions, which allow to successively perform Barbier-type organometallic reactions[9] of the intermediate aldehyde in the same flask. As concerns the synthesis of pyrroles, it is clear that our protocol should be applied to achiral 1,2-diimines, since the chirality of the N-substituent has no role in this process. Especially, the ability of the hydrated or anhydrous cerium salt to promote or catalyse the cyclisation of homopropargylic or homoallenylic amines is worth of investigation. The expeditious synthesis of the 1,2-aminoalcohols and their derivatives, particularly **7**[10] and **8**,[11] makes these compounds attractive for their use as ligands and auxiliaries in a variety of asymmetric transformations.[12]

## Acknowledgement

We are grateful to the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Roma, (National Project: "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni") and The University of Bologna for financial support.

## References

(1) (a) Neumann, W.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865. (b) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391. (c) Alvaro, G.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, *62*, 4180. (d) Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228. (e) Alvaro, G.; Grepioni, F.; Grilli, S.; Maini, L.; Martelli, G.; Savoia, D. *Synthesis* **2000**, 581. (f) Martelli, G.; Morri, S.; Savoia, D. *Tetrahedron* **2000**, *56*, 8367.
(2) Roland, S.; Mangeney, P. *Eur. J. Org. Chem.* **2000**, 611.
(3) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766.
(4) The deprotection of *O*-MEM ethers by $CeCl_3 \cdot 7\ H_2O$ in refluxing acetonitrile was reported when we had already obtained this results: (a) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Srividya, R.; Yadav, J. S. *Org. Lett.* **2001**, *3*, 1149. Similarly, $FeCl_3 \cdot 6\ H_2O$ has been used to deprotect acetals and thioacetals in $CH_2Cl_2$: (b) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684. See also: (c) Khamal, A.; Laxman, E.; Reddy, P. S. M. *Synlett* **2000**, 1476. Carbonyl compounds have been obtained from *N*,*N*-dimethylhydrazones by employing Ni, Hg and Mn complexes and 1 drop of water in $CHCl_3$: (d) Khamal, A.; Arifuddin, M.; Rao, M. V. *Synlett* **2000**, 1482.

(5) (a) Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553. (b) Poisson, J.-F.; Chemla, F.; Normant, J. F. *Synlett* **2001**, 305. (c) Poisson, J.-F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889.

(6) (a) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974. (b) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 5198. (c) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812. (d) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. (e) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201. (f) Aurrecoechea, J. M.; Arrate, M.; López, B. *Synlett* **2001**, 872.

(7) (a) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439. (b) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707. (c) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (d) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757. (e) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295. For a review of metal-initiated amination of alkenes and alkynes: (f)Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(8) The pyrrole should be also obtained by the analogous cyclisation of the partially formed aminoallene: Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871.

(9) It should be observed that even heating $CeCl_3 \cdot 7\ H_2O$ at 150 °C and 0.03 Torr for 12 h forms a material containing approximately 1 equiv of water, which reacts with MeLi to form methane: Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581.

(10) **Representative Procedure for the Preparation of 1,2-Aminoalcohols and Pyrroles**: Zn powder (1.40 g, 20 mmol) was heated at 150 °C for 5 min in a 50 mL two-neck flask under magnetic stirring in a flow of Ar, then was covered with anhyd THF (20 mL) at r.t. To the stirred mixture were added, in the order, the diimine **1** (1.32 g, 5 mmol), $CeCl_3 \cdot 7\ H_2O$ (1.86 g, 5 mmol) and then, slowly, a solution of prenyl bromide (1.12 g, 7.5 mmol) in THF (7 mL). After that the heterogeneous mixture had become greenish (ca 0.5 h), $CeCl_3 \cdot 7\ H_2O$ (3.72 g, 10 mmol) was then added and the mixture was heated at reflux temperature for 1 h, a yellowish colour being observed after that time. Then neat prenyl bromide (1.12 g, 7.5 mmol) was added and the mixture was stirred for 1 h at r.t. The reaction mixture was quenched by addition of sat. $NaHCO_3$ solution (10 mL) and the organic materials were extracted with $Et_2O$ (3 × 20 mL). The collected ethereal layers were dried over $Na_2SO_4$ and concentrated to leave a solid residue, which was chromatographed through a short column of $SiO_2$ to give 4(*R*),5(*R*)-*N*-[1(*S*)-phenylethyl]-5-amino-3,3,6,6-tetramethyl-1,7-octadien-4-ol **7** as a white solid: 1.00 g (66%). Crystallisation from *n*-pentane gave pure **7**: 0.81 g (54%); mp 65 °C; $[\alpha]_D^{25}$ –10.7 (*c* 0.68, CHCl3); $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 5 H), 5.84 (dd, *J* = 10.8 and 17.4 Hz, 1 H), 5.78 (dd, *J* = 10.8 and 17.4 Hz, 1 H), 5.09 (dd, *J* = 0.9 and 10.8 Hz, 1 H), 5.03 (dd, *J* = 0.9 and 17.4 Hz, 1 H), 4.90 (dd, *J* = 0.9 and 17.4 Hz, 1 H), 4.89 (dd, *J* = 0.9 and 10.8 Hz, 1 H), 3.88 (q, *J* = 6.6 Hz, 1 H), 3.24 (d, *J* = 1.8 Hz, 1 H), 2.51 (d, *J* = 1.8 Hz,1 H), 1.32 (d, *J* = 6.6 Hz, 3 H), 1.05 (s, 3 H), 1.0 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H); IR(nujol): 3317, 3300(broad), 1639 $cm^{-1}$; MS: *m/z* = 105(100), 232(20), 128(16), 69(13), 106(13), 98(12), 60(11), 79(10), 77(6), 202(5). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.67; H, 10.37; N, 4.65. Found: C, 79.65; H, 10.39; N, 4.63. Spectroscopic data of selected products are reported in the following; all products gave satisfactory elemental analyses. **4(**R**),5(**R**)-N-[1(**S**)-Phenylethyl]-5-amino-6,6-dimethyl-3-vinyl-1,7-octadien-4-ol 10**: dr 90:10; $[\alpha]_D^{25}$ –16.2 (*c* 1.10, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$–$D_2O$): δ = 5.85 (dd, *J* = 10.8 and 17.4 Hz, 1 H), 5.81–5.61 (m, 1 H), 5.50–5.28 (m, 1 H), 5.17–4.80 (m, 4 H), 4.72 (d, *J* = 17.2 Hz, 1 H), 4.42 (dd, *J* = 1.8 and 18.0 Hz, 1 H), 3.81 (q, *J* = 6.6 Hz, 1 H), 3.24 (dd, *J* = 1.4 and 9.2 Hz, 1 H), 2.46 (d, *J* = 1.4 Hz, 1 H), 1.67 (m, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.04 (s, 3 H), 1.01 (s, 3 H); IR: 3332, 3320(broad) $cm^{-1}$; MS: *m/z* = 105(100), 230(36), 126(15), 79(11), 106(10), 202(7). **5-Methyl-1-[1(**S**)-phenylethyl]-2-propynylpyrrole 14**: $^1$H NMR (200 MHz, $CDCl_3$): δ = 7.4–7.2 (m, 3 H), 7.03 (m, 2 H), 6.025 (d, *J* = 3.2 Hz, 1 H), 5.83 (d, *J* = 3.2 Hz, 1 H), 5.59 (q, *J* = 6.7 Hz, 1 H), 3.41 (dd, *J* = 2.6 and 7.0 Hz, 2 H), 2.08 (t, *J* = 2.6 Hz, 1 H), 2.0 (s, 3 H), 1.89 (d, *J* = 6.7 Hz, 3 H); IR: 3292, 3069, 3056, 3020, 2140, 1680, 1662, 1592 $cm^{-1}$; MS: *m/z* = 105(100), 119(54), 223(49), 118(24), 77(23), 104(23), 79(18), 103(17)

(11) **4(**R**), 5(**R**)-Di-(2-methyl-2-butyl)-1,3-oxazolidin-2-one 8**: In a Parr apparatus a mixture of MeOH (50 mL), **7** (0.62 g, 2 mmol), 10% Pd/C (60 mg) was submitted to $H_2$ pressure (45 psi) for 6 h. The mixture was filtered through a Celite pad and the filtered solution was concentrated to leave 5(*R*)-amino-3,3,6,6-tetramethyloctan-4(*R*)-ol as an oil: 0.35 g (87%). $[\alpha]_D^{25}$ +12.6 (*c* 0.88, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.26 (s, 1 H), 2.73 (s, 1 H), 1.50–1.10 (m, 4 H), 0.85 (m, 12 H), 0.73 (2 s, 6 H); MS: *m/z* = 100(100), 130(79), 60(38), 71(22), 55(17), 59(16). A solution of this compound (0.35 g, 1.7 mmol) and 1,1-carbonyldiimidazole (0.324 g, 2 mmol) in $CH_2Cl_2$ (8 mL) was stirred for 2 h, then $H_2O$ (5 mL) was added and the mixture was stirred for further 0.5 h. The organic phase was separated and the aq phase was extracted with $CH_2Cl_2$ (2 × 5 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and concentrated to leave **8** as a white solid: 0.33 g (86%); mp 85 °C; crystallisation from $Et_2O$ gave an analytical sample: mp 89 °C; $[\alpha]_D^{25}$ +71.8 (*c* 0.5, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$): δ = 6.24 (broad, 1 H), 4.06 (d, *J* = 2.1 Hz, 1 H), 3.27 (d, *J* = 2.1 Hz, 1 H), 1.50–1.15 (m, 4 H), 0.92–0.80 (m, 18 H); IR(nujol): 3265, 1751 $cm^{-1}$; irradiating the absorption at either δ = 4.06 (d) or δ = 3.27 (d) only a response (8%) at 0.81 (m) was observed; MS: *m/z* = 128(100), 86(58), 71(29), 156(13), 55(12), 129(10), 142(7). Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found C, 68.65; H, 11.10; N, 6.15.

(12) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.