Synthesis of Functionalized Pyrrolidines from *N*-(Benzylidene)- and *N*-(Alkylidene)-homoallylamines

Dirk De Smaele and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium

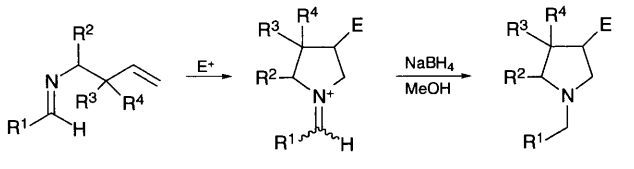
N-(Benzylidene)- and *N*-(alkylidene)-homoallylamines are cyclised by electrophiles, *e.g.* bromine or phenylselenenyl bromide, and by subsequent reduction to the corresponding 3-functionalised pyrrolidines; the stereochemistry was investigated, and reductive removal of the 3(or 4)-bromo- and 3(or 4)-phenylseleno-substituents was accomplished.

Electrophile induced heteroatom cyclisations onto carbon–carbon π-bonds are a versatile method for the construction of heterocycles.[1,2] The direct electrophile induced cyclisation of alkenylamines to nitrogen heterocycles has rarely been employed due to side reactions associated with this process.[2,3] The intramolecular aminomercuration of alkenylamines offers an alternative in some cases,[4,5] but few primary alkenylamines have been cleanly cyclised into azaheterocycles.[6] Consequently, *N*-protected alkenylamino compounds, *e.g.* carbamates,[7-10] carboxylic amides,[11] sulfonylamides,[12] imidates,[13,14] thioimidates,[15,16] ureas,[17] isoureas[18] and imines,[19,20] have been successfully used for this cyclisation reaction, due to the intervention of a reduced nucleophilic nitrogen atom. This electrophile induced cyclisation has been recently applied to oxygen-substituted alkenylamino compounds, *e.g.* *N*- or *O*-alkenylhydroxylamines,[21,22] and *O*-alkenyl hydroxamic acids.[23] Similarly, also alkenyloximes,[24,25] oxime alkenyl ethers[26,27] and alkenyl oxime ethers[28] proved to be good sources for the corresponding heterocycles.

Up to now, there have been only two reports on the electrophile induced cyclisation of alkenyl imines in which the olefinic double bond resides in the alkylidene skeleton.[19,20] Here, results on the electrophile mediated cyclisation of *N*-alkenyl imines, *i.e.* imines with the olefinic double bond in the *N*-substituent, are reported for the first time. It will be shown that imines, derived from primary homoallylamines, undergo regioselective cyclisation to pyrrolidine derivatives. This route enables the use of *N*-homoallyl imines as protected homoallylamines in this cyclisation process.

N-Homoallyl imines **1**, easily accessible by a classical imination process with a suitable aldehyde in the presence of a drying agent ($MgSO_4$), react smoothly with electrophiles such as bromine or phenylselenenyl bromide in dichloromethane at 0 °C to give intermediate iminium salts **2**, which are reduced by sodium borohydride to afford functionalised pyrrolidines **3** (Scheme 1).

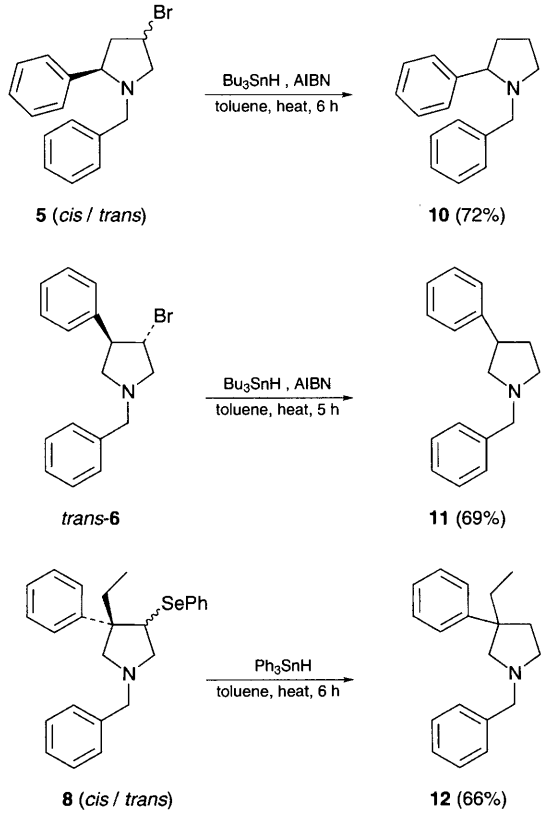
The unsubstituted *N*-(benzylidene)allylamine **1** ($R^2 = R^3 = R^4 = H$) reacted with bromine in dichloromethane (0 °C, 30 min) to give the uncyclised bromine addition product, *N*-(benzylidene)-3,4-dibromobutylamine in 97% yield which was cyclised into 1-benzyl-3-bromopyrrolidine **3** by treating with sodium borohydride in methanol for 2 h under reflux (Table 1). All the other substituted *N*-(benzylidene)-homoallylamines **1b–e** and *N*-(alkylidene)homoallylamine **1f** with different substituent pattern at the homoallyl side chain reacted with either bromine or phenylselenenyl bromide to give the intermediate iminium salts **2**, which were subsequently reacted with sodium borohydride in methanol to afford the 3-functionalised pyrrolidines **3–9** (Scheme 1). The fact that the latter reduction step for entry 3 proceeds smoothly at 0 °C for 1 h is indicative for the occurrence of a cyclic intermediate **2**, prior to the second step. However, it proved to be advantageous to perform the final reductive step at reflux temperature for 1–2 h in order to obtain a complete conversion into pyrrolidines **3–9**. The mechanism of the electrophilic reaction involves initial complexation of the electrophile with the olefinic double bond and subsequent attack of the bromonium ion or seleniranium ion by the bromide counter ion (for imines **1a,b**) or by the nitrogen atom of the imine in the substituted homoallyl derivatives (for imines **1c–f**). The reaction of *N*-(benzylidene)-1-phenyl-3-butenylamine **1c** with bromine and subsequently with sodium borohydride gave access to a 1 : 1 mixture of *trans*- and *cis*-pyrrolidines **5**, showing that there is a lack of diastereoselectivity in this process (Table 1; entry 3). A dia-



1a–f **2** **3–9**

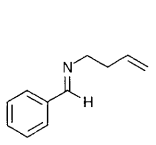
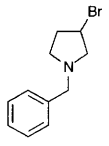
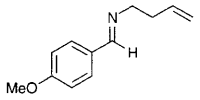
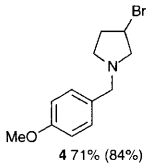
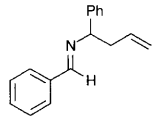
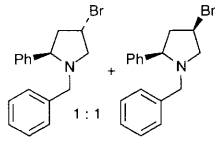
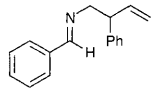
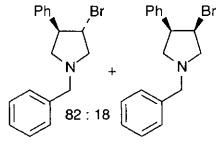
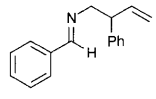
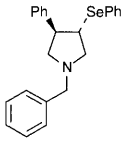
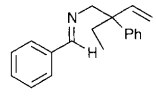
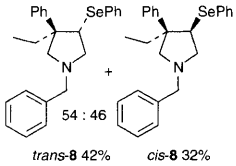
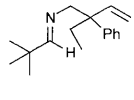
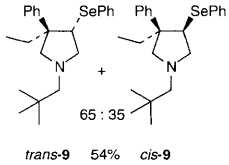
3 R^1 = Ph; $R^2 = R^3 = R^4$ = H; E = Br
4 R^1 = 4-$MeOC_6H_4$; $R^2 = R^3 = R^4$ = H; E = Br
5 $R^1 = R^2$ = Ph; $R^3 = R^4$ = H; E = Br
6 $R^1 = R^3$ = Ph; $R^2 = R^4$ = H; E = Br
7 $R^1 = R^3$ = Ph; $R^2 = R^4$ = H; E = SePh
8 $R^1 = R^3$ = Ph; R^2 = H; R^4 = Et; E = SePh
9 R^1 = Bu^t; R^3 = Ph; R^2 = H; R^4 = Et; E = SePh

Scheme 1



Scheme 2

Table 1 Electrophile induced cyclisation of *N*-homoallyl imines[a]

Entry	*N*-Alkenylimine	Electrophile	Reaction Product[b] Isolated Yield (%) [Crude yield (%)]
1	 **1a**	Br_2	 **3** 78% (82%)
2	 **1b**	Br_2	 **4** 71% (84%)
3	 **1c**	Br_2	 *trans*-**5** 61% *cis*-**5** (73%) 1 : 1
4	 **1d**	Br_2	 *trans*-**6** 39% *cis*-**6** 18% (74%) 82 : 18
5[c]	 **1d**	PhSeBr	 *trans*-**7** 42% (69%)
6[d]	 **1e**	PhSeBr	 *trans*-**8** 42% *cis*-**8** 32% (77%) 54 : 46
7[e]	 **1f**	PhSeBr	 *trans*-**9** 54% *cis*-**9** (74%) 65 : 35

[a] After reaction of the *N*-homoallyl imine with the electrophile (1–1.05 equiv., 0 °C, CH_2Cl_2, 30 min), the final step consists of the reduction of the intermediate reaction product with sodium borohydride in methanol at 0 °C (for iminium intermediates) or reflux temperature (for uncyclised and iminium intermediates). [b] Pure isolated products by flash chromatography. The low yields of some isolated pyrrolidines are due to the small operation scale during the chromatographic separation (adsorption phenomena on silica gel) because the crude yields are very good. All pyrrolidines **3–9** were completely characterised by spectroscopic methods (^1H and ^{13}C NMR, IR, MS) and elemental analysis. [c] The reaction mixture contained almost pure *trans*-**7**. [d] ^1H NMR integration of the reaction mixture revealed at 54 : 46 ratio for compounds *trans*-**8** and *cis*-**8**, respectively. [e] Compounds *trans*-**9** and *cis*-**9** were obtained as a mixture of isomers (65 : 35) after flash chromatography.

stereoselectivity was observed for the cyclisation of the isomeric *N*-(benzylidene)-2-phenyl-3-butenylamine **1d** which provided *cis*- and *trans*-pyrrolidines **6** after the two-step process (Table 1; entry 4). A very slight diastereoselectivity was observed for the cyclisation of *N*-(2 = ethyl-2-phenyl-3-butenyl) imines **1e,f** with phenylselenenyl bromide, affording mixtures of *cis*- and *trans*- 3-ethyl-3-phenyl-4-phenylselenopyrrolidines **9**.

Radical induced removal of the 3-bromo substituent was easily accomplished using tributyltin hydride in toluene in the presence of azobisisobutyronitrile affording 1-benzyl-2(or 3)-phenylpyrrolidines **10** and **11** in 72 and 69% yield after purification by flash chromatography (Scheme 2). The reductive removal of the phenylseleno group is best performed utilising triphenyltin hydride in toluene,[29] giving 1-benzyl-3-ethyl-3-phenylpyrrolidine **12** in 66% isolated yield (flash chromatography) (Scheme 2).

Received, 26th May 1995; Com. 5/03395K

References

1 K. C. Nicolaou, N. A. Petasis and D. A. Claremon, in *Organoselenium Chemistry*, ed. D. Liotta, Wiley, 1987, ch. 2, p. 127–162.
2 G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.
3 W. K. Staas and L. A. Spurlock, *J. Org. Chem.*, 1974, **39**, 3822; D. S. C. Black and J. E. Doyle, *Aust. J. Chem.*, 1978, **31**, 2247; M. Wada, H. Aiura and K.-y. Akiba, *Heterocycles*, 1987, **26**, 929.
4 M. B. Gasc, A. Lattes and J. J. Périé, *Tetrahedron*, 1983, **39**, 703.
5 J. J. Périé, J. P. Laval, J. Roussel and A. Lattes, *Tetrahedron*, 1972, **28**, 675.
6 D. E. Horning and J. M. Muchowski, *Can. J. Chem.*, 1974, **52**, 1321.
7 D. L. J. Clive, V. Farina, A. Singh, C. Kwong Wong, W. A. Kiel and S. M. Menchen, *J. Org. Chem.*, 1980, **45**, 2120.
8 K. E. Harding and S. R. Burks, *J. Org. Chem.*, 1984, **49**, 40.
9 A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1986, **51**, 1724.
10 H. Takahata, O. Takehara, N. Ohkubo and T. Momose, *Tetrahedron: Asymmetry*, 1990, **1**, 561.
11 A. Toshimitsu, K. Terao and S. Uemura, *J. Org. Chem.*, 1986, **51**, 1724.
12 Y. Tamaru, S.-i. Kawamura, T. Bando, K. Tanaka, M. Hojo and Z.-i. Yoshida, *J. Org. Chem.*, 1988, **53**, 5491.
13 K. Terao, A. Toshimitsu and S. Uemura, *J. Chem., Soc. Perkin Trans 1*, 1986, 1837.
14 S. Knapp and A. Levorse, *J. Org. Chem.*, 1988, **53**, 4006.
15 H. Takahata, T. Takamatsu and T. Yamazaki, *J. Org. Chem.*, 1989, **54**, 4812.
16 H. Takahata, T. Takamatsu, Y.-S. Chen, N. Ohkubo, T. Yamazaki, T. Momose and T. Date, *J. Org. Chem.*, 1990, **55**, 3792.
17 C. Betancor, E. I. León, T. Prange, J. A. Salazar and E. Suárez, *J. Chem. Soc., Chem. Commun.*, 1989, 450.
18 R. Freire, E. I. León, J. A. Salazar and E. Suárez, *J. Chem. Soc., Chem. Commun.*, 1989, 452.
19 N. De Kimpe and M. Boelens, *J. Chem. Soc., Chem. Commun.*, 1993, 916.
20 N. De Kimpe and M. Boelens, *Tetrahedron Lett.*, 1994, **35**, 1994.
21 D. R. Williams, M. H. Osterhout and J. M. McGill, *Tetrahedron Lett.*, 1989, **30**, 1327.
22 M. Tiecco, L. Testaferri, M. Tingoli and C. Santi, *Tetrahedron Lett.*, 1995, **36**, 163.
23 M. Tiecco, L. Testaferri, M. Tingoli and F. Marini, *J. Chem. Soc., Chem. Commun.*, 1995, 237.
24 R. Grigg, M. Hadjisoteriou, P. Kennewell, J. Markandu and M. Thornton-Pett, *J. Chem. Soc., Chem. Commun.*, 1993, 1340.
25 M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli and F. Marini *J. Chem. Soc., Perkin Trans. 1*, 1993, 1989.
26 M. Tiecco, L. Testaferri, M. Tingoli and L. Bagnoli, *J. Chem. Soc., Chem. Commun.*, 1995, 235.
27 M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli and C. Santi, *Tetrahedron*, 1995, **51**, 1277.
28 R. Grigg, J. Markandu, T. Perrior, Z. Qiong and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1994, 1267.
29 D. L. J. Clive, G. J. Chittattu, V. Farina, W. A. Kiel, S. M. Menchen, C. G. Russel, A. Singh, C. Kwong Wong and N. J. Curtis, *J. Am. Chem. Soc.*, 1980, **102**, 4438.