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Samarium(II)-iodide catalysed addition of *N*-chloroamines to double bonds, an iodide-catalysed reaction

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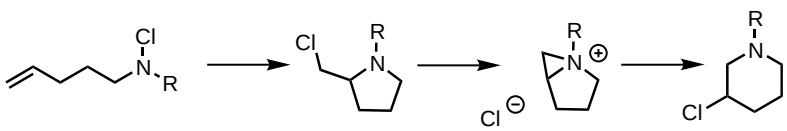
Abstract—*N*-Pentenyl-*N*-chloroamines react under virtually neutral conditions under samarium(II)-iodide catalysis to the corresponding piperidines. These conditions allow the complete rearrangement of 2-(chloromethylpyrrolidines), the proposed primary products of the reaction, via an aziridinium ion to the corresponding 3-chloro-piperidines. The reaction does not seem to proceed via free radicals, as a radical cascade cyclisation could not be observed. Therefore not the samarium(II), but the iodide seems to catalyze the reaction. © 2001 Elsevier Science Ltd. All rights reserved.

Piperidines are valuable structures for the synthesis of alkaloids and pharmacologically active compounds.[1] A straightforward method for synthesizing these heterocycles is the formation of the carbon–nitrogen bond. This can be achieved by a catalytic hydroamination of carbon–carbon double bonds,[2] a process which is difficult to perform as it is almost thermoneutral.[3] We therefore decided to form the carbon–nitrogen bond by aminochlorination of a double bond, a process which is not only exothermic but produces an additional carbon–chlorine bond that can be used for further transformations. This reaction can be performed via aminyl radicals, which add to double bonds under acidic conditions.[4] It has found application for the formation of the kinetically favourable pyrrolidines from *N*-pentenyl-*N*-chloroamines as can be seen from natural-product synthesies.[5]

However, it is less suitable for the formation of piperidines.[6] Furthermore, the strongly acidic conditions are not tolerated by a variety of functional- and protecting groups, thereby limiting the scope of this reaction. Therefore, it is highly desirable to find reaction conditions that are not as harsh. Under such almost neutral conditions the initially formed 2-chloromethyl-pyrrolidine should rearrange via an aziridinium ion to a 3-chloro-piperidine[7] (Scheme 1), thereby allowing the formation of piperidines via a kinetically favoured 5-*exo*-cyclisation.

To achieve this transformation the acidity of the reaction medium needs to be triggered carefully, as free aminyl radicals[8] do not readily attack double bonds.[9] In a recent paper[10] we reported that copper(I)-chloride can be used as a catalyst under mild conditions, however the oxidation potential of chloroamines does not allow the use of phosporous ligands for the catalyst to trigger the reaction. We were therefore looking for catalysts that allow the use of oxygen ligands and thought that samarium diiodide might be a suitable catalyst, starting the reaction by reducing the *N*-chloroamine to an aminyl radical, chloride and samarium(III), which should be Lewis acidic enough to activate the radical.[11] To check this concept, we added 10% samarium diiodide to a solution of the pentenylchloroamine **1a** in THF (Scheme 2).[†]



Scheme 1. Synthesis of piperidines via a 5-*exo*-cyclisation.

Keywords: amination; catalysis; cyclisation; piperidines.

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† In all examples Bu stands for *n*-butyl.

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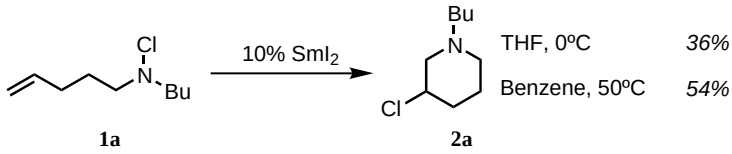


Scheme 2. SmI_2-catalysed cyclisation of *N*-pentenyl-*N*-chloroamine.

The piperidine **2a** was isolated as the only addition product, therefore, under these reaction conditions, the rearrangement is complete.[12] Unfortunately, the catalysis seems to stop after a few cycles and instead of the desired heterocycle pentenylamine is isolated together with unreacted chloroamine. In our mind this could be due to the decrease of the Lewis acidity of the medium, as an amine is formed, that might occupy the coordination sites of the catalyst (product inhibition). To overcome this problem, we decided to raise the reaction temperature and use benzene as a noncoordinating solvent. Under these conditions[‡] the catalysis proceeded smoothly, giving the addition product in good yield (Scheme 2). This reaction can be used for the cyclisation of a variety of *N*-pentenyl-*N*-chloroamines, giving the desired piperidines in good yield (Table 1).[13]

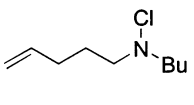
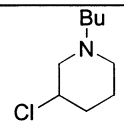
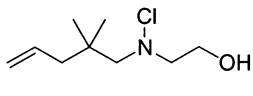
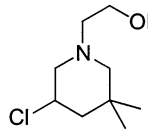
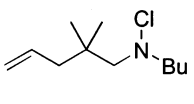
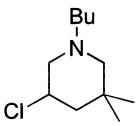
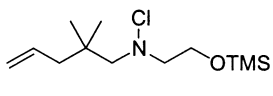
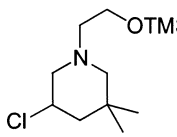
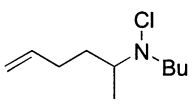
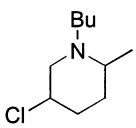
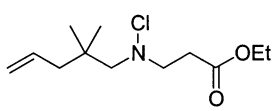
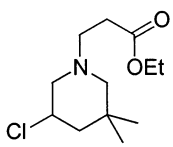
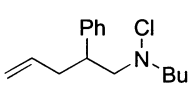
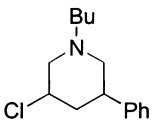
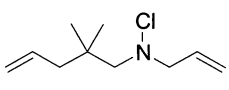
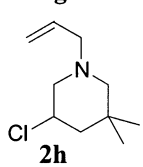
Furthermore, acid sensitive functionalities are tolerated. Free hydroxy groups **1e**, esters **1g** and even silyl ethers **1f** are neither affected nor do they inhibit the catalysis in any way.

To check whether this reaction indeed proceeds via free radicals, we tried to perform a cascade cyclisation using the *N*-allyl-pentenylchloroamine **1h** (Scheme 3). However, only the monocyclic product **2h** could be isolated in good yield, while not even traces of the anticipated bicyclic product **3** could be detected.

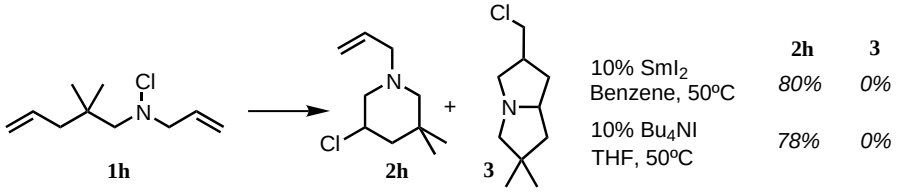
This result is in contrast to the bicyclic products obtained with titanium(III)-chloride under acidic conditions,[14] and suggests, that a carbon radical is not formed during the reaction. We supposed that the iodide might play a key-role in the reaction pathway and therefore performed the reaction using tetrabutylammonium iodide as a catalyst (Scheme 3).[15] Interestingly, the yield of piperidine was similar to the samarium(II)-iodide catalysed reaction. Therefore, we suggest that this reaction is catalysed by iodide rather than samarium(II). As the reaction clearly does not proceed via free radicals, there are two possible mechanisms. The *N*-chloroamine could oxidise iodide to iodine. This in turn could activate the double bond,

Table 1. SmI_2-catalysed cyclisation of chloroamines

SmI_2-catalysed cyclisation of chloroamines

Chloroamine	Piperidine	Yield (%)	Chloroamine	Piperidine	Yield (%)
 **1a**	 **2a**	54	 **1e**	 **2e**	54
 **1b**	 **2b**	81	 **1f**	 **2f**	54
 **1c**	 **2c**	77	 **1g**	 **2g**	78
 **1d**	 **2d**	75	 **1h**	 **2h**	80

[‡] In a typical procedure the catalyst (0.1 molar solution in THF) was added under argon to a solution of 3.0 mMol chloroamine in 5 mL benzene at 50°C and the reaction is stirred at this temperature for 12 h. After removal of the solvent the product was purified by chromatography.



Scheme 3. Iodide-catalyzed non-radical cyclisation of *N*-chloroamines.

leading to the cyclisation product in which chloride substitutes iodide, thereby liberating the catalyst. To check this possibility we treated a mixture of the corresponding secondary amine of **1b** with one equivalent of iodine and three equivalents of tetrabutylammonium chloride under the reaction conditions of our cyclisation. Only traces of **2b** were obtained in this experiment, proving, that this can not be the mechanism.[16]

We therefore suppose that an *N*-iodoamine[17] or higher oxidised iodo compounds[18] are formed in the reaction and that these add intramolecularly to the double bond.

We are currently further investigating this new reaction and its mechanism.

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12. The piperidine is formed during the reaction and not during work-up, what we checked by NMR studies.
13. Spectral data for **1e:** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.99$ (s, 6H), 2.09 (dt, 2H, $^3J=7.5$ Hz, $^4J=1.1$ Hz), 2.23 (s, 1H), 2.95 (s, 2H), 3.12 (m, 2), 3.81 (m, 2H), 5.05 (m, 2H), 5.83 (ddt, 1H, $^3J=16.7$, 10.6, 7.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=25.7$, 35.7, 44.9, 59.9, 68.1, 75.1, 117.5, 134.9 ppm. **1f:** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.13$ (s, 9H), 0.94 (s, 6H), 2.06 (dt, 2H, $^3J=7.4$ Hz, $^4J=0.9$ Hz), 2.91 (s, 2H), 3.10 (t, 2H, $^3J=5.9$ and 6.3 Hz), 3.82 (t, 2H, $^3J=5.9$, 6.3 Hz), 5.03 (m, 2H), 5.83 (ddt, 1H, $^3J=16.1$, 10.9, 7.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=-0.5$, 25.6, 35.8, 44.8, 60.6, 68.4, 75.3, 117.3, 135.2 ppm. **1g:** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.95$ (s, 6H), 1.28 (t, 3H, $^3J=7.2$ Hz), 2.06 (dt, 2H, $^3J=7.5$ Hz, $^4J=1.0$ Hz), 2.68 (t, 2H, $^3J=6.8$ and 7.0 Hz), 2.88 (s, 2H), 3.26 (t, 2H, $^3J=6.9$ Hz), 4.16 (q, 2H, $^3J=7.1$ Hz), 5.03 (m, 2H), 5.81 (ddt, 1H, $^3J=16.5$, 10.5, 7.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=14.2$, 25.6, 33.5, 35.6, 44.8, 46.2, 60.5, 61.9, 117.4, 135.1, 171.1 ppm. **1h:** ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=0.95$ (s, 6H), 2.07 (dt, 2H, $^3J=7.4$ Hz, $^4J=1.2$ Hz), 2.82 (s, 2H), 3.59 (dt, 2H, $^3J=6.4$ Hz, $^4J=1.2$ Hz), 5.01 (m, 2H), 5.24 (m, 2H), 5.81 (ddt, 1H, $^3J=16.2$, 10.7, 7.4 Hz), 5.94 (ddt, 1H, $^3J=17.6$, 10.0, 6.4 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=25.7$, 35.5, 44.8, 69.2, 73.2, 117.2, 119.0, 134.0, 135.2 ppm. **2e:** ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=0.95$ (s, 3H), 1.05 (s, 3H), 1.38 (dd, 1H, $^2J=12.4$ Hz, $^3J=12.4$ Hz), 1.88 (d, 1H, $^2J=11.0$ Hz), 1.96 (d, 1H, $^2J=10.9$ Hz), 2.10 (dd, 1H, $^2J=10.7$ Hz, $^3J=10.7$ Hz), 2.44 (d, 1H, $^2J=10.9$ Hz), 2.51 (dt, 1H, ^{2}J=12.7 Hz, ^{3}J=5.2 Hz), 2.58 (dt, 1H, ^{2}J=12.7 Hz, ^{3}J=5.5 Hz), 2.64 (s, 1H), 3.18 (d, 1H, $^2J=10.7$ Hz, $^3J=4.4$ Hz), 3.60 (t, 2H, $^3J=5.4$ Hz), 4.08 (ddt, 1H, $^3J=11.6$, 10.7, 4.4 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=25.0$, 29.2, 33.2, 48.0, 53.6, 57.8, 58.7, 61.7, 64.3 ppm. Anal. calcd for $C_9H_{18}NOCl$: C, 56.39; H, 9.46; N, 7.31. Found: C, 56.56; H, 9.06; N, 7.29. HRMS: calcd for $C_9H_{19}NOCl$ (M+H) 192.1155. Found 192.1129. **2f:** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.12$ (s, 9H), 0.91 (s, 3H), 1.04 (s, 3H), 1.32 (dd, 1H, $^2J=12.6$ Hz, $^3J=11.9$ Hz), 1.86 (d, 1H, $^2J=11.5$ Hz), 1.92 (d, 1H, $^2J=12.6$ Hz), 2.07 (dd, 1H, $^2J=10.8$ Hz, $^3J=10.8$ Hz), 2.42 (d, 1H, $^2J=10.9$ Hz), 2.53 (m, 2H), 3.18 (d, 1H, $^3J=7.8$ Hz), 3.67 (t, 2H, $^3J=5.8$ und 6.8 Hz), 4.06 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-0.5$, 25.2, 29.4, 33.5, 48.3, 54.1, 59.8, 60.5, 62.6, 65.3 ppm. Anal. calcd for $C_{12}H_{26}$-

NOClSi: C, 54.62; H, 9.93; N, 5.31. Found: C, 54.21; H, 9.78; N, 5.05. **2g:** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (s, 3H), 0.99 (s, 3H), 1.25 (t, 3H, $^3J = 7.1$ Hz), 1.31 (dd, 1H, $^2J = 12.5$ Hz, $^3J = 12.0$ Hz), 1.80 (d, 1H, $^2J = 11.6$ Hz), 1.91 (d, 1H, $^2J = 12.8$ Hz), 2.01 (dd, 1H, $^2J = 10.5$ Hz, $^3J = 10.5$ Hz), 2.39 (d, 1H, $^2J = 10.8$ Hz), 2.45 (t, 2H, $^3J = 6.7$ Hz), 2.68 (m, 2H), 3.15 (d, 1H, $^2J = 10.3$ Hz), 4.03 (m, 1H), 4.13 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 25.0, 29.2, 32.7, 33.2, 48.2, 53.2, 53.9, 61.8, 64.4, 172.3 ppm. Anal. calcd for $C_{12}H_{22}NO_2Cl$: C, 58.17; H, 8.95; N, 5.65. Found: C, 57.94; H, 8.88; N, 5.64. **2h:** ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.88$ (s, 3H), 1.01 (s, 3H), 1.29 (dd, 1H, $^2J = 12.4$ Hz, $^3J = 12.2$ Hz), 1.67 (d, 1H, $^2J = 11.1$ Hz), 1.90 (m, 2H), 2.40 (dt, 1H, $^2J = 11.1$ Hz, $^4J = 1.8$ Hz), 2.92 (ddt, 1H, $^2J = 13.7$ Hz, $^3J = 6.5$ Hz, $^4J = 1.4$ Hz), 2.97 (ddt, 1H, $^2J = 13.7$ Hz, $^3J = 6.2$ Hz, $^4J = 1.4$ Hz), 3.14 (dd, 1H, $^2J = 10.7$ Hz, $^3J = 4.4$ Hz), 4.05 (ddt, 1H, $^3J = 12.0$, 10.7, 4.4 Hz), 5.12 (m, 2H), 5.77 (ddt, 1H, $^3J = 17.1$, 10.2, 6.4 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.2$, 29.3, 33.2, 48.3, 54.2, 61.1, 61.9, 64.5, 117.5, 135.2 ppm. HRMS: calcd for $C_{10}H_{18}NCl$ 189.1098. Found 189.1076. For the analysis the hydrochloride was prepared, anal. calcd for $C_{10}H_{19}NCl_2$: C, 53.58; H, 8.54; N, 6.25. Found: C, 53.23; H, 8.60; N, 5.99. For the spectral data of the other compounds see Ref. 10.

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