Stereoselective Preparation of Bicyclic Lactams by Copper- or Ruthenium-catalysed Cyclization of *N*-Allyltrichloroacetamides: A Novel Entry to Pyrrolidine Alkaloid Skeletons

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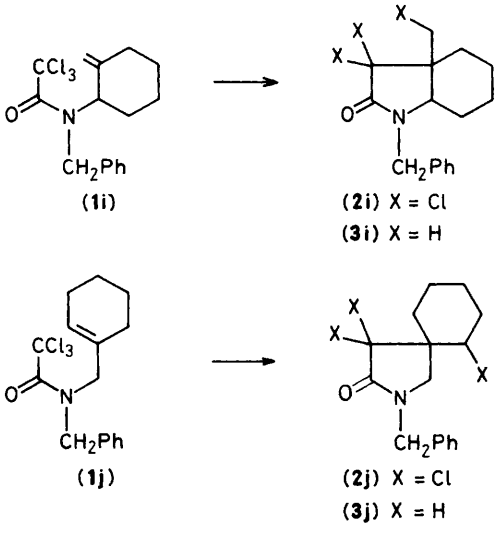
Cyclization of certain *N*-allyltrichloroacetamides provides a stereoselective preparative method for several bicyclic lactams.

Pyrrolidines bearing bicyclic skeletons are components of various alkaloids[1] or amino acid derivatives with potent physiological activities.[2] The efficient construction of the pyrrolidine ring is important in their syntheses. We reported previously that *N*-allyltrichloroacetamides cyclized to the corresponding trichlorinated γ-butyrolactams,[3] which are attractive precursors for various substituted pyrrolidines produced on reduction. In this paper we report an application of this cyclization to the effective preparation of several γ-lactams having spiro- or bi-cyclic systems. This cyclization provides a highly stereoselective route to hexahydro-oxindole derivatives including the mesembrine alkaloid skeleton.

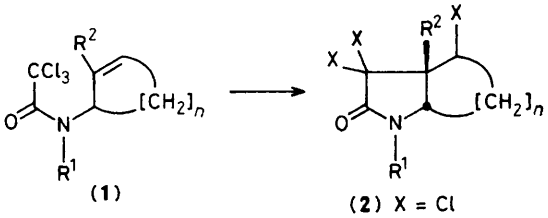
N-Allyltrichloroacetamides (**1**) having an appropriate cyclohexenyl or cyclopentenyl group, were easily cyclized to the corresponding trichlorinated γ-lactams (**2**) *via* CuCl or $RuCl_2(PPh_3)_3$ catalysis. Furthermore, reductive dechlorination of (**2**) by Bu_3SnH (140 °C, 1—5 h) gave the corresponding lactams (**3**) in over 80% yields (Scheme 1, Table 1). An intriguing feature of this cyclization is the production of new quaternary carbons by carbon–carbon bond formation. Thus, spiro-lactam (**2j**) and the hexahydro-oxindole (**2i**), bearing an angular chloromethyl group, were obtained in high yields. The cyclization of 2-phenyl-2-cyclohexenyltrichloroacetamide (**1e**) failed, probably because of steric hindrance by the phenyl group on cyclization. Fortunately, the *N*-substituted analogues (**1f**) and (**1g**) were successfully cyclized to (**2f**) and (**2g**), respectively, with stoicheiometric amounts of CuCl.

Interestingly, (**2**) was obtained as a single stereoisomer in spite of the possible formation of four diastereoisomers, since there are three chiral centres at two angular positions and at the one adjacent to the γ-chlorine atom. Selective formation of *cis*-fused hexahydro-oxindoles, (**2c**) and (**2d**), was confirmed by ^1H n.m.r. coupling constants between angular protons below 7 Hz, whereby the relative configuration of the γ-chlorine of (**2**) is ambiguous at present. Similarly, the *cis*-stereochemistry of (**2f**) and (**2g**) was identified by comparison of the spectroscopic data of (**3e**) and (**3f**) to those in the literature.[4] These results indicate that the present cyclization proceeds with *cis*-selectivity in forming hexahydro-oxindole skeletons.

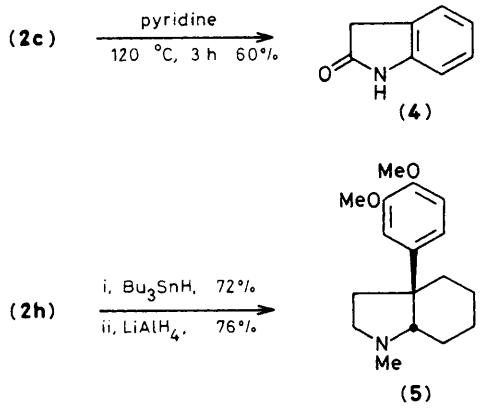
Compounds (**2**) are important intermediates to certain alkaloids[1] having a bicyclic pyrrolidine ring (Scheme 2). Dehydrochlorination of (**2c**) by pyridine provides a simple synthesis of oxindole (**4**). Furthermore, (**2h**) bearing the mesembrine alkaloid skeleton was prepared by the present highly *cis*-selective cyclization from (**1h**). Compound (**2h**) underwent reductive dechlorination (Bu_3SnH) and successive



Scheme 1



	n	R^1	R^2
a;	1	H	H
b;	1	CH_2Ph	H
c;	2	H	H
d;	2	CH_2Ph	H
e;	2	H	Ph
f;	2	Me	Ph
g;	2	CO_2CH_2Ph	Ph
h;	2	Me	3,4-$(MeO)_2C_6H_4$



Scheme 2

Table 1. Cyclization of *N*-allyltrichloroacetamides (**1**) to trichlorinated spiro- and bi-cyclic lactams (**2**).

Entry	(1)	Procedure[a]	Temp. (°C)	Time (h)	Product, % yield
1	**a**	A	140	3	(**2a**), 71
2	**a**	B	140	3	(**2a**), 71
3	**b**	A	110	1	(**2b**), 89
4	**b**	B	110	1	(**2b**), 88
5	**c**	A	140	3	(**2c**), 76
6	**c**	B	140	3	(**2c**), 71
7	**d**	A	110	1	(**2d**), 91
8	**d**	B	110	1	(**2d**), 90
9	**f**	A[b]	120	3	(**2f**), 45
10	**f**	B	140	3	(**2f**), 20
11	**g**	A[b]	110	1	(**2g**), 78
12	**g**	B	140	1	(**2g**), 50
13	**h**	A[b]	120	2	(**2h**), 47
14	**i**	A	110	1	(**2i**), 85
15	**i**	B	110	1	(**2i**), 88
16	**j**	A	110	1	(**2j**), 81
17	**j**	B	110	1	(**2j**), 89

[a] Method A: heating in acetonitrile in the presence of CuCl (30 mol%). Method B: heating in benzene or xylene in the presence of $RuCl_2(PPh_3)_3$ (5 mol%). [b] A stoicheiometric amount of CuCl was used to improve the yield.

reduction ($LiAlH_4$) to yield the known mesembrane, (**5**)[5] a degradation product of mesembrine alkaloids.

Efficient construction of ring systems by carbon–carbon bond formation is an attractive synthetic tool. Free radical cyclizations have recently received much attention to solve this problem. According to this strategy, several pyrrolidine syntheses were successful by means of reductively generated α-[6] or β-amino[7,8] radicals. Their regio- or stereo-chemical features in forming bicyclic skeletons, however, have not been fully optimized. Despite the rather indirect method of preparation of the bicyclic pyrrolidine rings, the present reaction shows one versatile route to them, the utility which should be stressed being the high *cis*-selectivity in producing hexahydro-oxindole skeletons, including ones having angular substituents.

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