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Control of the Stereoselectivity in the Synthesis of 1-Methyl-2,5-disubstituted Pyrrolidines by Mercury(II)-initiated Cyclization of Substituted Alk-4-enylamines

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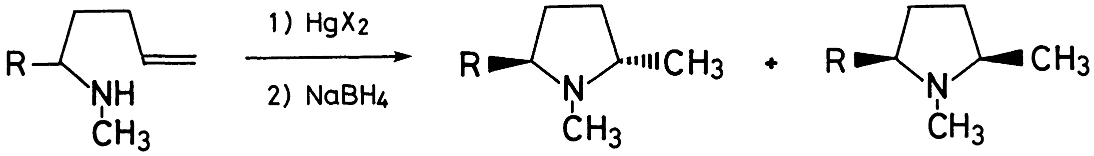
The stereoselectivity in the synthesis of cis- and trans-1-methyl-2,5-disubstituted pyrrolidines by mercury(II)-initiated cyclization of substituted alk-4-enylamines can be controlled by choosing the appropriate mercury salt and solvent.

In the synthesis of substituted pyrrolidines by mercury(II)- or silver(I)-initiated cyclization of substituted alk-4-enylamines, a recent attention has been focused on the stereoselectivity of the cyclization.1-3) For example, it has been reported that a mercury(II)-initiated cyclization of alk-4-enylamides or carbamates can give selectively trans-2,5-disubstituted pyrrolidines1) and that its stereoselectivity can be achieved only when a kinetic control is attained.2) A silver(I)-initiated cyclization of alka-4,5-dienylamine derivatives has been reported to give stereoselectively cis-2,5-disubstituted pyrrolidines.3)

We recently reported a stereoselective synthesis of cis-1-methyl-2,5-disubstituted pyrrolidines by means of the cyclization of an aminyl radical generated by anodic oxidation.4) In this paper we report that the stereoselectivity of the mercury(II)-initiated cyclization to give trans- or cis-1-methyl-2,5-disubstituted pyrrolidines can be controlled by changing the reaction conditions.

Mercury(II)-initiated cyclization of alkenylamines **1a**-**1e** was carried out in water-tetrahydrofuran(THF)(1:1), THF, or chloroform containing mercury(II) chloride or mercury(II) acetate. Representative results containing a combined yield of trans- (**2**) and cis-1-methyl-2,5-disubstituted pyrrolidines (**3**), the ratio of the trans and cis isomers, and the reaction conditions are shown in Table 1.

When the cyclization of **1a**-**1e** is conducted in a 1:1 mixture of water and THF with mercury(II) chloride, trans-2,5-disubstituted pyrrolidines **2a**-**2e** are obtained



1a $R = C_6H_5$

1b $R = p\text{-}CH_3C_6H_4$

1c $R = p\text{-}CH_3OC_6H_4$

1d $R = CH_3$

1e $R = C_2H_5$

2a~e

3a~e

Table 1. Mercury(II)-initiated Cyclization of Substituted Alk-4-enylamines (**1a**-**1e**) under Various Conditions

Run	Amine	HgX_2	Solvent	Concn. of **1**	Yield of **2**+**3**$^{a)}$	Isomer ratio$^{a)}$		
				mol dm^{-3}	%	**2**	:	**3**
1	**1a**	$HgCl_2$	H_2O-THF	0.10	64	87	:	13
2		$HgCl_2$	THF	0.025	36	10	:	90
3		$HgCl_2$	$CHCl_3$	0.05	50	4	:	96
4		$Hg(OAc)_2$	THF	0.025	56	88	:	12
5	**1b**	$HgCl_2$	H_2O-THF	0.10	82	84	:	16
6		$HgCl_2$	THF	0.025	53	2	:	98
7	**1c**	$HgCl_2$	H_2O-THF	0.025	86	93	:	7
8		$HgCl_2$	THF	0.025	40	25	:	75
9	**1d**	$HgCl_2$	H_2O-THF	0.025	28	93	:	7
10		$HgCl_2$	THF	0.025	43	36	:	64
11	**1e**	$HgCl_2$	H_2O-THF	0.025	55	90	:	10
12		$HgCl_2$	THF	0.025	50	20	:	80

a) Determined by GLC using an internal standard method(THEED 15% on Uniport B).

stereoselectively, while cis-2,5-disubstituted pyrrolidines **3a**-**3e** are the exclusive products when THF or chloroform is used as the solvent. On the other hand, a mercury(II) acetate-initiated cyclization gave predominantly trans isomers **2a**-**2e** even in THF or chloroform. Thus, the combination of the solvent and the mercury salt leading to the predominant formation of trans isomer (**2**) are $HgCl_2/H_2O$-THF, $Hg(OAc)_2$/THF, or $Hg(OAc)_2/CHCl_3$ and those leading to the selective formation of cis isomer (**3**) are $HgCl_2$/THF or $HgCl_2/CHCl_3$. The reaction of **1** in a lower concentration also results in an enhancement of the selectivity for the trans isomer. The reason for the observed change of stereoselectivity by alternating the solvent and the mercury(II) salt is not clear. The stereoselectivity, however, might be associated with the homogeneity of the solution during the cyclization since we found that when alkenylamine **1** was added to the solution of mercury(II) chloride in THF or chloroform, finely dispersed white precipitates were formed and the heterogeneous solution gave cis isomers predominantly. On the other hand, the solution containing mercury(II) chloride in water-THF, mercury(II) acetate in THF, or merury(II) acetate in chloroform was homogeneous and gave trans isomers selectively.

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