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Probing the diastereoselectivity in the cyclization of cationic aminyl radicals

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Abstract

The diastereoselective intramolecular cyclization of cationic aminyl radicals into the corresponding pyrrolidines has been investigated. The selectivities obtained are good to excellent.

The intramolecular addition of C-centered radicals onto olefins forming the corresponding five-membered cyclic derivatives has emerged as a powerful tactic in organic synthesis.[1,2] In this respect it is somewhat surprising that the cyclization of N-centered radicals into pyrrolidines has not received greater attention, since it should have potential for the synthesis of naturally occurring alkaloids.[3,4] The diastereoselectivity of these cyclizations has therefore, except for some scattered examples,[5–8] not been thoroughly investigated. As a part of an ongoing study we became interested in resolving this issue by defining the factors important for obtaining optimal selectivities in the intramolecular addition of cationic aminyl radicals to olefins. It has previously been shown that such radicals can be generated by several different methods. For the present investigation *N*-chloroalkenylamines **1**, which can be converted into pyrrolidines **2** either by a redox or an atom transfer process, were selected as precursors with the expectation that **2** would contain suitable functionality for further transformations (Scheme 1).[9]

The results from the cyclizations of *N*-chloroalkenylamines **3a**–**d**, prepared by standard techniques, are collected in Table 1. Cyclization of **3a** using the redox couples CuCl:$CuCl_2$ and $FeCl_2$:$FeCl_3$, employing the Stella conditions (THF:H_2O:HOAc),[10] gave *cis*- and *trans*-substituted pyrrolidines **4a** and **5a** (Table 1, entries 1 and 2). The stereochemical outcome of the cyclization was determined by converting the mixture of **4a**, **5a** into **6a**, **7a**, stereospecifically, followed by inspection of the relevant coupling constants in the ^{1}H NMR spectrum (vide infra). The cyclization proceeded in good yield with both redox couples, although the *cis*-selectivity was more pronounced when using CuCl:$CuCl_2$. Cyclization of **3a** with $TiCl_3$:$TiCl_4$ (H_2O:HOAc), which is believed to promote a radical chain mechanism, resulted in a lower yield (entry 3).[9] An improvement was observed when the same reagent combination was used

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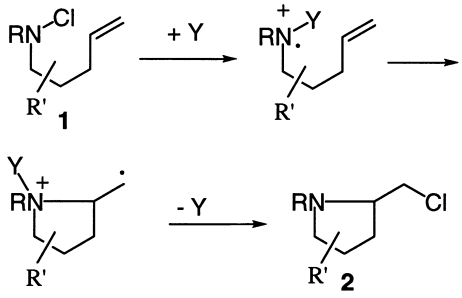


Scheme 1. General scheme for the cyclization of *N*-chloroalkenylamines

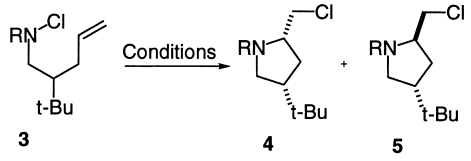
in dichloromethane, resulting in an increased yield and selectivity (entry 4). Having demonstrated the efficiency of $TiCl_3$ as an initiator for this reaction we proceeded by investigating the influence of other acids on the diastereoselectivity, and of lowering the reaction temperaure (entries 5–10).[11–15] Among those tested only $BF_3 \cdot Et_2O$ and $Sn(OTf)_2$ could match $TiCl_4$ in terms of selectivity, giving **4a**:**5a** in good to excellent ratios (entries 6 and 9), although the latter Lewis acid resulted in an inferior yield. Next the effect of varying the *N*-substituent was probed. Cyclization of derivatives **3b** and **3c** gave the corresponding pyrrolidines in lower selectivity as compared to **3a** under otherwise identical conditions (compare entry 6 with entries 11 and 12). Finally, subjecting **3d**, having an *N*-2-methoxyethyl substituent, to $TiCl_3$:Ti(O*i*-Pr)Cl_3 gave pyrrolidines **4d**:**5d** in a 7:1 ratio (entry 13). This experiment indicates that additional chelation of the substrate to the Lewis acid is not beneficial and this line of investigation was not pursued further.

The preferential formation of *cis*-isomers **4** in these reactions can be rationalized by the Beckwith–Houk model for the cyclization of the analogous C-centered radicals.[16–18] The intramolecular addition of the initially formed neutral aminyl radical to an olefin moiety is reversible with the ring opened form being favored at equilibrium.[19] However, upon complexation with a Lewis acid the cationic radical cyclizes rapidly and irreversibly, as has been detailed by Newcomb and co-workers,[11] and in all cases the major product arises from a 'chair' transition state in which the *t*-Bu moiety functions as a conformational lock (Scheme 2, M=H, Lewis acid). From the data in Table 1 no apparent correlation between the size or the strength of the acid used for complexation to the aminyl radical and the observed diastereoselectivity can be found; nor is it obvious why **3b**–**d** cyclizes with lower selectivity than **3a**. These points are currently being investigated.

It was also of interest to probe the potential of the cyclization products for further synthetic transformations. Thus, it was found that the stability of pyrrolidines **4** and **5** varied markedly in different solvents. While they were relatively stable in ethers and aromatic solvents a quantitative and stereospecific rearrangement into piperidines **6** and **7**, respectively, was observed in chlorinated solvents (Scheme 3). Similar transformations relying on regioselective opening of aziridinium cations have been observed previously and are expected to broaden the scope of the chemistry decribed above.[20–22]

In conclusion, we have shown that the cyclization of *N*-chloroalkenylamines into the corresponding pyrrolidines occurs with good to excellent diastereoselectivity, depending on the type of *N*-substituents and Lewis acid employed. Further studies of this type of cyclization are under way and will be reported in due course.

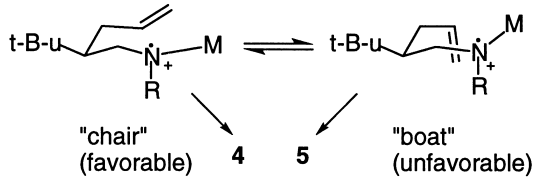
Table 1
Cyclization of *N*-chloroalkenylamines **3** into **4** and **5**



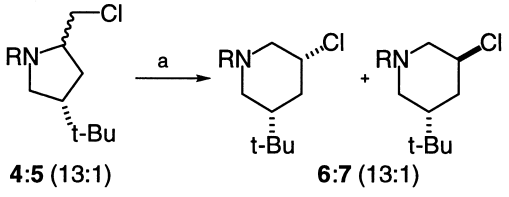
3 **4** **5**

Entry	**3**	R	Conditions	T [°C]	Yield [%][a]	Ratio **4**:**5**[f]
1	a	Bu	$CuCl:CuCl_2$[b]	-20	93	6:1
2	a	Bu	$FeCl_2:FeCl_3$[b]	-20	83	3:1
3	a	Bu	$TiCl_3:TiCl_4$[c]	-20	22	5.0:1
4	a	Bu	$TiCl_3:TiCl_4$[d]	-30	59	8:1
5	a	Bu	$TiCl_3:TiCl_4$[d]	-78	62	9:1
6	a	Bu	$TiCl_3:BF_3$[d]	-78	93	13:1
7	a	Bu	$TiCl_3:Ti(Oi\text{-}Pr)Cl_3$[d]	-78	94	9:1
8	a	Bu	$TiCl_3:MgBr_2$[d]	-78	93	7:1
9	a	Bu	$TiCl_3:Sn(OTf)_2$[d]	-78	38	12:1
10	a	Bu	$TiCl_3:H^+$[e]	-20	90	5:1
11	b	Bn	$TiCl_3:BF_3$[d]	-78	97	4:1
12	c	*p*-MeOBn	$TiCl_3:BF_3$[d]	-78	100	6:1
13	d	C_2H_4OMe	$TiCl_3:Ti(Oi\text{-}Pr)Cl_3$[d]	-78	93	7:1

[a] Isolated yields. The initially formed pyrrolidines were rearranged into piperidines **6** and **7** (Scheme 3). [b] In deoxygenated $THF:H_2O:HOAc$ (1:2:2). [c] In deoxygenated $H_2O:HOAc$ (1:1). [d] In deoxygenated CH_2Cl_2. [e] In deoxygenated THF. [f] Ratios determined by ^1H NMR.



Scheme 2. Proposed structure for the cationic aminyl radicals derived from **3**



4:**5** (13:1) **6**:**7** (13:1)

Scheme 3. (a) $CHCl_3$, room temperature, 100% ($t_{1/2}$ ~ 1 h)

Acknowledgements

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