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EFFECTS OF THE RING SIZE ON THE REGIOSELECTIVITY OF AMINO-CLAISEN REARRANGEMENT OF UNSYMMETRICALLY FUSED ANILINIUM DERIVATIVES

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Abstract - The site of meta rearrangement in quaternary amino-Claisen rearrangement is found to be controlled by the size of the fused rings. This regioselectivity is also predictable from the magnitudes of the chemical shifts differences between the two meta carbons.

Currently we are interested in the regioselectivity of amino(N)-Claisen rearrangement of unsymmetrically substituted anilinium derivatives[1]. The observation[1a] that the rearrangement of **1a** gave **3a** with high regioselectivity prompted us to investigate the other ring systems to see the generality of this kind of selectivity and the results are reported herein.

Quaternary salts **1b** (decomp. 183-185°C), and **1c** (decomp. 177-179°C) were prepared by the allylation of 9-methoxy-1,2,4,5,6,7-hexahydroazepino [3,2,1-hi] indole **2b** (Hydrobromide, mp 192-192.5°C) and 10-methoxy-2,3,5,6,7,8-hexahydro-1H-azepino [3,2,1-ij]quinoline **2c** (Hydrobromide, mp 240-241°C), respectively[2]. Rearrangements of **1b** and **1c** were carried out under two reaction conditions (Chart 1) and the results are summarized in Table 1. Products were analyzed by gas liquid chromatography (glc) as well as high pressure liquid chromatography (hplc) and identified with the selected authentic specimens, **3b**, **5b**, **3c**, **4c** and **5c**.[3]

Salt **1b** required rather forcing reaction conditions for the rearrangements. In this reaction, ally group migrated with high regioselectivity.

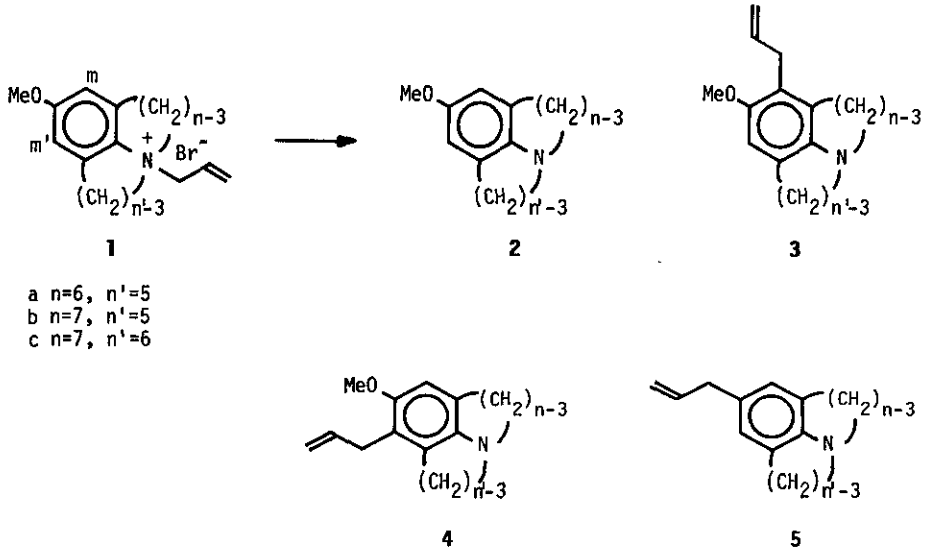


Chart 1

On the other hand, under the two reaction conditions 1c reacted quite smoothly but the selectivity was poor [3c : 4c = 53 : 47]. In the presence of weak base (reaction condition B), deallylation was substantial and the substitution reaction became the major reaction. The differences of the chemical shifts between the two *meta* carbons $\Delta(\delta m - \delta m')$, the twist angles between the lone pair of nitrogen and the aromatic π-orbitals (θ)[4] and the pKa values[5] for 2 are listed in Table 2. The twist angle (θ) increases from 2a to 2c. The similar trend was observed in the pKa values. In ^{13}C nmr spectrum of 1 and 2 *m*-carbon appeared always at lower field than *m*'-carbon. Thus allyl group on nitrogen migrated preferentialy to the carbon at the lower field, *i.e.* to the carbon with less electron density. As seen from $\Delta(\delta m - \delta m')$ for 1 and 2 the twist angle for 1 is different from that for 2

Table 1

S.M.	R.C.[a]	C.Y.(%)[b]	Products Compositions (%)[c]			
1a[d]	A(8h)	77	2a: 27	3a: 68	4a: -	5a: -
1a[d]	B(8h)	97	2a: 13	3a: 11	4a: -	5a: 56
1b	A(6h)[e]	72	2b: 26	3b: 73	4b: -	5b: -
1b	B(20h)	66	2b: 43	3b: 4	4b: -	5b: 4[f]
1c	A(6h)	98	2c: 9	3c: 44	4c: 40	5c: -
1c	B(6h)	88	2c: 15	3c: 7	4c: 6	5c: 53

[a] Reaction conditions: A solution of the starting material (S.M.) in glycerol-water (2 : 1) was heated at 140°C (bath temperature) for the time indicated in the absence (A) or in the presence (B) of sodium hydrogen carbonate. [b] Crude yield was calculated by assuming complete rearrangements. [c] Compositions (%) in the crude product were obtained by the analysis with glc(10%SE-30, 3 mm x 2 m, 200-250°C, 4°C min^{-1}; N_2 30 ml min^{-1}) for 1a and 1b and with hplc (micro-Porasil: 3.9 mm x 30 cm; Hexane : Chloroform : Ethyl acetate = 90 : 6 : 4; flow rate: 1 ml min^{-1}) for 1c. [d] These results are taken form the literature 1a. [e] In a sealed tube. [f] Obtained by hplc analysis.

According to the analysis with Dreiding model the order of the twist angle for 1 is 1c < 1a < 1b . This trend is reflected in the feasibility of the rearrangement (Table 1). The reaction of 1 is regarded as a consecutive [3.3],[3,3],[1,2]sigmatropic rearrangement as reported in another quaternary N-Claisen rearrangements[1].

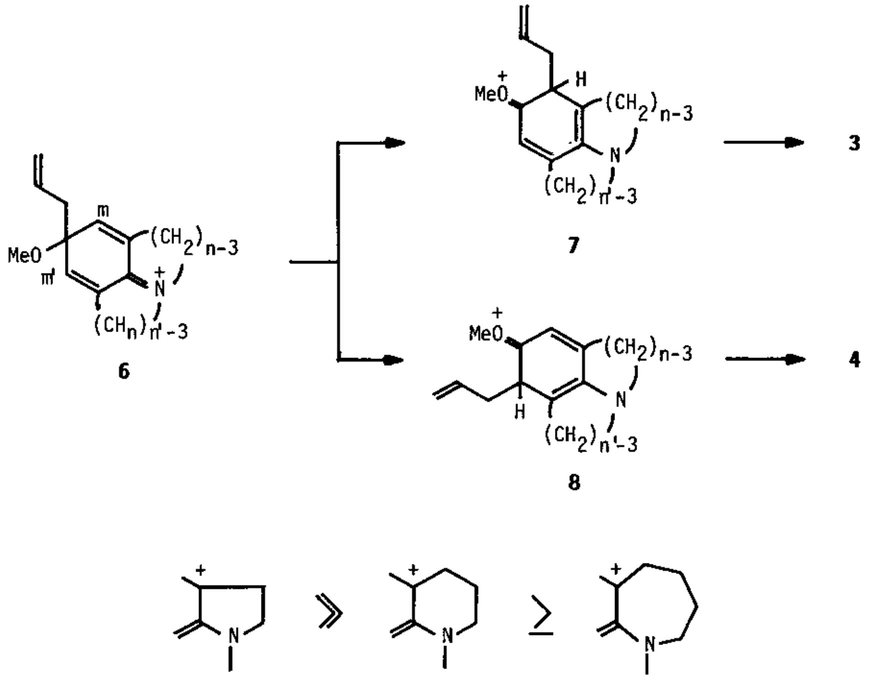
Table 2

	2a (1a)	2b (1b)	2c (1c)
$\Delta(\delta m - \delta m')$ppm	4.7 (3.5)	5.6 (8.7)	2.2 (4.1)
θ	37^{o}	44^{o}	50^{o}
pKa	5.36	5.91	6.27

θ: The twist angles between the lone pair of nitrogen and the aromatic π-orbitals were calculated with demethoxylated 2 according to the literature 4. pKa: Hydrobromides of 2 were dissolved in water and titrated.

Assuming that the regioselectivity is determined by the valence-bond resonance forms of the lowest energy[1a], the relative stabilities of 7 and 8 derivable from 6 by [1,2]sigmatropic rearrangement should determine the regioselectivity of the rearrangement (Chart 2). Refrecting the relative product ratios of 3 to 4 (Table 1) to the relative stabilities of the intermediate 7 to 8, the relative hyperconjugative stabilizations for the fused rings might be assumed as follows. Hyperconjugation is the most effective in staggered conformation[6] and the order of the effectiveness observed above is consistent with that obtained in the hydrolyses of benzyl chlorides whose aromatic rings were fused with different size of rings[7]. By using these relative hyperconjugative stabilization and comparing the chemical shifts of two <u>meta</u> carbons, it became possible to predict the probable site for allyl group to migrate in quaternary N-Claisen rearrangement. The magnitude of regioselectivity is deduced as follows.

Since allyl group of 6 migrates preferentialy to a more positive carbon, $\Delta(\delta m-\delta m')$ for 6 should be reflected in the magnitude of regioselectivity. As the direct measurement of the chemical shifts for 6 is not possible, compound 2 was used for



Hyperconjugative Stabilization

Chart 2

this purpose. The conformations of the fused rings for 2 correspond with 6 and no severe steric interaction between allyl group and the fused ring is present as it is present in 1. By using $\Delta(\delta m - \delta m')$ we can expect the high regioselectivity when $\Delta(\delta m - \delta m')$ for 2 is around 5 ppm and the poor one when around 2 ppm.[8]

In conclusion, it became possible to predict the regioselectivity of quaternary N-Claisen rearrangement and to propose the criterion for gaining high regioselectivity. This conclusion may wide the utility of quaternary N-Claisen rearrangement for synthetic purposes.

REFERENCES AND NOTES

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2. Compound **2b** (oil, hydrobromide: mp 192-192.5°C) was prepared from 7-methoxy-1-benzazepine by using intramolecular Friedel-Crafts alkylation (Y.Tamura, J.Uenishi, H.Maeda, H.Choi, and H.Ishibashi, *Synthesis*, 1981, 534) and **2c** was synthesized by refluxing 7-methoxy-1-benzazepine with 1,3-bromochloropropane (H.Katayama, E.Abe, and K.Kaneko, *J.Heterocyclic Chem.*, 1982, **19**, 925).
3. The specimens, **3b** (oil, picrate: mp 149-149.5°C), **3c** (oil, hydrobromide: decomp. 212-213°C) and **4c** (oil) were synthesized by the cyclization of 6- and 8-allyl-7-methoxy-1-benzazepines as described above. The samples **5b** (oil, picrate: mp 108-122°C) and **5c** (oil) were prepared by N-Claisen rearrangement[1b] of 3-allyl-1,2,4,5,6,7-hexahydroazepino [3.2.1-hi] indolenium bromide (decomp. 183-185°C) and 4-allyl-2,3,5,6,7,8-hexahydro-1H-azepino[3,2,1-ij]quinolinium tetrafluoroborate (mp 121-122.5°C).
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8. 9-Methoxy-1-oxajulolidine has $\Delta(\delta m - \delta m') = 6.45$ ppm and its N-allylated quaternary bromide showed *m*-Claisen rearrangement with high regioselectivity[1a].

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