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REGIO- AND DIASTEREOSELECTIVE CYCLOADDITION OF *N*-METHYL NITRONES DERIVED FROM 3-(ALLYLAMINO)PROPIONALDEHYDES

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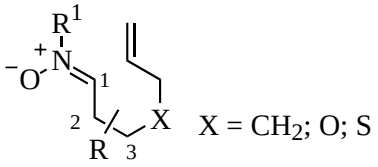
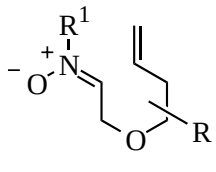
Abstract- Regio- and stereochemistry of intramolecular cycloaddition of *N*-methyl nitrones derived from 3-(allylamino)propionaldehydes was discussed; the methyl substituent at the 3-position in the nitrones (**11**) provided a highly controlled course of the cycloaddition to give predominantly *syn-cis*-fused adducts (**12**), while the reaction of the corresponding 2-methyl nitrone (**7a**) gave *syn-cis*- and *anti-cis*-fused (**8a**) and *syn*- and *anti*-bridged adducts (**9a**).

Since the regio- and stereoselectivity of intramolecular nitrone–alkene cycloaddition (INAC) was firstly discussed by LeBel,[1] the control of the regio- and stereochemistry in the INAC has been an urgent subject to be solved. Among the challenging studies aiming to the goal, Shing *et al.* recently demonstrated that the stereochemical courses of the intramolecular cycloaddition reaction of *N*-methyl nitrones derived from 3-*O*-allyl-D-hexoses were dependent on the relative configuration at the C-2 and C-3 positions.[2] Therein, they discussed the relative stabilities of the chair-like transition states leading to fused and bridged cycloadducts utilizing molecular models. Similar approaches have been independently made by Aurich,[3] Shipman,[4] Singh,[5] and Bhattacharjya[6] and the expected results have been accomplished. However, the nitrones employed by them were limitted to the highly functionalized systems derived from sugars and seemed consequently to be special cases in the INAC.

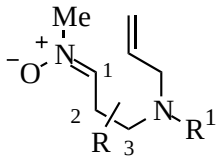
Scheme 1



(Aurich[7]; 1990)



(Knight[8]; 1999)



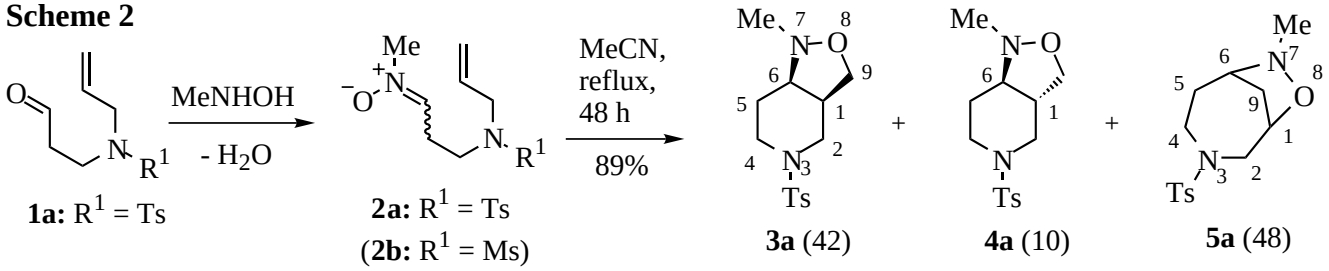
(this work)

In a previous paper,[7] Aurich *et al.* reported that the heteroatoms incorporated into the chain connecting two reaction components affected the regioselectivity in the INAC; the substituent on the 2- or 3-position caused a little effect on the yields and regioselectivity when the substituet on the nitrone nitrogen was less hindered, *e.g.*, R^1 = Me. Recently, Knight *et al.* pointed out that the substituents on the chain connecting ether oxygen and olefinic dipolarophile moiety exerted the stereocontrol in the INAC.[8] In this

communication, we will report the high degree of stereocontrol in the cycloaddition reaction of *N*-methyl nitrones derived from 3-(allylamino)propionaldehydes (Scheme 1).

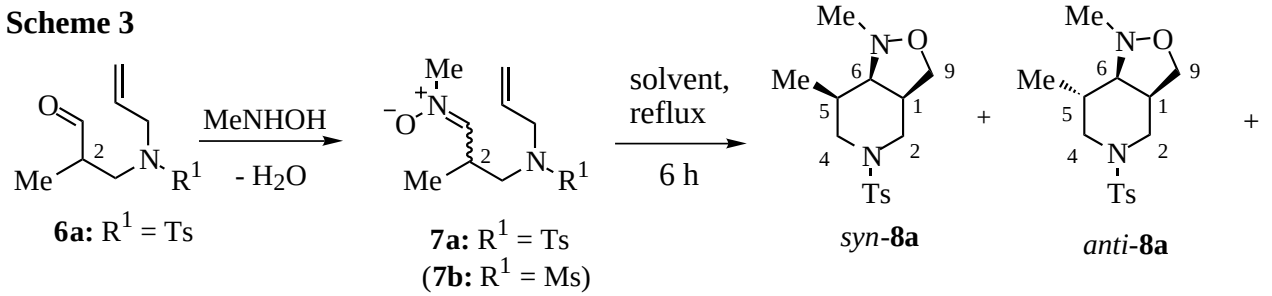
The solution of 3-(*N*-allyltosylamino)propionaldehyde (**1a**), *N*-methylhydroxylamine hydrochloride (2.0 equiv.), and triethylamine (2.3 equiv.) in acetonitrile (MeCN) was heated under reflux for 48 h to give three isomeric cycloadducts, *cis*- (**3a**) and *trans*-fused cycloadduct (**4a**) and bridged cycloadduct (**5a**), in ratio of 42:10:48, respectively (Scheme 2). Although the regioselectivity (fused *vs* bridged cycloadduct) of this reaction was poor (52:48), considerable improvement of the stereoselectivity (*cis*- *vs trans*-fused cycloadduct) was observed in comparison with the related results (X = O) reported by Aurich[7] (Scheme 1). The formatiom of *cis*-fused cycloadduct could be ascribed to the *exo*-approach of the (*Z*)-nitrone (***Z*-2a**) and the *endo*-approach of the (*E*)-one (***E*-2a**), and that of *trans*-fused cycloadduct to the *exo*-approach of the (*E*)-one (***E*-2a**), respectively from the previous discussion in a literature.[7]

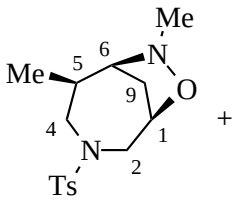
Scheme 2



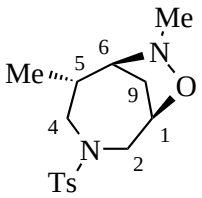
Similar reaction of 2-methyl substituted nitrone (**7a**) gave a mixture of two sets of diastereomeric cycloadducts, *cis*-fused **8a** and bridged **9a** and the ratio of the fused cycloadducts became somehow higher (Scheme 3). The ^{1}H NMR spectrum of the crude reaction mixture did not provide any evidence for the formation of *trans*-fused cycloadducts. The diastereofacial selectivity in this cycloaddition (*syn*- *vs anti*-cycloadduct) was not so high as expected (*syn*/*anti* = 51/7 - 48/12 for **8a** and 31/7 - 30/12 for **9a**). The kind of the solvents utilized slightly effected both total yields and ratio of the products.

Scheme 3





syn-**9a**



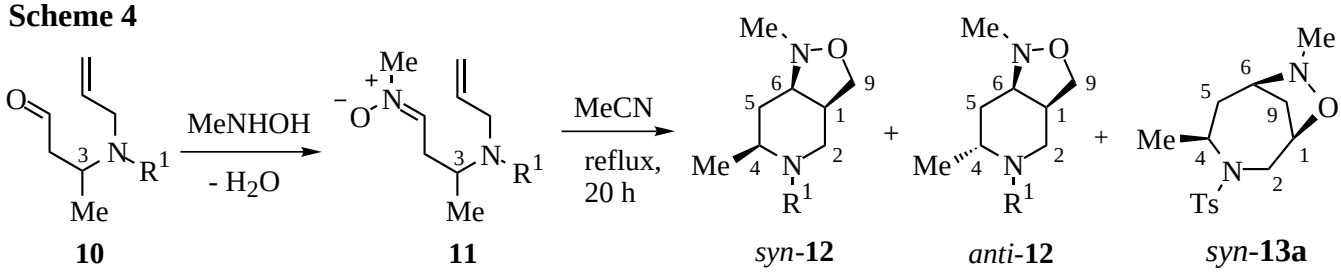
anti-**9a**

run	Solvent	Yield (%)	Ratio of products *syn*-**8a** : *anti*-**8a** : *syn*-**9a** : *anti*-**9a**			
1	EtOH	89	42	12	34	12
2	MeCN	85	48	14	31	7
3	Benzene	89	51	7	30	12

Interestingly, a different pattern of selectivity was found in cycloaddition of nitrone (**11a**) bearing a methyl

group at the 3-position; the formation of bridged adduct (**13a**) was depressed and *syn-cis*-fused adduct (**12a**) was formed predominantly with a high degree of diastereofacial selectivity (*syn*/*anti* = 92/3). To elucidate the effect of the substituent on the alkenylamino nitrogen, similar reaction of two other nitrones (**11b**, **c**) was examined; in the case of **11b** (R^1 = Ms) *syn-cis*- and *anti-cis*-fused adducts (**12b**)[9] were formed with *syn/anti* ratio of 94/6. On the other hand, *syn-cis* adduct (**12c**) was formed exclusively in the reaction of nitrone (**11c**) (R^1 = CO_2Et) (Scheme 4).

Scheme 4

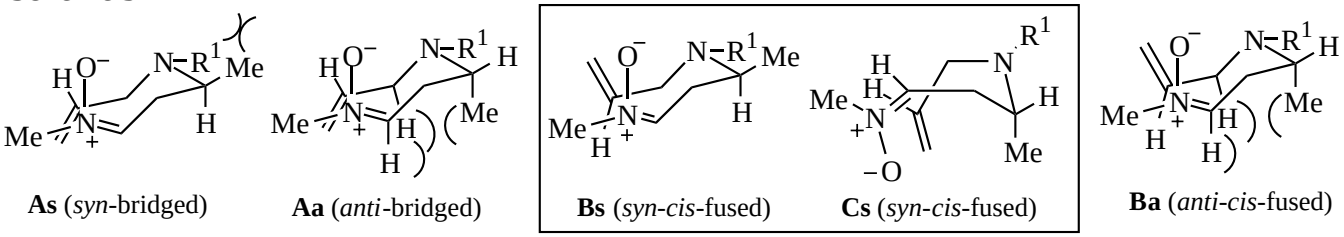


run	Nitrone	R^1	Yield (%)	Ratio of Products *syn*-**12** :	*anti*-**12** :	*syn*-**13**
1	**11a**	Ts	85	92	3	5
2	**11b**	Ms	84	94	6	0
3	**11c**	CO_2Et	76	100	0	0

Taking account for a rotation barrier for *N*-aryl aldonitrones ($\Delta G^{\ddagger}$: more than 30 kcal/mol),[10] the isomerization between the *Z*- and *E*-nitrones in the present system seems to be ruled out. In order to obtain further information, the heats of formation[11] of the corresponding *Z*- and *E*-nitrones (**11b**) and the model *N*-mesyl nitrones (**2b** and **7b**) were examined; since the difference of heats of formation between the *Z*- and *E*-isomer ($\Delta\Delta H^{\ddagger}_{E\text{-}Z}$) in **11b** was relatively large (more than 5.3 kcal/mol), the intervention of only *Z*-isomer in these cycloaddition of nitrone (**11b**) seems to be plausible. On the other hand, the both of *Z*- and *E*-isomers in nitrone (**2b**) ($\Delta\Delta H^{\ddagger}_{E\text{-}Z}$ = more than 2.3 kcal/mol) and **7b** ($\Delta\Delta H^{\ddagger}_{E\text{-}Z}$ = more than 1.8 kcal/mol) could be participated to the cycloaddition as proposed by Aurich.[7] The selective formation of *syn-cis* fused adducts (**12**) from nitrone (**11**) was explainable; the possible four chair-like transition states (TSs **A** and **B**) and one boat-like transition state (**Cs**) leading to bridged and fused adducts are illustrated in Scheme 5. In TS **As** leading to *syn*-bridged adduct, the equatrial methyl group at the 3-position causes a serious $A_{1,2}$-strain with the substituent (R^1) on the amino nitrogen along the formation of isoxazolidine ring. On the other hand, in TSs **Aa** and **Ba** leading to *anti*-bridged and *anti-cis*-fused adduct, respectively, the steric repulsion between the axial methyl group at the 3-position and the azomethine and allylic protons becomes serious due to 1,3-diaxial interaction. Consequently, chair-like TS **Bs** and/or boat-like TS **Cs**[13] leading to *syn-cis*-fused adduct become the favorable ones in the reaction of nitrones (**11**) (Scheme 5).

Stereoselective intramolecular nitrone–alkene cycloaddition of nitrones (**11**) and reductive cleavage of the resulting isoxazolidine ring would provide a useful tool for the stereoselective preparation of polyfunctionalized piperidine derivatives. The intramolecular cycloaddition of related nitrones is currently explored and will be reported elsewhere together with the experimental details of this communication.

Scheme 5



As (*syn*-bridged) **Aa** (*anti*-bridged) **Bs** (*syn-cis*-fused) **Cs** (*syn-cis*-fused) **Ba** (*anti-cis*-fused)

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9 *syn*-**12b:** ^{1}H NMR ($CDCl_3$) δ = 1.34 (d, J = 6.8, 3 H, 4-Me_{ax}), 1.62 (td, J = 7.3 and 14.2, 1 H, 5-H_{ax}), 2.07 (td, J = 5.5 and 14.2, 1 H, 5-H_{eq}), 2.66 (ov, 4 H, SO_2Me and 6-H_{eq}), 2.70 (m, 1 H, 1-H_{ax}), 3.13 (dd, J = 11.9 and 13.7, 1 H, 2-H_{ax}), 3.49 (dd, J = 3.7 and 8.5, 1 H, 9-H_{eq}), 3.68 (dd, J = 6.3 and 13.7, 1 H, 2-H_{eq}), 4.00 (m, 1 H, 4-H_{eq}), 4.07 (br t, J = 7.8, 9-H_{ax}). The irradiation of 2-H_{ax} caused an enhancement of the signal intensity of 4-Me (3.6%), 7-H_{ax} (3.2%), and 9-H_{eq} (5.0%).

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11 The nitrone molecules were built up utilizing MacroModel molecular modeling program.[12] The conformers with lower energy were researched by Monte Carlo method and optimized by PRCG method utilizing MacroModel Amber force field. All conformers ranged in the energy window of 12.0 kcal/mol more than the most stable conformer were collected.

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13 We wish to acknowledge the referee of this journal, who pointed this possible TS out.