FIRST EXAMPLE OF INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION OF NON-STABILIZED AZOMETHINE YLIDE GENERATED FROM TERTIARY AMINE *N*-OXIDE

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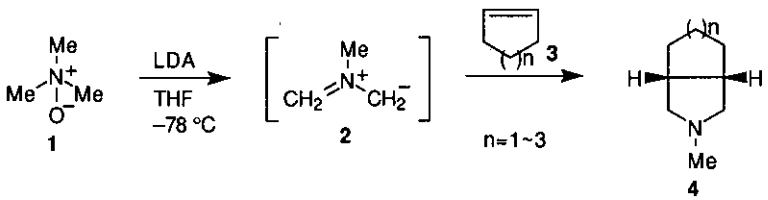
Abstract —— The reaction of two optically active 1-alkyl-3,4-diallyloxypyrrolidine 1-oxides, (**9**) and (**15**), under basic conditions has been examined. The 1-benzyl derivative (**9**), on reaction with lithium diisopropylamide, furnished a single pyrrolidine derivative (**11**) by intramolecular 1,3-dipolar cycloaddition of an *N*-benzylidene azomethine ylide (**10**), while the 1-methyl derivative (**15**) reacted with *tert*-butyllithium in the presence of trimethylaluminum to afford only a single 7-azabicyclo[2.2.1]heptane derivative (**19**) by spontaneous intramolecular 1,3-dipolar cycloaddition of the endocyclic azomethine ylide (**17**).

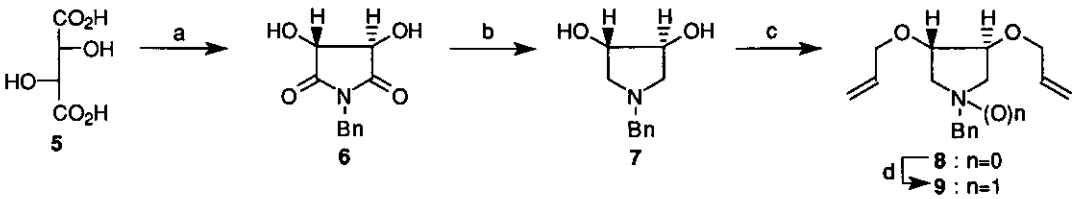
It is curious to note that intramolecular 1,3-dipolar cycloaddition of a non-stabilized azomethine ylide generated from a tertiary amine *N*-oxide precursor has never been reported so far, though a number of intermolecular examples of the reaction have been reported[1] (**Scheme 1**). Since the tertiary amine *N*-oxide mediated intermolecular 1,3-dipolar cycloaddition reaction, first reported by Roussi and co-workers,[1a] can be performed under very mild conditions using substrates having no activating groups both in the amine oxide component and the dipolarophile component, it seems to be synthetically useful if it can be carried out in an intramolecular way where regio- and stereochemical controls may be achieved much more efficiently than in the intermolecular pathway.[2] In order to develop the intramolecular 1,3-dipolar cycloaddition of an amine, we examined the reaction using two chiral model compounds and here disclose some interesting results observed.



Scheme 1

By following the established procedure[3] (3*S*,4*S*)-1-benzyl-3,4-dihydroxypyrrolidine (**7**), mp 103.0-103.5 °C, $[\alpha]_D^{30}$ +8.28° (*c* 1.10, $CHCl_3$) [lit.,[3] mp 109-110 °C, $[\alpha]_D^{22}$ +8.3° (*c* 1.1, $CHCl_3$)], was prepared from L-tartaric acid (**5**) in two steps in 61% overall yield *via* the imide (**6**). The hydroxypyrrolidine (**7**) was then treated with allyl bromide and sodium hydride in a mixture of DMF and THF in the presence of tetra-*n*-butylammonium

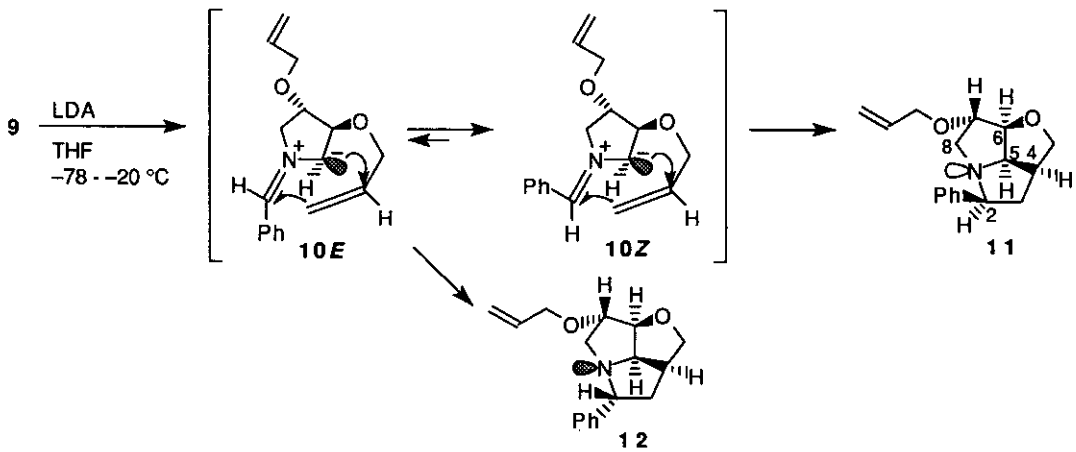
iodide to give the diallyl ether (**8**), $[\alpha]_D^{29}$ +39.50° (*c* 1.07, $CHCl_3$) having a C_2-symmetric structure in 82% yield. Exposure of **8** to *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate[4] effected chemoselective *N*-oxidation to form the 1-oxide (**9**) in 75% yield (**Scheme 2**).



Scheme 2

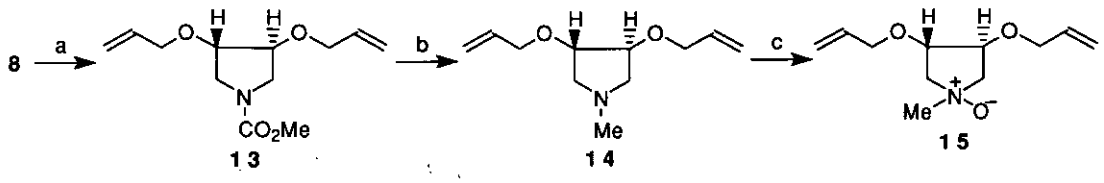
Reagents: a) benzylamine, xylene, reflux; b) $LiAlH_4$, THF, reflux; c) NaH, allyl bromide, DMF-THF (1:5), room temperature; d) *tert*-BuOOH, $VO(acac)_2$, CH_2Cl_2, room temperature.

Upon treatment with 3.5 equiv. of lithium diisopropylamide in THF,[1] **9** afforded the tricyclic amine (**11**), $[\alpha]_D^{29}$ +104.50° (*c* 1.00, $CHCl_3$), as an only isolable product in 35% yield as a single stereoisomer. Stereochemistry of **11** was determined by NOE experiment in which significant interactions between 8β-*H* and some aromatic hydrogens and between 8α-*H* and both 5α-*H* and 6α-*H* were recognized. The observed stereochemical outcome clearly indicated that the benzylidene azomethine ylide (**10Z**) having *Z* configuration was involved as an activated intermediate to give the *endo*-phenyl adduct (**11**) selectively instead of forming the *exo*-phenyl adduct (**12**) *via* the alternative *E*-ylide (**10*E***) presumably to alleviate steric congestion in the latter transition state (**Scheme 3**).



Scheme 3

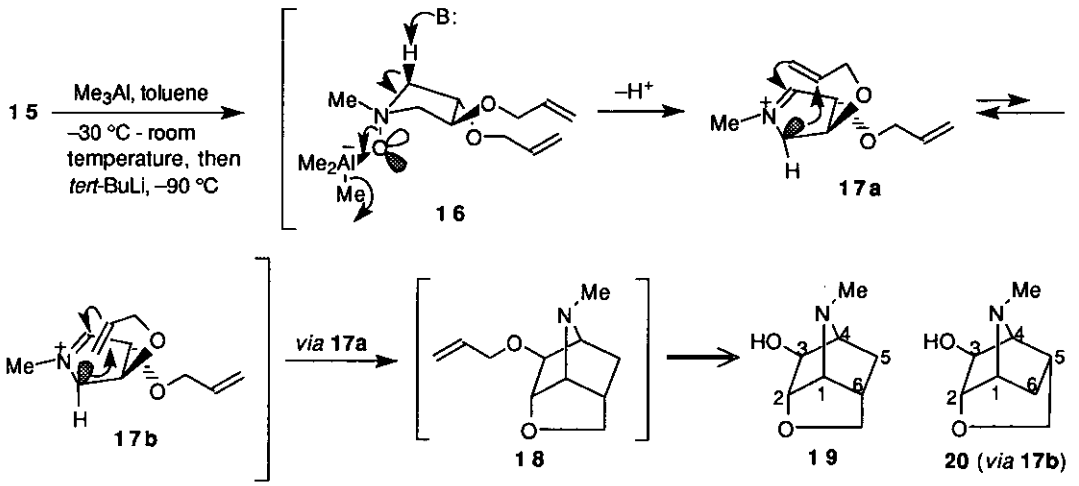
On the other hand, the *N*-methylamine oxide (**15**) was prepared[5] from the *N*-benzylamine (**8**) in three steps in 83% overall yield *via* the carbamate (**13**), $[\alpha]_D^{29}$ +4.01° (*c* 1.02, $CHCl_3$), and the methylamine (**14**), $[\alpha]_D^{29}$ +17.73° (*c* 1.00, $CHCl_3$) (**Scheme 4**).



Scheme 4

Reagents: a) $ClCO_2Me$, benzene, room temperature; b) $LiAlH_4$, THF, reflux; c) *tert*-BuOOH, $VO(acac)_2$, CH_2Cl_2, room temperature.

Under the same basic conditions described above, **15** was found to be inert, and none of adducts could be detected in the reaction mixture. Even under more forcing conditions using stronger bases at higher temperature in a variety of solvents, **15** failed to give any cycloadducts. However, we found that the intramolecular 1,3-dipolar cycloaddition does occur with **15** when trimethylaluminum[6] was added to the reaction medium prior to the basic treatment. The cycloaddition however took place in an unexpected way. Thus, on treatment with 2.0 equiv. of trimethylaluminum at –30 °C~room temperature followed by 4.5 equiv. of *tert*-butyllithium at –90 °C in toluene, **15** furnished the tricyclic amine (**19**), $[\alpha]_D^{29}$ +21.19° (*c* 0.59, $CHCl_3$), having 7-azabicyclo[2.2.1]heptane framework in 27% yield as a only isolable cycloadduct indicating the exclusive involvement of the endocyclic azomethine ylide (**17a**) in the reaction. The structure of the product (**19**) was confirmed by ^{1}H-nmr (500 MHz) spectroscopy which could readily distinguish **19** from the isomeric structure (**20**) generated *via* an alternative conformation (**17b**) in which suitable orbital interactions cannot be attained. Thus, decoupling experiment revealed that the proton at C_1 center is coupled with two vicinal protons at C_2 and C_6 centers allowing, and eliminated the alternative structure (**20**) where the C_1-proton bears three vicinal protons. The unexpected formation of the product (**19**) having 7-azabicyclo[2.2.1]heptane structure could be rationalized by considering the endocyclic azomethine ylide (**17**) which in turn underwent intramolecular 1,3-dipolar



Scheme 5

cycloaddition to give rise to the tricyclic adduct (**18**) whose allyl ether moiety was cleft under the conditions presumably by base promoted allyl bond migration.[7] The observed regiospecific generation of the endocyclic azomethine ylide (**17**) may be due to the initial formation of the aluminum complex[6] (**16**) having the axial N-O bond with the outward metal-oxygen bond which then was eliminated with specific removal of the axial C_2-hydrogen anti-parallel to the O-Al bond. However, the exact reason of the regioselective removal of the second hydrogen from the pyrrolidine ring rather than the methyl group is presently unclear (**Scheme 5**).

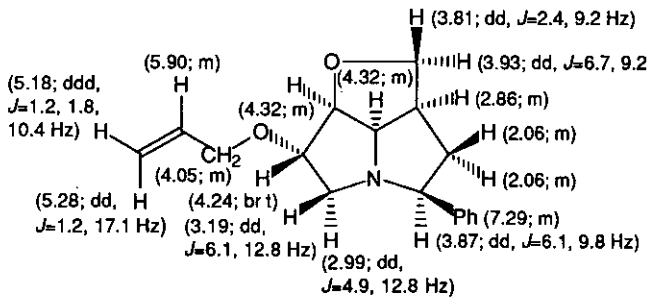
In conclusion, we have shown for the first time that the intramolecular 1,3-dipolar cycloaddition does occur for two non-stabilized azomethine ylides generated from the tertiary amine *N*-oxide precursors to give rise to the corresponding cycloadducts in regio- and stereospecifical manners, respectively. Extension of the present findings for the enantiocontrolled synthesis of the pyrrolidine natural products is currently under way in our laboratory.

ACKNOWLEDGEMENTS

We thank the Japan Society for the Promotion of Science for Japanese Junior Scientist for a fellowship to Y. S.

REFERENCES

1. a) R. Beugelmans, G. Negron, and R. Roussi, *J. Chem. Soc., Chem. Commun.*, **1983**, 31. b) R. Beugelmans, L. Benadjila-Iguertsira, J. Chastanet, G. Negron, and G. Roussi, *Can. J. Chem.*, 1985, **63**, 725. c) J. Chastanet and G. Roussi, *J. Org. Chem.*, 1985, **50**, 2910. d) J. Chastanet and G. Roussi, *Heterocycles*, 1985, **23**, 653. e) R. Beugelmans, J. Chastanet, and G. Roussi, *ibid.*, 1987, **26**, 3197. f) J. Chastanet and G. Roussi, *J. Org. Chem.*, 1988, **53**, 3808. g) G. Roussi and J. Zhang, *Tetrahedron Lett.*, 1988, **29**, 3481. h) B. De, J. F. DeBernardis, and R. Prasad, *Synth. Commun.*, 1988, **18**, 481. i) A. G. H. Wee, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1363. j) G. Roussi and J. Zhang, *Tetrahedron*, 1991, **47**, 5161.
2. cf. W. Carruthers, 'Cycloaddition Reactions in Organic Synthesis,' ed. by J. E. Baldwin and P. D. Magnus, Pergamon Press, Oxford, 1990.
3. Y. Arakawa and S. Yoshifuji, *Chem. Pharm. Bull.*, 1991, **39**, 2219.
4. L. Kuhnen, *Chem. Ber.*, 1966, **99**, 3384; M. N. Sheng and J. G. Zajacek, *Org. Synth. Coll. Vol.*, 1988, **6**, 501.
5. cf. M. Hanaoka, K. Nagami, Y. Hirai, S. Sakurai, and S. Yasuda, *Chem. Pharm. Bull.*, 1985, **33**, 2273.
6. Interaction of organoaluminum reagents with amine oxides has been reported, see: G. W. Kabalka and R. J. Newton, Jr., *J. Organomet. Chem.*, 1978, **156**, 65.
7. cf. J. Gigg and R. Gigg, *J. Chem. Soc. (C)*, **1966**, 82.
8. ^{1}H-Nmr spectra (500 MHz) of compounds **11** and **19**:



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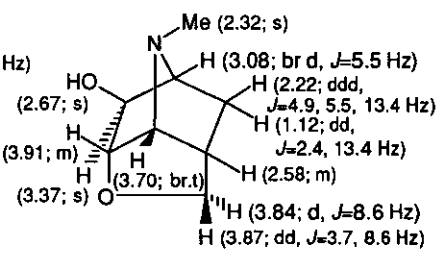

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Received, 25th May, 1992