THE NITROGENATED ALLYLIC SYSTEM AS AN INTRAMOLECULAR NUCLEOPHILE: A NEW ROUTE TO PYRAZOLES†

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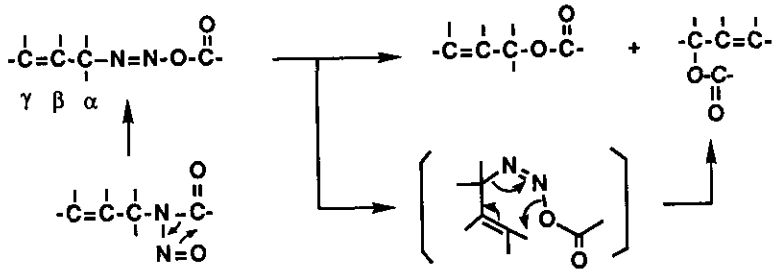
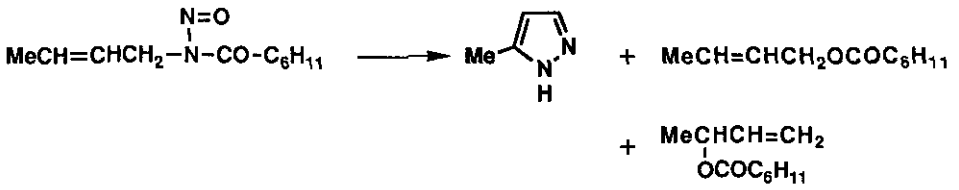
Abstract —— A new route to pyrazoles *via* the cyclization of *N*-allyl-*N*-nitrosoamides is described.

The thermal *N*-nitrosoamide rearrangement (Huisgen-White rearrangement)[2] constitutes the key step of the sequence that furnishes the α-ketonic cleavage *via* the tandem oximation - Beckmann rearrangement and serves as an alternative to the Baeyer-Villiger lactonization of cyclic ketones in the case where the latter is unsuccessful.[3] Despite the intensive work by E. H. White,[4] the olefinic amides especially of the allylamine system have never been examined to date. In association with the mechanistic aspects of the *N*-nitrosolactam rearrangement into bicyclic lactones,[5] we attempted to estimate the product distribution between α- and γ-carbon substitutions in the *N*-allylamide system, the latter being possibly derived *via* the pathway as depicted.



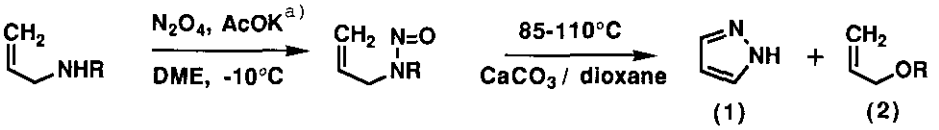
We examined, as a model experiment, the rearrangement of *N*-crotyl-*N*-nitrosocyclohexanecarboxamide and found that 2-methylpyrazole was formed in a considerable amount besides the products of rearrangement, crotyl cyclohexanecarboxylate and 3-buten-2-yl cyclohexanecarboxylate in a ratio of 4.3 : 1.

†This paper is dedicated to the memory of the late Professor Tetsuji Kametani.



In order to clarify the requirements of the present new pyrazole cyclization, several amides of allylamine were subjected to the sequence. The results are shown in Table I.

Table I. Reaction Products from *N*-Allyl-*N*-nitrosoamides.

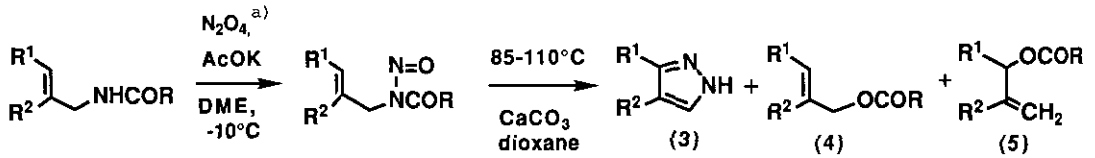


amides R	yield (%)[b] (1)	(2)
COMe	42	—[c]
COBn	59	28
CO^{c}Hex	41	12
CO^{t}Bu	26	2
COPh	39	24
CO_2Me	8+36[d]	—[c]
$COCH_2Cl$	—	16
3,4-dimethoxybenzoyl	41	23
Ms	—	63

a) The nitrosation was performed according to the procedure of White (E. H. White, *J. Am. Chem. Soc.*, 1955, 77, 6008); anhydrous potassium acetate was used instead of anhydrous sodium acetate as a base.
b) Given in the one of overall procedure involving nitrosation and thermolysis.
c) Failed to be collected owing to its high volatility.
d) 1-Methoxycarbonylpyrazole was isolated in 36% yield along with pyrazole (8%).

The structural requirements for the cyclization were next examined. The results are shown in Table II.

Table II. Reaction Products from *N*-(Substituted Allyl)-*N*-nitrosoamides.



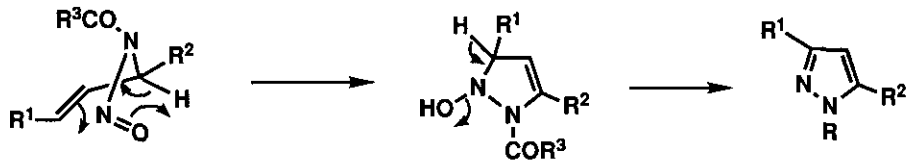
amide R^1	R^2	R	yield (%)b) (3)	(4+5)
Me	H	Me	21	— c)
Me	H	Bn	22	54 (3.6:1) d)
Me	H	cHex	21	27 (4.3:1) d)
H	Me	Me	58	— c)
H	Me	Bn	54	29
$-(CH_2)_3-$		Me	11	47
$-(CH_2)_4-$		Me	30	40
$-(CH_2)_4-$		Bn	14	53
$-CH_2-CH=CH-CH_2-$		Me	28	46
$-CH_2-CH=CH-CH_2-$		Bn	13	64
p-MeC_6H_4	H	Me	—	29

a) The nitrosation was performed according to the procedure for the experiments in Table I.
b) Given in overall one of the two step sequence.
c) Failed to be collected owing to its high volatility.
d) Determined on the basis of the nmr signal integration for the protons on the acyloxylated carbon.

The γ-homologation disfavors the cyclization possibly owing to the steric interference in the nitrogenous access to the allylic γ-carbon, the first stage of the cyclization, in the intermediate diazoalkanoate. Some additional requirements such as solvent effects are currently under investigation.

The most ordinary method for the pyrazole synthesis is the one involving the reaction of 1,3-diketones with hydrazine derivatives.[6] Recent methods for 5-silylated[7] and 3,4,5-trisubstituted pyrazoles[8] are also based on the reaction of

ketonic species with diazo or hydrazo species. The present ring-closure reaction is a new procedure for the pyrazole ring system, and the mechanism is tentatively postulated as depicted below.



To our knowledge, this is the first example, though intramolecular, of the nucleophilic addition of olefins at the γ position of the allylic π system which is heterogenated at the α position with an element more electronegative than carbon. The α-metalated allylic system, which is the one heterogenated with an element less electronegative than carbon, is known to react at the γ position as a nucleophile.[9] The allylic system which is α-heterogenated more electronegatively, however, is nucleophilic only at the β position and gives an anti-Markovnikov addition product exclusively.[10] The 'ene' reaction of the α-oxygenated allylic system with chlorine was also reported to result in the β-chlorination exclusively.[11]

NOTES AND REFERENCES

1. Present adress: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01, Japan.
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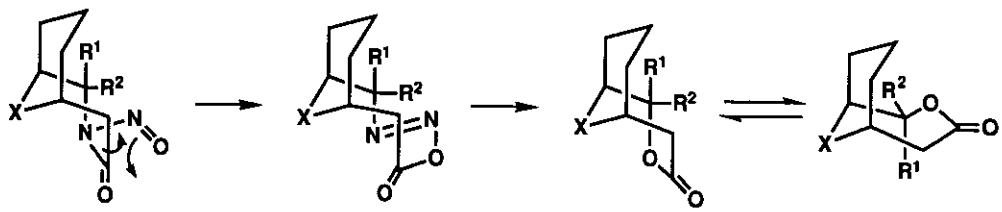
3. Cf. T. Momose and O. Muraoka, Tetrahedoron Lett., **1978**, 1125; T. Momose, O. Muraoka, S. Atarashi, and T. Horita, Chem. Pharm. Bull., 1979, **27**, 222.
4. For related papers, see E. H. White and H. M. Lim, J. Org. Chem., 1987, **52**, 2162 and references cited therein.

5. N-Protected 9-azabicyclo[3.3.1]nonan-3-one oxime gives a bicyclic lactone via the sequential Beckmann rearrangement-nitrosation-thermolysis in good yield:



T. Momose and C. H. Eugster, unpublished work. The work was presented in part at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1989. Abstracts of Papers, III, p. 124.

6. A. N. Kost and I. I. Grandberg, "Advances in Heterocyclic Chemistry: Progress in Pyrazole Chemistry," Vol. 6, A. R. Katritzky and A. J. Boulton, Ed.; Academic Press: London, 1966; pp. 347-429.

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8. T. A. Lentz and C. F. Beam, J. Heterocycl. Chem., 1987, **24**, 555.

9. See, for example, a) reviews: E.W. Colvin, "Silicon in Organic Synthesis", Butterworths: London, 1981; Chapter 9, pp. 97-124; Y. Yamamoto and K. Maruyama, Heterocycles, 1982, **18**, 357; A. Hosomi, Acc. Chem. Res., 1988, **21**, 200; b) recent papers: J. Nokami, T. Tamaoka, H. Ogawa, and S. Wakabayashi, Chemistry Lett., **1986**, 541; V. J. Jephcote, A. J. Pratt, and E. J. Thomas, J. Chem. Soc., Perkin Trans. I, **1989**, 1529; K. Sato, M. Kita, and H. Sakurai, J. Am. Chem. Soc., 1989, **111**, 6429; and references cited therein.

10. See, for example, A. L. Henne and S. Kaye, J. Am. Chem. Soc., 1950, **72**, 3369.

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Received, 5th October, 1989