Tetrahedron Letters,Vol.30,No.32,pp 4207-4210,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

EFFICIENT SYNTHESIS OF N-SUBSTITUTED LACTAMS FROM (N-ARYLSULFONYLOXY) AMINES AND CYCLIC KETONES

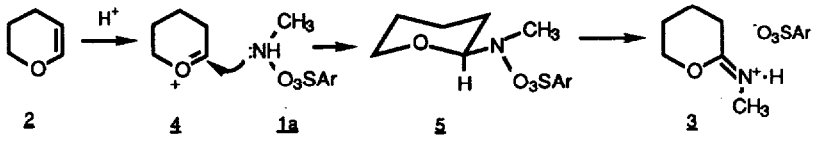
Robert V. Hoffman* and James M. Salvador
Department of Chemistry
New Mexico State University
Las Cruces, New Mexico 88003-0001

A new method is reported for the direct preparation of N-substituted lactams from cycloalkanones. N-(p-nitrobenzenesulfonoxyl) methylamine 1a (CH_3NH-$OSO_2C_6H_4NO_2$) was reacted with a series of cycloalkanones to give good yields of N-methyl lactams. An addition-rearrangement pathway accounts for the ring-expanded lactam products. A series of N-alkyl-N-arylsulfonoxyl amines were generated *in situ* and reacted with cyclobutanone to give N-alkyl pyrrolidinones in high yields.

There are several methods for the insertion of nitrogen into existing carbocyclic rings. Both the Beckmann rearrangement[1] and its variants[1b] and the Schmidt reaction[1c,2] can be used to convert cyclic ketones to ring expanded lactams. A variation of the Schmidt reaction can also be used to convert cyclic alcohols or olefins to ring expanded cyclic imines under acid catalysis.[3] Chloramines[4a] have also been used as ring expansion substrates in a few cases. In all of these reactions, however, only N-unsubstituted products can be produced.

The insertion of N-substituted nitrogen into rings is less well-known. In addition to a photochemical rearrangement of oxaziridines,[5] the insertion of N-substituted nitrogen into rings has been accomplished by Wasserman in his preparation of β-lactams from cyclopropanones.[6] Because a stable carbinolamine is required as an intermediate, this method is restricted to cyclopropanones. Barton described the conversion of cyclic ketones to nitrones followed by rearrangement to N-substituted amides using tosyl chloride in wet pyridine.[7] While seemingly general, overall yields are not high (20-50%), and N-alkyl hydroxylamines, which often must be synthesized, are required to produce N-substituted amides.

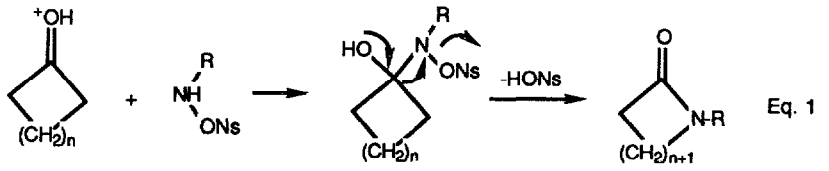
We recently observed that the reaction of N-(p-nitrobenzenesulfonyloxy)methylamine , 1a, with 3,4-dihydro-2H-pyran , 2, gave the imidate salt 3.[8] Evidence suggested that the imidate product results from acid catalyzed addition of 1a to 2 to give tetrahydropyran intermediate 5, followed by cationic, carbon to nitrogen hydride rearrangement. A key reaction in the sequence is the nucleophilic addition of 1a to oxonium ion 4 which yields the rearrangement precursor 5.



2 4 1a 5 3

If nucleophilic addition N-(p-nitrobenzenesulfonoxyl)amines (NSA) to oxonium ions is a general reaction, then oxonium ions formed by the protonation of cyclic ketones could serve as substrates and give (N-arylsulfonoxyl)carbinolamine intermediates 6. (Eq. 1) Carbon-to-nitrogen rearrangement in 6 would lead to lactam products, reminiscent of the β-lactam

synthesis of Wasserman[6] without the need for stable carbinolamine intermediates, and analogous to Barton's procedure[7] without the need for preparation of nitrone intermediates. We are pleased to report that the reactions of N-(p-nitrobenzenesulfonoxyl)amines, 1, with cyclic ketones give N-substituted lactams directly and efficiently.



1a-h 6 Eq. 1

In a typical reaction, cyclobutanone (50.4 mg, 0.72 mmol) was added to a cooled (-78 C) suspension of 1a (R=CH_3) (0.80 mmol) in chloroform-d (1.0 mL). The mixture was allowed to warm to room temperature with shaking. Triethylamine (218 mg, 2.2 mmol) was added and the solvent was removed on a rotary evaporator. Kugelrohr distillation (1.5 torr, 60°C) of the residue gave spectroscopically pure 1-methyl-2-pyrrolidinone (67.6 mg, 0.68 mmol, 94% yield).

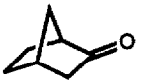
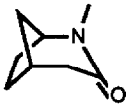
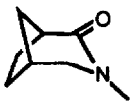
The mechanism of the reaction presumably involves the acid catalyzed[9] nucleophilic addition of 1a to the carbonyl group to give a carbinolamine type intermediate,6, which yields the ring expanded amide salt by cationic carbon to nitrogen migration of a ring bond. Treatment with base delivers the amide product. (Eq. 1). That the reaction is acid catalyzed is shown by the addition of 2,6-di-tert-butyl-4-methyl pyridine (4.4 mg, 0.021 mmol, 0.2 eq) to the reaction mixture. No reaction was observed to take place by pmr for more than three hours, until the base had been neutralized by acidic products from the decomposition of 1a, after which ring expansion proceeded normally. With no base present the reaction is complete in a matter of minutes at room temperature.

By the same procedure a variety of cyclic ketones were treated with 1.1 equivalents of 1a (Table1). Good to excellent yields are obtained from the reactions of 4, 5, and 6-membered ring ketones with 1a. In general reaction times increase with ring size from a few minutes for cyclobutanone to twelve hours for cyclohexanone derivatives. Ring strain plays a large role in increasing the rate and efficiency of the ring expansion. Cyclobutanone (Entry 1) and norbornanone (Entry 7) react in minutes to give high yields of products. Less strained cyclic ketones react more slowly. In ketones where addition of 1a is surpressed by steric congestion in the tetrahedral intermediate, as in Entry 8, the reaction is slow and poor yields result from competing decomposition of 1a.

Secondary alkyl migration is favored over primary alkyl group migration in ring expansions of unsymmetric cyclic ketones. The selectivity (4:1) is similar to that observed in cationic ring expansions in N-(arylsulfonyloxy)amines,[10] and to migratory preferences found in carbon-to-oxygen migrations in the Baeyer-Villiger reaction, an oxygen analog of the present rearrangement.[11] The mixture of products for norcamphor is also similar to those observed in the Baeyer-Villeger reaction of camphor systems.[12]

NSA 1b-h are less stable than 1a , and were generated *in situ* in the presence cyclobutanone to give N-substituted-pyrrolidinones.(Eq. 2) The instability of the NSA must be balanced by a high reactivity of the cycloalkanone to give efficient addition-rearrangement. Thus cyclobutanone was the preferred cyclic ketone as it reacts rapidly with NSA's and gives efficient rearrangement. Less reactive cycloalkanones gave poor results when the NSA was generated *in situ* . The starting amine was added dropwise to a stirred mixture of cyclobutanone and p-(nitrobenzenesulfonyl) peroxide (pNBSP)[14] in dichloromethane at -78°C. After the addition was complete the reaction was stirred at room temperature for 2

Table 1. The Reaction of Cyclic Ketones with N-(p-Nitrobenzenesulfonyloxy) Methylamine, 1a, in Chloroform at 25°C.

Entry	Ketone	Product[a]	Yield(%)[b]
1.	Cyclobutanone	N-methylpyrrolidinone	96
2.	2-Methylcyclopentanone	N,6-dimethylpiperidinone	82
3.	Cyclohexanone	N-methylcaprolactam	73
4.	2-Methylcyclohexanone	N,7-dimethylcaprolactam : N,3-dimethylcaprolactam	84 (4:1)
5.	3-Methylcyclohexanone	N,6-dimethylcaprolactam: N,4-dimethylcaprolactam	62 (1:1)
6.	4-t-Butylcyclohexanone	5-t-butyl-N-methylcaprolactam	68
7.		 	100 (3:2)
8.	Cycloheptanone	N-methylazacyclooctanone	12

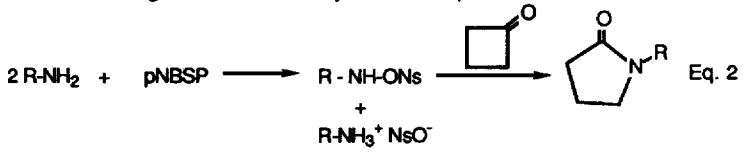
a. Product identification was accomplished by comparison of spectra with the literature data. b. Yields are isolated yields of pure products and are the average of two experiments.

Table 2. Yields of N-Substituted Pyrrolidones from the Reaction of N-Substituted-p-(nitrobenzenesulfonoxyl) Amines Generated *in situ* with Cyclobutanone.

R- NH-ONs	Yield (%)[a]
R=methyl, 1a	92
2,2-dimethoxyethyl, 1b,	73
allyl, 1c	62
propargyl, 1d	86
n-butyl, 1e	100
benzyl, 1f	86
i-propyl, 1g	21
cyclohexyl, 1h	18

a. Reported yields are isolated yields of pure products, and are the average of two experiments.

hours and worked up as described previously. Best results were obtained with a 3-fold excess of the reagents required to generate the NSA according to the stoichiometry shown in equation 2.[13]



Eq. 2

From the yields shown in Table 2, it is evident that a variety of N-substituted primary amines can be incorporated into the N-substituted lactam product effectively. While NSA's derived from most primary amines gave good yields of N-

substituted-pyrrolidinones, those generated from secondary amines gave poor yields, and that from tert-butyl amine gave no isolable product. Sterically bulky NSA probably do not add readily to oxonium ions, thus ring expanded products are not produced efficiently.

Within the limitations noted, however, a general approach to N-substituted lactams from cyclic ketones is now available. We are continuing to develop this method at present.

Acknowledgement

This work was supported in part by the National Science Foundation (CHE83-04000 and CHE87-09853) and the MBRS Program of the National Institutes of Health.

References:

1. a. McCarty, C. G. in "The Chemistry of the Carbon-Nitrogen Double Bond", Patai, S., Ed., Interscience, New York, NY, 1970, p 408-439. b. Tamura, Y; Minamikawa, J.; Ikeda, M., Synthesis, 1977, 1. c. Krow, G. R., Tetrahedron, 1981, 37, 1283. d. Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura. Y.; Sakane, S.; Hattori, K.; Yamamoto, H.; J. Am. Chem. Soc., 1983, 105, 2831. e. Sakane, S.; Matsumura, Y.; Yamamura, Y.; Ishida, K.; Yamamoto, H., J. Am. Chem. Soc., 1983, 105, 672.
2. a. Koldobski, G. I.; Tereshchenka, G. F.; Gerasimova, E. S.; Bagal, L. I., Russ. Chem. Rev., 1971, 40, 835. b. Smith, P. A. S. in "Molecular Rearrangements", Vol. 1, de Mayo, P., Ed., Interscience, New York, 1963, Chapter 8.
3. a. Boyer, J. H.; Canter, F. C., J. Am. Chem. Soc., 1955, 77, 3287. b.Sasaki, T.; Eguchi, S.; Okano, T., J. Org. Chem., 1984, 49, 444.
4. a.For example: Tonnis, J. A.; Wnuk, T. A.; Dolan, M. J.; Kovacic, P., J. Org. Chem., 1974, 39, 766, and references therein. b.
5. Oliveros, E.; Riviere, M.; Lattes, M., Nouv. J. Chim., 1979, 3, 739.
6. a. Wasserman, H. H.; Glazer, E. A.; Hearn, M. J., Tetrahedron Lett., 1973, 4855. b. Wasserman, H. H.; Adickes, H. W.; de Ochoa, O. E., J. Am. Chem. Soc., 1971, 93, 5586.
7. a. Barton, D.H.R.; Day, M. J.; Hesse, R. H.; Pechet, M. M., Chem. Commun., 1971, 945. b. ibid., J. Chem. Soc., Perkins Trans. 1, 1975, 1764. c. Jeffs, P. W.; Molina, G., Chem. Commun., 1973, 3.
8. Hoffman, R. V.; Salvador, J. M., J. Chem. Soc., Perkins Trans., I, in press.
9. Preparations of 1a-h invariably contain acidic impurities which serve as the acid catalyst for the reaction. Hoffman, R. V.; Belfoure, E. L., Synthesis, 1983, 34.
10. a. Hoffman, R. V.; Buntain, G. A., J. Org. Chem., 1988, 53, 3316. b. Hoffman R. V.; Kumar, A., J. Org. Chem., 1985, 50, 1859.
11. a. House, H.O., Modern Synthetic Reactions; 2nd Ed. W.A. Benjamin Inc. Menlo Park Cal., 1972, p. 321-329. b. Hawthorne, M. F.; Emmons, W. D.; McCallum, K. S., J. Am. Chem. Soc., 1958, 80, 6393. c. Doering, W. v. E.; Speers, L., J. Am. Chem. Soc., 1950, 72, 5515.
12. a. Sauers, R.R.; Beisler, J. A., J. Org. Chem., 1964, 29, 210. b. Meinwald, J.; Frauenglass, E., J. Am. Chem. Soc., 1960, 82, 5235.
13. This is very likely due to the fact that the conversion of amines to NSA under these conditions occurs in about 30-40% yield. Thus a three-fold excess of reagents corresponds to a 1-1.2:1 ratio of NSA to cyclobutanone.
14. Dannley, R. L.; Gagen, J. E.; Stewart, O. J., J. Org. Chem., 1970, 35, 3076.

(Received in USA 27 April 1989)