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Rearrangements of Bicyclic Nitrones to Lactams: Comparison of Photochemical and Modified Barton Conditions

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The rearrangement of nitrones to lactams can be carried out by photochemical activation or by treatment with Tf_2O followed by KOH-promoted rearrangement (a modification of conditions originally introduced by Barton). Substrates in which the nitrone is part of a fused bicyclic ring system have traditionally proven problematic for this kind of reaction. In this study, a series of mono-, bi-, and tricyclic ring-fused nitrones were prepared to investigate the dependence of products on nitrone ring size and tether length. Results indicated that photochemical rearrangement of nitrones in benzene afforded reasonably good yields (30−68%) of lactams, while the two-step nonphotochemical process provided slightly better average yields (30−95%) of the same targets.

The photolysis of oximes to afford amides, the photo-Beckmann rearrangement, and the corresponding reaction of nitrones provides easy access to medium ring lactams.[1] In particular, these methods often have the advantage of allowing successful ring expansions of substrates that are sensitive to the acidic conditions of the classical Beckmann rearrangement.[2] In most cases, the rearrangements of nitrones have been studied in substrates containing the nitrone in an exocyclic orientation to a single ring (Figure 1a). Although these compounds are readily prepared by the intermolecular reactions of ketones with hydroxylamines, in most cases they afford a mixture of regioisomeric lactams. This is because the intermediate oxaziridine presumably forms nonstereoselectively from the starting nitrone, which may itself be a mixture of isomers. An alternative to the photochemical nitrone rearrangement was introduced by Barton et al., who described treatment of the nitrone with toluenesulfonyl chloride, presumably to transform the nitrone oxygen into a competent leaving group in the presence of pyridine.[3]

On the other hand, rearrangement of endocyclic, ring-fused nitrones has attracted much less attention, despite the fact that the bicyclic lactams formed by the rearrangement of such species are of considerable value for alkaloid synthesis (Figure 1b). Of the few examples that have been reported, yields are variable and sometimes complex mixtures of products are obtained.[4] Still, this process has considerable potential due to the fact that rearrangement of a single isomeric nitrone should afford a single lactam due to the stereoelectronic principles that govern the reactions of the intermediate oxaziridine (i.e., it is usually the group antiperiplanar to the lone pair on nitrogen that migrates[5]). In practice, this advantage has been lessened by the fact that many workers have generated the nitrone or the oxaziridine by oxidation of a secondary amine, which is not always regioselective. In addition, we have also noted some advantages in using this technique over a close synthetic equivalent (the intramolecular Schmidt reaction of alkyl azides and ketones[6]) because Lewis or protic acids are not involved.[7]

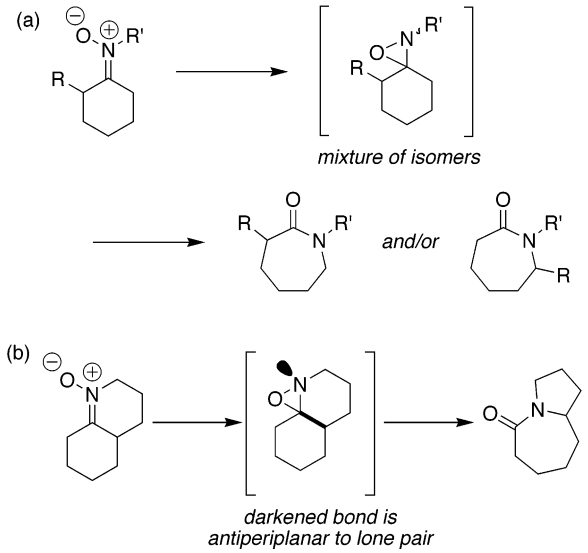

FIGURE 1. Rearrangements of (a) exocyclic and (b) endocyclic nitrones.

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(1) (a) Lamchen, M. *Mech. Mol. Migr.* **1968**, *1*, 1−60. (b) Spence, G. G.; Taylor, E. C.; Buchardt, O. *Chem. Rev.* **1970**, *70*, 231−265.
(2) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420.
(3) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1971**, 945−946.
(4) (a) Black, D. S. C.; Watson, K. G. *Aust. J. Chem.* **1973**, *26*, 2505−2513. (b) Black, D. S. C.; Johnstone, L. M. *Aust. J. Chem.* **1984**, *37*, 577−585. (c) Black, D. S. C.; Johnstone, L. M. *Aust. J. Chem.* **1984**, *37*, 587−597. (d) Johnson, G. P.; Marples, B. A. *Tetrahedron Lett.* **1985**, *26*, 4115−4118. (e) Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declercq, J.-P. *Org. Lett.* **2001**, *3*, 3067−3070.

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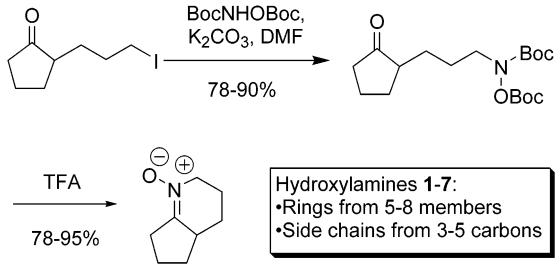
SCHEME 1



In this paper we report studies on the utility of the synthesis and rearrangement reactions of bicyclic nitrones. Nitrones were prepared by intramolecular addition of substituted hydroxylamines to ketones, to maximize regiochemical control in the nitrone formation step. Rearrangement reactions with both photochemical means and a new variant of the Barton protocol were then compared across a series of substrates.

Results and Discussion

Preparation of Endocyclic Nitrones. Despite a vast number of literature methods available for the preparation of nitrones,[8] many of them—especially those based on oxidation of a secondary amine directly to the nitrone (as often used to generate endocyclic nitrones)—do not adequately control regiochemistry. A useful approach that typically provides a single C=N double bond isomer is the condensation of an *N*-substituted hydroxylamine with a ketone. Surprisingly, intramolecular versions of this reaction are rare.[9] The direct installation of a hydroxylamine protected as various bis-carbonates into complex substrates is readily accomplished with either halide displacement[10] or Mitsunobu reaction.[11] It was anticipated that *N*,*O*-deprotection and subsequent condensation of bis-*tert*-butoxycarbonyl (Boc)-protected hydroxylamines with a ketone would directly afford the nitrones of interest (Scheme 1).

The required iodoalkyl ketones were readily obtained via hydrazone alkylation as previously described.[6] Displacement of the appropriate iodoalkyl ketone with *N*,*O*-diBoc-hydroxylamine[10] was followed by treatment with trifluoroacetic acid in DCM (4 Å MS; followed by acid neutralization with solid $NaHCO_3$) or a protocol in which the hydroxylamine was initially formed by treatment with TFA in DCM, followed by evaporation, replacement of the solvent with benzene, and reflux with a Dean–Stark trap (see Supporting Information for details). In general, the nitrones were purified and characterized prior to the rearrangement step, although this precaution is probably not necessary in many cases.

SCHEME 2

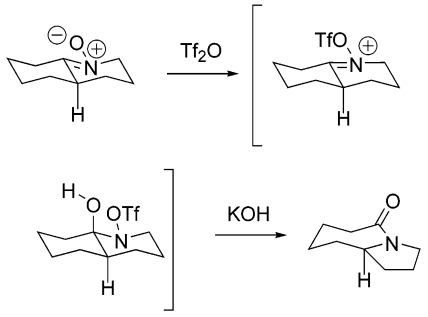
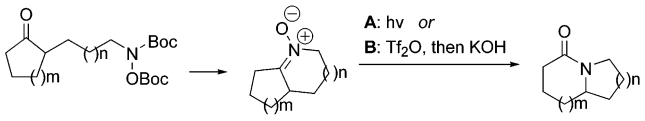


TABLE 1. Nitrone Rearrangements



entry	nitrone	*m*	*n*	yield of nitrone, %	rearrangement method	lactam	yield of lactam, %
1	**8**	1	2	85	A	**15**	50
2	**8**	1	2		B	**15**	40
3	**9**	2	1	90	A	**16**	68
4	**9**	2	1		B	**16**	75
5	**10**	2	2	80	A	**17**	65
6	**10**	2	2		B	**17**	70
7	**11**	2	3	88	A	**18**	35
8	**11**	2	3		B	**18**	40
9	**12**	3	2	95	A	**19**	50
10	**12**	3	2		B	**19**	70
11	**13**	4	1	78	A	**20**	56
12	**13**	4	1		B	**20**	60
13	**14**	4	2	87	A	**21**	45
14	**14**	4	2		B	**21**	35

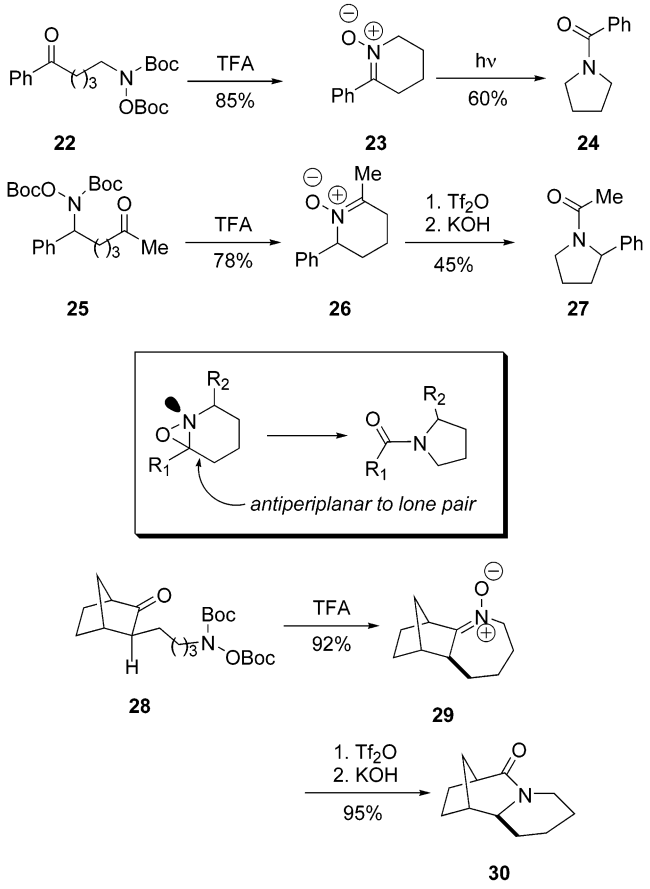
Nitrone Rearrangement. Two methods for the rearrangement of these bicyclic nitrones were examined. As shown above (Figure 1), the photochemical rearrangement of nitrone involves initial oxaziridine formation followed by the migratory rearrangement to yield lactams. These reactions were conveniently carried out in a vintage Merry-Go-Round photolysis apparatus (0.02–0.03 M, 254 nm, benzene, quartz tubes). Benzene has been shown to be a useful solvent for some oxaziridine rearrangements, possibly due to sensitization effects.[12]

Given the spotty history of this reaction as presented in the literature,[4] we thought it desirable to have a nonphotochemical alternative for the rearrangement step. Accordingly, we slightly modified Barton's protocol (treatment of nitrone with toluene-*p*-sulfonyl chloride in pyridine)[3] to a two-step process of trapping the nitrone oxygen with Tf_2O followed by a semipinacol-like KOH-promoted rearrangement (Scheme 2). The results for nitrones **8**–**14** are collected in Table 1.

In the bicyclic series, the photolysis process afforded the desired bicyclic lactams with modestly reasonable yields (35–68%). The lowest yields were associated with

(5) Lattes, A.; Oliveros, E.; Rivière, M.; Belzecki, C.; Mostowicz, D.; Abramskj, W.; Piccinni-Leopardi, C.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *104*, 3929–3934.
(6) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.
(7) Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577–2579.
(8) (a) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495. (b) Adams, J. P.; Paterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695–3705. (c) Jones, R. C. F.; Martin, J. N. *Chem. Heterocycl. Compd.* **2002**, *59*, 1–81.
(9) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865–4873.
(10) Mellor, S. L.; Chan, W. C. *Chem. Commun.* **1997**, 2005–2006.
(11) (a) Stewart, A. O.; Brooks, D. W. *J. Org. Chem.* **1992**, *57*, 5020–5023. (b) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, *42*, 2593–2595.
(12) (a) Post, A. J.; Nwaukwa, S.; Morrison, H. *J. Am. Chem. Soc.* **1994**, *116*, 6439–6440. (b) Wolfe, M. S.; Dutta, D.; Aubé, J. *J. Org. Chem.* **1997**, *62*, 654–663.

SCHEME 3

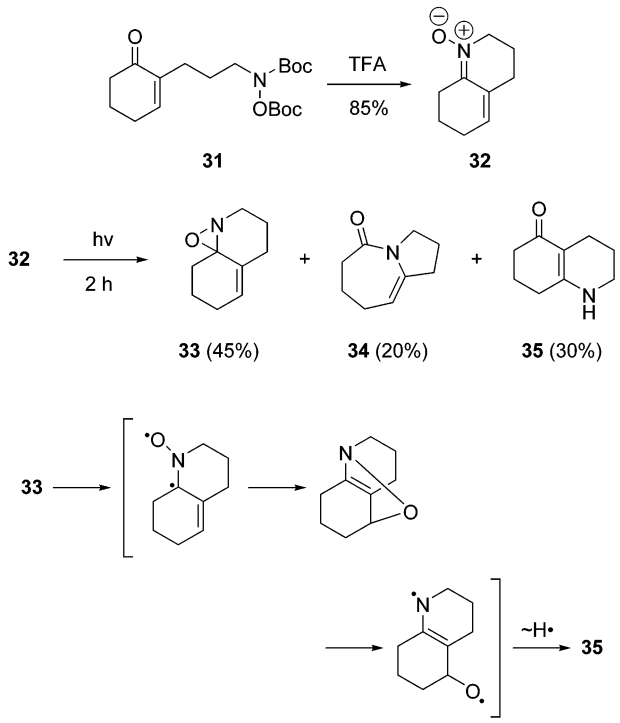


difficult ring sizes (entries 7, 8, 13, and 14). Only fused (as opposed to bridged) lactams were isolated, in accord with stereoelectronically preferred bond migrations associated with the intermediate oxaziridines (see Figure 1).[5] In comparison, the average yields of lactam formation using Method B were slightly better. In neither case were discrete byproducts isolated. It is noteworthy that two medium ring lactams (**18** and **21**) obtained here in reasonably good yields were inaccessible from the intramolecular Schmidt reaction, further establishing the present route as an alternative to that method.[6]

Several more examples were assayed to further establish the scope of the reaction. For example, two acyclic ω-hydroxylamino ketones were prepared as above (Scheme 3; the preferred method is shown in the scheme, but yields of both ring expansion methods are reported for these examples in the Supporting Information). Ring expansion of each gave exclusively ring-contracted amides **24** and **27** shown as a direct consequence of selective migration of bond antiperiplanar to the lone pair of nitrogen electrons in the intermediate oxaziridine. This particular example was also chosen to emphasize the utility of intramolecular nitrone formation as opposed to secondary amine oxidation; for example, oxidation of 2-phenyl-6-methylpiperidine would be expected to afford, possibly exclusively, the *isomer* of nitrone **26**. We also note the very good yields obtained with the norbornane-based tricyclic compound **29**.

As enones are also reluctant participants in the intramolecular Schmidt reaction, nitrone **32** was prepared and examined (Scheme 4). Unfortunately, compound **32**

SCHEME 4



gave poor yields (10−20%) with both rearrangement conditions. Interestingly, under photolytic conditions, this was the only substrate that produced isolable oxaziridine (**33**) in this study, indicating that the problem is with the further reactivity of this species (as opposed to its formation). Also, the unexpected vinylogous amide **35** was formed during the photochemical reaction; extended photolysis for two additional hours led to **35** as the exclusive product by examination of the crude ^{1}H NMR spectrum. One possible mechanism for the formation of **35** is given, based on the idea that the presence of the double bond facilitates initial C−O bond cleavage of the oxaziridine. Presumably, the lactam **34** decomposes upon extended photolysis. However, these points have not been carefully examined due to the lack of synthetic utility of this reaction.

Summary

The rearrangement reactions of endocyclic nitrones were examined by using photochemical techniques and modified Barton conditions. Both methods afforded good yields of the isomeric lactams. Thus, the overall conversion of an ω-iodoalkyl ketone to the corresponding *N*,*O*-bis-Boc-hydroxylamine followed by rearrangement provides an attractive alternative to synthetically equivalent methods such as the intramolecular Schmidt reaction.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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