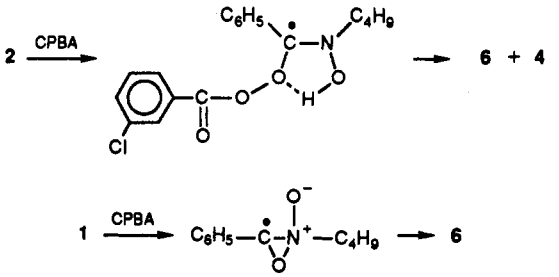
of PBN or substituted PBN present the aminoxyl yield is in the range of 0.05–7.8%. PBN in benzene appears to give the highest yield. In acetonitrile the concentration of **5** exceeds **6** (except for *p*-BrPBN) whereas in benzene the reverse is true. When water is added to acetonitrile the substituted PBN's are less soluble. However, the acyl aminoxyl **6** is formed in 1:1 acetonitrile and water, e.g., for R = H, *p*-Br, a^N = 8.25 and 8.09 G, respectively. When samples of PBN and *m*-chloroperbenzoic acid are mixed in the cold (200 K) no aminoxyl radical reaction is found. The first EPR signal is produced when the temperature is increased to 263 K. Maximum intensity is reached at 313 K for **5** and 293 K for **6**. The greater sensitivity of **6** to heat is indicated by the complete disappearance of its signal by 320 K. The formation of **5** and **6** does not depend on light (all experiments were run in the dark) or air (all experiments were run under nitrogen). The presence of oxygen broadens the lines, but the same mixture of **5** and **6** appears to be present. A 0.02 M concentration of PBN was able to detect the presence of as little as 0.001% (5.79×10^{-5} M) CPBA in acetonitrile. With α-D PBN (C_6H_5C-$DN(O)C_4H_9$) initial formation of **5** and **6** is slightly slower than for normal PBN. The observed isotope effects on the rate of formation of **5** and **6** were 2.56 and 2.45, respectively.

The precise mechanism of aminoxyl radical production in the reaction of *m*-chloroperbenzoic acid with *C*-phenyl-*N*-*tert*-butylnitrone is still not clear. Evidence indicates that a "molecule-induced" free-radical reaction not greatly affected by polar substituents or polarity of solvent is occurring. A small isotope effect with α-D PBN indicates bond breaking of the benzylic carbon–hydrogen bond is involved prior to or in the rate-determining step. No evidence for the intermediacy of **3** is found although small amounts of this aminoxyl may be undetected in a mixture spectrum. Thus, a combination of concerted and intermolecular redox reactions is indicated. If there is any significance to the fact that the estimated isotope effects for the initial formation of **5** and **6** are the same it would seem that the production of these aminoxyls may depend on the same benzylic carbon–hydrogen bond-breaking step. The reactions which accommodate this possibility are as follows:



Further investigations are underway since it is important to know whether the reaction between acyl hydroperoxides (peracids) and nitrones is general. This molecular reaction may have significant impact on the use of spin traps in biological systems.

Acknowledgment. The authors recognize the financial support for a studentship for C.-R.L. provided by the National Taiwan University and facilitated by Prof. T.-I. Ho. Assistance in this work from Dr. Y. Kotake is also gratefully acknowledged.

Supplementary Material Available: Experimental details (1 page). Ordering information is given on any current masthead page.

$TiCl_4$-Mediated Reactions of Alkyl Azides with Cyclic Ketones

Jeffrey Aubé,* Gregory L. Milligan, and Craig J. Mossman

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045-2506

Received January 3, 1992

Summary: The reaction of cyclic ketones with alkyl azides to afford N-alkyl lactams can be effected by $TiCl_4$.

The Schmidt reaction of ketones with hydrazoic acid is an important method for the preparation of N-unsubstituted lactams.[1] Since alkyl azides do not react under standard Schmidt conditions,[2] a variety of other methods have been reported for the formal insertion of a primary amine adjacent to a ketone. These include the reactions of ketones with *N*-[(arylsulfonyl)oxy]amines,[3] the reactions of substituted amines with cyclopropanones (limited to β-lactam synthesis)[4] and multistep methods involving oxaziridine[5] or nitrone[6] intermediates. Clearly, given the ready availability of a wide variety of alkyl azides, the extension of the Schmidt reaction to those reactants would be a welcome development. We recently reported that the *intramolecular* Schmidt reaction of keto azides occurs readily under protic or Lewis acid conditions to give bicyclic lactams.[7] In this paper, we consider the problem

(1) (a) Wolff, H. *Org. React.* **1946**, *3*, 307–336. (b) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley and Sons: New York, 1963; Vol. 1, pp 457–591. (c) Uyeo, S. *Pure Appl. Chem.* **1963**, *7*, 269–283. (d) Abramovich, R. A.; Kyba, E. P. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 221–329. (e) Banthorpe, D. V. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 397–440. (f) Kyba, E. P. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: Orlando, 1984; pp 2–34.

(2) (a) Briggs, L. H.; De Ath, G. C.; Ellis, S. R. *J. Chem. Soc.* **1942**, 61–63. (b) Smith, P. A. S. *J. Am. Chem. Soc.* **1948**, *70*, 320–323. (c) For a few examples of benzamides obtained by the reaction of benzaldehyde with alkyl azides, see: Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–954. These authors report that the reaction fails with ketones.[11]

(3) (a) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1989**, *30*, 4207–4210. (b) Hoffman, R. V.; Salvador, J. M. *Tetrahedron Lett.* **1991**, *32*, 2429–2432. (c) Hoffman, R. V. *Tetrahedron* **1991**, *47*, 1109–1135.

(4) (a) Wasserman, H. H.; Adickes, H. W.; Espejo de Ochoa, O. *J. Am. Chem. Soc.* **1971**, *93*, 5586–5587. (b) Wasserman, H. H.; Glazer, E. A.; Hearn, M. J. *Tetrahedron Lett.* **1973**, 4855–4858.

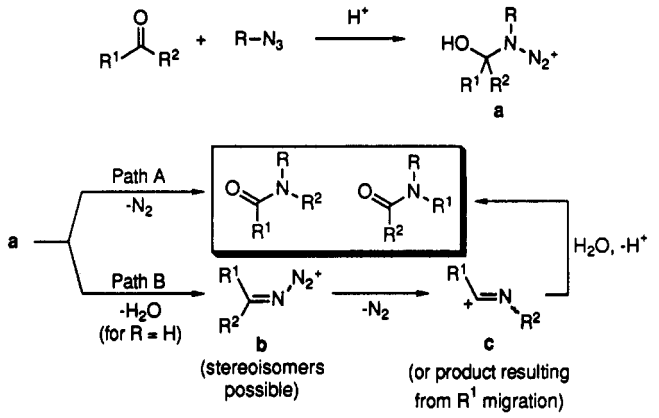
(5) For a review, see: Haddadin, M. J.; Freeman, J. P. In *Small Ring Heterocycles*; Hassner, A., Ed.; John Wiley and Sons: New York, 1985; Vol. 42, Part 3, pp 283–350.

(6) (a) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* **1971**, 945–946. (b) Jeffs, P. W.; Molina, G. *J. Chem. Soc., Chem. Commun.* **1973**, 3–4. (c) Barton, D. H. R.; Day, M. J.; Hesse, R. H.; Pechet, M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1764–1767. (d) Prager, R. H.; Raner, K. D.; Ward, A. D. *Aus. J. Chem.* **1984**, *37*, 381–387.

(7) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966.

0022-3263/92/1957-1635$03.00/0

Scheme I



of carrying out this reaction without the benefit of intramolecularity.

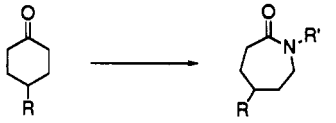
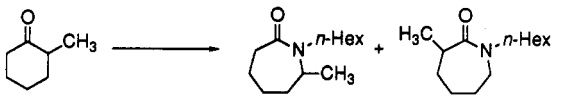
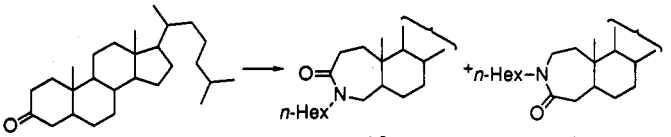
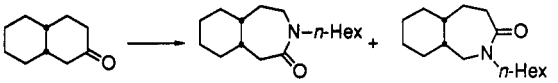
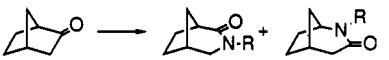
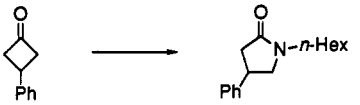
Although a number of reagents could trigger the intramolecular Schmidt reaction, $TiCl_4$ proved to be particularly effective.[7] Indeed, all attempts to carry out the intermolecular reaction of *n*-hexyl azide or benzyl azide with cyclohexanone under protic or $BF_3{\cdot}OEt_2$ catalysis met with failure. However, excellent results could be obtained using $TiCl_4$ to activate the ketone; the reaction of cyclohexanone with *n*-hexyl azide is typical of the conversions reported in this communication. Thus, 2.5 equiv of $TiCl_4$ was added to a mixture of cyclohexanone and 2.0 equiv of *n*-hexyl azide at 0 °C in CH_2Cl_2; an exothermic reaction and gas evolution ensued. After the reaction was allowed to warm to rt and stirred ca. 16 h, a standard $NaHCO_3$ workup followed by column chromatography gave *N*-hexyl caprolactam in 80% yield. In experiments using equimolar amounts of ketone and azide, aldol-type self-condensation of cyclohexanone led to substantial amounts of byproduct; this undesired reaction pathway could be minimized using the excess of azide described above. These conditions were used to survey the reactions of other ketones as summarized in Table I. Details for the preparation of the alkyl azides used and the general experimental procedure are provided in the supplementary material.

Best results were obtained with unhindered cyclohexanones, although the single cyclobutanone examined gave an acceptable yield of product. We have been unable so far to obtain reasonable yields of ring-expansion product from simple cyclopentanones or 2-methylcyclohexanone, possibly due to steric hindrance, competing enolization, or both. We do note that the major product obtained in the latter reaction resulted from the migration of the more substituted carbon, consonant with results obtained using hydrazoic acid (entry 7).[1] Likewise, the marginally major product obtained from reactions of alkyl azides with norcamphor was **19a** or **b**, again consistent with the behavior of hydrazoic acid in this system (entries 12 and 13).[8] As expected, unsymmetrical ketones containing substituents nonadjacent to the reacting ketone gave equimolar mixtures of isomeric lactams.

Several mechanistic pathways have been proposed for the Schmidt reaction (Scheme I), each beginning with the addition of azide to activated ketone affording intermediate a (R = H for the classical Schmidt reaction). Most texts and reviews invoke the multistep process summarized as path B: initial dehydration to give iminodiazonium ion b, rearrangement with concomitant loss of nitrogen yielding c, and finally rehydration and tautomerization to lead to the amide products.[1b] This route has been favored

(8) Krow, G. R. *Tetrahedron* 1981, *37*, 2697–2724.

Table I. Reactions of Ketones with Alkyl Azides

entry	ketone	azide	product(s)[a]	yield (%) (isomer ratio)
				
1	1, R = H	*n*-HexN3	**2a**, R = H, R' = *n*-Hex[b]	80
2	1	BnN3	**2b**, R = H, R' = Bn	88
3	3, R = *t*-Bu	*n*-HexN3	**4a**, R = *t*-Bu, R' = *n*-Hex	63
4	3	BnN3	**4b**, R = *t*-Bu, R' = Bn	65
5	5, R = Ph	*n*-HexN3	**6a**, R = Ph, R' = *n*-Hex	48
6	5	BnN3	**6b**, R = Ph, R' = Bn	70
				
	7		**8** **9**	
7	7	*n*-HexN3	**8** + **9**	5-19 (**8** : **9** = 1.7 : 1)
				
	10		**11**	
8	10	*n*-HexN3	**11a**, R = *n*-Hex	100
9	10	BnN3	**11b**, R = Bn	98
				
	12		**13** **14**	
10	12	*n*-HexN3	**13** + **14**	99 (**13** : **14** = ca. 1:1)
				
	15		**16** **17**	
11	15	*n*-HexN3	**16** + **17**	50 (**16** : **17** = ca. 1:1)
				
	18		**19** **20**	
12	18	*n*-HexN3	**19a** + **20a**, R = *n*-Hex	40 (**19a** : **20a** = ca. 5 : 1)
13	18	BnN3	**19b** + **20b**, R = Bn	46 (**19b** : **20b** = ca. 2 : 1)
				
	21		**22**	
14	21	*n*-HexN3	**22**[c]	<5
				
	23		**24**	
15	23	*n*-HexN3	**24**	51

[a] All new products gave satisfactory spectral (^1H and ^{13}C, IR, MS) and HRMS or CHN data (see supplementary material). [b] Oliveros, E.; Rivière, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3*, 739–753. [c] Murahashi, S.-I.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* **1986**, *108*, 7846–7847.

mainly because of the observation that tetrazoles are common byproducts of the Schmidt reaction (resulting from the reaction of c with another molecule of hydrazoic acid), but also because azides did not react under conditions similar to those employing hydrazoic acid.[2] Thus, it was hypothesized that path B had to be operative because the formation of b was not possible when R ≠ H. Reactions in which tetrazoles are not observed may be explained by invoking path A; for example, regiochemical differences,[8,10] the dependence of products obtained under conditions of varying acid strength,[9] and the obtention of amides from reactions of alkyl azides with benzaldehyde but not with various ketones[2c,11] have been explained by invoking changes in mechanism. Our previous paper[7] and the present disclosure show unambiguously that intermediates similar to a (R = alkyl) can directly rearrange via path A to the corresponding amide under appropriate conditions.

In conclusion, we have shown that some ketones undergo $TiCl_4$-catalyzed Schmidt reactions with alkyl azides to give N-substituted lactams in synthetically useful yields. Furthermore, we have demonstrated that, in some cases, the Schmidt reaction of simple ketones can proceed by direct rearrangement of an azidohydrin intermediate.

Acknowledgment. This work was supported by the National Institutes of Health. J.A. acknowledges an Eli Lilly Granteeship (1989–1991). C.J.M. is the recipient of a National Institutes of Health predoctoral fellowship.

Supplementary Material Available: Representative experimental procedures for preparation of azides and rearrangement reactions, spectral data, and ^1H and ^{13}C NMR spectra (51 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) (a) Fikes, L. E.; Shechter, H. *Tetrahedron Lett.* **1976**, 2525–2528. (b) Fikes, L. E.; Shechter, H. *J. Org. Chem.* **1979**, *44*, 741.

(10) Di Maio, G.; Permutti, V. *Tetrahedron* **1966**, *22*, 2059–2067.

(11) Several papers describing rearrangements arising from Schmidt-type intermediates in the reactions of ketones and alkyl azides were published: (a) Boyer, J. H.; Morgan, L. R., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 2020–2021. (b) Boyer, J. H.; Morgan, L. R., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 3369–3372. (c) Boyer, J. H.; Morgan, L. R., Jr. *J. Org. Chem.* **1959**, *24*, 561–562. However, see: (d) Boyer, J. H.; Krueger, W. E.; Modler, R. *J. Org. Chem.* **1969**, *34*, 1987–1989 for a cautionary note. We thank Dr. Evan Kyba for bringing this reference to our attention.

A Highly Convergent Asymmetric Synthesis of the C(19)–C(27) Segment of Rifamycin S: An Application of Enantiodifferentiating Acetalization with Menthone

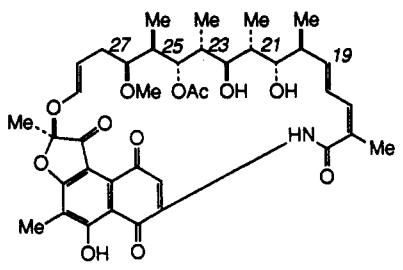
Toshiro Harada,* Yasuhiro Kagamihara, Sachi Tanaka, Kazuhiko Sakamoto, and Akira Oku*

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto, 606, Japan

Received December 30, 1991

Summary: An enantiodifferentiating transformation of 1,3-alkanediols by kinetic acetalization with menthone is developed and used in a highly convergent asymmetric synthesis of the C(19)–C(27) segment of the ansa chain of rifamycin S.

Rifamycin S (1) is a well-known member of the ansamycin antibiotic group.[1] Following the landmark total synthesis reported by Kishi and co-workers in 1980,[2] much effort has been directed toward the synthesis of the stereochemically rich ansa chain and, thereby, toward the development of effective means of controlling contiguous stereogenic centers.[3,4] We report here a highly convergent asymmetric synthesis of the C(19)–C(27) segment **13** that utilizes two-direction chain synthesis[5] (Scheme I). Crucial terminus differentiation of σ-symmetric intermediate **8** was enantioselectively achieved by using a novel, kinetic acetalization with *d*-menthone.



1

The symmetric sequence of seven contiguous stereogenic centers in the C(19)–C(27) segment was constructed efficiently in three steps from dialkenyl carbinol derivative **2**. Double hydroboration of **2** with 9-BBN furnished diol **3** with high stereoselectivity (anti,anti:anti,syn = 13:1).[6] Swern oxidation[7] of **3** afforded the corresponding di-

(1) (a) Rinehart, K. L., Jr.; Shield, L. S. *In Progress in the Chemistry of Organic Natural Products*; Hertz, W., Grisebach, H., Kirby, G. M., Eds.; Springer-Verlag: New York, 1976; Vol. 33, p 231. (b) Wehrli, W. *Top. Curr. Chem.* **1977**, *72*, 22. (c) Brufani, M. *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Wiley: New York, 1977; Vol. 1, p 91.

(2) (a) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi, Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (b) Kishi, Y. *Pure Appl. Chem.* **1981**, *53*, 1163. (c) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.

(3) (a) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, 335. (b) Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749. (c) Masamune, S.; Imperiali, B.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5528. (d) Nakata, M.; Enari, H.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3283. (e) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (f) Fraser-Reid, B.; Magdzinski, L.; Molino, B. *Ibid.* **1984**, *106*, 731. (g) Hanessian, S.; Pougney, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289. (h) Rama Rao, A. V.; Yadav, J. S.; Vidyasagar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 55. (i) Tschamber, T.; Waespe-Sarcevic, N.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 621. (j) Danishefsky, S. J.; Myles, D. C.; Harvey, D. F. *J. Am. Chem. Soc.* **1987**, *109*, 862. (k) Ziegler, F. E.; Cain, W. T.; Kneisley, A.; Stirchak, E. P.; Wester, R. T. *Ibid.* **1988**, *110*, 5442. (l) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron. Lett.* **1989**, *30*, 1293. (m) Roush, W. R.; Palkowitz, A. D.; Anodo, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(4) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

(5) (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563. (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583.

(6) Harada, T.; Matsuda, Y.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21.

0022-3263/92/1957-1637$03.00/0