Regioselective Functionalization. 7.[1] Unexpected Preferences for Bridgehead Migration in Schmidt Rearrangement Syntheses of Novel 2,6-Diazabicyclo[3.2.*x*]alkan-3-ones ($x = 1-3$)

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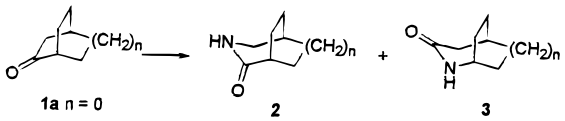
Regioselective syntheses of 2,6-diazabicyclo[3.2.*x*]alkan-3-ones ($x = 1-3$) **34** by insertion of nitrogen next to the bridgehead (BH) of 2-azabicyclo[2.2.*x*]alkanones **32** with hydroxylamine-*O*-sulfonic acid are described. The ketones **32** under Schmidt reaction conditions (HN_3/H_2SO_4) afford major amounts of BH migrated lactams **34** but also, when $x = 2$ or 3, the methylene (M) migrated lactams, 3,6-diazabicycl[3.2.*x*]alkan-2-ones **37**. The present N-insertion reactions favoring BH migration with azabicyclic ketones contrast markedly with reactions of the related carbocycles **1a,b**, which give only methylene migrated lactams **2a,b** with HN_3/H_2SO_4. Schmidt reactions of 3-*anti*/*syn*-methyl- and 3-*anti*-phenyl-2-azabicyclo[2.2.2]octan-5-ones **17**, **20**, and **23** (64:36 ± 9, BH:M) follow the reaction pattern of the parent ketone **14**, but the 3-*syn*-phenyl ketone **26** gives major (65%) methylene migration. The results offer insights into the BH vs M migration dichotomy for the Beckmann and Schmidt reactions of bridged bicyclic ketones.

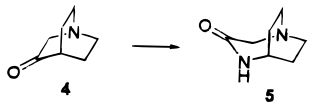
Introduction

In the formation of bridged bicyclic lactams from ketones, it has been generalized that the regiochemistry of nitrogen insertion upon Beckmann or Schmidt rearrangements is opposite.[2] For example, the Schmidt rearrangement of ketones **1a,b** (Eq 1) affords solely the



1a n = 0 **1b** n = 1 **2** **3**

methylene migrated lactams **2a,b**, whereas Beckmann rearrangements of the oximes of **1a,b** generally afford mainly bridgehead migrated lactams **3a,b**.[3−5] An exception to this generalization is the observation that quinuclidin-3-one **4** (Eq 2) affords bridgehead migrated



4 **5**

lactam **5** under both Schmidt and Beckmann conditions in 50% and 28% yields, respectively. The 1-amino group, or its protonated conjugate acid, *eliminated* the migratory ability of the C-2 methylene.[6−8] Because of the importance of heteroatom insertion reactions as synthetic methods,[9,10] there is a need to better understand those factors that control the regioselectivity of such reactions.

Recently, in an investigation of the Schmidt and Beckmann rearrangements of 7-*syn*- and 7-*anti*-substituted norbornan-2-ones **6** (Eq 3) we observed significant

(1) For the previous paper in this series, see: Krow, G. R.; Cheung, O. H.; Hu, Z.; Lee, Y. B. *J. Org. Chem.* **1996**, *61*, 5574.

(2) This comment has appeared in a number of reviews. (a) Krow, G. R. *Tetrahedron* **1981**, *37*, 1283. (b) Benz, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, p 404. (c) Gawley, R. *Organic Reactions* **1988**, *35*, 1−420. (d) For another review of the Schmidt reaction, see: Wolff, H. *Org. React.* **1946**, *3*, 307.

(3) For Beckmann and Schmidt reactions of ketone **1a** ($n = 1$), see: ref 1 and (a) Elderfield, R. C.; Losin, E. T. *J. Org. Chem.* **1961**, *26*. 1703. (b) Potti, B. D.; Nobles, W. L. *J. Pharm. Sci.* **1968**, *57*, 1785.

(4) For Beckmann and Schmidt reactions of ketone **1b** ($n = 2$), see: (a) Reinesch, G.; Bara, H.; Klave, H. *Chem. Ber.* **1966**, *99*, 856. The Schmidt reaction gave a 56% yield of methylene migrated lactam **2b**, whereas the Beckmann reaction using polyphosphoric acid on the derived oxime of ketone **1b** gave bridgehead migrated lactam **3b** in 57% yield. (b) Beckmann reaction with benzenesulfonyl chloride/NaOH (25% yield of lactam **3b**): Hall, H. K. *J. Am. Chem. Soc.* **1960**, *82*, 1209. (c) Beckmann rearrangement with TosCl/pyridine (84% of lactam **3b**): Morita, K. I.; Suzuki, Z. *J. Org. Chem.* **1966**, *31*, 233.

(5) (a) For the Schmidt reaction of dibenzo[2.2.2]octan-2-one (a single lactam product via methylene insertion in 10% yield), see: Blaser, R.; Imfeld, P.; Schindler, O. *Helv. Chim. Acta* **1969**, *52*, 2197. (b) The Beckmann reaction of the corresponding dibenzo[2.2.2]octan-2-one oxime afforded solely cleavage product. Wawzonek, S.; Hallum, J. V. *J. Org. Chem.* **1959**, *24*, 364.

(6) Mikhlina, E. E.; Vorebleva, V. Y.; Shedchenko, V. I.; Rubtsov, M. V. *Zh. Org. Khim.* **1965**, *1*, 1336; *Chem. Abstr.* **1965**, *63*, 13257.

(7) Paquette and Scott have observed that Schmidt reactions of fused ring α-aminoketones give only distal methylene migration in moderate (44−65%) yields: Paquette, L. A.; Scott, M. *J. Org. Chem.* **1968**, *33*, 2379. In a competition among the β-methylene groups of ketones **9** and **10**, preferential migration of the methylene carbon distal from the carbon atom at the bridge fusion is observed.

9 **10**

(8) Ring size and reaction conditions are important. (a) For the Schmidt reaction of bicyclo[3.2.1]octan-2-one, a single lactam was reported to be formed via methylene insertion in 40% yield: Arya, V. P.; Shenoy, S. J. *Indian J. Chem.* **1972**, *10*, 815. Repetition of this work resulted in isolation of a 62:38 mixture of methylene:bridgehead migrated lactams in 50% yield: Krow, G. R.; Szczepanski, S. *J. Org. Chem.* **1982**, *47*, 1153. Lactam ratios in the Beckmann rearrangement were highly dependent upon reaction conditions and ranged from 95:5 to 31:69 bridgehead:methylene migration products. (b) For HOSA and camphor, see: Krow, G. R.; Szczepanski, S. *Tetrahedron*, **1980**, *56*, 499.

(9) For recent reviews of nitrogen insertions, see: ref 2 and (a) Shioiri, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 6, pp 798, 820. (b) For a recent discussion of the mechanism of the Schmidt reaction, see: Sprecher, M.; Kost, D. *J. Am. Chem. Soc.* **1994**, *116*, 1016.

(10) For a recent review of oxygen insertion reactions, see: Krow, G. R. *Org. React.* **1994**, *43*, 251.

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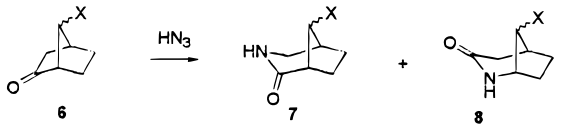
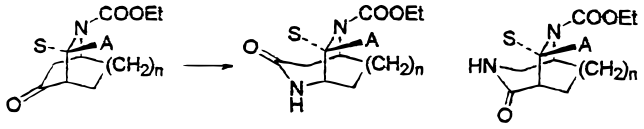


effects of β-halide, -alkoxy, -methoxycarbonyl and -*O*-tosyl substituents on the course of these reactions.[1] Although Schmidt reactions of the parent norbornan-2-one (**1a**) gave solely methylene migrated lactam **2a**, the functionalized ketones **6**, except for the *anti*-7-bromoketone, gave mixtures of lactams **7** and **8** formed by competing methylene and bridgehead migration. Both Schmidt (48−78%) and Beckmann (36−77%) reactions of ketones **6** were accompanied by cleavage products in the significant amounts indicated in the parentheses.

As part of an effort to clarify the role of neighboring nitrogen substitution on the course of heteroatom insertions and to develop regioselective synthetic routes to bridged diazaheterocycles,[11] we have prepared 2-azabicyclo[2.2.1]alkanone **11** (n = 0) and 2-azabicyclo[2.2.2]-alkanone **14** (n = 1), related to the carbocycles **1a** and **1b**, respectively. The 3-*anti*/*syn*-methyl- and 3-*anti*/*syn*-phenyl-2-azabicyclo{2.2.2]octan-5-ones **17**, **20**, **23**, and **26** were prepared to determine if steric effects near the carbonyl group influenced the course of nitrogen insertions. To determine the effect of a larger tether on the regiochemistry of nitrogen insertions, the ketone **29** also was prepared. The nitrogen atom in all of these azabicyclic ketones is β to both of the potentially migrating methine and methylene groups attached to the carbonyl.[12] We here report the influence of the β-*N*-ethoxycarbonyl substituent on the course of hydroxylamine-*O*-sulfonic acid (HOSA) Beckmann and hydrazoic acid Schmidt rearrangements of these selected bicyclic *N*-acylaminoketones.

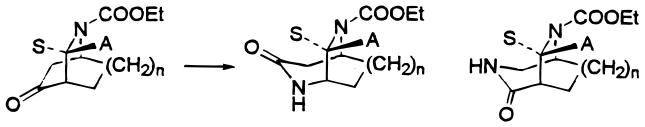


n = 0 **11** A = S = H	**12**	**13**
n = 1 **14** A = S = H	**15**	**16**
17 A = Me, S = H	**18**	**19**
20 A = H, S = Me	**21**	**22**
23 A = Ph, S = H	**24**	**25**
26 A = H, S = Ph	**27**	**28**
n = 2 **29** A = S = H	**30**	**31**

Results

HOSA and Schmidt Reactions. The ketones in Table 1 were prepared by our previously described regioselective ketofunctionalization method from known azabicycloalkenes (see Experimental Section).[13] Beckmann rearrangements of the ketones were performed in the presence of HOSA in refluxing acetic acid or formic acid to afford lactams.[1] Schmidt reactions were carried out with sodium azide in concentrated sulfuric acid at 0−25 °C. No attempts were made to isolate cleavage products. Upon workup, the crude lactam mixtures were subjected to NMR analysis; lactam ratios were determined by comparison of integrated intensities for appropriate nonoverlapping proton resonances. The structures in which the inserted nitrogen is adjacent to the bridgehead can be readily identified by observation of the two protons next to the lactam carbonyl group. These appear at δ 2.7−3.23 and δ 2.45−2.65 and are characterized by large 15−19 Hz vicinal coupling constants. A broad peak at δ 2.62−3.20 for the bridgehead proton characterizes the structures with the lactam carbonyl adjacent to the bridgehead. The reactions of the bicyclic ketones with HOSA, shown in Table 1, indicate that only bridgehead migrated lactams were obtained in all cases studied. Under conditions of the Schmidt reaction, also shown in Table 1, mixtures of lactams were observed except for ketone **11**, which gave in low yield only lactam **12** derived by bridgehead migration.

Table 1. Beckmann and Schmidt Reactions of *N*-Ethoxycarbonylazabicyclo[2.2.1], [2.2.2], and [3.2.2]-alkanones



entry	ketone	n	A (*anti*)	S (*syn*)	lactams yield,[a] %	type of lactam % BH:% M[b]
			HOSA[c] Beckmann Reaction			
1	**11**	0	H	H	38	100 (**12**):0 (**13**)
2	**14**	1	H	H	79	100 (**15**):0 (**16**)
3	**17**	1	Me	H	93	100 (**18**):0 (**19**)
4	**20**	1	H	Me	73	100 (**21**):0 (**22**)
5	**23**	1	Ph	H	76	100 (**24**):0 (**25**)
6	**26**	1	H	Ph	90	100 (**27**):0 (**28**)
7	**29**	2	H	H	99	100 (**30**):0 (**31**)
			Schmidt Reaction[d]			
8	**11**	0	H	H	38	100 (**12**):0 (**13**)
9	**14**	1	H	H	62	73 (**15**):27 (**16**)
10	**17**	1	Me	H	43	70 (**18**):30 (**19**)
11	**20**	1	H	Me	72	55 (**21**):45 (**22**)
12	**23**	1	Ph	H	50	73 (**24**):27 (**25**)
13	**26**	1	H	Ph	97	35 (**27**):65 (**28**)
14	**29**	2	H	H	82	67 (**30**):33 (**31**)

[a] Yields of lactam mixtures are after chromatographic separation except for entries 13 and 14. [b] BH = lactam formed by bridgehead migration. M = lactam formed by methylene migration. Lactam ratios of crude mixtures were determined using comparisons of the ^{1}H NMR peaks adjacent to carbonyl or NH peaks and were within ±9 of the isolated values. [c] HOSA = hydroxylamine-*O*-sulfonic acid in refluxing formic or acetic acid. [d] HN_3/H_2SO_4 at 0−25 °C.

Discussion

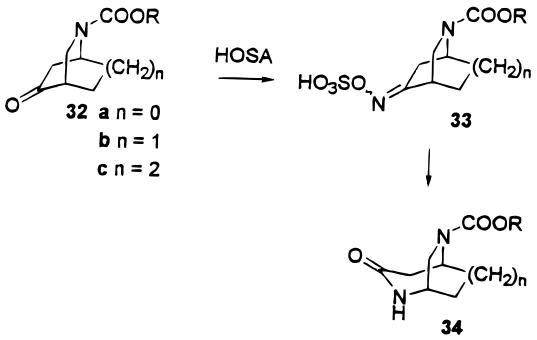
HOSA Reactions. As shown in Table 1, reaction of the strained 2-azabicyclo[2.2.1]heptanone **11** (entry 1) with HOSA gave the bridgehead lactam insertion product **12**. This preference for bridgehead migration correlates with the formation of bridgehead insertion product **3a** from bicyclo[2.2.1]heptan-2-one (**1a**).[1,3] In reference to the

(11) Fray, A. H.; Augeri, D. J.; Kleinman, E. F. *J. Org. Chem.* **1988**, *53*, 896. A synthetic route to 3,6-diazabicyclo[3.2.1]octanes and 3,6-diazabicyclo[3.2.2]nonanes related to lactam structures **13** and **16** has been reported.

(12) For regioselective Schmidt reactions of β-aminoketones in which the nitrogen atom is β to only one of the potentially migrating methylene groups and the group nearest nitrogen uniquely migrates, see: (a) Plostniecks, J. *J. Org. Chem.* **1966**, *31*, 634. (b) Afsah, E. M.; Metwally, M. A.; Khalifa, M. M. *Monatsh. Chem.* **1984**, *115*, 303. (c) Sakakida, Y.; Kumanireng, A. S.; Kawamota, H.; Yokoo, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 478.

(13) Krow, G. R.; Johnson, C. A.; Guare, J. P.; Kubrak, D.; Henz, K. J.; Shaw, D. A.; Szczepanski, S. W.; Carey, J. T. *J. Org. Chem.* **1982**, *47*, 5239.

Scheme 1. HOSA Rearrangements of Ketones 32



low (38%) yield of lactam **12**, we note that the strained 2-azabicyclo[2.2.1]heptan-2-one **11** could not be prepared by Jones oxidation of the precursor alcohol in sulfuric acid because of decomposition of material; thus, reactions of ketone **11** under acidic HOSA or Schmidt conditions were terminated after 1 h.[14]

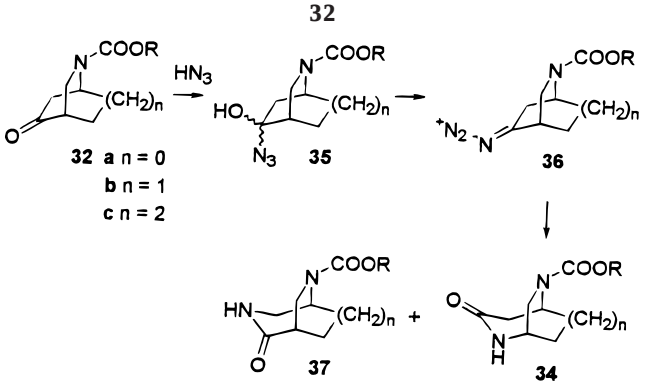
Yields of lactams from HOSA rearrangement of the azabicyclo[2.2.2]octanones **14**, **17**, **20**, **23**, and **26** (entries 2−6) are generally high (73−93%) and are comparable to that observed for the parent bicyclo[2.2.2]octan-2-one **1b** (68%).[4] Independently, a preferential decomposition of the methylene migrated lactam **16** under the forcing acidic conditions has been observed; the methylene migrated lactam **16** has a half-life of about 3.5 h in refluxing 7:1 formic/sulfuric acids.[15] The less strained 2-azabicyclo[3.2.2]nonan-8-one **29** (entry 7) gave bridgehead migrated lactam **30** essentially quantitatively (99% yield).

The reaction outcomes with HOSA and the ability of methylene migrated lactam **16** to survive the reaction conditions are consistent with the mechanism shown in Scheme 1.[1] Following conversion of ketones **32** to oxime-*O*-sulfonic acids **33**, there follows either a regioselective bridgehead rearrangement of the *anti*-isomer of **33** (*O*-sulfonic acid is *anti* to the bridgehead carbon) to give lactam **34** and/or a nonlactam bridgehead cleavage product. Both of these processes are preferred over rearrangement of the isomeric *syn*-oxime-*O*-sulfonic acid isomer of **33**.

Schmidt Reactions. The most striking result in Table 1 (entry 8) is the Schmidt reaction of 2-azabicyclo[2.2.1]-heptanone **11** to give *only bridgehead migrated* lactam **12**. Similarly, a preference for bridgehead migration was observed for Schmidt reaction of 2-azabicyclo[2.2.2]-octanone **14** (entry 9). These results do not correlate with formation of only methylene migrated lactams **2a** and **2b** from the carbocycles bicyclo[2.2.1]heptan-2-one (**1a**) and bicyclo[2.2.2]octan-2-one (**1b)** with sodium azide/sulfuric acid.[1,3,4]

For the Schmidt reaction of ketone **14**, a roughly 2:1 mixture of lactams **15**/**16**, in which bridgehead migration

Scheme 2. Schmidt Rearrangements of Ketones 32



is favored, was observed. The ratios are kinetic in origin, because various mixtures of lactams **15**/**16** were recovered unchanged after 2−12 h at 25 °C in H_2SO_4.

The major difference in product formation between Schmidt reactions of the azabicyclic ketones (entries 9−13) and the related carbocycle, bicyclo[2.2.2]octanone **1b**, is the formation of major amounts of bridgehead migrated lactams from the heterocycles. Bridgehead: methylene migrated lactam ratios of 64:36 ± 9 are observed for Schmidt reactions of ketones **14**, **17**, **20**, and **23** (entries 9−12). For this heterocyclic ring system, the reaction of the 3-*syn*-phenyl ketone **26** (entry 13) to give a 35:65 mixture of lactams **27** and **28** is the only example of methylene migration as the major process.

The less strained azabicyclo[3.2.2]nonanone **29** (entry 14) reacts similarly in the Schmidt reaction to its homolog, azabicyclo[2.2.2]octanone **14** (entry 9). A roughly 7:3 mixture of bridgehead and methylene migrated lactams **30** and **31** is obtained.

Possible mechanisms for the Schmidt rearrangements are shown in Scheme 2. Addition of hydrazoic acid to ketones **32** affords stereoisomeric azidohydrins **35**, which lead to mixtures of *anti*/*syn*-iminodiazonium ions **36**, likely favoring an excess of *anti*-stereoisomers.[1] In the absence of a cleavage process, regioselective migration of ions **36** to give mainly bridgehead migrated lactams **34**, rather than methylene migrated lactams **37**, would occur.[1]

Isolation of regiochemical mixtures during the Schmidt reactions and not from the HOSA reactions of ketones **32b,c** can be attributed to the effects of differing temperatures[14] and leaving groups for the two reactions. The Schmidt reactions, in which the strong nucleofuge nitrogen is the leaving group, were carried out at 0−25 °C. The neighboring electron-withdrawing *β*-*N*-ethoxycarbonyl substituent should destabilize a bridgehead carbocation formed upon cleavage of an *anti*-iminodiazonium ion **36**. Because the propensity for bridgehead cleavage processes is reduced, bridgehead migration products **34** now are formed competively with methylene migration products **37**. This retardation of bridgehead cleavage by the *β*-*N*-ethoxycarbonyl substituent in the heterocycles **32a,b** also accounts for the failure of the Schmidt reaction outcomes for the heterocycles to correlate with their carbocyclic analogues **1a,b**, in which the lactams formed are only methylene migrated ones, **2a,b**. The HOSA reactions, in which the weaker nucleofuge H_2SO_4 is the leaving group, required the temperatures of refluxing acetic or formic acids. Under these conditions, either bridgehead cleavage or migration of the more electron-

(14) A 60% yield of bridgehead migrated lactam **28** was obtained when the oxime of ketone **27** was stirred with PPSE (trimethylsilyl polyphosphate), but only a 23% yield was obtained upon treatment of the same oxime with benzenesulfonyl chloride/sodium hydroxide: Ph.D. Thesis, Szczepanski, S. W., Temple University, 1985.

(15) A 1:1 mixture of lactams **15** and **16**, after 3.5 h at reflux in 7:1 formic acid/sulfuric acid (Beckmann conditions related to entry 2), gave only 66% recovery of a 2:1 mixture of lactams **15** and **16**. This corresponds to 88% recovery of bridgehead migrated lactam **15** and 44% recovery (about 50% loss) of the methylene migrated lactam **16**. The total absence of methylene migrated lactam **16** is inconsistent with its rapid selective hydrolysis during reaction. Also, such a selective hydrolysis does not occur in the selective formation of methylene migrated lactam **2a** from ketone **1a**.

rich methine group dominates over processes involving the less electron-rich methylene group. Additionally, even if small amounts of methylene migrated lactams were formed, they might have been selectively decomposed under the acidic conditions of the reaction (see above).

The isolation of only bridgehead migrated lactam **34a** during the Schmidt reaction of ketone **32a** can be explained by selective bridgehead migration/cleavage reactions of an *anti*-iminodiazonium ion **36a** and/or complete decomposition in H_2SO_4 acid of any strained methylene migrated lactam **37a** that might have formed. It is not apparent why Schmidt reaction of the 3-*syn*-phenyl ketone **26** of Table 1 (entry 13) should favor a slight excess of methylene migration to give lactam **28**. This outcome is kinetically determined, as a 3:7 mixture of lactams **27** and **28** remains unchanged after 2 h in H_2SO_4.

The data in Table 1 do not preclude competitive rearrangement of tetrahedral azidohydrin intermediates **35b** to give lactam mixtures. However, major amounts of methylene migrated lactam **28** might be expected from an azidohydrin rearrangement pathway, so this process cannot be generally dominant for reactions of the heterocyclic ketones of Table 1.[17]

Experimental Section

General Methods. Thin-layer chromatography was performed on precoated plates of silica gel GF 250 microns (Analtech, Inc.). Preparative thin-layer chromatography was performed on silica gel GF 500 or 1000 microns containing a fluorescent indicator (Analtech, Inc.). Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh). Melting points are uncorrected. Solvents were removed under reduced pressure. ^{1}H NMR spectra were recorded at 100, 300, or 500 MHz, and ^{13}C NMR at 75 MHz in $CDCl_3$ solvent. Ketones **11**, **14**, **17**, **20**, **23**, **26**, and **29** were prepared by a previously described route from known alkenes;[13,18,19] the 3-*anti* stereochemical designation places the 3-substituent away from the carbonyl bridge. Lactam ratios of crude mixtures were determined by comparison of the integrated intensities of the resonances for the protons adjacent to carbonyl or the NH peaks. Exact mass measurements were taken on an RMH-2 Hitachi Perkin-Elmer mass spectrometer at the University of Pennsylvania Mass Spectrometer Center.

General Procedure for the Beckmann Reactions.[1] A mixture of the ketone (0.2−1.3 mmol) and excess hydroxylamine-*O*-sulfonic acid (25−50% excess) in 97% formic or glacial acetic acid (4−10 mL) was heated at reflux for 1−4 h. The reaction mixture was basified with 3 N NaOH and extracted with chloroform or CH_2Cl_2. The combined organic layers were washed with water, dried, and filtered. Removal of solvent afforded a crude mixture, which was analyzed by NMR. The crude lactams could be further purified by chromatography. Cleavage products, which primarily remained in the water layer, were not purified or characterized.

6-Ethoxycarbonyl-2,6-diazabicyclo[3.2.1]octan-3-one (12). From ketone **11** (140 mg, 0.76 mmol) and HOSA (130 mg, 1.15 mmol) in glacial acetic acid (5 mL) after 1 h, there was obtained according to the general procedure 57 mg (38%) of lactam **12**: mp 130−132 °C; ^{1}H NMR δ 7.3 and 7.2 (br, 1H), 4.4 and 4.3 (br, 1H), 4.20 (q, J = 7 Hz, 2H), 3.94 (br, 1H), 3.65 and 3.6 (d, J = 10.8 Hz, 1H), 3.4 (two dd, J = 10.8, 3 Hz, 1H), 2.8 and 2.7 (d, J = 18 Hz), 2.45 (d, J = 18 Hz, 1H), 2.00 (m, 2 H), 1.25 (t, J = 7 Hz, 3H); ^{13}C NMR δ 170.6, 154.2, 60.7, 55.4, 51.6, 50.8, 39.2, 34.4, 14.2; HRMS calcd for $C_9H_{14}N_2O_3$ 198.1005, found 198.0995.

6-Ethoxycarbonyl-2,6-diazabicyclo[3.2.2]nonan-3-one (15). From ketone **14** (250 mg, 1.27 mmol) and HOSA (215 mg, 1.9 mmol) in 97% formic acid (6 mL) after 3 h, there was obtained according to the general procedure 214 mg (79%) of lactam **15** as an oil: ^{1}H NMR δ 7.73 (br, 1H), 4.28 (br, 1H), 4.12 (q, J = 7 Hz, 2H), 3.72 (br, 1H), 3.43 (br, 2H), 2.87 (d, J = 18 Hz, 1H), 2.52 (dd, J = 18, 4 Hz, 1H), 2.03 (br, 2H), 1.87, br, 2H), 1.20 (t, J = 7 Hz, 3H); ^{13}C NMR δ 174.0, 155.3, 60.9, 48.5, 45.5, 44.4, 41.9, 26.0, 25.6, 14.2; HRMS calcd for $C_{10}H_{16}N_2O_3$ 212.1161, found 212.1148.

6-Ethoxycarbonyl-7-*anti*-methyl-2,6-diazabicyclo[3.2.2]-nonan-3-one (18). From ketone **17** (98 mg, 0.46 mmol) and HOSA (63 mg, 0.56 mmol) in 97% formic acid (5 mL) after 3 h, there was obtained according to the general procedure 98 mg (93%) of lactam **18** as an oil: ^{1}H NMR δ 8.74, 8.64 (two d, J = 7 Hz, 1H), 4.32 (br, 1H), 4.28−4.08 (br, 3H), 3.34 (br, 1H), 3.02 (dt, J = 19, 5 Hz, 1H), 2.56 (two d, J = 19 Hz, 1H), 2.30−1.88 (br, 4H), 1.30 (m, 6H); ^{13}C NMR δ 174.4, 155.0, 60.7, 54.0, 50.3, 45.1, 40.9, 25.3, 22.4, 18.3, 14.1; HRMS calcd for $C_{11}H_{18}N_2O_3$ 226.1318, found 226.1309.

6-Ethoxycarbonyl-7-*syn*-methyl-2,6-diazabicyclo[3.2.2]-nonan-3-one (21). From ketone **20** (100 mg, 0.47 mmol) and HOSA (80 mg, 0.71 mmol) in glacial acetic acid (5 mL) after 2.5 h, there was obtained according to the general procedure 72 mg (67%) of lactam **21** as an oil: ^{1}H NMR δ 7.36 (br, 1H), 4.47 (br, 1H), 4.10 (q, J = 7 Hz, 2H), 3.96 (br, 1H), 3.26 (br, 1H), 2.70 (dt, J = 19, 2.7 Hz, 1H), 2.56 (dd, J = 19, 4.5 Hz, 1H), 2.10 (m, 2H), 1.70 (m, 2H), 1.25 (d, J = 7 Hz, 3H), 1.20 (t, J = 7 Hz, 3H); ^{13}C NMR δ 174.2, 155.1, 61.1, 54.8, 50.1, 44.2, 43.5, 26.7, 23.8, 18.6, 14.4; HRMS calcd for $C_{11}H_{18}N_2O_3$ 226.1318, found 226.1329.

6-Ethoxycarbonyl-7-*anti*-phenyl-2,6-diazabicyclo[3.2.2]-nonan-3-one (24). From ketone **23** (320 mg, 1.17 mmol) and HOSA (200 mg, 1.76 mmol) in glacial acetic acid (10 mL) after 2.5 h, there was obtained according to the general procedure 260 mg (76%) of lactam **24** as an oil: ^{1}H NMR 70 °C δ 7.33 (m, 5H), 7.20 (br, 1H), 5.30 (br, 1H), 4.60 (br, 1H), 4.12 (br, 2H), 3.68 (br, 1H), 3.23 (two dd, J = 18, 4 Hz, 1H), 2.65 (dd, J = 18, 2 Hz, 1H), 2.24 (br, 1H), 1.94 (m, 2H), 1.78 (m, 1H), 1.10 (br, 3H); ^{13}C NMR δ 174.2, 155.5, 139.7, 128.0, 126.7, 124.9, 62.3, 61.1, 51.7, 45.1, 41.9, 25.1, 22.1, 14.1; HRMS calcd for $C_{16}H_{20}N_2O_3$ 288.1474, found 288.1454.

6-Ethoxycarbonyl-7-*syn*-phenyl-2,6-diazabicyclo[3.2.2]-nonan-3-one (27). From ketone **26** (67 mg, 0.24 mmol) and HOSA (41 mg, 0.37 mmol) in glacial acetic acid (4 mL) after 3 h, there was obtained according to the general procedure 62 mg (90%) of lactam **27** as an oil: ^{1}H NMR δ 7.42−7.00 (m, 5H), 6.92 (shift varies with concentration, 1H, br), 5.05−4.50 (br, 2H), 4.27−3.77 (br, 2H), 3.48 (br, 1H), 2.91 (d, J = 19 Hz, 1H), 2.59 (dd, J = 19, 3.9 Hz, 1H), 2.15 (br, 1H), 2.07−1.77 (m, 3H), 1.25, 0.83 (two m, 3H); ^{13}C NMR δ 173.3, 155.7, 140.6, 128.0, 126.6, 125.3, 63.1, 60.9, 50.9, 44.6, 42.9, 26.8, 24.9, 13.9; HRMS calcd for $C_{16}H_{20}N_2O_3$ 288.1474, found 288.1476.

10-Ethoxycarbonyl-2,10-diazabicyclo[3.3.2]decan-3-one (30). From ketone **29** (125 mg, 0.59 mmol) and HOSA (100 mg, 0.88 mmol) in glacial acetic acid (5 mL) after 4 h, there was obtained according to the general procedure 132 mg (98%) of lactam **30**: mp 111−112 °C (THF−petroleum ether); ^{1}H NMR δ 7.28 and 7.38 (br, 1H), 4.63 and 4.47 (br, 1H), 4.16 (q, J = 6 Hz, 2H), 4.00 (dd, J = 14, 6 Hz, 1H), 3.75 (br, 1/2 H), 3.65 (d, J = 14 Hz, 1H), 3.55 (d, J = 14 Hz, 1H), 2.83 (d, J = 15, 4 Hz, 1H), 2.63 (dd, J = 15 Hz, 4 Hz, 1H), 2.10−1.62 (br, 6H), 1.28 (t, J = 6 Hz, 3H); ^{13}C NMR δ 175.4, 155.1, 61.1, 51.1, 49.6, 49.1, 38.5, 32.7, 31.3, 18.4, 14.2. Anal. Calcd for

(16) Reduced reactivity might allow *syn*- and *anti*-iminodiazonium ions **36** to interconvert competitively with Schmidt rearrangement and cleavage processes at lower temperatures. This is not likely, however, because preferential reaction of *anti*-iminodiazonium ions **36** in the Schmidt reaction would lead to solely bridgehead migration products **34**, which was not observed.

(17) $TiCl_4$-catalyzed reaction of hexyl azide with norbornanon-2-one (**1a**) results in a 5:1 ratio of lactams resulting from insertion of nitrogen mainly adjacent to methylene and in a minor amount next to bridgehead carbon. This reaction is believed to occur via azidohydrin intermediates, because iminodiazonium ions cannot be formed: Aube, J.; Milligan, G.; Mossman, C. *J. Org. Chem.* **1992**, *57*, 1635.

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$C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.48; H, 8.07; N, 12.37.

General Procedure for the Schmidt Reactions. To a cold (0 °C) solution of the ketone (0.4−3 mmol) in concentrated sulfuric acid (3−7 mL) was added sodium azide (1.1−1.25 equiv). After the mixture was stirred at 0 °C for the indicated time, the reaction was brought to 25 °C, basified with 3 N NaOH, and extracted with chloroform or methylene chloride. The combined organic layers were dried, and solvent was removed to give lactams, which could be further purified by crystallization or chromatography. Cleavage products, which primarily remained in the water layer, were not purified or characterized. Lactam ratios were determined by integration of ^{1}H NMR peaks for the protons next to amide carbonyl resonances, unless otherwise noted.

Schmidt Reaction of *N*-Ethoxycarbonyl-2-azabicyclo-[2.2.1]heptan-5-one (11): Lactam 12. From ketone **11** (290 mg, 1.58 mmol) in H_2SO_4 (5 mL) after 1 h, there was obtained according to the general procedure 247 mg of a crude oil containing a single lactam and olefinic cleavage products. Flash column chromatography afforded 120 mg (38%) of lactam **12**.

Schmidt Reaction of *N*-Ethoxycarbonyl-2-azabicyclo-[2.2.2]octan-5-one (14): 6-Ethoxycarbonyl-2,6-diazabicyclo-[3.2.2]nonan-3-one (15) and 6-Ethoxycarbonyl-3,6-diaza-bicyclo[3.2.2]nonan-2-one (16). From ketone **14** (100 mg, 0.5 mmol) in H_2SO_4 (5 mL) after 2 h at 25 °C, there was obtained according to the general procedure 95 mg (88%) of a 2:1 mixture of lactams **15** and **16**. When the isolated lactam mixture was stirred in H_2SO_4 for two h at 25 °C and reisolated, the ratio of lactams remained 2:1. Flash column chromatography afforded at R_f = 0.47 lactam **15** and at R_f = 0.58 (acetone) a pure sample of lactam **16**: ^{1}H NMR δ 6.45 (br, 1H), 4.59 (br, 1H), 4.17 (q, J = 7 Hz, 2H), 3.84 (d, J = 12 Hz, 1H), 3.56 (br, 2H), 3.26 (d, J = 14 Hz, 1H), 2.78 (br s, 1H), 2.21−1.62 (br, 4H), 1.25 (t, J = 7 Hz, 3H); ^{13}C NMR δ 177.0, 155.2, 61.2, 47.9, 47.0, 44.1, 40.7, 25.1, 21.5, 14.4; HRMS calcd for $C_{10}H_{16}N_2O_3$ 212.1161, found 212.1147.

Schmidt Reaction of *N*-Ethoxycarbonyl-3-*anti*-methyl-2-azabicyclo[2.2.2]octan-5-one (17): 6-Ethoxycarbonyl-7-*anti*-methyl-2,6-diazabicyclo[3.2.2]nonan-3-one (18) and 6-Ethoxycarbonyl-7-*anti*-methyl-3,6-diazabicyclo[3.2.2]-nonan-2-one (19). From ketone (620 mg, 2.93 mmol) in H_2-SO_4 (5 mL) after 3 h at 0 °C, there was obtained according to the general procedure 198 mg of lactam **18** and 88 mg of lactam **19** (286 mg total, 43% yield, 70:30 ratio of lactams **18** and **19**). Flash column chromatography (acetone) afforded a pure sample of lactam **19**: ^{1}H NMR δ 7.20, 6.86 (two br, 1H), 4.46, 4.37 (two br, 1H), 4.33−4.02 (br, 3H), 3.59−3.47 (m, 1H), 3.20, 3.17 (two s, 1H), 2.62 (br, 1H), 2.23−1.87 (m, 4H), 1.32 (m, 6H); ^{13}C NMR δ 177.0, 154.8, 60.8, 49.4, 47.5, 46.9, 46.6, 25.5, 19.3, 17.1, 14.2; HRMS calcd for $C_{11}H_{18}N_2O_3$ 226.1318, found 226.1313.

Schmidt Reaction of *N*-Ethoxycarbonyl-3-*syn*-methyl-2-azabicyclo[2.2.2]octan-5-one (20): 6-Ethoxycarbonyl-7-*syn*-methyl-2,6-diazabicyclo[3.2.2]nonan-3-one (21) and 6-Ethoxycarbonyl-7-*syn*-methyl-3,6-diazabicyclo[3.2.2]-nonan-2-one (22). From ketone **20** (334 mg, 1.58 mmol) in H_2SO_4 (4 mL) after 2.5 h at 0 °C, there was obtained according to the general procedure after column chromatography (50% ether/acetone) 252 mg (72%) of a 55:45 mixture (comparison of NH integrals at δ 7.36 and 6.22) of lactams **21** and **22** . Flash column chromatography (acetone) afforded a pure sample of lactam **22**: ^{1}H NMR δ 6.22 (br, 1H), 4.82, 4.66 (two s, 1H), 4.20 (m, 2H), 3.96 (m, 1H), 3.44 (d, J = 11.5 Hz, 1H), 3.34 (m, 1H), 2.72 (m, 1H), 2.18 (m, 2H), 1.90−1.64 (br, 2H), 1.25 (d, J = 7 Hz, 3H), 1.20 (t, J = 7 Hz, 3H); ^{13}C NMR δ 175.5, 155.2, 61.2, 51.5, 49.6, 47.0, 46.3, 22.8 (two C), 18.9, 14.5; HRMS calcd for $C_{11}H_{18}N_2O_3$ 226.1318, found 226.1337.

Schmidt Reaction of *N*-Ethoxycarbonyl-3-*anti* -phenyl-2-azabicyclo[2.2.2]octan-5-one (23): 6-Ethoxycarbo-nyl-7-*anti*-phenyl-2,6-diazabicyclo[3.2.2]nonan-3-one (24) and 6-Ethoxycarbonyl-7-*anti*-phenyl-3,6-diazabicyclo-[3.2.2]nonan-2-one (25). From ketone **23** (186 mg, 0.68 mmol) in H_2SO_4 (4.6 mL) after 2.5 h at 0 °C and 2.5 h at 25 °C, there was obtained according to the general procedure 140 mg (71%) of a 73:27 mixture of lactams **24** and **25**. Flash column chromatography (acetone) afforded (50% combined yield) pure samples of lactams **24** (68 mg) and **25** (26 mg): ^{1}H NMR of **25** δ 7.32 (m, 5H), 6.6 and 6.31 (br, 1H), 5.35 and 5.28 (s, 1H), 4.76 and 4.65 (br, 1H), 4.10 (br, 2H), 3.73 (m, 1H), 3.27 (dd, J = 12.5, 2 Hz, 1H), 3.04 (br, 1H), 2.19 (br, 1H), 1.90 (m, 2H), 1.54 (m, 1H), 1.24 and 0.96 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 176.5, 155.6, 140.3, 128.3, 126.8, 125.3, 61.5, 57.4, 48.7, 47.8, 29.6, 25.4, 17.3, 14.3; HRMS calcd for $C_{16}H_{20}N_2O_3$ 288.1474, found 288.1483.

Schmidt Reaction of *N*-Ethoxycarbonyl-3-*syn*-phenyl-2-azabicyclo[2.2.2]octan-5-one (26): 6-Ethoxycarbonyl-7-*syn*-phenyl-2,6-diazabicyclo[3.2.2]nonan-3-one (27) and 6-Ethoxycarbonyl-7-*syn*-phenyl-3,6-diazabicyclo[3.2.2]-nonan-2-one (28). From ketone **26** (106 mg, 0.37 mmol) in H_2SO_4 (6 mL) after 3 h at 0 °C, there was obtained according to the general procedure 108 mg (97%) of a 35:65 mixture of lactams **27** and **28**. Crystallization (THF/chloroform) afforded a pure sample of lactam **28**: ^{1}H NMR δ 7.32−7.21 (m, 5H), 5.80 (br, 1H), 5.12−4.83 (br, 2H), 4.20−4.40 (br, 2H), 3.55 (d, J = 18 Hz, 1H), 3.25−3.15 (m, 2H), 2.30−2.22 (m, 2H), 1.94−1.78 (m, 2H), 1.30 and 0.96 (t, J = 7 Hz, 3H); ^{13}C NMR δ 174.3, 155.6, 140.3, 127.9, 125.3, 124.8, 61.2, 59.3, 48.5, 47.4, 46.9, 23.4, 22.7, 14.1; HRMS calcd for $C_{16}H_{20}N_2O_3$ 288.1474, found 288.1480. A 3:7 mixture of lactams **27** and **28** (63 mg) in concentrated H_2SO_4 (1.5 mL) was stirred at 25 °C for 2 h. Customary workup afforded a 3:7 mixture of **27** and **28** (58 mg).

Schmidt Reaction of *N*-Ethoxycarbonyl-6-azabicyclo-[3.2.2]nonan-8-one (29): 10-Ethoxycarbonyl-2,10-diazabi-cyclo[3.2.2]decan-3-one (30) and 10-Ethoxycarbonyl-3,-10-diazabicyclo[3.2.2]decan-2-one (31). From ketone **29** (118 mg, 0.56 mmol) in $CHCl_3$ (10 mL) and H_2SO_4 (0.5 mL) after 2 h at 0 °C and 13 h at 25 °C, there was obtained according to the general procedure 104 mg (83%) of a 67:33 mixture (δ 2.83 vs δ 3.00) of lactams **30** and **31**. Flash column chromatography (acetone) did not separate the lactams, but major peaks could be identified for lactam **31**: ^{1}H NMR δ 7.60 (br s, 1H), 4.67 and 4.45 (m, 1H), 4.15 (t, J = 6 Hz, 2H), 3.87 (q, J = 6 Hz), 3.65−3.55 (m, 2 H), 3.35 (br, 1 H), 3.00 (br, 1 H), 2.20−1.50 (br, 6H), 1.25 (t, J = 6 Hz, 3H); ^{13}C NMR δ 175.9, 154.6, 60.7, 52.4, 50.6, 45.2, 44.0, 43.5, 30.5, 26.7, 13.9; HRMS calcd for $C_{11}H_{18}N_2O_3$ 226.1317, found 226.1309.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for all lactams and experimental procedures for syntheses of ketones **11**, **26**, and **29**. This material is contained in 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.

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