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Regioselective Functionalization. 5.[1] Nitrogen Insertion Reactions of Bicyclo[3.2.1]octan-2-one. Reexamination of Bridgehead vs. Methylene Migratory Preferences

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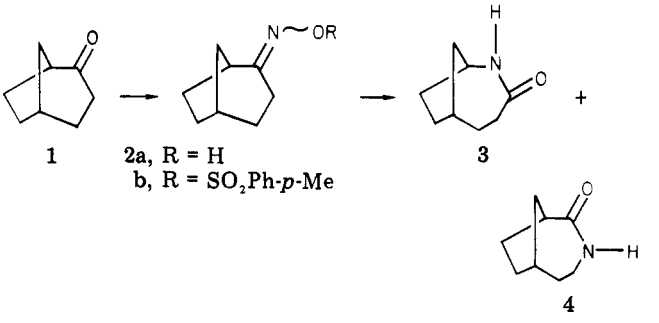
Earlier reports of totally regioselective *bridgehead* nitrogen insertion upon rearrangement of the oxime of bicyclo[3.2.1]octan-2-one (1), by using benzenesulfonyl chloride/sodium hydroxide as a Beckmann catalyst, but completely regioselective *methylene* migration upon reaction of ketone 1 with hydroxylamine hydrogen sulfate in sulfuric acid have been found to be inaccurate. Lactams **3**, formed by bridgehead migration, and **4**, arising from methylene migration, are afforded under both sets of reaction conditions as shown by ^1H and ^{13}C NMR analyses of crude reaction mixtures. Upon examination of a number of nitrogen insertion reaction conditions, the most regioselective formation of bridgehead nitrogen insertion product **3** (95%) can be effected by reacting ketone 1 with hydroxylamine-*O*-sulfonic acid in formic acid. The preference for nitrogen insertion adjacent to methylene was highest for reaction of ketone 1 with hydroxylamine hydrochloride/sulfuric acid which gave a 69% preference for lactam **4**. This exceeds the methylene migratory preference for the Schmidt reaction of ketone 1 with hydrazoic acid, which gives 62% lactam **4**.

Insertion of nitrogen adjacent to the carbonyl functionality of bridged bicyclic ketones formally provides an attractive route to bridged bicyclic nitrogen heterocycles.[2] Central to synthetic efforts in this area, however, is the discovery of synthetic methods whereby there is regiochemical control of heteroatom insertion when the ketone carbonyl is flanked by chemically different groups.[3] We thus were intrigued by reports that with bicyclo[3.2.1]octan-2-one (**1**) as substrate there is a dependency of the preferred regiochemistry of hydroxylamine-mediated nitrogen insertion related to the choice of acid or base catalysis in the Beckmann rearrangement. Specifically, oxime **2a**, of unspecified stereochemistry, has been reported by Hall[4] to rearrange with benzenesulfonyl chloride/sodium hydroxide to a single lactam (**3**, mp 85–87 °C) derived by bridgehead carbon migration. By contrast, a one-pot reaction of ketone **1** with hydroxylamine hydrogen sulfate/sulfuric acid has been reported by Arya and Shenoy[5] to give a second lactam (**4**, mp 106 °C) formed by methylene migration. The synthetic implications of these reports has prompted us to reinvestigate the above and related nitrogen insertion reactions of ketone **1**.

Our results for lactam formation with bicyclo[3.2.1]octan-2-one (**1**) under various sets of experimental conditions



are shown in Table I. The outcome of repetition of the base-catalyzed rearrangement conditions used by Hall[4] for isomerization of the ketoxime **2a**, found to be a 2:1 *E*/*Z* mixture, is shown by entry 1. Examination of the crude reaction mixture by 360-MHz ^1H NMR ($CDCl_3$) indicated a mixture of lactam **3** [δ 3.63 (q, H_1) and lactam **4** [δ 3.33 (m, H_4)], with a slight preference for lactam **3** (57%) formed by bridgehead migration. Distillation of the reaction mixture afforded a white solid (mp 85–87 °C) as reported by Hall;[4] however, this solid proved to be a 60:40

(1) For previous papers in this series, see: (a) Krow, G. R.; Fan, D. M. *J. Org. Chem.* **1974**, *39*, 2674. (b) Krow, G. R.; Johnson, C. *Synthesis* **1979**, 50. (c) Krow, G.; Rodebaugh, R., Grippi, M.; Carmosin, R. *Synth. Commun.* **1972**, *2*, 211. (d) Krow, G. R.; Szczepanski, S. *Tetrahedron Lett.* **1980**, 4593.

(2) For previous papers on alternative synthetic routes to bridged bicyclic amines, see: (a) Krow, G. R.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978**, 1971. (b) Krow, G. R.; Damodaran, K. M.; Fan, D. M.; *rodebaugh*, R.; Gaspari, A.; Nadir, U. *J. Org. Chem.* **1977**, *42*, 2486 and footnote 1 therein.

(3) (a) Krow, G. *Tetrahedron* **1981**, *37*, 1283. (b) *Ibid.* **1981**, *37*, 2697.

(4) Hall, H. K. *J. Am. Chem. Soc.* **1960**, *82*, 1209.

(5) Arya, V. P.; Shenoy, S. J. *Indian J. Chem.* **1972**, *10*, 815.

0022-3263/82/1947-1153$01.25/0

Table I. Lactam Formation Using Bicyclo[3.2.1]octan-2-one (1)

entry	derivative	conditions	lactam ratio[a] % 3	lactam ratio[a] % 4	% yield[b]	ref
1	oxime[c]	$PhSO_2Cl/NaOH$[d]	57	43	48	e
2	oxime	$BF_3/Cl_2CHCHCl_2$[f]	73	27	44	g
3	oxime	PPSE[h]	54	46	46	i
4	oxime tosylate	CH_3COOH/HCl[j]	59	41	60	k
5		$NH_2OSO_2H/HCOOH$[l]	95	5	97	m
6	oxime	$H_2SO_4/HCOOH$[n]	86	14	39	m
7		$NH_2OH\cdot HCl/H_2SO_4$[o]	31	69[p]	53	q
8	oxime	H_2SO_4[r]	50	50	77	
9		$HN_3/H_2SO_4/PPA$[s]	38	62	50	q

[a] Reported isomer ratios (±3%) are those determined by comparing the integrated area for H_1 of lactam **3** at δ 3.63 (q) with that of H_4 of lactam **4** at δ 3.33 (m) at 360 MHz. [b] Yields are TLC isolated. Reactions were run on a 350–1000-mg scale. Except for entry 7, yields are not adjusted for recovered oxime **2a**. [c] Mp 93–94 °C; **2a** was assigned as a 1:2 mixture of *Z/E* oxime stereoisomers on the basis of the ratio of ^{13}C NMR C=N resonances (see the Experimental Section and ref 15). [d] 30 °C/90 min. [e] See ref 4; Hall reported 100% lactam **3** (33% yield) from oxime **2a** (mp 93.5–94.5 °C). [f] 110 °C/12 h. [g] See ref 6. [h] PPSE = trimethylsilyl polyphosphate/25 °C/21 h. [i] See ref 7. [j] 95 °C/20 min. [k] See ref 8. [l] reflux/3 h. [m] See procedure of ref 9. [n] Sulfuric acid (1 molar equiv)/reflux/3 h. [o] 116 °C/30 min. [p] Isomer ratios were determined at 90-MHz by comparing the integrated peak intensity at δ 3.63 for lactam **3** with one-third the integrated peak intensity centered at δ 3.10 for H_4, $H_{4'}$, and H_1 of lactam **4**. [q] See ref 5. Arya and Shenoy reported 100% lactam **4** (36% yield) on using hydroxylamine hydrogen sulfate/sulfuric acid/116 °C/15 min. We recovered 35% oxime **2a** at this reaction time. [r] 116 °C/30 min. [s] PPA = polyphosphoric acid/5–25 °C/19 h.

mixture of lactams **3** and **4** and *not* solely lactam **3** as reported.

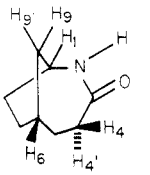
In an attempt to improve the bridgehead regioselectivity of the Beckmann migration with **2a** we first varied the rearrangement catalysts. Conley and Ghosh[6] have reported regioselective lactam formation from bridgehead migration in norbornanone oxime using boron trifluoride catalysis in refluxing tetrachloroethane. Oxime **2a** under these conditions (entry 2) afforded a mixture of lactams **3** and **4** enriched in the bridgehead-migrated lactam **3** (73%). The trimethylsilyl polyphosphate reagent of Imamoto[7] converted oxime **2a** (entry 3) to a mixture of lactams only slightly favoring the bridgehead migrated lactam **3** (54%).

Fleming and Woodward[8] have used acetic acid/hydrochloric acid as a Beckmann rearrangement catalyst with the capability to isomerize oxime tosylates. In the event that one of a pair of diastereoisomeric oxime tosylates rearranges faster than the other, the regioselectivity of the Beckmann rearrangement can be decoupled from the configuration of the starting oxime tosylate mixture, and one lactam regioisomer can be obtained. However, the oxime tosylate **2b** (entry 4) afforded a mixture of lactams **3** and **4** only slightly favoring bridgehead-migrated lactam **3** (59%).

Pure lactam **3** (mp 114–115 °C) was best obtained by Olah's procedure[9] in which ketone **1** in formic acid (entry 5) was caused to react with hydroxylamine-*O*-sulfonic acid. The result was nearly pure lactam **3** (95%), and the trace of lactam **4** was readily removed by a recrystallization from tetrahydrofuran/hexane. The same preference for lactam **3** (86%) resulted when the oxime **2a** (entry 6) was treated with 1 equiv of sulfuric acid in formic acid solvent; however, isolated yields were lower in this case.

In an attempt to prepare pure lactam **4** we repeated (entry 7) the one-pot acid-catalyzed reaction conditions employed by Arya and Shenoy[5] for rearrangement of ketone **1**. We obtained not pure **4** as reported but a 31:69 mixture of lactams **3** and **4**, favoring the latter. Notably, two recrystallizations of the mixture of lactams from 10:1 hexane/tetrahydrofuran did afford white crystals (mp 102.5–103.5 °C) of nearly pure lactam **4**. Although the conditions of entry 7 suggest rearrangement of an oxime **2a** with sulfuric acid, when preformed oxime **2a** was treated with sulfuric acid (entry 8), the slight selectivity for isolation of lactam **4** (50%) was lost.

Arya and Shenoy[5] reported that hydrazoic acid/sulfuric acid treatment of ketone **1** resulted in totally methylene-migrated lactam **4**. Under the same conditions (entry 9) we have found only a 62:38 preference for lactam **4** over lactam **3**. Arya and Shenoy were misled perhaps in the assignment of structure **4** to the mixture of lactams **3** and **4** by an incorrect interpretation of the 90-MHz NMR spectrum of **4**.[10] They assigned a downfield multiplet centered at δ 3.1 to H_1, H_9, and $H_{9'}$ and a multiplet at δ



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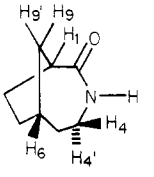


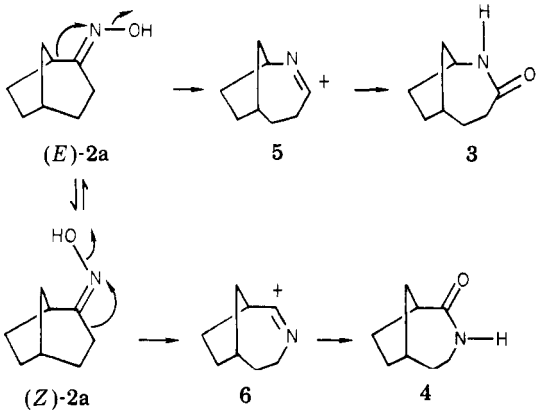
4

2.5 to H_4 and $H_{4'}$. Actually, the multiplet at δ 3.1 represents H_1, H_4, and $H_{4'}$, and the multiplet at 2.5 represents H_6. In a mixture of lactams **3** and **4**, the multiplet at δ 2.5 represents H_4, $H_{4'}$, and H_6 of **3**, as well as H_6 of **4**. The broad multiplet centered at δ 3.10 for H_1, H_4, and $H_{4'}$ of lactam **4** includes in its tail the peak at δ 3.63 for H_1 of lactam **3**. At 360 MHz the mixture of lactams **3** and **4** shows clearly separated peaks at δ 3.63 (H_1) for lactam **3** and at δ 2.92 (H_1), 3.05 ($H_{4'}$), and 3.33 (H_4) for lactam **4**; thus enabling the assignments of lactam ratios in the mixtures of Table I.

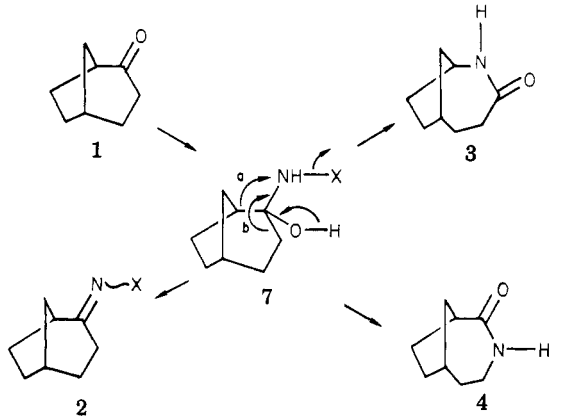
The most probable mechanistic schemes to explain the results of Table I are outlined in Schemes I and II.[3a] In the trigonal mechanism of Scheme I, migration of the bond antiperiplanar to the oxime N–O bond leads from the oxime (*E*)-**2a** to iminium ion **5**, which upon hydration, proton loss, and tautomerization gives lactam **3** formed by bridgehead migration. The corresponding oxime (*Z*)-**2a**

(6) Conley, R. T.; Ghosh, S. "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Wiley: New York, 1971; pp 230–233.
(7) Imamoto, T.; Hideki, Y.; Yokoyama, M. *Tetrahedron Lett.* **1981**, 1803.
(8) Fleming, I.; Woodward, R. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1653.
(9) Olah, G. A.; Fung, A. P. *Synthesis* **1979**, 537.
(10) We also made incorrect assignments of the 90-MHz NMR signals in ref 3a, p 1296. The lactam ratios of Table IV, entries 5 and 7, therein should be changed as noted in Table I herein.

Scheme I. Trigonal Mechanism for the Beckmann Rearrangement of Oxime 2a



Scheme II. Tetrahedral Mechanism for the Beckmann Rearrangement of Ketone 1



leads via iminium ion **6** to the lactam **4** formed by methylene migration. The observed ratio of lactams **3** and **4** would reflect the 2:1 ratio of *E*/*Z* oximes **2a**[11] in the absence of competing Beckmann fragmentation pathways.[3a] Entries 1 and 3 of Table I, for which oxime interconversion is unlikely, and perhaps entry 4, if Beckmann rearrangement were more rapid than oxime isomerization, may fit this mechanistic picture if some preferential fragmentation at the bridgehead carbon is assumed.

Under strongly acidic conditions whereupon *Z*/*E* oximes **2a** can interconvert, if oxime interconversion is rapid relative to rearrangement, the observed ratio of lactams **3** and **4**, in the absence of competing fragmentation pathways for ions **5** and **6**, would reflect the bridgehead vs. methylene carbon migratory preference under the reaction conditions. Entries 2 and 4–8, utilizing acid catalysis, can be accommodated by such a mechanistic scheme, if one assumes preferential migration of the bridgehead carbon for entries 2, 5, and 6, some bridgehead cleavage for entries 4 and 8, and major amounts of bridgehead cleavage for entry 7.

In the tetrahedral mechanism of Scheme II, an intermediate **7**, presumably formed by exo attack[12] of a nucleophilic azide or hydroxylamine species at the carbonyl carbon of ketone **1**, can rearrange in a synchronous manner by either bridgehead migration (bond a) to give lactam **3** or by methylene migration (bond b) to give lactam **4**. The ratio of lactams **3** and **4** would be a function of the relative migratory aptitudes of the bridgehead and methylene carbons. Migratory abilities are known from work on the Schmidt[3a] and Baeyer–Villiger[3b] rearrangements to depend upon the identity and orientation of the leaving group, on the solvent and catalyst, and on electronic variables, torsional strain, and other conformational factors associated with the reactive substrate. Under the conditions of the Schmidt rearrangement, the results of Table I (entry 9) may be accommodated by a Scheme II mechanism,[3a] while under other sets of conditions, whereupon intermediate **7** is capable of formation, the entries 5 and 7 may fit the Scheme II pattern. Of course, a mixture of Scheme I and Scheme II mechanisms is not precluded for entries 5, 7, and 8.

It is not possible for us to refine the mechanisms for the nitrogen insertion methods of Table I further at this time. Hopefully, further empirical studies of other bicyclic ketones will remedy this situation.[1d]

In conclusion, the ring expansion of ketone **1** by insertion of nitrogen, in contradiction of prior reports,[4,5] is complicated by formation of the two isomeric lactams **3** and **4**. These exhibit nearly identical TLC behavior. Our inability to isolate pure *E* or *Z* stereoisomers of oxime **2a** precluded regioslective formation of pure lactams **3** and **4** by stereospecific Beckmann rearrangements of the individual *E* and *Z* oximes.[11] Nevertheless, experimental conditions have been found which enable the isolation of either lactam **3** or **4** in >95% purity following selective crystallization from suitably enriched lactam mixtures.

Experimental Section

General Methods. Proton magnetic resonance spectra were reecorded at 90 MHz on a Perkin-Elmer R-32 spectrometer and at 360 MHz on a Brucker WH-360 spectrometer; ^{13}C-NMR spectra were recorded at 25.16 MHz on a Varian XL-100 spectrometer fitted with a Nicolet 1180 pulse system. Chemical shifts are reported in δ units from an internal standard (tetramethylsilane) in deuteriochloroform. Low-resolution mass spectra were taken with a Perkin-Elmer RMU-6H. IR spectra were taken with a Perkin-Elmer 137 Infracord spectrophotometer. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) analyses were carried out by using precoated silica gel GF plates (Analtech). Flash chromatography[13] was carried out by using Merck silica gel 60 (230–400 mesh). Bicyclo[3.2.1]octan-2-one (**1**) and formic acid (95–97%) were purchased from Aldrich Chemical Co. Hydroxylamine-*O*-sulfonic acid was purchased from Alfa (Ventron). All organic solutions which were dried in the workup were stirred with magnesium sulfate and filtered. Pure samples of 2-azabicyclo[4.2.1]nonan-3-one (**3**) and 3-azabicyclo-[4.2.1]nonan-2-one (**4**) were obtained by crystallization of the mixtures obtained from Table I, entries 5 and 7, respectively, from tetrahydrofuran/hexane. Proton magnetic resonance assignments were made possible with the aid of spin-decoupling experiments; relevant physical properties of lactams **3** and **4** are given below; the symbol (q) refers to a quartet in the ^{1}H NMR spectrum.

2-Azabicyclo[4.2.1]nonan-3-one (3): mp 115–116 °C (lit.[4] mp 85–87 °C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.50 (br s, NH), 3.63 (q, J = 7.5 Hz, H_1), 2.50 (m, H_4, $H_{4'}$, H_6), 2.20 (m, H_8, coupled to H_1 but not H_6), 1.70–1.53 (m, 7 H); ^{13}C NMR δ 177.8 (C=O), 52.4, 41.9, 37.0, 33.6, 33.0, 28.7 (2C); IR (KBr) 3200, 1650 cm^{-1}; mass spectrum, *m*/*e* 139.

3-Azabicyclo[4.2.1]nonan-2-one (4): mp 102.5–103.5 °C (lit.[5] mp 106 °C); ^{1}H NMR (360 MHz) δ 7.73 (br s, NH), 3.33 (m, H_4), 3.05 (m, $H_{4'}$), 2.92 (broadened s, H_1), 2.52 (m, H_6), 2.01 (m, H_8, $H_{9'}$), 1.90–1.53 (m, 6 H); ^{13}C NMR δ 181.51 (C=O), 46.43, 38.98, 37.83, 37.15, 34.29, 29.78, 26.92; IR (KBr) 3230, 1660 cm^{-1}; mass spectrum, *m*/*e* 139.

Bicyclo[3.2.1]octan-2-one Oxime (2a). To a solution of bicyclo[3.2.1]octan-2-one (**1**; 1.0 g, 8.0 mmol) and hydroxylamine

(11) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; p 1008. "The group which migrates is generally the one trans to the hydroxyl, and this is often used as a method of determining the configuration of the oxime."

(12) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1977**, *55*, 841.

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

hydrochloride (0.83 g, 12 mmol) in 20 mL of ethanol was added potassium hydroxide (4.18 g) dissolved in 10 mL of water. The solution was refluxed for 4 h, cooled, neutralized with 20% hydrochloric acid, extracted with chloroform, and dried, and the solvent was removed to yield 1.03 g (93%) of oxime **2a**. Recrystallization from ether gave a solid, mp 93.5–95 °C (lit.[14] mp 93.5–94.5 °C). ^{13}C NMR gave a series of 16 lines corresponding to the *E* and *Z* oxime **2a** configurations. An integrated ratio of approximately 2:1 (65–67% to 33–35%) was found for the C=N peaks at δ 163.8 and 164.2, as measured by using a 10-s pulse delay.[15,16] After three recrystallizations of 475 mg of the oxime **2a** from ether/petroleum ether, 230 mg (48%) of the same 2:1 *E*/*Z* oxime mixture **2a** (mp 93.5–94.5 °C) was obtained. We were unable to find suitable TLC conditions to separate the *E*/*Z* stereoisomers of **2a**.

Nitrogen Insertion Methods of Table I. Entry 1. To a stirred solution of bicyclo[3.2.1]octan-2-one oxime (**2a**; 440 mg, 3.2 mmol) in 44 mL of 5 N sodium hydroxide was added benzene sulfonyl chloride (620 mg, 3.5 mmol) dropwise over 15 min, keeping the temperature below 30 °C.[4] The solution was stirred at this temperature for 90 min, extracted with chloroform, and dried, and the solvent was removed to yield 570 mg of a yellow oil. Preparative TLC (acetone) of this oil yielded 210 mg (48%) of a mixture of lactams **3** and **4** [ratio of 65:35 by ^{13}C NMR (C=O);[16] see Table I]. Distillation [110 °C (0.25 mm)] afforded upon solidification in the condenser a white solid (mp 85–87 °C) shown by ^{1}H NMR (see Table I, footnote *a*) to be a 60:40 mixture of lactams **3** and **4**.[4]

Entry 2. To a solution of bicyclo[3.2.1]octan-2-one oxime (**2a**; 370 mg, 2.7 mmol) in 10 mL of 1,1,2,2-tetrachloroethane was added 1 mL of boron trifluoride etherate.[6] The solution was heated under nitrogen to 105–110 °C for 12 h. The solution was cooled, washed with saturated sodium bicarbonate until neutral, and dried, and the solvent was removed to yield 318 mg of a brown oil. TLC produced 164 mg (44%) of a white solid mixture of lactams **3** and **4** [ratio of 86:14 by ^{13}C NMR (C=O);[16] see Table I].

Entry 3. A benzene solution of trimethylsilyl polyphosphate (PPSE, 6 mL) and bicyclo[3.2.1]octan-2-one oxime (**2a**; 240 mg, 1.7 mmol) was stirred at room temperature under nitrogen for 21 h.[7] Water (10 mL) was added, the solution was extracted with chloroform and dried, and solvent was removed to yield 202 mg of a thick yellow oil. Flash chromatography (acetone) yielded 110 mg of a mixture of lactams **3** and **4** (see Table I for ratio).

Entry 4. A solution of *O*-*p*-toluenesulfonylbicyclo[3.2.1]octan-2-one oxime (**2b**; 345 mg, 1.2 mmol) was dissolved in 10 mL of glacial acetic acid and 5 mL of concentrated hydrochloric acid.[8] The solution was heated to 95–97 °C for 20 min, cooled, made alkaline with 20% potassium hydroxide, and extracted with dichloromethane. Drying and removal of the solvent yielded 98 mg (60%) of a mixture of lactams **3** and **4** [ratio of 63:37 by ^{13}C NMR (C=O);[16] see Table I].

Entry 5. To a stirred solution of bicyclo[3.2.1]octan-2-one (**1**; 600 mg, 4.8 mmol) in 12 mL of formic acid was added hydroxylamine-*O*-sulfonic acid (820 mg, 7.2 mmol).[9] After being stirred for 3 h under reflux, the solution was cooled in an ice bath and made alkaline with 20% sodium hydroxide. The aqueous layer was extracted with chloroform and dried, and the solvent was removed to give 650 mg (97%) of a mixture of lactams **3** and **4** [ratio of 95:5 by ^{13}C NMR (C=O);[16] see Table I].

Entry 6. A mixture of bicyclo[3.2.1]octan-2-one oxime (**2a**; 577 mg, 4.1 mmol) and 1 molar equiv of concentrated sulfuric acid was refluxed in formic acid (10 mL) for 3 h.[9] Upon cooling, the solution was made alkaline with 20% sodium hydroxide, extracted with dichloromethane and ether, dried, and concentrated to yield 485 mg (84%) of a crude semisolid. Flash chromatography (acetone) yielded 233 mg (39%) of a solid mixture of lactams **3** and **4** (see Table I for the ratio).

Entry 7. A solution of bicyclo[3.2.1]octan-2-one (**1**; (1.0 g, 8.0 mmol) in 14 mL of concentrated sulfuric acid was added dropwise to a solution containing hydroxylamine hydrochloride (970 mg, 14 mmol) in concentrated sulfuric acid (3 mL).[5] The solution was gradually warmed over 65 min to 115 °C and maintained at 115–116 °C for 15 min. Upon cooling in an ice bath, the solution was cautiously made alkaline with 40% sodium hydroxide. The aqueous solution was extracted with chloroform and ether, and the combined organic layers were dried and concentrated to yield 951 mg of a thick yellow oil. Preparative TLC (acetone) of a 240-mg sample yielded 118 mg (42%) of oxime **2a** and 87 mg (31%) of a white solid mixture of lactams **3** and **4** [ratio of 38:62 by ^{13}C NMR (C=O);[16] see Table I].

Entry 8. A solution of bicyclo[3.2.1]octan-2-one oxime (2a; 530 mg, 3.8 mmol) in 15 mL of concentrated sulfuric acid was brought to 114 °C over 50 min and held between 114–116 °C for 13 min. Upon cooling, the solution was made alkaline with 20% sodium hydroxide and extracted with chloroform. Drying and removal of solvent yielded 410 mg (77%) of a mixture of lactams **3** and **4** (see Table I for the ratio).

Entry 9. Sodium azide (440 mg, 6.8 mmol) was added to 1.0 mL of warm water and stirred until dissolved. The solution was cooled to 5 °C in an ice bath, and chloroform (10 mL) was added followed by concentrated sulfuric acid (0.6 mL). The solution was stirred at this temperature for 30 min, after which the layers were separated. The aqueous layer was extracted with chloroform, combined with the organic layer, dried, and kept cool in an ice bath until used. To a solution of bicyclo[3.2.1]octan-2-one (**1**; 500 mg, 4.0 mmol) and phosphorus pentoxide (150 mg, 1.1 mmol) in concentrated sulfuric acid (4 mL) chilled in an ice bath was added the hydrazoic acid solution dropwise, keeping the temperature between 5 and 8 °C.[5] The solution was stirred at this temperature for 3 h and then at room temperature for 16 h. The solution was made alkaline with 20% sodium hydroxide, and the layers were separated. The aqueous layer was extracted with chloroform, the combined organic layers were dried, and the solvent was removed to yield a yellow oil. TLC (acetone) of the residue yielded 278 mg (50%) of a mixture of lactams **3** and **4** [ratio of 50:50 by ^{13}C NMR (C=O);[16] see Table I].

Acknowledgment. Support of this work by the National Cancer Institute (Grant No. CA 24596) and the American Cancer Society (Grant No. IN 88J) is gratefully acknowledged.

Registry No. **1**, 5019-82-9; (*E*)-**2a**, 80584-61-8; (*Z*)-**2a**, 80584-62-9; **2b**, 80584-63-0; **3**, 4438-25-9; **4**, 39974-10-2; benzenesulfonyl chloride, 98-09-9; hydroxylamine-*O*-sulfonic acid, 2950-43-8.

(14) Sasaki, T.; Eguchi, S.; Hiraki, O. *J. Org. Chem.* **1976**, *41*, 1803.
(15) Hawkes, G. E.; Herwig; K. Roberts, J. D. *J. Org. Chem.* **1974**, *39*, 1017.
(16) Computer generated peak heights were used.