The Beckmann Rearrangement of Cyclohex-2-enone Oximes. Synthesis of 4,5-Diphenyl-2,3,4,5-tetrahydro-1*H*-azepin-2-one

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The Beckmann rearrangement of either *syn* or *anti* 3,4-diphenyl-cyclohexenone oxime **2a,b** in polyphosphoric acid produces only one of the two possible isomeric unsaturated caprolactams **1**. Under neutral conditions, only the *syn* oxime tosylate **9b** rearranges to lactam **1**, the *anti* oxime tosylate **9a** remains unchanged. These results support earlier reports that alkyl migration is preferred over vinyl migration in the Beckmann rearrangement of unsaturated cyclic ketoximes. Structure proof of the lactam was made using deuterium exchange and HMQC nmr experiments.

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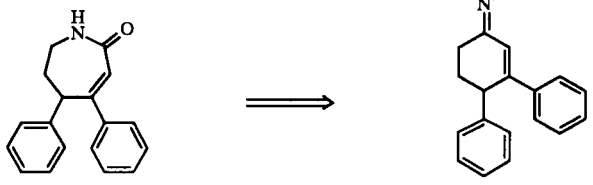
In connection with our pesticide discovery effort, we required a quantity of 4,5-diphenyl-2,3,4,5-tetrahydro-1*H*-azepin-2-one (**1**) as an intermediate. We felt that the most practical approach to **1** was by the Beckmann rearrangement of oxime **2** (Scheme 1) [1-4]. We had two concerns with this strategy; unsymmetrical oximes invariably give mixtures of isomeric lactams and the competing Semmler-Wolff aromatization of cyclohexenone oximes often produce anilines as by-products [5].

Scheme 1

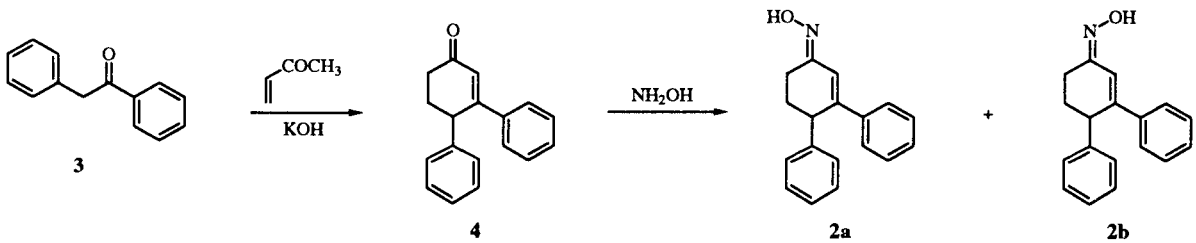


1 **2**

As a general rule, the ratio of products from the Beckmann rearrangement of unsymmetrical ketoximes can be predicted from the ratio of starting *syn* and *anti* oxime isomers. The group that migrates is opposite to the leaving group on the oxime nitrogen. A review of the literature, however, indicates that this "rule" does not always apply in the rearrangement of cyclohexenone oximes. Although both isomers are usually obtained, the lactam resulting from migration of the alkyl group often predominates [2-4, 6]. Thus, the nature of the migrating group rather than its geometric relationship to the oxime appears to control the outcome of the migration for cyclic unsaturated ketoximes. Based on these findings, we expected to obtain **1** along with the unwanted lactam isomer **5**.

The required 3,4-diphenylcyclohexenone (**4**) was prepared in excellent yield by the condensation of deoxybenzil with methy vinyl ketone (Scheme 2) [7]. Treatment of **4** with hydroxylamine hydrochloride and pyridine in ethanol gave a mixture of the two oximes **2a** and **2b** in a 10:3 ratio favoring **2a**. Since **2a** was expected to produce the undesired lactam **5** from the Beckmann rearrangement, we tried but were unsuccessful in significantly altering the ratio of oximes using other reaction conditions. When **2b** was heated at 110° in polyphosphoric acid, a single rearranged product was formed (Scheme 3). The structure was identified as the expected lactam **1** from a deuterium exchange nmr experiment. The 16 line multiplet for the amine methylene collapsed to an octet upon treatment with deuterium oxide (Figure 1) and the vinyl proton remained unchanged. When oxime **2a** was subjected to the same reaction conditions as **2b**, a single lactam was also formed accompanied by a small amount of 3,4-diphenylaniline. Instead of the expected lactam **5**, the product was found to be *identical to the one obtained from* **2b**. As a further structural proof, lactam **1** was hydrogenated to **6**, benzylated, **7**, and then reduced with lithium aluminum hydride to give the symmetrical hexa-

Scheme 2



3 **4** **2a** major **2b** minor

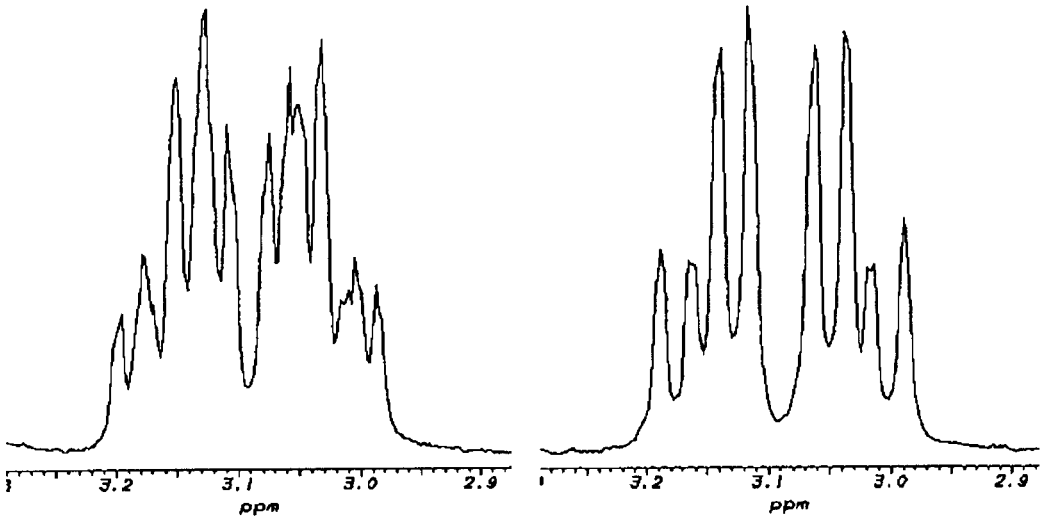


Figure 1. ^{1}H NMR spectrum for H-7 of Compound 1 in DMSO-d_6 (left) and DMSO-d_6 and deuterium oxide (right).

hydroazepine **8** (Scheme 4). The nmr HMQC spectrum of **8** (Figure 2) unequivocally confirms **1** as the sole Beckmann rearrangement product.

One explanation for the absence of lactam **5** in the above reaction is that oxime **2a** isomerizes to **2b** prior to rearrangement (Scheme 5). There is experimental evidence

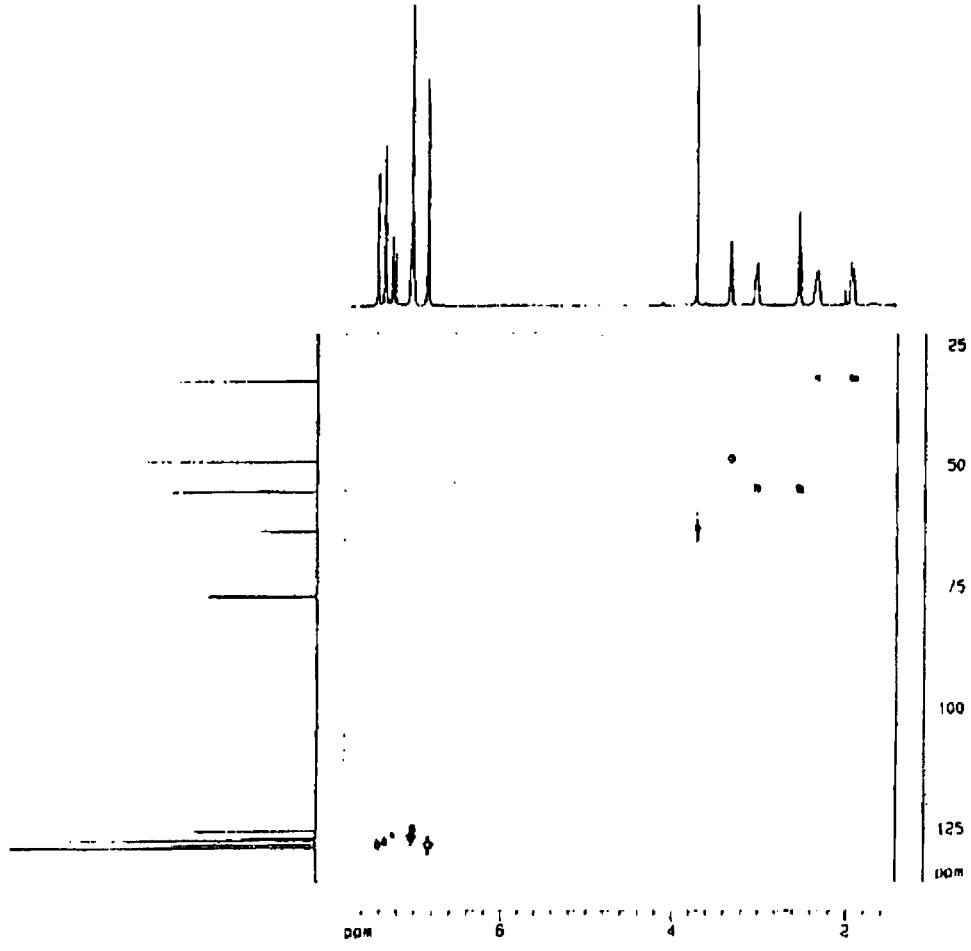
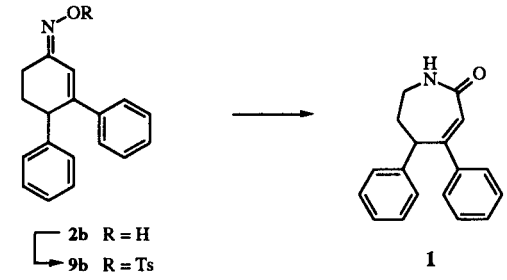
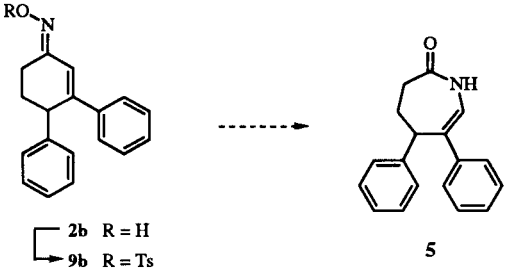


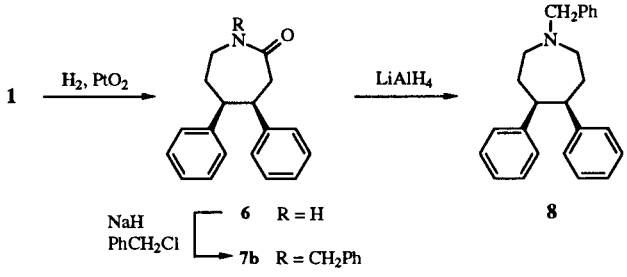
Figure 2. HMQC Spectra for Compound **8**.

Scheme 3





Scheme 4



which suggests that five and six member ring *anti* vinyl ketoximes are not readily rearranged under Beckmann conditions due to considerable strain in the transition state [8,9]. If isomerization of the oximes is faster than rearrangement, **1** would be expected to be the major product. Since polyphosphoric acid and other strong acids are known to catalyze geometric isomerization of oximes [10-12], we decided to repeat the reaction using the oxime tosylates, **9a** and **9b**. Oxime tosylates can undergo the Beckmann rearrangement under neutral conditions reducing the possibililty of isomerization [6]. When the oxime tosylates **9a** and **9b** were heated for 2 hours at 80° in aqueous dioxane, only **9b** was converted into **1**. Tosylate **9a** remained unchanged even after eight hours at 80°. These results favor the isomerization hypothesis as shown in Scheme 5 and support claims that alkyl migration is strongly preferred over vinyl migration in the Beckmann rearrangement of unsaturated cyclic ketoximes.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were recorded on a General Electric QE300 spectrometer (300 MHz ^{1}H and 75.5 MHz^{13}C) and a Bruker AMX2-500 (500 MHz ^{1}H and 125 MHz^{13}C). Deuteriochloroform was used as the nmr solvent unless otherwise specified. Chemical shifts are expressed in parts per million downfield from internal tetramethysilane (^{1}H) and deuteriochloroform (^{13}C). Infrared spectrum were recorded on a Nicolet 5ZDX FT-IR spectrometer using potassium bromide pellets. Elemental analyses were determined at FMC Corporation, Analytical Services Department or at Quantitative Technologies, Inc., Whitehouse, New Jersey. Chromatography was performed using EM Silica Gel 60 (0.040-0.063 mm). Solvents and reagents were used as purchased.

Synthesis of 3,4-Diphenylcyclohexenone (**4**).

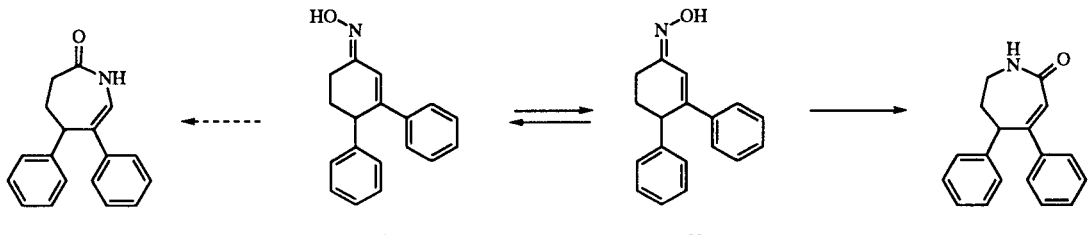
To a solution of deoxybenzil (25 g, 128 mmoles) in tetrahydrofuran (300 ml) at -30° was added dropwise a solution of potassium hydroxide (2.4 g) in 95% ethanol (15 ml) over 5 minutes followed by methyl vinyl ketone (11 ml, 128 mmoles) over 10 minutes. The yellow-orange solution was gradually warmed to ambient temperature and then heated at 50° for 1 hour. The mixture was cooled to ambient temperature and then poured into ice-water (700 ml) with stirring. The resulting solid was collected, air dried, and then triturated with 1:1 (v/v) ethyl ether/petroleum ether (100 ml) to afford 28 g (83%) of a tan solid, mp 97-98°: ^{1}H nmr: δ 2.16-2.64 (m, 4H), 4.32 (t, 1H, J = 4Hz), 6.71 (s, 1H), 7.24-7.48 (m, 10H); ^{13}C nmr: δ 31.9, 32.7, 43.1, 126.8, 126.9, 128.0, 128.6, 128.8, 129.8, 137.9, 140.2, 159.3, 199.6; ir: ν 1662 (C=O) cm^{-1}; ms: m/z 249 (MH$^+$).

Anal. Calcd. for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.95; H, 6.48.

Synthesis of *syn* and *anti* 3,4-Diphenylcyclohexenone Oxime (**2**).

To a solution of **4** (26.2 g, 0.106 mole) in warm ethanol (400 ml) was added pyridine (40 ml) followed by a solution of hydroxylamine hydrochloride (8.6 g, 0.124 mole) in water (30

Scheme 5



ml). The solution was warmed over a steam bath for 30 minutes and then poured into ice water (1 l). The tacky solid was removed and dissolved in methylene chloride (200 ml). The filtrate was extracted with methylene chloride (200 ml). The combined methylene chloride extracts were washed with water (100 ml), saturated aqueous sodium chloride (100 ml), and then dried over anhydrous magnesium sulfate and filtered. The solvent was removed *in vacuo* and the crude product was chromatographed on silica gel (1 kg) with 1:7 (v/v) ethyl acetate and heptane to yield 14.3 g (51%) of **2a** (higher Rf isomer) and 4.1 g (15%) of **2b** (lower Rf isomer).

Compound **2a** was a tan solid, mp 62-64°, ^{1}H nmr: δ 2.16 (m, 3H), 2.98 (m, 1H), 4.20 (br s, 1H), 6.93 (s, 1H), 7.26 (m, 2H), 7.42 (m, 8H), 9.13 (br s, 1H); ms: m/z 263 (M^+).

Anal. Calcd. for $C_{18}H_{17}NO \cdot 0.25H_2O$: C, 80.72; H, 6.59; N, 5.23. Found: C, 80.88; H, 6.66; N, 5.05

Compound **2b** was a tan solid, mp 117-118°, ^{1}H nmr: δ 2.07 (m, 1H), 2.34 (m, 1H), 2.40 (m, 2H), 4.26 (br s,1H), 7.26 (m, 8H), 7.49 (m, 2H), 7.62 (s, 1H), 9.50 (brs, 1H); ms: m/z 263 (M^+).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.96; H, 6.57; N, 5.20.

Beckman Rearrangement of **2b**. 4,5-Diphenyl 1,5,6,7-tetrahydroazepin-2-one (**1**).

To polyphosphoric acid (10 ml) at 110° was added **2b** (2 g, 11.4 mmoles) portionwise over 5 minutes. The mixture was stirred and heated for 1 hour resulting in a deep red-brown syrup. The syrup was poured slowly into ice water (100 ml) and then extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfated, filtered, and then concentrated *in vacuo* to a solid, 1.8 g (90%), mp 176-177°; ^{1}H nmr (DMSO-d_6): δ 1.96 (m, 1H), 2.33 (m, 1H), 3.09 (qq, 2H), 4.55 (t, 1H), 6.04 (s, 1H), 7.02-7.38 (m, 10H), 7.93 (br s, 1H); ^{1}H nmr (DMSO-d_6 and deuterium oxide): δ 3.09 (dq, 2H, missing bs at 7.93); hrms Calcd. for $C_{18}H_{17}NC$): m/z 264.1388. Found: 264.1405.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.58; H, 6.45; N, 5.13.

Beckman Rearrangement of **2a**.

A mixture of **2a** (1.1 g, 4.2 mmoles) and polyphosphoric acid (6 ml) was heated at 110° for 1 hour. After workup as in **2b**, 1 g of solid was obtained. Recrystallization from ethyl acetate afforded 0.55 g (50%) of a tan solid, identical to **1**. When the reaction was allowed to run longer (4-6 hours) or at higher temperature (120-150°), a small amount of higher Rf oily material was isolated, identified as 3,4-diphenylaniline; ms: m/z 245 (M^+).

Synthesis of *N*-Benzyl-*cis*-4,5-diphenyl-1,5,6,7-tetrahydroazepin-2-one (**7**).

To a solution of **1** (8.0 g, 0.3 mmole) in methanol (250 ml) was added platinum oxide (0.25 g) and the mixture was hydrogenated at 40 psi hydrogen pressure. The uptake hydrogen was slow, requiring nearly 24 hours to complete the reduction. The mixture was filtered to remove the catalyst and concentrated *in vacuo* to afford a quantitative yield of **6** as a tan solid which was used without further purification, mp 189-192° ; ^{1}H nmr: δ 6.04 singlet missing; ms: m/z 266 (MH^+).

A solution of **6** (4 g, 15.1 mmoles) and *N,N*-dimethylformamide (75 ml) was stirred at ambient temperature under nitrogen as sodium hydride (0.66 g, 16.6 mmoles of 60% in mineral oil) was added portionwise. The mixture was heated at 60° until the evolution of hydrogen ceased (10 minutes) and then cooled. Benzyl chloride (1.9 ml, 15.11 mmoles) was added dropwise and the mixture was stirred at ambient temperature for 16 hours. The mixture was poured into ice cold saturated aqueous ammonium chloride (200 ml) and then extracted with ethyl acetate (2 x 250 ml). The organic phase was washed with saturated aqueous ammonium chloride (100 ml), dried over magnesium sulfate, filtered and then concentrated *in vacuo* to afford a solid. The solid was recrystallized from a mixture of ethyl acetate (15 ml) and heptane (30 ml) to yield 2.4 g (47%) of a tan solid, mp 147-149°; ^{1}H nmr: δ 1.82 (m, 1H), 2.19 (m, 1H), 3.13 (m, 2H), 3.19 (m, 1H), 3.34 (m, 1H), 3.61 (m, 1H), 3.77 (m, 1H), 4.77 (q, 2H), 6.66-7.41 (m, 15H); hrms Calcd. for $C_{25}H_{25}NO$: m/z 356.2014. Found: 356.2028.

Anal. Cacld. for $C_{25}H_{25}NO \cdot 0.5H_2O$; C, 83.41; H, 7.14; N, 3.89. Found; C, 83.67; H, 7.17; N, 3.98.

Synthesis of *N*-Benzyl-*cis*-4,5-diphenyl-2,3,4,5,6,7-hexahydroazepine (**8**).

A solution of **7** (1.8 g, 5.1 mmoles) in tetrahydrofuran (20 ml) was added dropwise to a mixture of lithium aluminum hydride (0.42 g, 11 mmoles) and tetrahydrofuran (10 ml) with stirring under nitrogen at 0°. After stirring at 0° for 45 minutes, water (0.4 ml) was cautiously added followed by 10% aqueous sodium hydroxide (0.6 ml) and then water (0.8 ml). The mixture was diluted with tetrahydrofuran (25 ml), filtered through a small bed of celite, and then concentrated *in vacuo* to an oil which was chromatographed on preparative silica gel plates with 8:2 (v/v) heptane/ethyl acetate to afford 1.4 g (81%) of a tan solid, mp 73-75°; ^{1}H nmr (500 MHz): δ 1.96 (d, 2H, H-3, H-6), 2.35 (q, 2H, H-3, H-6), 2.56 (m, 2H, H-2, H-7), 3.13 (d, 2H, H-2, H-7), 3.32 (d, 2H, H-4, H-5), 3.73 (s, 2H, *N*-benzyl), 6.80-7.43 (m, 15H, phenyl's). ^{13}C nmr (125 MHz): δ 32.4, 49.3, 55.6, 63.7, 125.5, 126.8, 127.3, 128.2, 128.9, 129.0, 139.6, 144.7: ms: m/z 341 (M^+).

Anal. Calcd. for $C_{25}H_{27}N$: C, 87.93; H, 7.97; N, 4.10. Found: C, 87.72; H, 8.00; N, 4.10.

Synthesis of *anti* 3,4-Diphenylcyclohex-2-enone Oxime Tosylate (**9a**).

To a stirred solution **2a** (1.0 g, 3.8 mmoles) in dichloromethane (10 ml) was added pyridine (1 ml) and then *p*-toluenesulfonyl chloride (0.72 g, 3.8 mmoles). After 18 hours, the mixture was diluted with water (100 ml) and dichloromethane (50 ml). The organic layer was washed with 10% hydrochloric acid (50 ml), saturated aqueous sodium bicarbonate (50 ml), dried over magnesium sulfate, filtered, and then concentrated *in vacuo* to yield 1.5 g (98%) of a white foam; ^{1}H nmr: δ 2.01 (m, 1 H), 2.19 (m, 2H), 2.46 (s, 3H), 2.91 (m, 1H), 4.19 (m, 1H), 6.83 (s, 1H), 7.15-7.37 (m, 12H), 7.92 (m, 2H).

Anal. Calcd. for $C_{25}H_{23}NO_3S$: C, 71.92; H, 5 55; N, 3.36. Found: C, 71.64; H, 5.68; N, 3.16.

Synthesis of *syn* 3,4-Diphenylcyclohex-2-enone Oxime Tosylate (**9b**).

This compound was prepared as in **9a** from 1.0 g of **2b** to afford 1.5 g (98%) of a tan foam; ^{1}H nmr: δ 2.04 (m, 1H), 2.27 (m, 1H), 2.36 (m, 2H), 2.46 (s, 3H), 4.24 (m, 1H), 7.13-7.44 (m, 13H), 7.93 (m, 2H).

Anal. Calcd. for $C_{25}H_{23}NO_3S$: C, 71.92; H, 5 55; N, 3.36. Found: C, 71.63; H, 5.70; N, 3.17.

Beckman Rearrangement of **9b**.

A solution of **9b** (0.5 g, 1.2 mmoles), ethanol (5 ml), dioxane (5 ml) and water (1 ml) was heated at 80° for 2 hours. The solvents were removed *in vacuo* and the residue was chromatographed on preparative silica gel plates with ethyl acetate to afford 0.20 g (71%) of a white solid identical to **1**.

Acknowledgement.

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REFERENCES AND NOTES

[1] R. K. Smalley, Comprehensive Heterocyclic Chemistry, Vol 7, A. R. Katritzky, C. W. Rees and W. Lwowski, eds, Pergamon Press, Oxford, 1984, p 491.

[2] D. Craig, Comprehensive Organic Synthesis, Vol 7, B. M. Trost, I. Fleming and S. V. Ley, eds, Pergamon Press, Oxford, 1991, p 689.

[3] L. G. Donaruma and W. Z. Heldt, Organic Reactions, Vol **11**, R. Adams, A. H. Blatt, V. Boekelheide, T. L. Cairns, A. C. Cope, D. Y. Curtin and C. Niemann, eds, John Wiley & Sons, Inc., New York, 1960, p 1.

[4] R. E. Gawley, Organic Reactions, Vol **35**, A. S. Kende, ed, John Wiley & Sons, Inc., New York, 1988, p 1.

[5] R. T. Conley and S. Ghosh, Mechanisms of Molecular Migrations, Vol **4**, B. S. Thyagarajan, ed, Wiley-Interscience, New York, 1971, p 197.

[6] G. I. Hutchison, R. H. Prager, and A. D. Woog, *Aust. J. Chem.*, **33**, 2477 (1980).

[7] H. E. Zimmerman, X. Jian-hua, R. K. King and C. E. Caufield, *J. Am. Chem. Soc.*, **107**, 7724 (1985).

[8] C. A. Grob and P. Wenk, *Tetrahedron Letters*, 4191 (1976).

[9] P. T. Lansbury and N. R. Mancuso, *Tetrahedron Letters*, 2445 (1965).

[10] P. A. Smith and E. P. Autoniades, *Tetrahedron*, **9**, 210 (1960).

[11] F. Fernandez and C. Perez, *J. Chem. Res.; (S)*, 340 (1987).

[12] C. G. McCarty, The Chemistry of the Carbon-Nitrogen Double Bond, S. Parai, ed, Interscience, London, 1970, p 363.