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CONCERTED CYCLOADDITION OF CHLOROSULFONYL ISOCYANATE TO α-PINENE STEPWISE REARRANGEMENT OF THE β-LACTAM CYCLOADDUCT TO A γ-LACTAM†

G. T. FURST, M. A. WACHSMAN, J. PIERONI, J. G. WHITE and E. J. MORICONI*
Department of Chemistry, Fordham University, New York, U.S.A.

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Abstract—Chlorosulfonyl isocyanate adds to α-pinene in concerted fashion to give the unrearranged N-chlorosulfonyl-β-lactam **2** (75%). Thermolysis of cycloadduct **2** affords the rearranged N-chlorosulfonyl-γ-lactam **6** (60%) via a sequence of transient carbonium ions (**4** ⇌ **5**). Reductive hydrolysis of **2** and **6** gave, respectively, the NH-β-lactam **3** (70%) and the NH-γ-lactam **7** (70%). Proof of structure of the rearranged γ-lactams **6** and **7** are provided, respectively, by X-ray crystallographic analysis and the application of the Eu(dpm)$_3$ NMR shift reagent.

We have viewed the regioselective and stereospecific addition of chlorosulfonyl isocyanate (CSI) to *cis* and *trans* alkenes,[1a,2] bridged bicyclic olefins,[1b] conjugated dienes,[1c] and certain acetylenes[1d] as $_{\pi}2_s + _{\pi}2_a$ cycloaddition reactions in which the CSI functions as the antarafacial component. In the case of conjugated dienes,[1c] the initially formed 1,2-cycloadducts thermally rearrange via dipolar intermediates to N- and O-1,4-cycloadducts. Clearly here, β-lactam formation precedes rather than follows the generation of Graf's 1,4-dipole.[1e,3]

Most recently, Barton and Rogido have also viewed the cycloaddition of CSI to 2-cyclopropylpropene[4a] and diphenylmethylenecyclopropane[4b] as a concerted process, initially affording an N-chlorosulfonyl-β-lactam which in each case subsequently rearranged via thermal heterolysis.

We should like to report here the concerted cycloaddition of CSI to rearrangement-prone α-pinene (**1**)[5] to give the unrearranged N-chlorosulfonyl-β-lactam product (**2**). Thermolysis of cycloadduct **2** generates a sequence of transient carbonium ions (**4** ⇌ **5**) reminiscent of the acid-catalyzed hydration of **1** to borneol.[6] However, before an analogous intramolecular 6,2-hydrogen shift can occur, the rearranged carbonium ion **5** is trapped by the anion of the attached uniparticulate CSI‡ to form the N-chlorosulfonyl-γ-lactam (**6**).

Thus, stirring equimolar amounts of **1** and CSI in ether solution at −70° for two hr led to 3-chlorosulfonyl-2,8,8-trimethyl-3-azatricyclo [5.1.1.9^{2,5}] nonan-4-one (**2**) (75%). β-Lactam **2** rearranges on standing overnight at room temp to a brown oil which is chromatographed on a silica gel column and eluted with ether-hexane to give 4-chlorosulfonyl-7,8,-trimethyl-4-azatricyclo [4.2.1.0^{3,7}] nonan-5-one (**6**)(60%). Reductive hydrolysis of **2** with NaOH-acetone-H_2O at −30° and **6** with alkaline Na_2SO_3 at room temp afforded, respectively, the NH-β-lactam **3** (70%) and the NH-γ-lactam **7** (70%). γ-Lactam **7** was converted to the imino-ether-BF_4 salt **8** (80%) with an equimolar amount of $(C_2H_5)_3O^+BF_4^-$ in CH_2Cl_2 solution under N_2 at room temp. Reduction of **8** with a four-fold molar excess of $NaBH_4$ in refluxing ethanol converted it to the tricyclic amine **9** (40%) which could also be obtained via reduction of **7** with LAH in dry THF at reflux for 72 hr.

Confirmatory evidence for the γ-lactam structure of rearranged product **7** began with the application of the Eu(dpm)$_3$ NMR shift reagent.[8] The chemical shift of each of the assigned protons varied linearly with the molar ratio of Eu(dpm)$_3$ to **7**. The Eu shift parameter ΔEu§ (Fig 1) is greatest for the hydrogen closest to the europium.‖

X-Ray crystallographic analysis of **6** ultimately delineated its structure as drawn in Fig 2. The crystals are orthorhombic with $a = 7{\cdot}808 \pm 0{\cdot}001$, $b = 11{\cdot}850 \pm 0{\cdot}001$, $c = 14{\cdot}157 \pm 0{\cdot}001$ Å, $\gamma = \beta = \alpha = 90°$. The space group was found to be $P2_12_12_1$ with four molecules per unit cell or one molecule per crystal asymmetric unit. Data were collected on a four-circle diffractometer and the structure was solved by a combination of Patterson and heavy atom methods. It was refined to a conven-

*To whom correspondence should be addressed. Current address: Sandoz, A. G., Farben/Chemikalien-Departement, CH-4002 Basel, Switzerland.

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‡*cf.* the instances where addition of the uniparticulate electrophile CSI generates initially the carbonium ion and then intramolecularly traps it. For leading refs see L. A. Paquette, G. R. Allen, Jr. and M. J. Broadhurst, *J. Am. Chem. Soc.* **93**, 4053 (1971).

§As an approximation the hydrogen to CO oxygen bond distances were calculated using Dreiding models since the exact location of the europium atom in the complex is unknown.

‖Eu(dpm)$_3$ chemical shift effects on a series of simple lactams are currently being investigated in this laboratory and will be reported elsewhere.

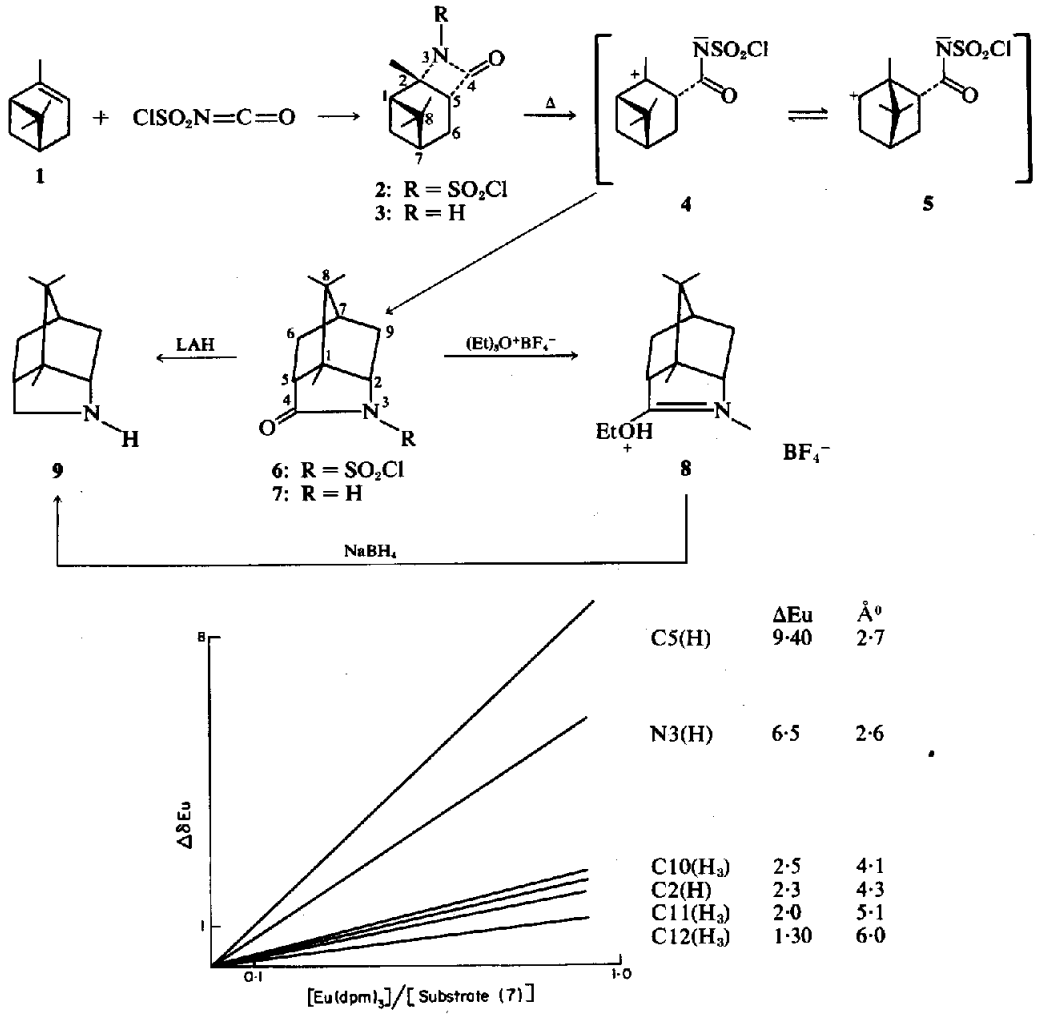

Fig 1. Plot of chemical shift parameter ΔEu vs molar ratio of Eu(dpm)$_3$/substrate (7) in $CDCl_3$.

tional R of 0·0938 with 615 observed and 670 unobserved reflections using Fourier and least square methods with isotropic temperature factors. The average bond distances are given in Fig 2 in Å and are in agreement with those expected for 6. The atomic position of one of the bridge methyl groups is at least certain because of high thermal motion in this region.

EXPERIMENTAL

M.ps are corrected. The IR spectra were recorded on a Perkin-Elmer 337 grating spectrophotometer. NMR spectra were obtained on Varian Associates A-60A and XL-100 spectrometers; chemical shifts are expressed in ppm (δ) downfield from TMS as an internal standard. Gas chromatographs were run on a Perkin-Elmer 880 with a flame ionization detector and using a column packed with 10% SE-30 on Chromosorb W. The mass spectra were obtained using the facilities of the Battelle Memorial Institute, High Resolution Mass Spectrometry Center sponsored by the National Institute of Health, Division of Research Resources Contract No. NIH-71-2483. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. CSI was obtained from the American Hoechst Corp.

3-Chlorosulfonyl-2,8,8-trimethyl-3-azatricyclo[5.1.1.0^{2,5}]*nonan-4-one* (2). CSI (21 g, 0·150 mole) was added dropwise to a stirred soln of 20 g (0·147 mole) α-pinene maintained at −60°. Addition was complete in 1 hr and the mixture was stirred for an additional hr. The white solid which precipitated was filtered and recrystallized from hexane to yield 30·6 g (75%) of 2, m.p. 59–62°; IR (CCl_4) 5·64 (C=O), 7·2 and 8·5 μ (SO_2); NMR ($CDCl_3$, δ) 0·92, 1·37 [6H, C(C<u>H</u>$_3$)$_2$], 1·83 (s, 3H, C<u>H</u>$_3$), and 3·35 (doublet of doublets, 1H, C<u>H</u>CO). (Found: C, 47·60; H, 5·75; N, 5·32. Calcd. for $C_{11}H_{16}NSO_3Cl$: C, 47·56; H, 5·81; N, 5·04%).

2,8,8-Trimethyl-3-azatricyclo[5.1.1.0^{2,5}]*nonan-4-one* (3). To 10 g (0·036 mole) of 2 in a flask maintained at −30° was added 75 ml acetone and 25 ml H_2O. 5% NaOHaq was then added until the mixture was just basic to litmus, and

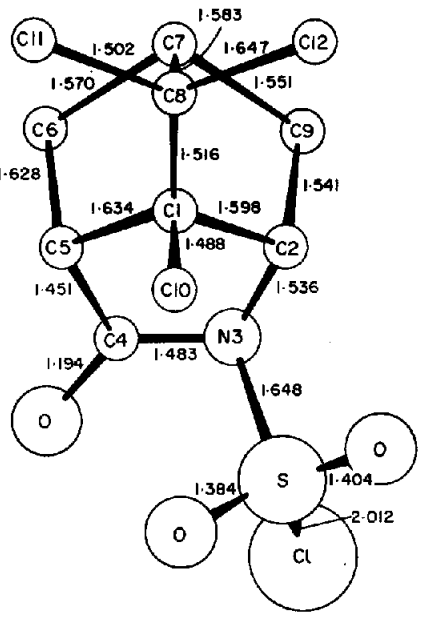

Fig 2. Geometry and bond lengths of **6**.

the whole stirred for an additional 30 min. While still cold, the mixture was extracted quickly with ether, and the ether extracts were dried over Na_2SO_4. Filtration, followed by evaporation of the filtrate to dryness afforded 4·5 g (70%) of **3**, m.p. 147–148° (ether-hexane); IR (KBr) 3·18 (NH) and 5·75 μ (C=O); NMR ($CDCl_3$, δ) 0·90, 1·30 [6H, $C(CH_3)_2$], 1·46 (s, 3H, CH_3), 2·85 (doublet of doublets, J=10 and 2·5 Hz, CHCO) and 7·1 (mound, 1H, NH). (Found: C, 73·74; H, 9·62; N, 7·76. Calcd. for $C_{11}H_{17}NO$: C, 73·70; H, 9·56; N, 7·82%).

4-Chlorosulfonyl-7,8,8-trimethyl-4-azatricyclo[4.2.1.$0^{3,7}$]*nonan-5-one* (**6**). N-Chlorosulfonyl-β-lactam **2** (10 g, 0·036 mole) was allowed to stand overnight at room temp. The white crystals of **2** decomposed to a brown oil (impure rearranged **6**) which was deposited on a silica gel column and eluted with ether-hexane (gradient 10–50%). Evaporation of solvent from the major fraction ultimately afforded 6·0 g (60%) of pure **6**, m.p. 75–76° (hexane); IR (KBr) 5·80 (C=O), 7·09 and 8·54 μ (SO_2); NMR (CCl_4, δ) 1·00 [s, 6H, $C(CH_3)_2$], 1·19 (s, 3H, CH_3), and 4·19 (broad d, 1H, J=8·0 Hz, CHN). (Found: C, 47·31; H, 5·99; N, 5·10. Calcd. for $C_{11}H_{16}NSO_3Cl$: C, 47·56; H, 5·81; N, 5·04%).

7,8,8-Trimethyl-4-azatricyclo[4.2.1.$0^{3,7}$]*nonan-5-one* (**7**). N-Chloro-sulfonyl-γ-lactam **6** (2·0 g, 0·0072 mole) was dissolved in 10 ml ether and added dropwise to a stirred soln of 20 ml of 25% Na_2SO_3 aq and 10 ml ether. The soln was kept slightly basic by the addition of a 10% KOH aq. Addition was complete in 15 min. The ether layer was separated and dried over Na_2SO_4. Filtration, followed by evaporation of the filtrate to dryness afforded 0·9 g (70%) of **7**, sublimes 160–210° (hexane); IR (KBr) 3·13 (NH) and 5·88 μ (C=O); NMR (CCl_4, δ) 0·94 [s, 6H, $C(CH_3)_2$], 1·10 (s, 3H, CH_3), 3·36 (broad d, 1H, J=9·0 Hz, CHN), and 8·22 (mound, 1H, NH). (Found: C, 73·76; H, 9·48; N, 7·73. Calcd. for $C_{11}H_{17}NO$: C, 73·70; H, 9·56; N, 7·82%).

Reaction of Meerwein's reagent with **7**. γ-Lactam **7** (1·71 g, 0·010 mole) dissolved in 15 ml of anhyd CH_2Cl_2 was added dropwise (20 min) to a soln of 1·70 g (0·010 mole) of triethyloxonium fluoborate in 20 ml of CH_2Cl_2 under N_2. The mixture was then stirred for 16 hr and then added to 100 ml of anhyd ether. Cooling to 0° precipitated white needles of the iminoether-BF_4 salt **8** (2·37 g, 80%), m.p. 85–86°; IR (KBr) 6·08 μ (C=N); NMR ($CDCl_3$, δ) 1·0 [s, 6H, $C(CH_3)_2$], 1·25 (s, 3H, CH_3), 1·58 (t, 3H, J=7·5 Hz, CH_2CH_3), 4·0 (broad d, 1H, CHN), and 4·75 (q, 2H, J=7·5 Hz, CH_2CH_3). (Found: C, 52·87; H, 7·77; N, 4·73. Calcd. for $C_{13}H_{22}NOBF_4$: C, 52·90; H, 7·52, N, 4·74%).

Sodium borohydride reduction of **8**.[9] To a stirred solution of 0·507 g (0·017 mole) of **8** in 50 ml abs EtOH was added 0·270 g (0·068 mole) of $NaBH_4$. The mixture was then refluxed for 16 hr, cooled to 25°, and added to 150 ml H_2O. The aqueous mixture was extracted with 3 × 25 ml ether. The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to dryness to leave a yellow residue. Crystallization from CCl_4 afforded **9** (0·116 g, 40%), m.p. 106–107° (CCl_4): NMR ($CDCl_3$, δ) 0·90 [s, 6H, $C(CH_3)_2$], 1·00 (s, 3H, CH_3), 1·29 (s, 1H, NH), and 3·10–3·95 (m, 3H, $CHNHCH_2$). (Found: *m/e*, 165·1522. Calcd. for $C_{11}H_9N$: *m/e*, 165·1517.)

Tricyclic amine **9** was alternately prepared from **7** via LAH reduction: a mixture of 0·309 g (0·172 mole) of **7** and 0·700 g (0·184 mole) of LAH in 20 ml of dry THF was refluxed for 72 hr. The excess LAH was decomposed by slow addition of 50 ml of H_2O. The soln was filtered and the filter cake washed with ether. The combined filtrates were extracted with 3 × 50 ml ether; the combined ether extracts were dried ($MgSO_4$), filtered and evaporated to dryness to give crude **9** as a yellow residue. Crystallization from light petroleum afforded white needles of pure **9** (0·198 g, 70%), m.p. 106–107°, and identical in all respects with that obtained from **8**.

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REFERENCES

[1a]E. J. Moriconi and J. F. Kelly, *J. Org. Chem.* **33**, 3036 (1968); [b]E. J. Moriconi and W. C. Crawford, *Ibid.* **33**, 370 (1968); [c]E. J. Moriconi and W. C. Meyer, *Ibid.* **36**, 2841 (1971); [d]E. J. Moriconi and Y. Shimakawa, *Ibid.* **37**, 196 (1972); [e]E. J. Moriconi, C. F. Hummel and J. F. Kelly, *Tetrahedron Letters*, 5325 (1969)

[2]L. A. Paquette, M. J. Wyvratt and G. R. Allen, Jr., *J. Am. Chem. Soc.* **92** 1763 (1970)

[3]R. Graf, *Angew. Chem.* Intern. Edit. **7**, 172 (1968)

[4a]T. J. Barton and R. J. Rogido, *Chem. Commun.* 878 (1972); [b]*Tetrahedron Letters* 3901 (1972)

[5]J. A. Berson, *Molecular Rearrangements* (Edited by P. de Mayo), Vol. I, p. 111. Interscience, New York, N.Y., (1963)

[6]J. Simonsen and L. W. Owen, *The Terpenes*. Vol. II, p. 163. Cambridge University Press (1949)

[8]See e.g., J. K. M. Sanders and D. R. Williams, *Ibid.*, **93**, 641 (1971); P. V. Demarco, T. K. Elzey, R. B. Lewis and E. Wenkert, *Ibid.* **92**, 5734, 5737 (1970) and the refs cited.

[9]R. F. Borch, *Tetrahedron Letters* 61 (1968)