"Chlorosulfonyl Isocyanate Reactions with *N*-(Alkoxycarbonyl)-2-Azabicyclo[2.2.0]hex-5-enes. Regiospecific Two Atom Insertion Pathways."

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***N*-(Benzyloxycarbonyl)-5-bromo-2-azabicyclo[2.2.0]hex-5-ene (1e).** Following the procedure of Fowler,¹ benzyl chloroformate (1.71 g, 10 mmol) in ether (5 mL) was added to a solution of sodium borohydride (0.84 g, 21 mmol) and 4-bromopyridine hydrochloride (1.94 g, 10 mmol) in absolute methanol (20 mL) cooled in dry ice-acetone. The mixture was stirred for four hr while the temperature of the reaction mixture was maintained below -65 °C. Enough water was added to dissolve the inorganic salts and the mixture was extracted with ether (4 x 20 mL). The combined organic layers were washed with water and dried over sodium carbonate. Removal of the solvent gave crude *N*-(benzyloxycarbonyl)-4-bromo-1,2-dihydropyridine (2.8 g), which decomposed upon attempted purification by silica gel or basic alumina chromatography. Accordingly, a 5% solution in acetone (56 g) of the crude dihydropyridine was irradiated in a Rayonet photochemical reactor using RP-3000 lamps for 96 h until no starting material remained. Removal of solvent gave an orange oil, which was purified by ammonia saturated silica gel chromatography (3:1 hexane:ether) to give 665 mg (23 %) of azabicycle **1e** as a yellow oil at $R_f = 0.24$ (3:1 hexane:ether): ¹H NMR δ 7.35 (s, 5H), 6.68 and 6.50 (two br, 1H), 5.12 (s, 2H), 4.89 (br, 1H), 3.97 (m, 1H), 3.62 (br, 2H); ¹³C NMR δ 156.8, 140.6 and 140.2, 136.4, 128.5, 128.2, 128.0, 114.5 and 114.0, 66.9, 63.9 and 63.4, 49.1 and 48.4, 44.9; HRMS m/z 315.4947 and 317.9930; calcd for C₁₃H₁₂^{79/81}Br NO₂Na (M + Na), 315.9949 and 317.9929.

***N*-(Benzyloxycarbonyl)-5-phenyl-2-azabicyclo[2.2.0]hex-5-ene (1f).** A stirred mixture of 5-bromoazabicycle **1e** (591 mg, 2 mmol) and Pd(PPh₃)₄ (80 mg, 0.8 mmol) in toluene (30 mL) under argon was successively treated with phenylboronic acid (260 mg, 2.13

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mmol) in ethanol (1 mL) and aq sodium carbonate (2 mL).¹⁵ The resulting mixture was heated to 70 °C and stirred for 8 hr, cooled and filtered. To the filtrate there was added brine (8 mL) and the mixture was extracted with CH₂Cl₂ (4 x 20 mL). The combined extracts were dried over sodium sulfate, filtered and the solvent was removed. Silica gel column chromatography (3:1 hexane:ether) gave 120 mg (20%) of unreacted **1e** and 390 mg (67%) of 5-phenylazabicyclo **1f** at R_f = 0.2 (3:1 hexane:ether): ¹H NMR δ 7.22 (m, 10H), 6.63 and 6.44 (two s, 1H), 5.01 (s, 2H), 4.77 (br, 1H), 3.76 (brm, 1H), 3.56 (brm, 1H), 3.44 (brm, 1H); ¹³C NMR δ 157.5, 153.3, 137.2, 132.9, 130.1, 129.6, 129.4, 129.1, 128.9, 125.6, 67.0, 62.0, 61.4, 50.4, 49.7, 36.9; HRMS *m/z* 314.1158, calcd for C₁₉H₁₇NO₂Na (M + Na) 314.1157.

10b

10b

10c

10d

10e

10f

10f

10h

10h

CH₃

CH₂

H₁
H₂

H₃

H₅

H₆

H₄

H₇

H₈

ppm

X-ray Structure Determination of Compound 9005 = 10a

Compound 9005, $C_9H_{12}N_2O_3$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences $h00: h=\text{odd}$, $0k0: k=\text{odd}$, and $00l: l=\text{odd}$) with $a=8.2895(2)\text{\AA}$, $b=19.8550(7)\text{\AA}$, $c=6.08250(10)\text{\AA}$, $V=1001.11(5)\text{\AA}^3$, $Z=4$ and $d_{\text{calc}}=1.302\text{ g/cm}^3$. X-ray intensity data were collected on an Rigaku R-Axis IIc area detector employing graphite-monochromated Mo- K_{α} radiation ($\lambda=0.71069\text{ \AA}$) at a temperature of 295°K . Indexing was performed from a series of 1° oscillation images with exposures of 3 minutes per frame. A hemisphere of data was collected using 12° oscillation angles with exposures of 5 minutes per frame and a crystal-to-detector distance of 82 mm. Oscillation images were processed using bioteX¹, producing a listing of unaveraged F^2 and $\sigma(F^2)$ values which were then passed to the teXsan² program package for further processing and structure solution on a Silicon Graphics Indigo R4000 computer. A total of 5882 reflections were measured over the ranges: $5.32 \leq 2\theta \leq 50.66^\circ$, $0 \leq h \leq 9$, $-23 \leq k \leq 23$, $-7 \leq l \leq 7$ yielding 1083 unique reflections ($R_{\text{int}} = 0.0341$). The intensity data were corrected for Lorentz and polarization effects but not for absorption.

The structure was solved by direct methods (SIR92³). Refinement was by full-matrix least squares based on F^2 using SHELXL-93⁴. All reflections were used during refinement (F^2 's that were experimentally negative were replaced by $F^2 = 0$). The weighting scheme used was $w=1/[\sigma^2(F_o^2) + 0.1171P^2 + 0.0802P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as constant contributions to the structure factors and were not refined. Refinement converged to $R_1=0.0606$ and $wR_2=0.1744$ for 919 reflections for which $F > 4\sigma(F)$ and

$R_1=0.0704$, $wR_2=0.1834$ and $GOF = 1.103$ for all 1083 unique, non-zero reflections and 128 variables⁵.

The maximum Δ/σ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were $+0.205$ and $-0.148 \text{ e}/\text{\AA}^3$.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Table 2. Anisotropic thermal parameters are in Table 3. Tables 4. and 5. list bond distances and bond angles. Figure 1. is an ORTEP⁶ representation of the molecule with 30% probability thermal ellipsoids displayed.

Figure 1. ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

References

1. bioteX: A suite of Programs for the Collection, Reduction and Interpretation of Imaging Plate Data, Chen, D., C.L. Day, J.D. Ferrara, T.L. Higashi, J.W. Pflugrath, B.D. Santarsiero, P.N. Swebston, J.M. Troup, B.R. Vincent and L. Xiong (1995).
2. teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).
3. SIR92: Altomare, A., Burla, M.C., Camalli, M., Cascarano, M., Giacovazzo, C., Guagliardi, A., Polidoro, G. (1994). *J. Appl. Cryst.*, in preparation.
4. SHELXL-93: Program for the Refinement of Crystal Structures, Sheldrick, G.M., University of Göttingen, Germany.
5. $R_1 = \sum ||F_o| - |F_c|| / \sum |F_o|$
 $wR_2 = \{ \sum w (F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2 \}^{1/2}$
 $GOF = \{ \sum w (F_o^2 - F_c^2)^2 / (n - p) \}^{1/2}$ where n = the number of reflections, and p = the number of parameters refined.
6. "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

Table 1. Summary of Structure Determination of Compound 9005

Formula:	C ₉ H ₁₂ N ₂ O ₃
Formula weight:	196.21
Crystal class:	orthorhombic
Space group:	P2 ₁ 2 ₁ 2 ₁ (#19)
Z	4
Cell constants:	
a	8.2895(2) Å
b	19.8550(7) Å
c	6.08250(10) Å
V	1001.11(5) Å ³
μ	0.99 cm ⁻¹
crystal size, mm	0.42 x 0.18 x 0.04
D _{calc}	1.302 g/cm ³
F(000)	416
Radiation:	Mo-K _α (λ=0.71069 Å)
2θ range	5.32–50.66°
hkl collected:	0 ≤ h ≤ 9; -23 ≤ k ≤ 23; -7 ≤ l ≤ 7
No. reflections measured:	5882
No. unique reflections:	1083 (R _{int} =0.0341)
No. observed reflections	919 (F > 4σ)
No. reflections used in refinement	1083
No. parameters	128
R indices (F > 4σ)	R ₁ =0.0606 wR ₂ =0.1744
R indices (all data)	R ₁ =0.0704 wR ₂ =0.1834
GOF:	1.103
Final Difference Peaks, e/Å ³	+0.205, -0.148

Table 4. Bond Distances in Compound 9005, Å

O1-C6	1.218(4)	O2-C7	1.208(5)	O3-C7	1.320(5)
O3-C8	1.450(6)	N1-C7	1.374(5)	N1-C6	1.401(4)
N1-C1	1.470(5)	N2-C6	1.348(5)	N2-C5	1.451(5)
C1-C2	1.508(8)	C2-C3	1.489(11)	C2-C5	1.570(7)
C3-C4	1.320(8)	C4-C5	1.490(8)	C8-C9	1.434(9)

Table 5. Bond Angles in Compound 9005, °

C7-O3-C8	115.5(4)	C7-N1-C6	123.6(3)	C7-N1-C1	119.3(3)
C6-N1-C1	116.7(3)	C6-N2-C5	122.3(3)	N1-C1-C2	109.7(4)
C3-C2-C1	117.6(5)	C3-C2-C5	84.6(5)	C1-C2-C5	110.4(4)
C4-C3-C2	95.4(5)	C3-C4-C5	94.1(6)	N2-C5-C4	119.6(4)
N2-C5-C2	113.9(4)	C4-C5-C2	85.7(4)	O1-C6-N2	123.3(3)
O1-C6-N1	122.9(3)	N2-C6-N1	113.5(3)	O2-C7-O3	124.7(4)
O2-C7-N1	123.3(4)	O3-C7-N1	112.0(3)	C9-C8-O3	108.4(5)