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THE PREPARATION AND REACTIONS OF 2-AZIDOCARBAPENEMS

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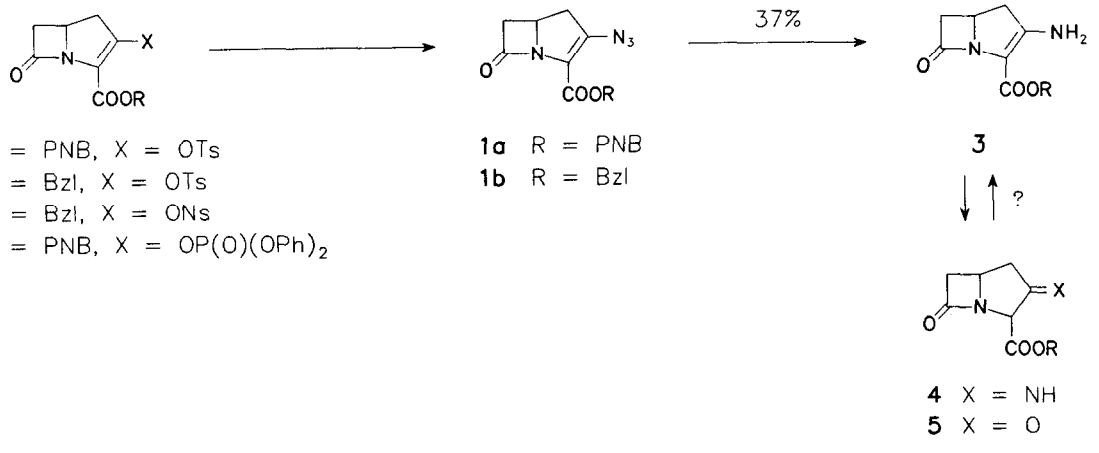
Summary. The preparation of 2-azasubstituted carbapenems is reported, wherein reactions of intermediate 2-azides provide the amine, 1,2,3-triazolines, 1,2,3-triazoles, and aziridines.

The extraordinary potency and spectrum of antibacterial activity of thienamycin has prompted the synthesis of a wide variety of analogs. Yet only one report of substitution of nitrogen for sulfur at the 2-position of the carbapenem nucleus has appeared.[1] We wish to report the preparation of 2-azido substituted carbapenems, and the reactions of these synthetically versatile azides with a variety of acetylenes and olefins to provide the amine, 1,2,3-triazolines, 1,2,3-triazoles, and aziridines.

The key intermediate azides **1a**[2] and **1b**[3] are obtained in 94% and 67% isolated yields, resp., by reaction of enol tosylates **2a**[4] and **2b**[4,5] with KN_3 (5:1 [v/v] CH_3CN/CH_2Cl_2, 0° C, 1.5 h). Nosylate **2c**[4] and phosphate **2d**[6] react in an analogous fashion to provide azides **1a** and **1b**, but in lower yields. Azides **1a** and **1b** are colorless, crystalline solids which decompose extensively upon standing overnight at ambient temperature, but which can be stored at -20° C for over a week with little loss.

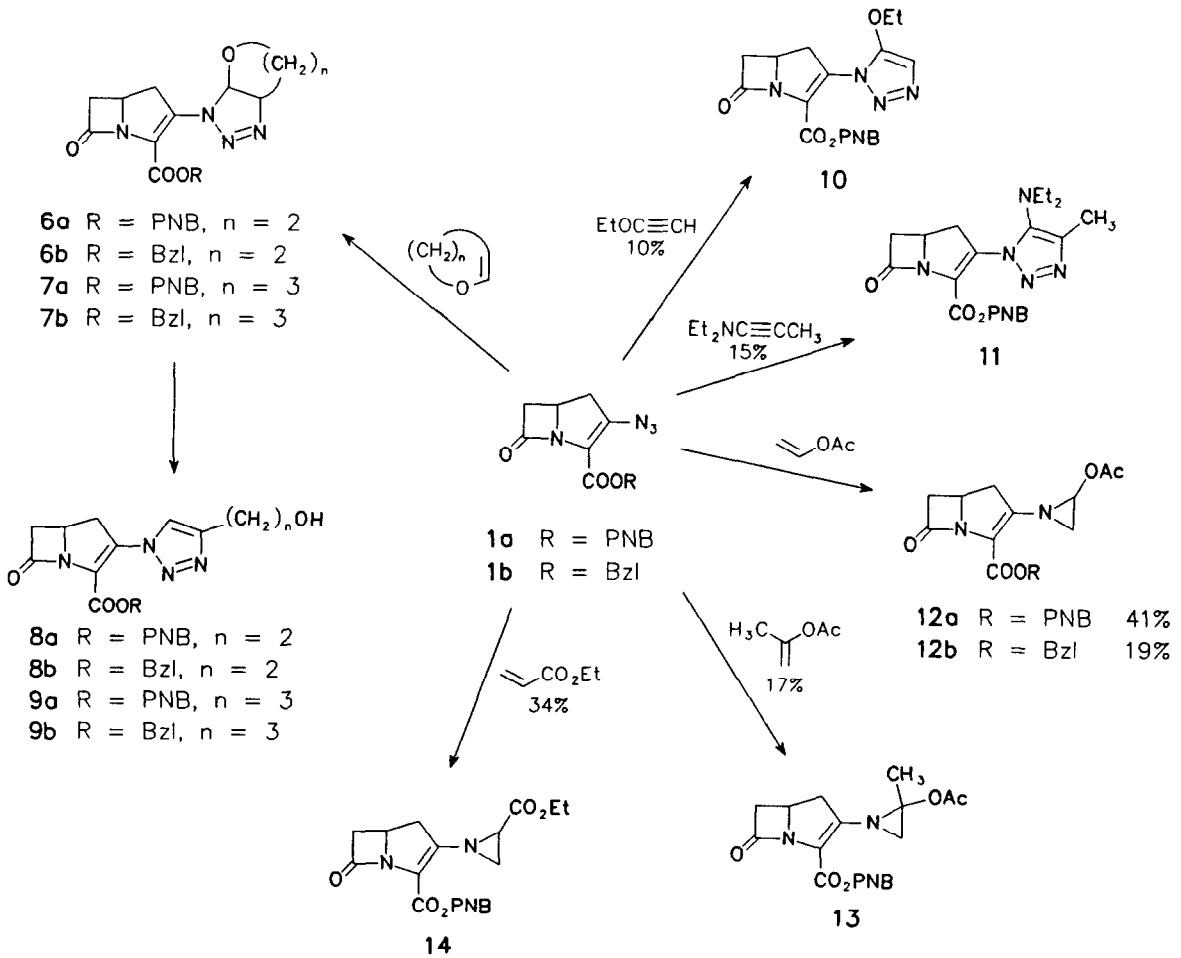


2a R = PNB, X = OTs
2b R = Bzl, X = OTs
2c R = Bzl, X = ONs
2d R = PNB, X = $OP(O)(OPh)_2$

1a R = PNB
1b R = Bzl

Like the recently reported cephem vinyl azides,[7] **1b** provides the enamine **3**[8] when hydrogenated (1 atm, $Pd/CaCO_3/Pb^{2+}$, dioxane, *t*BuOH, 25° C, 20 min). The enamine **3** was highly unstable, however, decomposing within hours when pure even at -78° C. Although no evidence for the imine tautomer **4** was observed, the strain in the carbapenem nucleus and the known propensity of the ketone **5** to undergo retro Diekmann reactions under mild conditions[5] suggest **4** may be an intermediate in an autocatalytic decompostion.

Azides **1a** and **1b** react slowly with dihydrofuran and dihydropyran (CH_2Cl_2, $NaHCO_3$, 4° C, 18 h to 6 d) initially to provide mixtures of isomers of the fused bicyclic 1,2,3-triazolines[9] **6a**[10] and **7a**,[11] and **6b**[12] and **7b**,[11] which subsequently isomerize under the reaction conditions to the hydroxyalkyl-1,2,3-triazoles[13] **8a**[14] and **9a**,[15] and **8b**[16] and **9b**,[17] resp. This observation stands in contrast to the reaction of cephem azides with dihydropyran, which afforded the iminoethers.[7] Although small amounts of iminoethers may be formed in our reaction mixtures, chromatographic and spectroscopic examination indicated that **6** and **7** predominated.



The low isolated yields of **8a-9b** apparently reflect the instability of these materials on contact with the chromatographic supports employed in their isolation, and not competitive side reactions *in situ*. Azide **1a** also reacts with ethoxyacetylene (neat, 25° C, 18 h) and more rapidly with 1-diethylamino-1-propyne (CH_2Cl_2, 0° C, 1.25 h) to provide low isolated yields of the 1,2,3-triazoles **10**[18] and **11**,[19] resp. The positions of the substituents on the triazole ring of **10** and **11** were assigned by analogy to literature precedents.[20] In contrast, cephem azides were reported to provide no triazoles in reaction with these reagents.[7]

In reactions with less electron rich olefins (CH_2Cl_2, $NaHCO_3$, 25° C, 2-3 d), 3-azidocarbapenems **1a** and **1b** formed aziridines. With vinyl acetate, azides **1a** and **1b** provided low yields of acetoxyaziridines **12a**[21] and **12b**,[22] while **1a** formed the acetoxymethylaziridine **13**[23] in reaction with isopropenyl acetate. Azide **1a** was sufficiently reactive to provide the carbethoxyaziridine **14**[24] in reaction with ethyl acrylate.

In all cases studied, hydrogenolytic removal of the PNB group provided highly unstable products of reduced microbiological activity relative to thienamycin.

REFERENCES

[1]K. Higashi, M. Takemura, M. Sato, and M. Furukawa, *J. Org. Chem.*, **50**, 1996 (1985).

[2]Mp 77° C (dec); R_f(5:1[v/v] Et_2O-EtOAc) 0.60; IR(neat): 2110, 1785, 1710 cm^{-1}; NMR: δ3.02 dd (J = 3, 16.5 Hz, 1H), 3.11 d (J = 9 Hz, 2H), 3.56 dd (J = 5, 16.5 Hz, 1H), 4.27 tdd (J = 3, 5, 9 Hz, 1H), 5.28 d (J = 13.5 Hz, 1H), 5.45 d (J = 13.5 Hz, 1H), 7.64 d (J = 8 Hz, 2H), 8.24 d (J = 8 Hz, 2H); UV (CH_2Cl_2) λ_{max} 269, 299 nm; MS (m/e): 329 (M^+), 315, 301, 287, 255, 136.

[3]Mp 84-84.5° C (dec); R_f(3:2 [v/v] PhMe-EtOAc) 0.60; IR(neat): 2110, 1785, 1710 cm^{-1}; NMR: δ2.99 dd (J = 3, 16 Hz, 1H), 3.07 d (J = 9 Hz, 2H), 3.52 dd (J = 5, 16 Hz, 1H), 4.25 m (1H), 5.30 d (J = 8 Hz, 1H), 5.33 d (J = 8 Hz, 1H), 7.37 m (5H); UV(CH_2Cl_2): λ_{max} 310 nm; MS (m/e): 256 (M^+-N_2), 243, 228, 214, 178, 162, 160, 137, 120, 107.

[4]U. S. Patent 4,357,342, Merck & Co., Inc., Nov. 2, 1982.

[5]R. W. Ratcliffe, T. N. Salzmann, and B. G. Christensen, *Tetrahedron Lett.*, 31 (1980).

[6]Prepared *in situ* from benzyl 2-oxocarbapenam-3-carboxylate (refs. 3 and 4 above), DMAP (0.2 eq.), *N,N*-diisopropylethylamine (1.2 eq.), and diphenyl chlorophosphate (1.05 eq.) in MeCN at 0° C.

[7]D. O. Spry and A. R. Bhala, *Heterocycles*, **22**, 2487 (1984).

[8]Ninhydrin positive; R_f(1:1 [v/v] PhMe-EtOAc) 0.20; IR: 3450, 3330, 1780, 1690 cm^{-1}; NMR: δ2.81 dd (J = 4, 16 Hz, 1H), 2.93 m (2H), 3.21 dd (J = 5, 16 Hz, 1H), 5.25 d (J = 13 Hz, 1H), 5.32 d (J = 13 Hz, 1H), 7.37 m (5H).

[9]Azides have been reported to react with cyclic vinyl ethers to provide exclusively 1,2,3-triazolines, see: R. Huisgen, L. Mobius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965); P. Scheiner, *J. Org. Chem.*, **32**, 2022 (1967); and B. Green and D. W. Liu, *Tetrahedron Lett.*, 2807 (1975). The regiochemistry of **6a-7b** is assigned by analogy to that described in these references.

[10]**6a**, 100% yield after 2.5 d; R_f(Et_2O) 0.43; IR(CH_2Cl_2): 1780, 1715 cm^{-1}; NMR: δ 2.36 and 2.54 m (2H), 2.97 dd (J = 3, 16 Hz) and 3.00 dd (J = 3, 16 Hz)(1H), 3.15 m (1H), 3.26 m (1H), 3.53 m (2H), 3.64 m (1H), 3.90 m (1H), 4.14 m (1H), 5.26 d (J = 14 Hz) and 5.52 d (J = 14 Hz) and 5.32 d (J = 15 Hz) and 5.46 d (J

= 15 Hz)(2H), 5.70 d (J = 6 Hz) and 5.80 d (J = 6 Hz)(1H), 7.67 broad d (J = 9 Hz, 2H), 8.14 d (J = 9 Hz, 2H).

[11] **7a** and **7b** were not isolated, but their existence is inferred by analogy and by their behavior on tlc.

[12] **6b**, 96% yield after 18 h; $R_f(Et_2O)$ 0.60; IR(CH_2Cl_2): 1780, 1710 cm^{-1}; NMR: δ2.32 m and 2.50 m (2H), 2.94 dd (J = 3, 17 Hz) and 2.96 dd (J = 3, 17 Hz) (1H); 3.14 m (1H), 3.24 m (1H), 3.48 m (2H), 3.60 m (1H), 3.84 m (1H), 4.10 m (1H), 5.30 m (2H), 5.72 d (J = 6 Hz) and 5.81 d (J = 6 Hz)(1H), 7.37 m (5H).

[13] Thermolytic or base-catalyzed elimination of alcohol from 1,2,3-triazolines to form 1,2,3-triazoles is known, see: R. Huisgen *et al.*, above ref. 6, and R. Huisgen and G. Szeimies, *Chem. Ber.*, **98**, 1153 (1965).

[14] **8a**, 26% yield after 9 d; $R_f(Et_2O)$ 0.08; IR(neat): 3600-3200, 1775, 1710 cm^{-1}; NMR: δ 2.52 t (J = 6.5 Hz, 2H), 2.96 dd (J = 3, 16.5 Hz, 1H), 3.35 dd (J = 8, 20 Hz, 1H), 3.54 dd (J = 5.5, 16.5 Hz, 1H), 3.71 t (J = 6.5 Hz, 2H), 3.82 dd (J = 10, 20 Hz, 1H), 4.20 m (1H), 5.28 d (J = 14 Hz, 1 H), 5.49 d (J = 14 Hz, 1H), 7.66 d (J = 9 Hz, 2H), 8.26 d (J = 9 Hz, 2H), 9.84 s (1H).

[15] **9a**, 23% yield after 46 h at 4° C and 51 h at 25° C; R_f(3:1 [v/v] Et_2O-EtOAc) 0.10; IR($CDCl_3$): 3600-3200, 1775, 1710 cm^{-1}; NMR: δ1.78 m (2H), 2.44 t (J = 7.5 Hz, 2H), 2.99 dd (J = 3, 17 Hz, 1H), 3.37 dd (J = 8, 20 Hz, 1H), 3.57 dd (J = 5, 17 Hz, 1H), 3.70 broad t (J = 6 Hz, 2H), 3.85 dd (J = 10, 20 Hz, 1H), 4.14 m (1H), 5.31 d (J = 14 Hz, 1H), 5.52 d (J = 14 Hz, 1H), 7.70 d (J = 9 Hz, 2H), 8.31 d (J = 9 Hz, 2H), 9.84 s (1H); UV(CH_2Cl_2) λ_{max} (ε): 272 (6000), 317 (8300) nm.

[16] **8b**, not isolated, $R_f(Et_2O)$ 0.10.

[17] **9b**, 6% yield after 6 d at 4° C; $R_f(EtO_2)$ 0.16; IR(CH_2Cl_2): 3600-3200, 1780, 1725 cm^{-1}.

[18] R_f(5:1 [v/v] Et_2O-EtOAc) 0.33; IR(CH_2Cl_2): 1785, 1735 cm^{-1}; NMR: δ1.32 t (J = 7 Hz, 3H), 3.23 dd (J = 3, 17 Hz, 1H), 3.44 d (J = 9 Hz, 2H), 3.67 dd (J = 6, 17 Hz, 1H), 4.13 q (J = 7 Hz, 2H), 4.46 m (1H), 5.28 d (J = 13 Hz, 1H), 5.40 d (J = 13 Hz, 1H), 7.54 d (J = 9 Hz, 2H), 8.26 d (J = 9 Hz, 2H), 8.26 s (1H); MS (m/e): 371, 329, 235, 207, 136.

[19] R_f(5:1 [v/v] Et_2O-EtOAc) 0.30; IR(CH_2Cl_2): 1785, 1730 cm^{-1}; NMR: δ0.92 t (J = 7Hz, 6H), 2.30 s (3H), 2.97 q (J = 7 Hz, 4H), 3.18 dd (J = 4, 17 Hz, 1H), 3.24 dd (J = 10, 18 Hz, 1H), 3.40 dd (J = 8, 18 Hz, 1H), 3.65 dd (J = 6, 17 Hz, 1H), 4.25 m (1H), 5.22 d (J = 14 Hz, 1H), 5.32 d (J = 14 Hz, 1H), 7.45 d (J = 9 Hz, 2H), 8.22 d (J = 9 Hz, 2H); MS (m/e): 440, 414, 412, 398, 384, 369, 357, 355, 341, 333.

[20] See T. L. Gilchrist and G. E. Gymer, *Advances in Heterocyclic Chemistry*, **16**, 33 (1974).

[21] R_f(5:1 [v/v] Et_2O-EtOAc) 0.20; IR(CH_2Cl_2): 1770, 1735 cm^{-1}; NMR: δ 1.90 dd (J = 6, 7 Hz, 1H), 2.10 t (J = 7 Hz, 1H), 2.13 s (3H), 2.76 broad d (J = 5 Hz, 2H), 2.85 dd (J = 2.5, 15 Hz, 1H), 3.25 dd (J = 5, 15 Hz, 1H), 4.12 m (1H), 4.87 dd (J = 6, 7 Hz, 1H), 5.27 s (2H), 7.49 d (J = 9 Hz, 2H), 8.25 d (J = 9 Hz, 2H).

[22] $R_f(Et_2O)$ 0.25; IR(CH_2Cl_2): 1770, 1735 cm^{-1}; NMR: δ 1.92 broad t (J = 6.5 Hz, 1H), 2.08 t (J = 7 Hz, 1H), 2.13 s (3H), 2.70 dd (J = 6, 17 Hz, 1H), 2.76 dd (J = 6, 17 Hz, 1H), 2.86 dd (J = 2, 15 Hz, 1H), 3.24 dd (J = 5, 15 Hz, 1H), 4.16 m (1H), 4.79 broad t (J = 7 Hz, 1H), 5.17 s (2H), 7.37 m (5H).

[23] R_f(5:1 [v/v] Et_2O-EtOAc) 0.25; IR(CH_2Cl_2): 1770, 1735 cm^{-1}; NMR: δ1.69 s (3H), 2.11 s (3H), 2.16 d (J = 7 Hz, 1H), 2.22 d (J = 7 Hz, 1H), 2.74 dd (J = 8, 17 Hz, 1H), 2.79 dd (J = 3, 16 Hz, 1H), 2.84 dd (J = 5, 17 Hz, 1H), 3.21 dd (J = 6, 16 Hz, 1H), 4.30 m (1H), 5.29 d (J = 12 Hz, 1H), 5.35 d (J = 12 Hz, 1H), 7.57 d (J = 9 Hz, 2H), 8.29 d (J = 9 Hz, 2H); MS (m/e): 402(M^+), 359, 342, 316, 300, 274, 258, 222.

[24] R_f(4:1 [v/v] Et_2O-EtOAc) 0.30; IR(CH_2Cl_2): 1780, 1735, 1710 cm^{-1}; NMR: δ1.30 t (J = 7 Hz, 3H), 1.65 broad t (J = 5 Hz, 1H), 1.93 m (1H), 2.6-2.8 m (4H), 2.95 dd (J = 5, 15 Hz, 1H), 4.05 m (1H), 4.21 q (J = 7 Hz, 2H), 5.32 s (2H), 7.25 d (J = 9 Hz, 2H), 8.30 d (J = 9 Hz, 2H); MS (m/e): 401(M^+), 355, 282, 265, 237, 223.

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