SYNTHESIS AND REACTIONS OF C(3)-AZIDO CEPHEM

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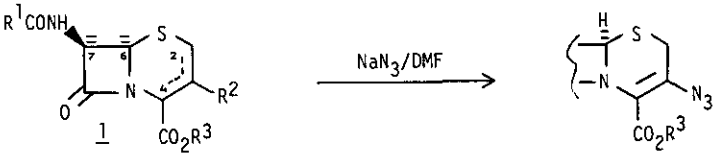
Abstract - The C(3)-azido cephem 2 reacts with Grignards to give triazines and with a variety of electron rich dipolarophiles to give C(3)-substituted amidines, imidates, iminolactones and aziridines.

The versatility of azides in organic synthesis is well known.[1] Azides, for example, can react with nucleophiles, electrophiles, dipolarophiles, they can be reduced to amines and they undergo photochemical and thermal decomposition to give highly reactive nitrenes. With this in mind we studied the chemistry of the C(3)-azido-Δ^3-cephem 2,[2] readily available by azide displacement of Δ^2- or Δ^3-C(3)-chloro or C(3)-tosylate 1.[3] The double bond in 2 preferentially assumes the Δ^3-configuration in order to obtain maximum delocalization of the azide electrons. In so doing the azide becomes electron deficient, so much so that it fails to react with dimethyl acetylenedicarboxylate to give the corresponding triazole.



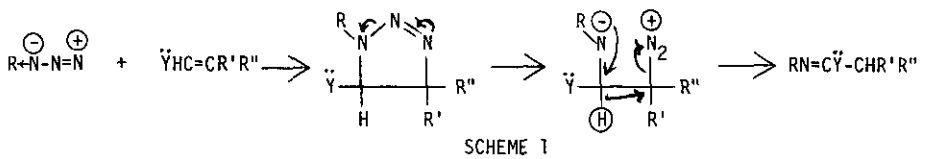
1 2 80-90%

R^1 =  CH_2, $PhOCH_2$, CH_3

R^2 = Cl, OTs

R^3 = CH_3, $CHPh_2$, PNB, $CH_2CH=CH_2$, CH_2CCl_3

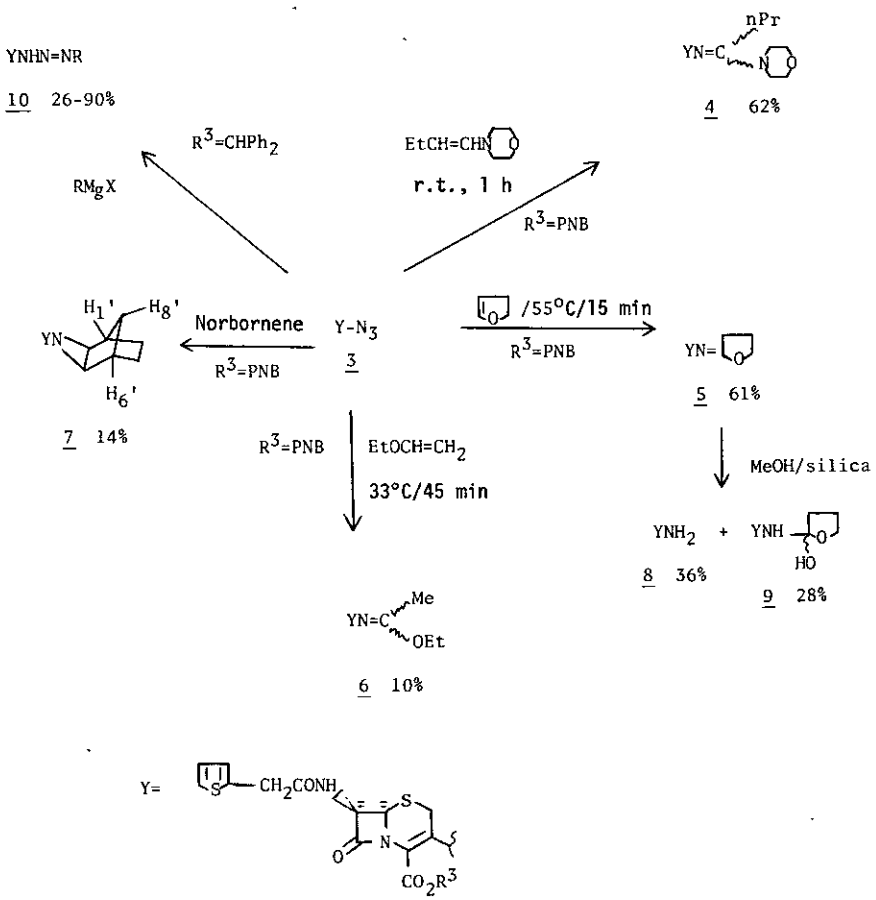
Electron deficient azides are known to react with difficulty with electron deficient dipolarophiles; one of the components in the cycloaddition must be electron rich.[1a] Such electron rich olefins normally react regioselectively with electron deficient azides to give a single adduct, a result of electronic control. The resulting unstable triazoline undergoes rearrangement via a diazonium zwitterionic intermediate to give aziridines, imidates or amidines.[4]



SCHEME 1

Thus the reaction of 3 (R^3=PNB) with the morpholine enamine of n-butyraldehyde[1a] at room temperature (1 h) gave 62% of chromatographed amidine 4,[5] while dihydrofuran[6] gave the iminolactone 5[7] in 61% yield and ethyl vinyl ether[8] gave the imidate 6[9] in only 10% yield. The activated, strained bicyclic olefin, norbornene,[10] gave the aziridine 7[11] in 14% yield. In most cases structures 4-7 have not been rigorously proven but rather assigned on the bases of analogous 1,3-dipolar cycloadditions with the same dipolarophile[1a,6,8,10] and an electron deficient azide. All gave the correct molecular ion and nmr spectra compatible with the given structure. Methanolysis of 5, followed by silica chromatography, gave 36% C(3)-amino cephem 8 and 28% of the hydrated product 9, in agreement with the work of Edwards and Brown[12] with ethyl azidoformate and 2,3-dihydropyran.[13]

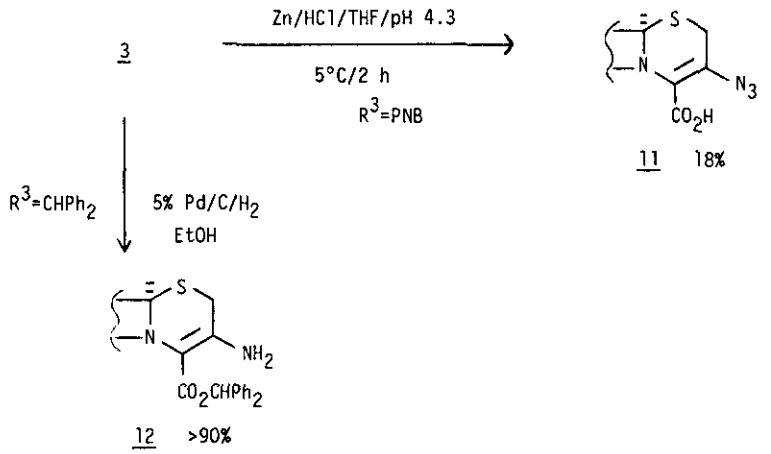
Conditions could not be found for obtaining the corresponding triazole from 3 (R=PNB) using ethoxyacetylene,[1a] or 1-diethylamino-1-propyne[14] or 1-benzoyl-2-morpholino-1-propene.[15] Nor could the tetrazole be obtained from the reaction of the azide with trichloroethylcyanoformate.[1a]



Removal of the PNB ester from 4 and 6 gave problems; however, use of the allyl ester followed by a McCombie type cleavage[16] gave the corresponding acids, which showed reduced microbiological activity relative to cephalothin.

Addition of methyl Grignard to the C(3)-azide 3 (R^3=$CHPh_2$) gave the crude triazene 10 (R=Me) in greater than 90% yield, however, chromatography on silica gel gave 50% C(3)-amino cephem 12, an apparent result of the triazene methylating water and indeed the crude triazene reacted with 3,5-dinitrobenzoic acid to give 51% 3,5-dinitromethylbenzoate.[17,18] The phenyl triazene 10 (R=Ph)[19] could be chromatographed, although in low yield (26%).

Hydrogenation of the C(3)-azide 3 (R^3=$CHPh_2$) over palladium on carbon gave the C(3)-amino 12 in quantitative yield, while Zn/HCl (pH 4.3) reduction[20] at 5°C for 2 h gave 18% of the C(3)-azido acid 11, which showed somewhat reduced microbiological activity relative to cephalothin.



ACKNOWLEDGEMENT

The authors wish to thank Wayne A. Spitzer for his encouragement and helpful discussions.

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1. (a) G. L'abbe, Chem. Rev., 1969, 69, 345.
(b) "The Chemistry of the Azido Group", ed. by S. Patai, Interscience, 1971.
2. Initial azide synthesis was done by W. A. Spitzer.
3. R^1=  , R^3=PNB: *m/e* 490 (M-10, $-N_2+H_2O$); ir ($CHCl_3$) 2105, 1780 cm^{-1}; nmr ($CDCl_3$) δ 3.57 (s, 2, C(2) protons), 3.83 (s, 2, thiophene), 5.00 (d, J=4 Hz, H_6), 5.73 (d, d, J=4, 8 Hz, 1, H_7).
4. (a) P. Scheiner, "Selective Organic Transformations", ed. by B. S. Thyagarajan, Wiley-Interscience, New York, 1970, Vol. 1, pp. 327-362.

(b) G. Bianchi, C. De Micheli, and R. Gandolfi, "The Chemistry of Double Bonded Functional Groups", ed. by S. Patai, John Wiley and Sons, Inc., New York, 1977, p. 460.

5. 4: m/e 613; ir ($CHCl_3$) 1768 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (t, 3, $CH_2CH_2CH_3$), 1.44 (m, 2, $\underline{CH_2}CH_3$), 2.26 (m, 2, $\underline{CH_2}CH_2CH_3$), 2.99, 3.10 (AB, J=12 Hz, 2, C(2) protons, 3.50, 3.69 (m, 4, morpholine), 3.90 (s, 2, thiophene), 5.10 (d, J=4 Hz, 1, H_6), 5.12, 5.30 (AB, 2, PNB), 5.49 (d, d, J=4.8 Hz, 1, H_7).

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7. 5: m/e 542; ir ($CHCl_3$) 1765 cm^{-1}; nmr ($DMSOd_6$) δ 2.00 (m, 2, furan $H_{4'}$), 2.50 (m, 2, furan $H_{3'}$), 3.46 (s, 2, C(2) protons), 4.23 (m, 2, furan $H_{5'}$), 5.16 (d, J=4 Hz, 1, H_6), 5.32 (AB, 2, PNB), 5.54 (d, d, J=4,8 Hz, 1, H_6).

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9. 6: m/e 544; ir ($CHCl_3$) 1772 cm^{-1}; nmr ($CDCl_3$) δ 1.25 (t, J=7 Hz, 3, CH_2CH_3), 1.73 (s, 3, CH_3), 3.12, 3.28 (AB, J=17 Hz, 2, C(2) protons), 3.88 (s, 2, thiophene), 4.10 (q, J=7 Hz, 2, CH_2CH_3), 5.50 (d, J=4 Hz, 1, H_6), 5.27 (m, 2, PNB), 5.60 (d, d, J=4,8 Hz, 1, H_7).

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11. 7: m/e 566; ir ($CHCl_3$) 1762 cm^{-1}; nmr ($CDCl_3$) δ 0.86 (d, J=10 Hz, 1, H_1, anti), 1.22 (m, 2, $H_{7'}$), 1.36 (d, $J_{8,8'}$=10 Hz, 1, H_1, syn), 1.51 (m, 2, $H_{6'}$), 2.46 (d, $J_{2',4'}$=4 Hz, 1, $H_{2'}$), 2.54 (Bs, 2, $H_{1'}$, $H_{5'}$), 2.62 (d, $J_{2',4'}$=4 Hz, $H_{4'}$), 3.01, 3.14 (AB, J=12 Hz, 2, C(2) protons), 3.90 (s, 2, thiophene protons), 5.07 (d, J=4 Hz, 1, H_6), 5.20, 5.40 (AB, 2, PNB), 5.38 (d, d, J=4.8 Hz, 1, H_7).

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13. Reaction of 3 (R^3=PNB) with dihydropyran (85°C/15 min) followed by silica chromatography gave 25% iminolactone plus 46% hydrated product.

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19. 10: R=Ph: m/e 609; ir ($CHCl_3$) 1775 cm^{-1}; UV (EtOH) 368 nm, ε 18,250; nmr ($CDCl_3$) δ 3.72 (s, 2, C(2) protons), 5.07 (d, J=4 Hz, 1, H_6), 5.67 (d, d, J=4,8 Hz, 1, H_7), 11.95 (s, 1, NH-N=NPh, replaceable with D_2O).

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