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STUDIES ON THE SYNTHESIS OF CORRINS AND RELATED LIGANDS. AN ALTERNATE SYNTHESIS OF "SEMICORRIN E"

Robert V Stevens* and Edward B. Reid

Department of Chemistry, Rice University, Houston, Texas 77001

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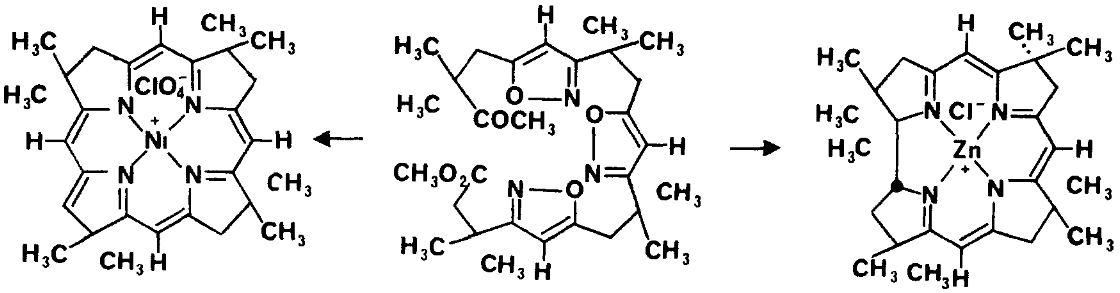
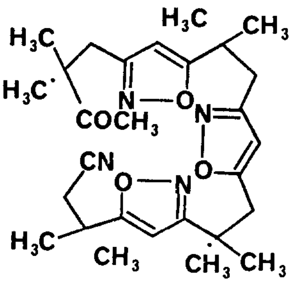
As part of a program whose ultimate goal is the total synthesis of vitamin B-12,[1] we have recently developed new methodology for construction of the macrocyclic corphin (1)[2] and corrin (3)[3] ligands. A key intermediate in these studies was the triisoxazole 2 which serves as a latent synthon for three of the vinylogous amidine chromophores common to each of these macrocycles However, as noted previously,[4] all of the structural features of these ligands can also be incorporated into the isomeric triisoxazole 4 which, in principle, can be assembled from the nitrile oxides and terminal acetylenes shown in diagram 5 It should be noted that all four subunits (5A-D) are, in principle, derivatives of acetylenic nitrile 5D. The possibility of constructing both macrocyclic ligands from this single starting material was sufficiently intriguing to prompt us to test the chemistry required to achieve this goal



1 2 3



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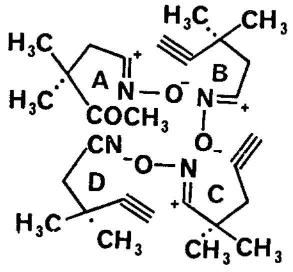

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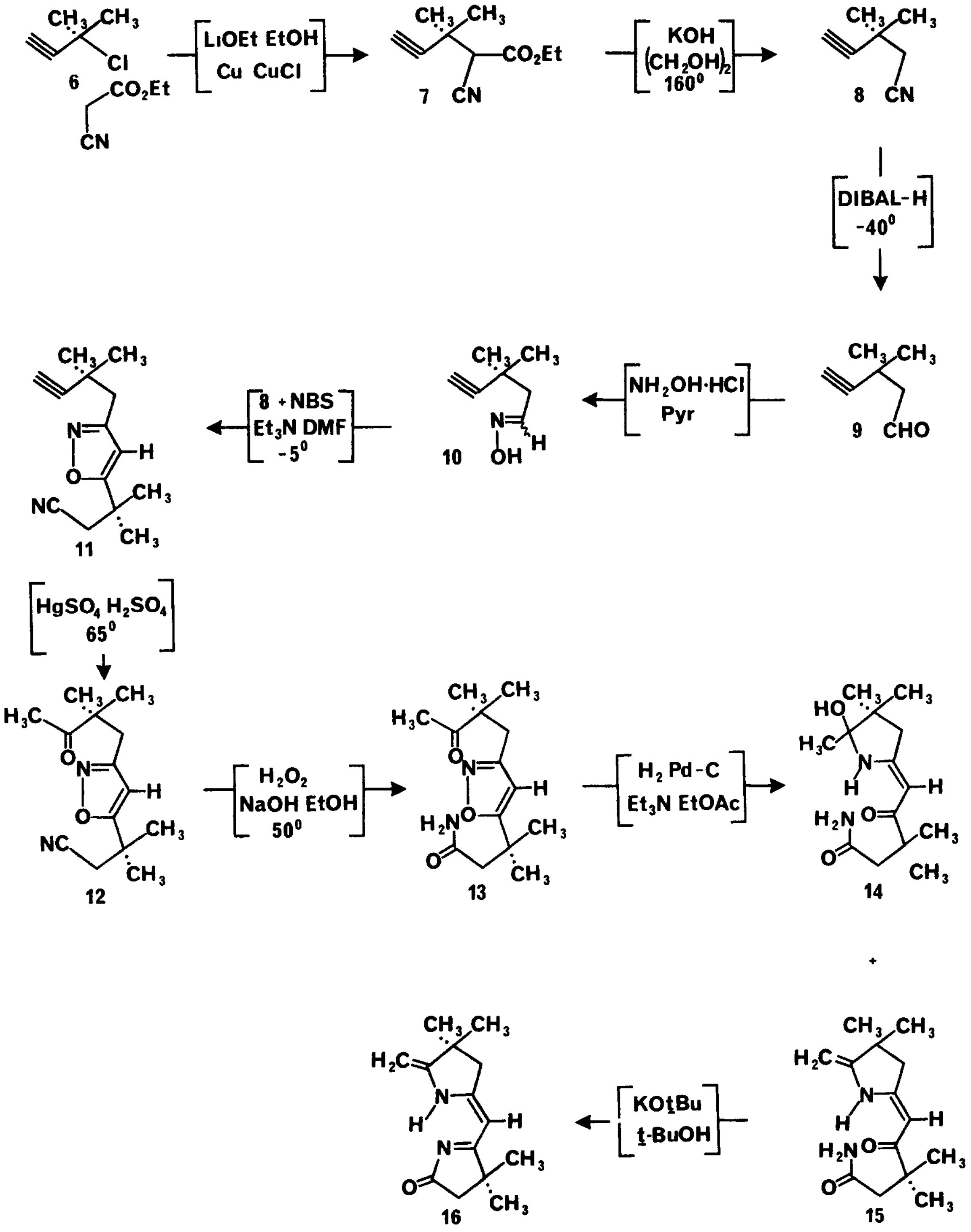
As in the case of diethyl malonate,[5] the direct alkylation of ethyl cyanoacetate with 3-chloro-3-methyl-1-butyne (6) gave very low yields of the desired adduct 7. However, in the reaction of similar halides with amines, Hennion[6] observed that a mixture of copper powder and CuCl enhanced greatly both the rate and yields of substitution. Application of this modification in the present case provided 45-52% yields of pure cyanoester 7 (bp 61-63°/0 3 mm)[7] Decarboethoxylation of 8 with KOH in hot ethylene glycol[8] gave the desired nitrile 8≡5D (bp 76-78°/41 mm) in 70% yield. Careful reduction of this intermediate with diisobutylaluminum hydride (DIBAL-H) yielded aldehyde 9 (75%, bp 136-138°) which was converted to a mixture of *syn*- and *anti*-aldoximes 10 (bp 95-96°/21 mm) by treatment with NH$_2$OH HCl in pyridine The mixture of aldoximes was converted *in situ* into the corresponding nitrile oxide (5C) in the presence of five equivalents of nitrile 8 by employing the NBS/Et$_3$N/DMF procedure employed previously[4] This afforded a 65-70% yield of isoxazole 11 which was converted to ketone 12 (85%, bp 155°/0 2 mm) by mercuric ion catalyzed Markovnikov hydration. Hydrolysis of nitrile 12 to amide 13 (85%, mp 97-97.5°) was achieved with alkaline H$_2$O$_2$. Catalytic hydrogenolysis of this isoxazole provided a solid (100%, mp 121-125°) whose pmr spectrum clearly demonstrated was a mixture of vinylogous amides 14 and 15. Treatment of this mixture with 2 5 equivalents of KO*t*Bu afforded "semicorrin E" (16) identical in all respects with an authentic sample[4]


6
LiOEt EtOH
Cu CuCl
7
KOH
(CH2OH)2
160°
8
DIBAL-H
-40°
9
NH2OH·HCl
Pyr
10
8 + NBS
Et3N DMF
-5°
11
HgSO4 H2SO4
65°
12
H2O2
NaOH EtOH
50°
13
H2 Pd-C
Et3N EtOAc
14
+
15
KOtBu
t-BuOH
16

This study clearly demonstrates the feasibility of assembling triisoxazole **4** from a single precursor (**8**≡**5D**) This exciting opportunity is presently being pursued

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References and Notes

(1) R. V. Stevens, *Proc 24th National Organic Symposium*, June 22-26, 1975, pp. 21-35.

(2) R. V. Stevens, C. G. Christensen, R. M Cory and E Thorsett, *J Am. Chem. Soc.*, **97**, 0000 (1975).

(3) R. V Stevens and E Thorsett, unpublished results

(4) R V Stevens, L E. DuPree, Jr., W L. Edmonson, L L Magid and M. P. Wentland, *J. Am. Chem. Soc* , **93**, 6638 (1971)

(5) O K Behrens, J. Corse, D E Huff, R G Jones, Q. F Soper and C. W. Whitehead, *J. Biol. Chem* , **175**, 771 (1948)

(6) G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem* , **30**, 3696 (1965) and references cited therein.

(7) The structures of all new compounds reported in this paper are supported by ir, pmr, and mass spectral analysis.

(8) F. S. Prout, R. J Hartman, E. P.-Y. Huang, C J. Korpics, and G. R Tichelaar, *Org Syn Coll. Vol* , **4**, 95 (1963).