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Rearrangement/Bromocyclization of O-Cyclohexenyl Carbamidates. Model Studies for Aminocyclitol Synthesis

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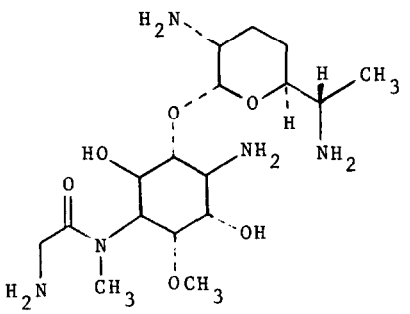
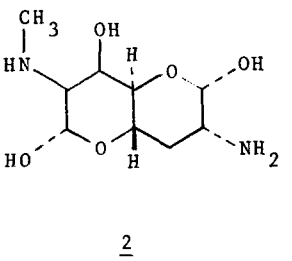
Summary: A three step method for conversion of 2-cyclohexen-1-ol (4) to the protected 1,2,3-methylamino-hydroxyl-bromocyclohexane 18 is described.

The cis-1,2-methylamino-hydroxyl functionality occurs frequently among aminocyclitol antibiotics.[1] Representative structures include fortimicin A (1)[2], the diaminooctose portion of apramycin (2)[3], and spectinomycin (3).[4] Evidence has been presented in the case of 1 that the N-methyl group at C-4 is actually required for biological activity.[5] In considering the total synthesis of aminocyclitol antibiotics from non-carbohydrate precursors, we initially focused on the problem of introducing the amino group onto a cyclohexyl ring. This had been achieved in a clever way by Overman, who described the [3,3] sigmatropic rearrangement of O-3-cyclohexenyl-trichloroacetamidate.[6] We have modified the rearrangement to provide 1) an N-methyl substituent, 2) a resultant N-protecting group which allows further useful transformation, and 3) some flexibility for the preparation of secondary amines in general. We wish to report that the rearrangement of O-3-cyclohexenyl-carbamidates, followed by bromocyclization of the unsaturated carbamate, provides a direct route to the cis-1,2-methylamino-hydroxyl functionality in suitable form for aminocyclitol synthesis.



1



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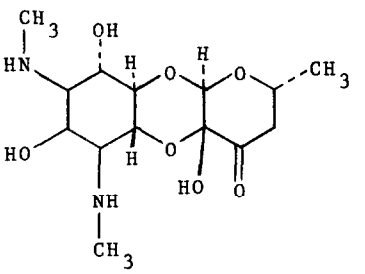
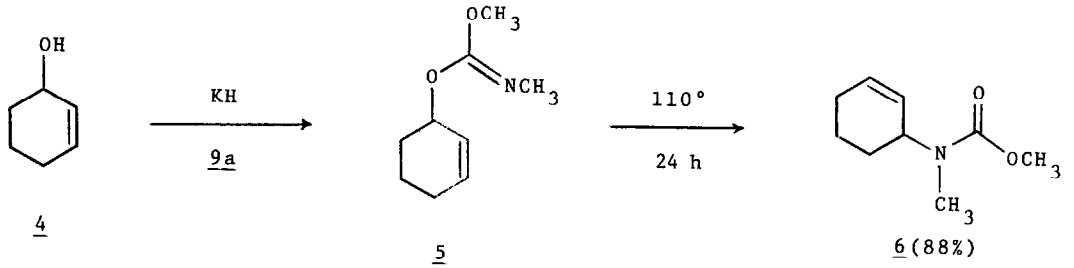


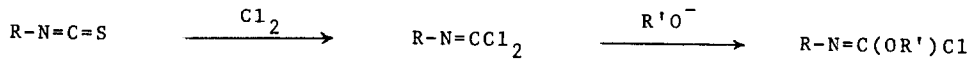
3

The requisite carbamidates were prepared by treatment of the potassium salt of the alcohol (KH, THF, 25°) with the appropriate imidoyl chloride (see below). In this way 2-cyclohexen-1-ol (4) was converted to carbamidate 5. Rearrangement of 5 occurred at 110°, giving 6 in 88% overall yield from 4. The reaction was most conveniently performed in CCl_4 solution in a sealed NMR tube so that progress of the reaction could be monitored.



4 5 6 (88%)

Four different imidoyl chlorides 9 a-d were obtained by chlorination[7] of the isothiocyanate 7, then displacement of one chloride of 8 by sodium methoxide or potassium benzyloxide in ether at 25°. The use of 9 b-d with several cyclic allylic alcohols to prepare N-allyl carbamates 10 - 15 is shown in the Table. Since different R groups tolerate the rearrangement, and a number of isothiocyanates 7 are available, this method should serve for the preparation of a variety of protected secondary amines. The nature of the carbamate protecting group may also be adjusted by changes in R' as illustrated by the synthesis of benzyloxycarbonyl-protected amine 12 (entry 3). Entries 4,5, and 6 establish that the rearrangement is probably of the [3,3] sigmatropic variety[6], since ^{1}H NMR spectra of the products 13 - 15 show that complete migration of the carbon-carbon double bond has occurred. Introduction of the substituted nitrogen at a hindered position (entry 4) is feasible, but a competing thermal elimination reaction (leading to $PhCH_2NHCO_2CH_3$) reduces the yield. A thiocarbamidate was also prepared and rearranged for comparison (entry 7).

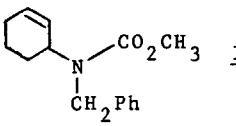
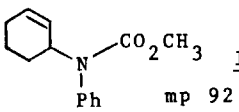
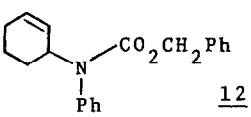
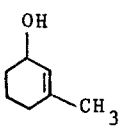
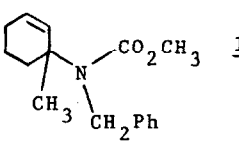
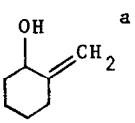
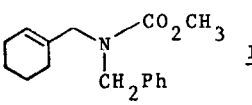
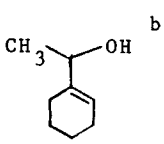
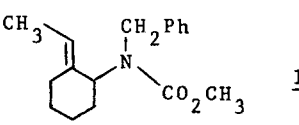
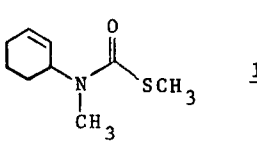


7 8 9

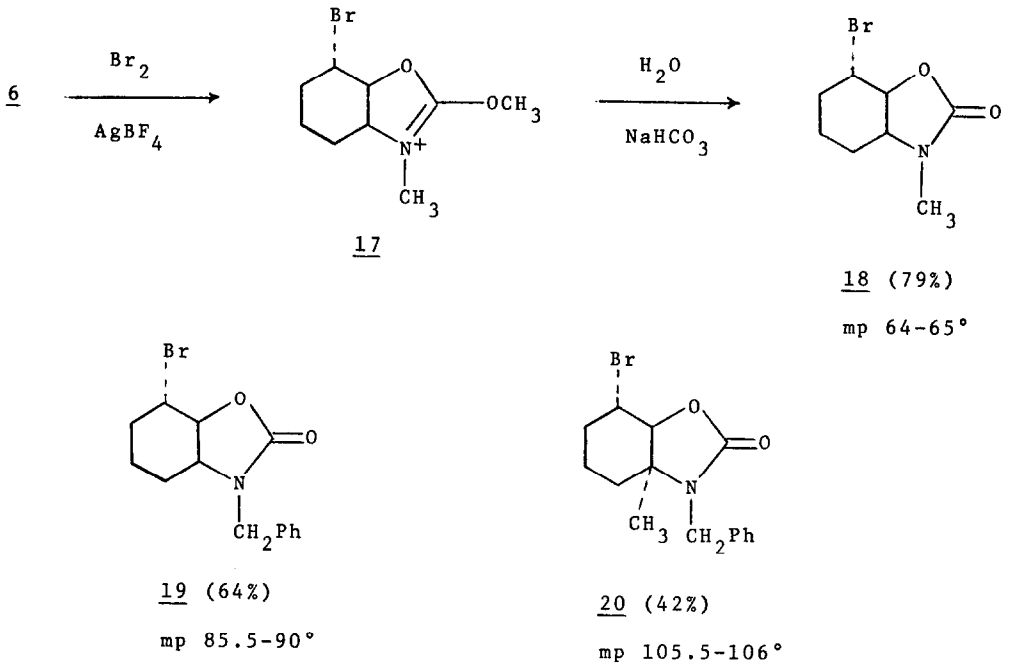
a. R = CH_3, R' = CH_3 c. R = Ph, R' = CH_3
b. R = CH_2Ph, R' = CH_3 d. R = Ph, R' = CH_2Ph

Treatment of 6 with Br_2 and $AgBF_4$ in CH_2Cl_2 solution at -78° caused disappearance of the starting material within 10 min (tlc analysis). We assume the formation of iminium salt 17 by analogy to other halocyclizations[8,9], although no characterization was attempted. Quenching the reaction at 25° with aqueous $NaHCO_3$ gave the crystalline bromocarbamate with structure 18, according to its IR and ^{1}H NMR spectra.[10] In the same way 10 and 13 gave 19 and 20, respectively. This bromocyclization reaction secures the cis-1,2-methylamino-hydroxyl functionality in protected form and provides a bromo substituent which is available for nucleophilic displacement, reductive removal, or dehydrobromination. The sequence allylic alcohol → bromocarbamate also provides potential access to N-substituted (as from 19) or ring-substituted (as from 20) aminocyclitol analogues.

Table. Synthesis of N-allyl carbamates

entry	allylic alchol	imidoyl chloride	conditions[c]	product (% yield)[d]
1	4	9b	110° 24 h	 10 (76)
2	4	9c	98° 48 h	 11 (70) mp 92.5-93.5°
3	4	9d	90° 24 h	 12 (70)
4		9b	80° 43 h	 13 (45)[e]
5	 [a]	9b	100° 30 h	 14 (73)
6	 [b]	9b	90° 72 h	 15 (63)[f]
7	4	g	110° 24 h	 16 (50)

a. Dreiding, A.A.; Hartman, J.A. J. Amer. Chem. Soc. 1953, 75, 3723.
b. This alcohol was prepared by $NaBH_3/CeCl$ reduction of 1-acetylcyclohexene. Gemal, A.L.; Luche, J.-L. J. Amer. Chem. Soc. 1981, 103, 5454.
c. The reactions were carried out on a 1-2 mmol scale in CCl_4 solution in a sealed NMR tube.
d. Yields (overall for two steps) refer to product isolated by chromatography on silica gel. The assigned structures are supported by IR and ^1H NMR spectra.
e. $PhCH_2NHCO_2CH_3$ was also isolated (50% yield). Compound 13 was shown to be stable to the reaction conditions.
f. Only one rearranged carbamate was isolated, presumably the E isomer.[6]
g. The thio analogue of 5 was prepared by treating the sodium salt of 4 with CH_3NCS, then CH_3I in THF at 25°.



We are currently exploring the application of these reactions to aminocyclitol total synthesis.

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References and Notes

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9. Iodocyclization of an unsaturated carbamate was used to great advantage in the synthesis of methyl α,L-garosaminide. Pauls, H.W.; Fraser-Reid, B. J. Amer. Chem. Soc. 1980, 102, 3956.
10. Compound 18 IR (KBr): 1760 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 60 MHz): δ 4.55 (app t, J - 6.5 Hz, 1H), 4.0-4.4 (m, 1H), 3.6-4.0 (m, 1H), 2.74 (s, 3H), 1.4-2.4 (m, 6H).

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