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NEW ROUTES TO CIS-1,2-HYDROXYAMINES AND RELATED SYSTEMS

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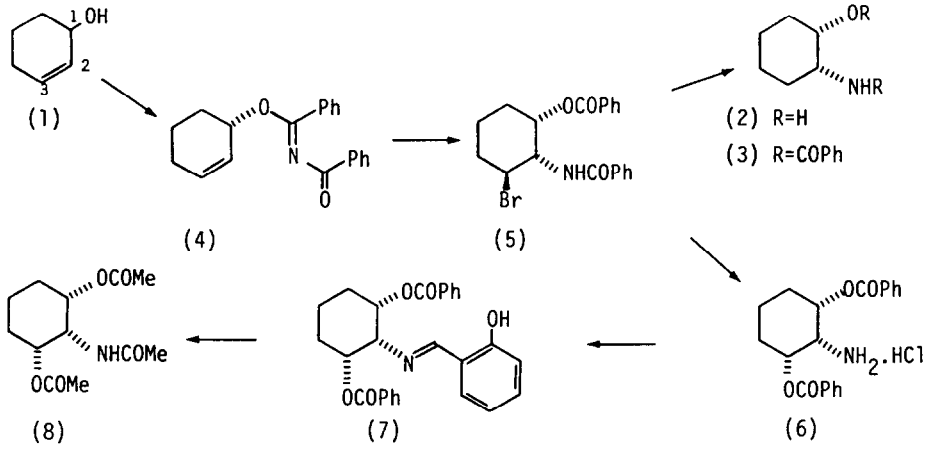
ABSTRACT: Use of modified Mitsunobu reactions followed by intramolecular cyclisations have been used to prepare cis-1,2-hydroxyamines, cis-1,3-hydroxyamines, 1,2,3-dihydroxyamines and 1,2,3-diaminoalcohols from allylic alcohols.

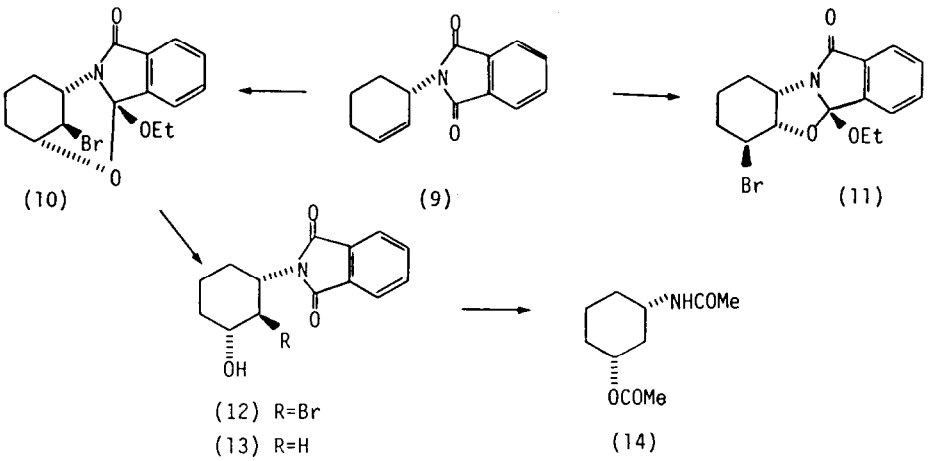
The cis-1,2-hydroxyamino- group occurs widely in natural products such as the aminocyclitol antibiotics[2] and amino sugars, eg. daunosamine[3] and acosamine.[4] Several workers have recently published routes to the 1,2-hydroxyamino system using an intramolecular cyclisation of a trichloroacetimidate[5] or a carbamate[6] group. Herein we describe new, efficient and controlled routes to the cis-1,2-hydroxyamino and cis-1,3-aminohydroxy systems as well as opening general routes to amino-alcohols containing oxygen and nitrogen substituents at three contiguous carbon centres.

Preparation of cis-2-aminocyclohexan-1-ol (2) from cyclohex-2-en-1-ol (1) was achieved by use of a modified Mitsunobu reaction.[7] Thus the alcohol (1) was converted to the imidate (4)[8], m.p. 148-150°C, using triphenylphosphine and diethyl azodicarboxylate in the presence of dibenzoylimide at room temperature. Cyclisation of the imidate (4) with N-bromosuccinimide in chloroform containing ethanol gave the bromo-amide ester (5), m.p. 160-162°C. Removal of the bromine atom with tributyltin hydride, followed by acid hydrolysis of the amide ester (3), m.p. 149-150°C, gave the cis-1,2-amino-alcohol (2) isolated as its hydrochloride, m.p. 182-184°C (lit.[9] 189-190°C) in overall 62% yield.



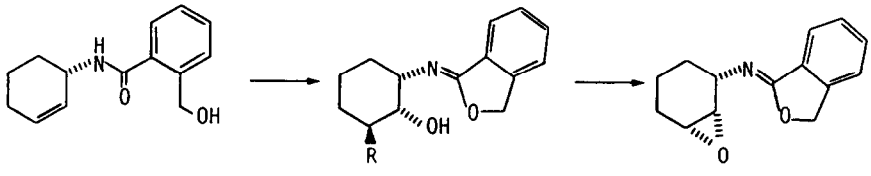
Attempted solvolysis of the bromo-ester (5), using 6M hydrochloric acid, resulted in neighbouring group participation by the benzamido group. ^{13}C N.m.r. analysis of the product aminodiester (6), m.p. 183-185°C, indicated that the oxygen and nitrogen substituents were all cis- orientated. The latter ester could be converted to the known acetamido-diacetate (8), m.p. 180-182°C (lit.[10] 177.5-179°C) by initial protection of the amino group, as the imine (7), m.p. 159-161°C, followed by base-catalysed hydrolysis and acetylation using acetic anhydride in pyridine. The overall yield of the diacetate (8), from the allylic alcohol (1), was 32%.

In an alternative approach to the title compounds the starting allylic alcohol (1) was initially reacted with phthalimide, under the Mitsunobu conditions, to give the protected allylic amine (9), m.p. 113-114 °C (lit.[11] 114.5°C) in 57% yield. Reaction of the amide (9) with N-bromosuccinimide in ethanolic chloroform gave the orthoamide (10) as a colourless gum. ^{13}C N.m.r. analysis indicated the presence of only one isomer and consistent with attack at C-3 of the cyclohexane ring by a carbonyl oxygen atom of the precursor phthalimide. In this case the 5-membered imide ring constrains the oxygen atom to attack in a 1,3 manner; the isomeric orthoamide to be expected from 1,2-attack, viz isomer (11), is, presumably much more strained.

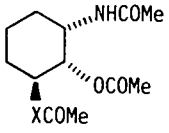


Acid hydrolysis of the orthoamide (10) afforded the bromo-alcohol (12), m.p. 171-173°C, thus confirming the structure of the intermediate. Reductive dehalogenation in the usual manner gave the alcohol (13), m.p. 205-207°C, which, after deprotection of the nitrogen and acetylation, gave the known cis-amido-ester (14), m.p. 116-118°C (lit.[12] 119-120°C) in overall 68% yield from the amide (9).

In order to direct attack of the oxygen atom at C-2 of the cyclohexane ring, the steric constraint of the phthalimide group in the imide (9) was initially removed by reduction with sodium borohydride to give the hydroxyamide (15), m.p. 114-116°C. Under the usual cyclisation conditions the bromo-alcohol (16), m.p. 166-168°C, was obtained. In this case ethanol was not necessary as a co-solvent since the hydroxymethyl group in the amide (15) acts as an internal nucleophile. Reductive dehalogenation of the amide (16) and base hydrolysis of the resulting imino-ether (17), m.p. 97-99°C, afforded cis-2-aminocyclohexan-1-ol (2), isolated as its hydrochloride, m.p. 180-182°C, in overall 49% yield.



(15) (16) R=Br (17) R=H (18)



(19) X=NH
(20) X=O

The bromo-alcohol (16) is a useful intermediate for the preparation of the other amino-alcohols. Thus treatment with silver oxide in tetrahydrofuran gives the epoxide (18). Under a variety of conditions opening of the epoxide always occurred at position C-3. Thus reaction with ammonia, followed by acetylation gave the acetamido-acetate (19), m.p. 203-205°C, in 71% yield from the imide (9).

Treatment of the epoxide (18) with perchloric acid followed by acetylation of the crude reaction mixture gave the amide diacetate (20), m.p. 147-149°C, in 67% yield from the imide (9).

Although the above reactions have been exemplified with cyclohexenol as starting material they are generally applicable to allylic alcohol allowing the production of a range of amino-alcohol derivatives in a regioselective and stereoselective manner.[13]

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