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AN IMPROVED SYNTHESIS OF

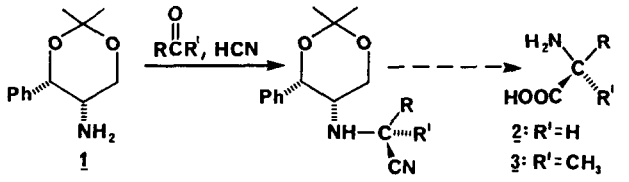
(4S,5S)-2,2-DIMETHYL-4-PHENYL-1,3-DIOXAN-5-AMINE

Ivan C. Nordin and James A. Thomas*

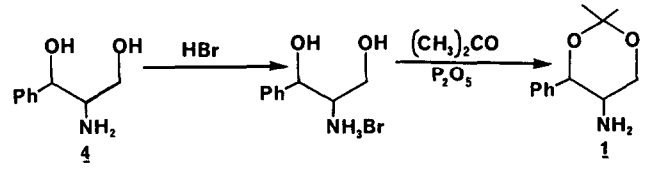
Warner-Lambert/Parke-Davis Co.
Pharmaceutical Research
Holland, MI. 49423 USA

ABSTRACT: The title compound is prepared in 78% yield using an improved one-pot procedure which does not require final purification.

The title compound (4S,5S)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-amine (1) is an effective reagent for the synthesis of optically active amino acids (2)[1] and ∝-methyl amino acids (3)[2,3] as shown in Scheme 1. The literature methods for the synthesis of 1 use a reaction scheme similar to Scheme 2, reporting 36%[4] and 56%[5] yields of 1, depending on work-up conditions.



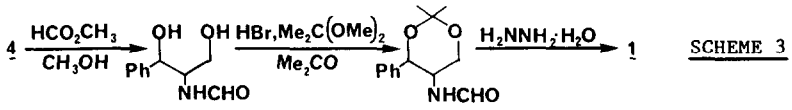
SCHEME 1



SCHEME 2

In our laboratories this scheme worked satifactorily on a small scale (ca. 0.1 mol). However, on increasing the reaction scale, this method became difficult due to the large amounts of acetone required, phosphate residues that required special disposal, and a crude product requiring fractional distillation prior to further usage.

We have developed an alternate synthesis which may be conducted in one pot, whose product is suitably pure for most purposes without distillation, and is easily scaled up. In the improved method, shown in Scheme 3, aminodiol 4 is treated with methyl formate in methanol; followed by treatment with acetone, 2,2-dimethoxypropane and catalytic HBr; and finally hydrazinolysis yields the desired compound 1 in 79% yield from 4.



SCHEME 3

An analogous sequence using acetic anhydride to give the N-acetyl protecting group also routinely gave 80% yields. However, the hydrazinolysis reaction took much longer (60+ hours) for completion. The product was equivalent in all respects to the N-formyl protected reaction variant.

EXPERIMENTAL *All solvents and reagents are used as commercially obtained with no further purification.* (1S,2S) 2-Amino-1-phenyl-1,3-propanediol was obtained from Quimica Sintetica, S.A., Madrid.

To a 2 L flask was added 200 g (1.196 mol) of 4, 1 L of methanol and 83 mL (85.5 g = 1.42 mol) of methyl formate[6]. The mixture was stirred at ambient temperature for 3.5 hours then the solvent was evaporated in vacuo. To the crystalline residue was added 1.5 L of acetone, 220 mL (187 g = 1.78 mol) of 2,2-dimethoxypropane and 80 mL of 1.0 M HBr (in methanol). The mixture was stirred in an ice water bath for 2.5 hours and the solvents were evaporated in vacuo. To the viscous residue was added 1 L of 85% hydrazine hydrate and the mixture was refluxed for 2 hours. The cooled mixture was extracted with 3 - 200 mL portions of toluene. The combined extracts were washed with a 50 mL portion of water, dried (Na_2SO_4), and evaporated to give 195.8 g (79%) of a yellow oil,

1: NMR ($CDCl_3$): 1.3(2H,s); 1.5(6H,s); 2.75(1H,ddd,J=2, 2,3 hz); 3.85(1H,dd,J=2, 12 hz); 4.3(1H,dd,J=3,12hz); 5.1(1H,d,J=2 hz); 7.35(5H,s).

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(6) For best results, the methyl formate should be stored over anhydrous sodium carbonate prior to use. Alternately, ca. 3.0 g of sodium methoxide may be added to the reaction as an acid scavenger.

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