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THE USE OF TRIPHENYLPHOSPHINE/DIETHYL AZODICARBOXYLATE (DEAD) FOR THE CYCLIZATION OF 1,4- AND 1,5-AMINO ALCOHOLS

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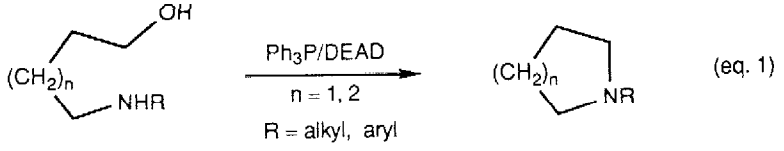
Summary: Application of the Mitsunobu reagent to the cyclization of 1,4- and 1,5-amino alcohols provided an assortment of azacycles in good to excellent yield.

As part of a project directed toward the synthesis of polyhydroxylated azacycles, we required a mild, convenient procedure for the cyclization of a series of amino alcohols. Previously, the Mitsunobu reagent[1] (Ph_3P/DEAD) has been used to produce aziridines from 1,2-amino alcohols[2] and azetidines from 1,3-amino alcohols[3] but to our knowledge this procedure had not been applied to the synthesis of larger azacycles.[4] Recently, we described the cyclization of a pair of 1,4-amino alcohols under Mitsunobu conditions to give 2-vinyl pyrrolidines.[5] We report here that treatment of a variety of 1,4- and 1,5-amino alcohols with Ph_3P/DEAD affords pyrrolidines, piperidines and related multicyclic systems in good to excellent yields (equation 1).

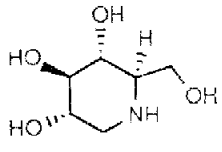


(eq. 1)

The general procedure for cyclization involved treatment of a 0.05-0.2M anhydrous tetrahydrofuran or dichloromethane solution of the amino alcohol with 1.0 or more equivalents of Ph_3P followed by an equimolar portion of DEAD. The reactions were carried out at room temperature under nitrogen and were monitored by TLC for disappearance of starting material. Addition of water and extractive workup with dichloromethane followed by purification of the crude product by flash chromatography[6] gave the desired azacycles in yields ranging from 70 to 95%. The substrates, conditions, and results are summarized in Table I.

The procedure was first applied to the synthesis of pyrrolidines from 1,4-amino alcohols. As previously reported,[5] the cyclization of allylic alcohol 1 (where R = CH_2Ph) cleanly produced 2-vinyl pyrrolidine 11 while its hydroxy epimer 2 produced pyrrolidine 12. These results are consistent with the usually observed[1] S_N2 displacement of the hydroxyl group in the Mitsunobu reaction, at least in the case of these allylic alcohols.[7] The process was also highly regioselective since no azepine products from S_N2' attack on the terminal alkene were observed with either 1 or 2. Using the less activated, but still hindered N-phenyl-5-amino-2-pentanol 3 as substrate provided an excellent yield of pyrrolidine 13, indicating that aryl as well as alkyl amines can be used in the cyclization.[8]

The methodology was extended to the synthesis of substituted piperidines which resemble the potent alpha-glucosidase inhibitor 1-deoxynojirimycin 22.[9] Cyclization of D-glucose-derived 4 under Mitsunobu conditions gave achiral tribenzyloxypiperidine 14.



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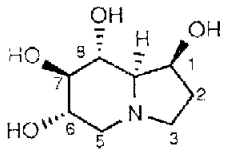

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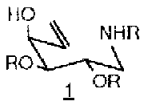
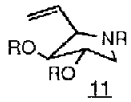
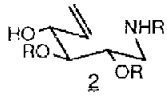
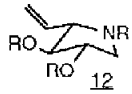
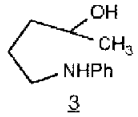
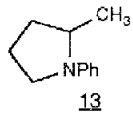
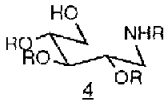
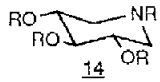
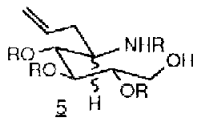
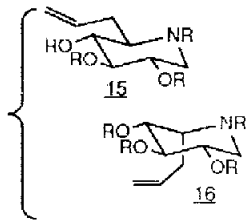
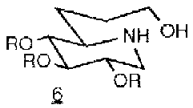
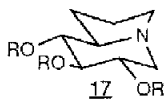
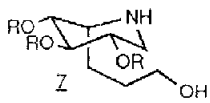
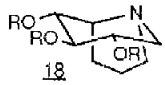
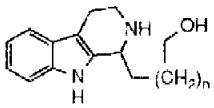
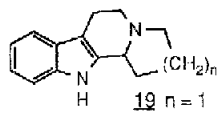
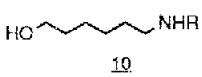
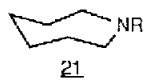
When the carbon bearing the nitrogen was substituted by an allyl group, ring formation still proceeded readily. Thus, when a 40:60 mixture of diastereomeric amino alcohols 5, derived from treatment of the hemiaminal of 2,3,4-tri-O-benzyl-L-xylose with allylmagnesium chloride, was treated with Ph_3P/DEAD, a similar but separable 40:60 mixture of allyl substituted piperidines 15 and 16 was isolated. (These piperidines were used as the precursors for 6 and 7, respectively.)

Similar conditions were used to form fused ring systems with bridgehead nitrogen atoms. Both 1-deoxy-6,7,8-tri-O-benzylcastanospermine 17 and its 9-epimer 18 were prepared by treatment of the appropriate 3-hydroxypropylsubstituted piperidines 6 and 7 with Ph_3P/DEAD.[10] These two compounds are related to the indolizidine alkaloid castanospermine 23,[11] a very potent inhibitor of certain alpha-glucosidases. Beta-carboline 8 was readily cyclized to afford tetracyclic 19; no product from displacement of the hydroxyl group by the indole nitrogen was isolated. Similarly, the one carbon homolog 9 was converted to 20 in good yield using this method.

Finally, we attempted to extend this approach to the synthesis of azepines by treatment of 1,6-amino alcohol 10 with Ph_3P/DEAD, but were unable to isolate any of the desired seven-membered ring 21, even using more dilute conditions which might have favored an intramolecular reaction.[12]

In summary, the treatment of 1,4- and 1,5-amino alcohols with Ph_3P/DEAD resulted in good to excellent yields of substituted azacycles including pyrrolidines, piperidines, and a variety of multicyclic systems.

TABLE I

SUBSTRATE [a]	EQUIV. EACH DEAD + Ph_3P	SOLVENT	TIME (HOURS)	% YIELD [b]	PRODUCT(S) [a,c]
 1	1.7	THF	2.5	95	 11
 2	1.1 1.1	CH_2Cl_2 THF	18 [d] 2	94 83	 12
 3	1.1	CH_2Cl_2	3	80	 13
 4	1.1	CH_2Cl_2	2	82	 14
 5	2.0	CH_2Cl_2	15 [d]	89	 15 16
 6	1.1	THF	1.5	95	 17
 7	1.0	THF	15 [d]	70	 18
 8 n = 1 9 n = 2	1.1 1.1	CH_2Cl_2 CH_2Cl_2	3 1	78 85	 19 n = 1 20 n = 2
 10	1.1	CH_2Cl_2	24 [d]	0	 21

[a] R = CH_2Ph [b] Yields are for chromatographically pure compounds. [c] All products gave satisfactory ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), CIMS, and IR spectra. [d] Overnight reaction.

Footnotes and References

1 Mitsunobu, O., Synthesis, 1981, 1.

2 Carlock, J. T., Mack, M. P., Tetrahedron Letters, 5133 (1978) and also Pfister, J. R., Synthesis, 1984, 969.

3 Sammes, P. G., Smith, S., J. Chem. Soc., Chem. Commun., 1983, 682.

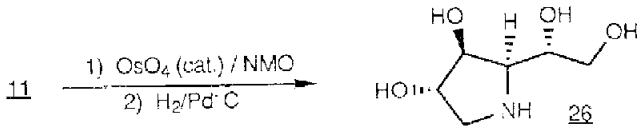
4 However, the use of Ph_3P/CCl_4 for the conversion of 24 to 25 has been reported: Barbry, D., Couturier, D., Ricart, G., Synthesis, 1980, 387.

24 25

5 Bernotas, R. C., Tetrahedron Letters, 31, 469 (1990).

6 Still, W. C., Kahn, M., Mitra, A., J. Org. Chem., 43, 2923 (1978).

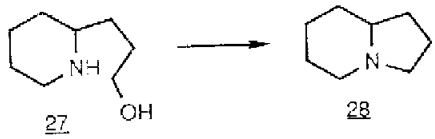
7 The stereochemistry at the vinyl-substituted carbon was established by conversion of 11 to known 26 (Fleet, G. W. J., Son, J. C., Tetrahedron, 44, 2637 (1988)) by oxidation of the alkene to a diol followed by hydrogenation. See reference 5.



8 Recently, cyclizations of N-tosyl 1,4- and 1,5-amino alcohols have been reported: Henry, J. R., Marcin, L. R., McIntosh, M. C., Scola, P. M., Harris, G. D., Weinreb, S. M., Tetrahedron Letters, 30, 5709 (1989).

9 Inouye, S., Tsuruoka, T., Ito, T., Niida, T., Tetrahedron, 23, 2125 (1968).

10 Delta-coniicine 28 has been synthesized from 27 in 42% yield using Ph_3P/CCl_4: Stoilava, V., Tritonov, L. S., Orahovats, A. S., Synthesis, 1979, 105.



27 28

11 Hohenschutz, L. D., Bell, E. A., et al, Phytochem., 20, 811 (1981).

12 In a related, tribenzyloxy-substituted substrate, a low yield (14%) of azepine was isolated.

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