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A SIMPLE METHOD OF PREPARATION OF 7-ALKYL-7-AZABICYCLO[2.2.1]HEPTANES[1]

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Abstract: *Action of triphenylphosphine - carbon tetrachloride on the trans-4-alkylaminocyclohexanols leads to 7-alkyl-7-azabicyclo[2.2.1]heptanes in the good yields. The starting aminoalcohols are easily available from the monoethylene ketal of 1,4-cyclohexanedione and primary amines in a four step process without isolation of intermediates.*

The recent isolation of epibatidine **1**, an alkaloid isolated from the skin of So. American frogs and shown to be several hundred times more active an analgesic than morphine[2], continues to attract interest and has resulted in several recent reports of its synthesis[3-9]. Yet, an efficient general method of formation of the 7-azabicyclo[2.2.1]heptane (**2e**) backbone, a key step in the synthesis of epibatidine or its analogs[10] is still missing. Two routes for construction of **2e** have been reported: (1) the reaction of pyrrole derivatives (acting as a Diels - Alder diene component or as an azomethine ylide in a 3+2 cycloaddition) with active dienophiles[3-5,10], or (2) the intramolecular 1-4 ring closure of derivatives of 4-aminocyclohehanol[6-9,11].

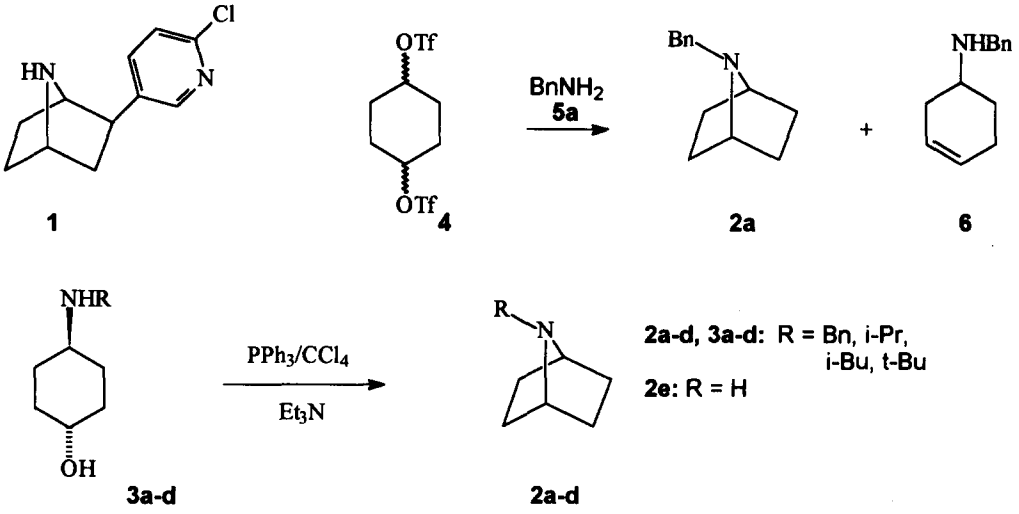
The Diels - Alder pathway (1) with active alkenes suffers from low yields, apparently due to the aromaticity of the starting pyrroles and the reversability of the resulting 7-aza[2.2.1]bicycloheptenes to pyrroles. For instance, we have tried unsuccessfully to perform the Diels - Alder reaction of *trans*-2-nitrostyrene or 2-nitro-1-(3'-pyridyl)ethene with N-Boc- or N-benzenesulfonylpyrrole under different conditions[12]. The successful 3+2 cycloaddition approach starting from dihydropyrroles[5] is a multiple step process and also requires activated olefins.

The route *via* cyclization of 4-aminocyclohexanols seems more reliable but is complicated either by requiring drastic reaction conditions[6] or several protection-deprotection or other additional steps[7-9,11]. An attempt to avoid these difficulties[11] by reaction of *trans*-4-aminocyclohexanol (**3e**) with diethoxytriphenylphosphorane led to **2e** in 26% yield together with its 7-ethyl derivative[13].

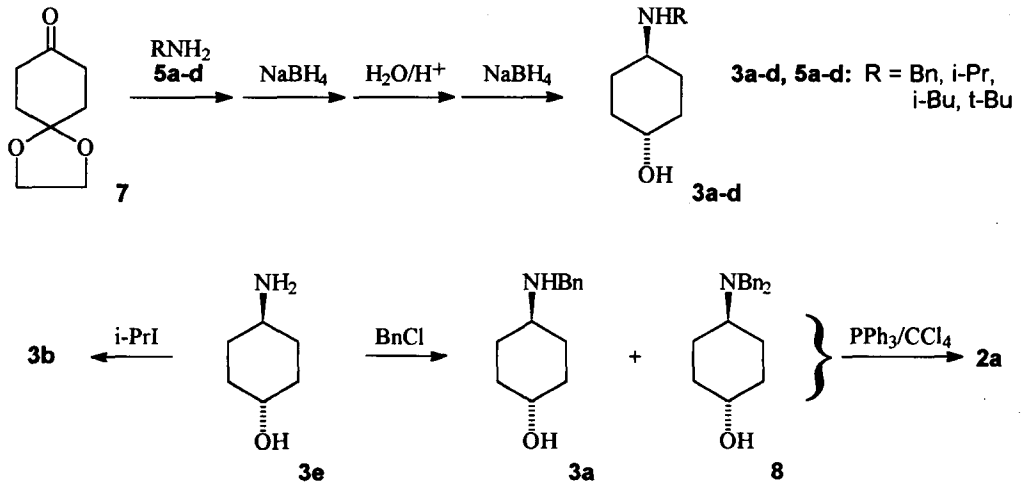
As a route to **2e** we first examined the reaction of bistriflate **4** of the 1:1 mixture of *cis*- and *trans*-cyclohexanediol. However, our attemps at this reaction using either isolated unstable **4** or *in situ* generated **4** with benzylamine **5a** lead to bicyclic amine **2a** in poor yield (8%) together with elimination product **6** in 23% yield.

We report here a simple synthesis of 7-alkyl-7-azabicyclo[2.2.1]heptanes by reaction of *trans*-4-alkylaminocyclohexanols with triphenylphosphine - carbon tetrachloride in the presence of triethylamine. Addition of carbon tetrachloride to the boiling mixture of aminoalcohol **3a-d**, triphenylphosphine, triethylamine in acetonitrile led to formation of bicyclic amine **2a-d** in 42-70% yield[14]. The reaction proceeded even with the

crowded N-t-butyl derivative (the yield decreased with steric crowding of the N-substituent). The bicyclic products **2a-d** were formed as a practically single amine-containing product, which simplified their isolation.

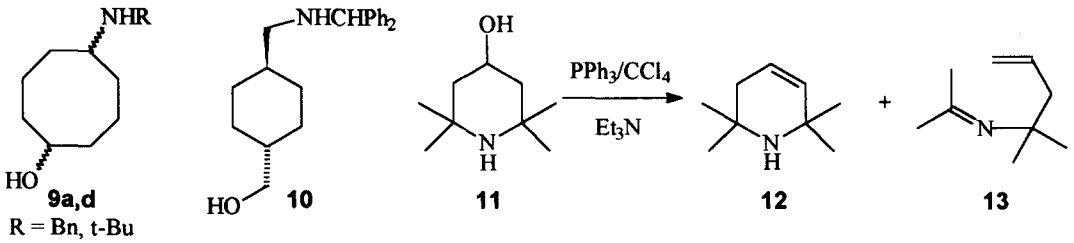


The starting *trans*-4-alkylaminohexanols **3a-d** were readily prepared from commercially available monoprotected 1,4-cyclohexanedione **7** or aminoalcohol **3e**. In the case of **7**, condensation with an amines **5a-d** led to Schiff bases which were reduced by sodium borohydride and deprotected by treatment with dilute HCl followed by sodium borohydride reduction under neutral conditions to afford the crude amino alcohols **3a-d** in 65-90% overall yield[15]. Isolation of the intermediate products was not required and the obtained aminoalcohols **3a-d** of 85-95% purity were suitable for subsequent cyclization. Alternatively, amine **3** was alkylated with benzyl chloride (1.1 equiv) or isopropyl iodide (10 equiv) in the presence of $NaHCO_3$ (EtOH, reflux) providing a mixture of secondary amine **3a** and tertiary amine **8** in the ratio of 2.4:1 or amine **3b** in 72 and 83% yield, respectively. A mixture of **3a** and **8** was used in the Ph_3P-CCl_4 procedure to give the bicyclic amine **2a** in 63% yield.



Triphenylphosphine - carbon tetrachloride have been used in the formation of 3-6 membered amino-containing rings from aminoalcohols[16] but the synthesis of **2a-d** is apparently the first example of cyclization to azabicyclic compounds.

Attemps to apply this method to formation of similar bicyclic amines were unsuccessful. A mixture of *cis*- and *trans*-5-benzyl- or 5-t-butylaminocyclooctanol **9a,d**[17] or *trans*-4-aminomethylcyclohexanemethanol **10** on treatment with PPh_3 - CCl_4 led to a mixture of amines (less than 3% yield) which didn't contain the expected bicycles[18]. This fact is in agreement with the observation[19] that terminal aminoalcohols under Mitsunobu conditions give the 3-6 membered azacycles in good yields but the formation of the seven membered ring is inferior. However the preparation of the small ring bicycles using PPh_3 - CCl_4 procedure also seems problematically: 4-piperidol exposed to these conditions gave a many component mixture and piperidol **11** was transformed to piperideine **12** and the fragmentation product **13** in 41 and 59% yields respectively.



9a,d R = Bn, t-Bu **10** **11** **12** **13**

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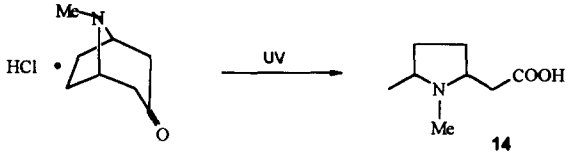

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14. *General procedure for preparation of* **2a-d**. To a boiling mixture of 10 mmol of aminoalcohols **3a-d**, 12-14 mmol of PPh_3, 12 mmol Et_3N and 25 mL of acetonitrile under argon was added 10 mmol of carbon tetrachloride in one portion. After 20-30 min of reflux, 30 mL of dilute HCl solution and chloroform were added to the cooled reaction mixture. The aqueous solution was treated with KOH to pH 11-12 and after chloroform extraction and evaporation the residue was dissolved in 10 mL of 0.001 M HCl solution and stirred with 8 mL of Dowex 50Wx4 (H^+-form). After filtration and washing to neutral pH the ion exchanger was treated with 25 mL of 1 M HCl solution, filtered, and the acidic solution was treated with KOH to pH 11-12. After chloroform extraction, drying and evaporation at 25^0, bicycles **2a-d** of about 90% purity (by NMR) were obtained. Chromatography on C_1 reversed phase silica led to pure **2a-d**. The ^{13}C NMR data are given for **2a** ($CDCl_3$): 28.50 (C-2, C-3, C-5, C-6); 52.00 ($N\underline{C}H_2$); 59.14 ($N\underline{C}H$); 126.59, 128.13, 128.52, 140.37 (Ph).
15. *General procedure for preparation of* **3a-d**. A solution of 10 mmol of **7** and 100 mmol of amine **5b-d** or 12 mmol in the case of **5a** in 10 mL of benzene was refluxed 4 h in the presence of 5 g of molecular sieves 4 A. After filtration and evaporation 10 mL of dry dioxane and 20 mmol of sodium borohydride were added and the mixture was stirred 1-2 days at 25^0. A 5% HCl solution was added slowly to pH 2-3 and after chloroform extraction an equal volume of THF was added to the aqueous solution. After 24 h at 25^0 the reaction mixture was extracted with dichloromethane, the water layer was neutralized with KOH to pH 7-8 and 20 mL of EtOH and 20 mmol of sodium borohydride were added. After 4 h at 25^0, dilute HCl solution and dichloromethane were added consecutively, the water phase was treated with KOH to pH 11-12 and extracted with chloroform. Evaporation of the dried organic phase afforded the crude products **3a-d** (in the case of **3a** amine **5a** was also present). The pure aminoalcohols **3a-d** were isolated by chromatography on C_1 reversed phase silica.
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17. A mixture of *cis*-, *trans*-isomers **9a** or **9d** (*ca* 2:3) was obtained similarly to **3a-d** in a *one pot* reaction sequence from 5-hydroxycyclooctanone and amine **5a,d** [(1) 110^0, toluene, molecular sieves; (2) $NaBH_4$, dioxane, 25^0].
18. An attempt to obtain substituted 9-azabicyclo[3.3.1]nonanes from the bistriflate of *cis*-1,5-cyclooctanediol and amine **3a** was also unsuccessful.
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