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NOTE

USE OF TRITIATED METHYLBORANE IN THE SYNTHESIS OF LABELLED PRIMARY AMINES

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SUMMARY

Tritiated methylborane prepared from tritium gas and methaneboronic acid was used to prepare [2-H^3]-trans-2-phenylcyclopentylamine from 1-phenylcyclopentene with a high specific activity (26Ci/mmol) in 20-40% yield.

Key Words: tritiated methylborane, tritiated primary amine, tritiated lithium hydride.

INTRODUCTION

Numerous interesting ligands for biochemical assays are primary amines or derivatives. Thus, an easy access to tritium labelled primary amines with a high specific activity is an important challenge. A synthesis via organoboranes appeared suitable and well documented. The synthesis of primary amines via hydroboration of double bonds and oxidation by hydroxylamine sulfate has been largely developed by Brown and coworkers (1,2). The oxidation by H_2NOSO_3H proceeds with the migration of only two groups over the three possible (3). In the asymmetric synthesis of cypenamine by monoisopinocampheylborane, Brown exchanges the Ipc group by a methyl to ensure complete oxidation of the phenylcyclopentyl group (3). However this approach is difficult to extend to a very small scale because the methylation must be done at -78°C. Thus, we decided to investigate the use of methylborane, as a specific reagent to synthesize primary amines. Synthesis of methylborane has been previously reported by Brown (4,5). However our previous experience in the synthesis of tritiated monoalkylboranes by means of alkylcatecholboranes prompted us to synthesize methylborane by a different route: from methylcatecholborane and aluminium hydride (6). We have extended this synthesis to the tritiated analog and used it to the synthesis of the tritiated cypenamine.

SYNTHESIS

The methylcatecholborane was prepared from commercially available methaneboronic acid and catechol by the azeotropic removal of the water formed by means of dichloromethane (7). It was characterized by its ^{11}B NMR and its ^1H NMR spectra (+34.7ppm from BF_3/Et_2O) and (CH_3-: 0.8ppm from TMS). Methylcatecholborane was diluted in anhydrous diglyme then added to a solution of AlH_3 in diglyme prepared from $LiAlH_4$ and $AlCl_3$. The resulting methylborane was characterized by its ^{11}B NMR spectrum: it

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demonstrated that we clearely obtained not only CH_3BH_2 as a dimer(+21.9ppm,q)(4) but also CH_3BH_2 complexed with diglyme (-10.3ppm,t) in the respective proportion of 40/60. The addition of 1-phenylcyclopentene to the reaction mixture and oxidation by H_2NOSO_3H yielded the trans 2-phenylcyclopentylamine. It was isolated as its benzamide: mp=162°C and characterized by ^{13}C NMR and mass (chemical ionisation) spectra. As we do not know if we have obtained the di- or trialkylborane or a mixture of both as an intermediate, the yield, calculated from methylcatecholborane, may vary from 40 to 80%.

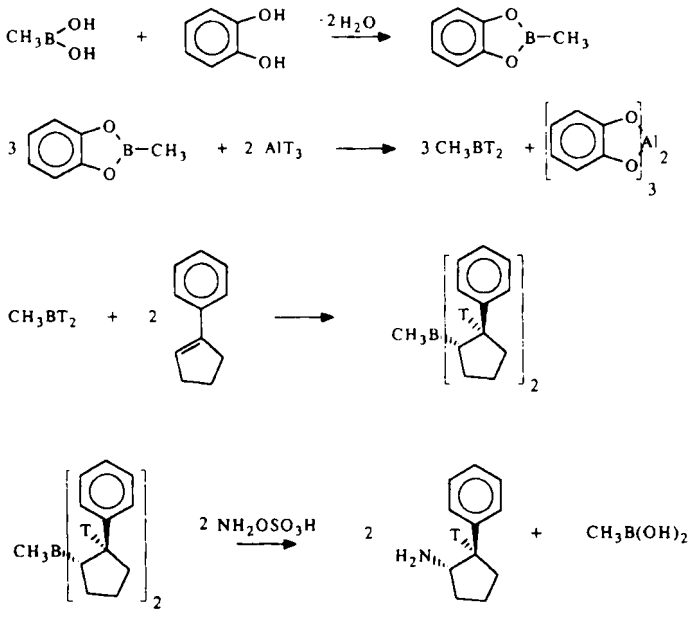
The same process was adopted to yield the tritiated methylborane. AlT_3 was prepared from butyllithium, tritium gas, TMEDA and $AlCl_3$, according to our previous work (6). Methylcatecholborane was added over AlT_3 in diglyme. Two equivalents of 1-phenylcyclopentene (over tritiated methylborane) were then introduced in the synthetic mixture. Surprisingly after oxidation by H_2NOSO_3H, no tritiated cypenamine was detected.

A carefull examination of the synthesis of LiT demonstrated that if TMEDA was not completely eliminated from the reaction mixture by a simple evaporation, even under a high vacuum, it formed a very stable complex with lithium hydride. Consequently we probably obtained $(CH_3BT_2)_2$:TMEDA, a complex which did not hydroborate 1-phenylcyclopentene.

LiT free from TMEDA was readily prepared from the complex by repetitive centrifugation in pentane in a 80% yield, calculated from tritium gas. Thus, pure LiT was obtained as a finely divided white powder. Using pure LiT, (2-^{3}H)-trans-2-phenylcyclopentylamine (tritiated cypenamine) was readily obtained from 1-phenylcyclopentene. For the indicated above reasons the radiochemical yield may vary from 20 to 40%. The characterization of the tritiated amine was made by means of ^3H NMR spectroscopy in methanol-D_4 (+2.9ppm) and mass spectrometry (chemical ionisation). The isotopic enrichment was 90% -i.e.- a specific activity of 26Ci/mmol. (theory 29Ci/mmol).

Work is in progress to generalize the scope to different kind of unsatured structures.

EXPERIMENTAL



Materials

All chemicals were from commercial sources (Aldrich) except for tritium gas (C.E.A.). Diglyme, catechol, TMEDA and 1-phenylcyclopentene (prepared in the laboratory) were purified by standard procedures and kept under nitrogen before use. All reactions were carried out under nitrogen in glassware dried at 150°C and cooled under nitrogen. NMR spectra were recorded on a Bruker AC 300 at 320.130 MHz for ^3H, on a Bruker WP 80 at 20.147 MHz and 25.699 MHz respectively for ^{13}C and ^{11}B. All the measurements were done in the FT mode with reference to tritiated water (external), TMS (internal), and boron trifluoride etherate (external). Mass spectra were recorded on a Quadrupole Finnigan Mat 4600. The purification of the tritiated amine was by preparative thin layer chromatography, KC18F, 20X20,1mm. The final radioactivity of the tritiated samples was counted in a Shlumberger ECT34 apparatus.

Methylcatecholborane -Methaneboronic acid (250mg, 4.18mmol) and catechol (460mg, 4.18mmol), freshly crystallized from diethyl ether and dichloromethane, were covered by 25ml of CH_2Cl_2, under nitrogen. The reactor was equipped with a Dean-Stark trap filled with molecular sieves (4Å). The reaction was then warmed to reflux during 2 hours, CH_2Cl_2 was distilled and completely eliminated under vacuum (10mm Hg) and the product as prepared was used in the next step.

Methylborane -$AlCl_3$ (93mg, 0.69mmol) was dissolved in 5ml of diglyme then cooled to 0°C. 2.2ml of a 0.96M solution of $LiAlH_4$ in diglyme was added to the solution of $AlCl_3$. Methylcatecholborane (4.18mmol) diluted in 5ml of diglyme was then added at 0°C. After 15 minutes the solution was analyzed by ^{11}B NMR.

Trans-2-phenylcyclopentylamine -AlH_3 was prepared as follows: $AlCl_3$ (98mg, 0.73mmol) was dissolved in 2.3ml of diglyme then cooled to 0°C. 2.3ml of a 0.96M solution of $LiAlH_4$ in diglyme was added to the solution of $AlCl_3$. This solution, containing AlH_3, was added to methylcatecholborane (0.586g, 4.38mmol), diluted in 5ml of diglyme and 1-phenylcyclopentene (1.3g, 9.02mmol) was then added neat via a syringe. The reaction mixture was stirred for 24 hours at room temperature and then quenched with 1ml of MeOH. Solid H_2NOSO_3H (1.3g, 13.2mmol) was added and the reaction was stirred for 2 days at room temperature. The reaction mixture was then hydrolysed with 100ml of 10% HCl, basified with 6g of solid NaOH and then extracted with 100ml of Et_2O. The organic layer was then washed with water to neutrality to eliminate diglyme then extracted with 10% HCl (2X50ml). The aqueous layer was basified by 6g of solid NaOH then extracted with Et_2O (2X50ml). The organic layer was washed with water to neutrality and then dried over Na_2SO_4. The solvent was removed under reduced pressure. The yield was 40-80% of yellowish oil which was diluted in 5ml of pyridine and benzoyl chloride was added. The benzamide was isolated by crystallization in Et_2O.

LiT -Tetramethyl ethylene diamine (TMEDA) (0.5ml) was added to 2.1ml of 1.6M butyllithium in hexanes. 0.8ml of this solution was hydrolyzed with water then titrated by 0.1N HCl (V_1). 0.8ml of the same solution was stirred under tritium gas atmosphere (50Ci, 0.86mmol) at 30-35°C, until no more gas absorption occurred. 3ml of pentane was added, the suspension of LiT was stirred for a few seconds and then centrifugated. The clear surpernatant solution was withdrawn. This operation was repeated two times. The

supernatant solutions were combined, hydrolyzed and then titrated by 0.1N HCl (V_2). V_1-V_2 = 7ml. The yield was 80% (calculated from tritium gas).

[2-^{3}H]-trans-2-phenylcyclopentylamine -Freshly prepared 1.1ml of 0.2M solution of $AlCl_3$ in diglyme (0.22mmol) was added to LiT (O.7mmol) at room temperature. Methylcatecholborane (45mg, 0.34mmol) (obtained as in the first step of the CH_3BH_2 synthesis) was added neat via a syringe and 1-phenylcyclopentene (100mg, 0.69mmol) was then added. After 24 hours at room temperature, solid H_2NOSO_3H (100mg, 0.88mmol) was added and the reaction was stirred for 2 days. The reaction mixture was then pourred into 10ml of 10% HCl, basified with 10% NaOH (25ml) and the aqueous layer was extracted with 50ml of Et_2O. The organic layer was then washed with water to neutrality then extracted with 10% HCl (2X25ml). The aqueous layer was basified with 10% NaOH (25ml) then extracted with Et_2O (3X25ml). The organic layer was washed with water to neutrality then dried over Na_2SO_4. 500mCi of the crude product were purified on a preparative thin layer chromatography, in a mixture of MeOH/H_2O/TEA (75/25/2). The radiochemical yield was 20-40% and the radiochemical purity was 99%.

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