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A SYNTHESIS OF ALKYNYL AZACYCLOALKANES BY THE COUPLING REACTION OF ALKYNYL BORANES AND LACTAMS

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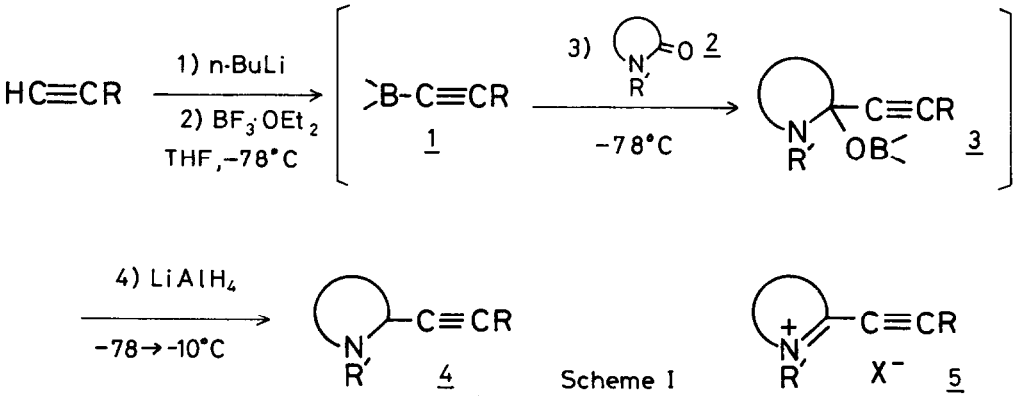
Abstract: Alkynyl azacycloalkanes are synthesized in good yields by the addition reaction of alkynyl boranes to lactams followed by a lithium aluminum hydride reduction of the adducts.

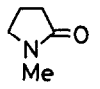
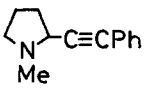
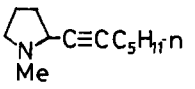
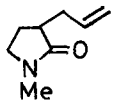
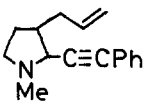
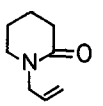
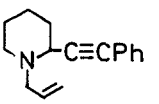
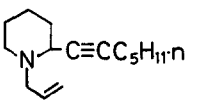
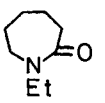
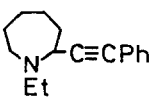
Azacycloalkanes such as pyrrolidines, piperidines and perhydroazepines are integral features of naturally occurring alkaloids. The development of the functionalization methods for these ring systems is therefore an important synthetic problem. One of the synthetic attempts in this direction has involved the nucleophilic addition of organometals to the cabonyl moiety of the corresponding lactams. Several examples were reported for the alkylation or arylation of lactams to synthesize saturated or unsaturated cyclic amines employing strong nucleophiles as organomagnesium[1] or organolithium[2] reagents. The alkynylation reaction of lactams, however, has not appeared in litterature.[3] Actually, our initial attempts to synthesize alkynyl pyrrolidines by utilizing lithium or magnesium acetylide were unsuccessful.

Previously, we have reported the reactions of alkynyl boranes (1), for the synthesis of β-hydroxyacetylenes and alkynyl ketones.[4] As a further synthetic investigation based on the useful reagents (1), we now wish to report a synthesis of alkynyl azacycloalkanes (4) by the alkynylation reaction of lactams (2).



Scheme I

Table. The Synthesis of Alkynyl Azacycloalkanes

entry	lactam	acetylene	product[a]	yield(%)[b]
1		HC≡CPh		80
2		HC≡CC$_5$H$_{11}$-n		64[c]
3		HC≡CPh		74[d]
4		HC≡CPh		74
5		HC≡CC$_5$H$_{11}$-n		69
6		HC≡CPh		56[e]

a) All the products gave satisfactory spectral data (NMR, IR, MS).

b) Isolated yields.

c) The crude products were treated with N,N,N',N'-tetramethylethylenediamine (TMEDA) at 80°C for 30 min and then purified.

d) A 1:1 mixture of stereoisomers.

e) 2,2-Bis(phenylethynyl)-1-ethylperhydroazepine was obtained as a by-product in 30 % yield.

Thus, alkynyl boranes (1), generated in situ from lithium acetylide and boron trifluoride etherate in tetrahydrofuran (THF) at -78°C, were treated with lactams (2) at the temperature. The resulted adducts (3) were then reacted with lithium aluminum hydride at -78°C to -10°C to afford the alkynyl azacycloalkanes (4) in good yields (Scheme I, Table).

It is considered that the adducts (3) readily expel a boronate to form novel alkynyl imminium salts (5), which, in turn, are reduced to amines (4) by the 1,2-addition of hydride.[5]

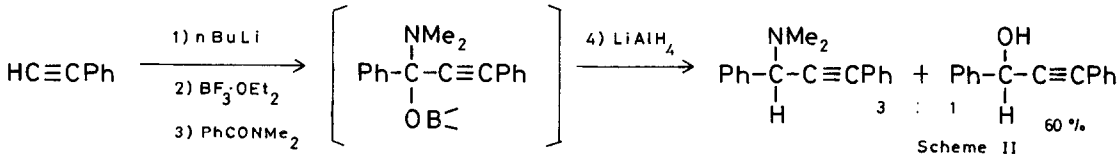
When lithium or magnesium acetylide was employed in place of the alkynyl boranes (1) at an ambient to refluxing temperature in THF, the yields of the desired product were less than 2 %. These results suggest the high reactivity of the alkynyl boranes (1) against lactam carbonyls and/or the high ability of the adducts (3) to form imminium salts (5).

In the synthesis of 2-(1-heptynyl)-1-methylpyrrolidine (entry 2), a considerable amount of a borane complex of the alkynyl amine was detected as a by-product In order to obtain the free amine, the crude products were treated with excess N,N,N',N'-tetramethylethylenediamine (TMEDA) at 80°C for 30 min.[6]

Several reducing reagents —— $LiAlH_4$, $NaBH_4$ and iso-Bu_2AlH —— were examined for the reduction of the intermediates (3). Though the yields of the azacycloalkanes (4) were comparable in each case, the use of the latter two reagents resulted in the formation of the borane complexes of the amines and regeneration of the free amines (4) by the treatment with TMEDA was required.

It was also found that, in the reaction of ε-caprolactam (entry 6), dialkynylated perhydroazepine was obtained as a by-product.[7]

A brief examination of the synthesis of an acyclic alkynyl amine was performed And, similar to the above mentioned synthesis of azacycloalkanes (4), 1-dimethylamino-1,3-diphenyl-2-propyne was obtained by the reaction of phenylacetylene and N,N-dimethylbenzamide. In addition, however, 1,3-diphenyl-2-propyn-1-ol was detected showing that C-N bond cleavage also occurred in the acyclic system (Scheme II).



Scheme II

A typical procedure is described for the synthesis of 1-methyl-2-(2-phenylethynyl)pyrrolidine: Under a nitrogen atomosphere, to a THF solution (3 ml) of phenylacetylene (306 mg, 3.0 mmol) was added a solution of n-butyllithium in n-hexane (1.92 ml, 3.0 mmol) at -78°C. After a 10 min's stirring, boron trifluoride etherate (0.4 ml, 3.2 mmol) was added to the solution and the mixture was stirred for 10 min at -78°C. Then, a THF solution (2 ml) of 1-methyl-2-pyrrolidone (99 mg, 1.0 mmol) was added to react for 30 min at the temperature. The excess alkynyl borane was then decomposed by the addition of ethanol (0.15 ml), and the adduct was treated with lithium aluminum hydride (100 mg, 2.7 mmol) elevating the temperature to -10°C over 2 h. The reaction was quenched by adding a small amount of ethanol and the aluminum salts were precipitated by adding a saturated aqueous solution of sodium sulfate. The supernatant liquid was collected by decantation and was dried over sodium sulfate. An usual work up by thin layer chromatography (silica gel) gave 1-methyl-2-(2-phenylethynyl)-pyrrolidine (148 mg, 80 %).

^{1}H-NMR ($CDCl_3$) δ 1.6-2.5 (4H, m), 2.46 (3H, s), 2.6-3.1 (2H, m), 3.29 (1H, t, J= 6.5 Hz), 7.0-7.5 (5H, m). ^{13}C-NMR ($CDCl_3$) δ 22.4, 23.3, 32.3, 39.7, 53.4, 54.6, 56.9, 84.2, 88.8, 123.3, 127.7, 128.0, 131.5. IR (neat) 690, 755, 1595 cm^{-1}. MS m/e 195 (M^+), 194 (M^+-1).

Acknowledgement

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References and Notes

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