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Nucleophilic Ring Opening of Tetrahydro-1,3-oxazines and 1,3-Oxazolidines by Alkynyl anions: A Novel Synthesis of β-Aminoacetylenes

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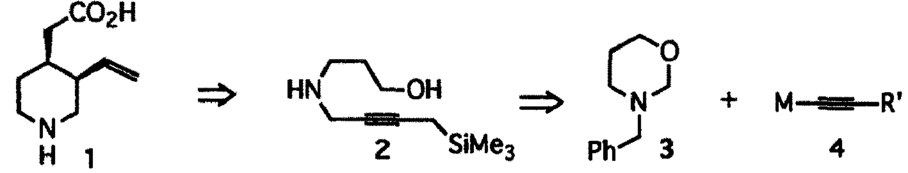
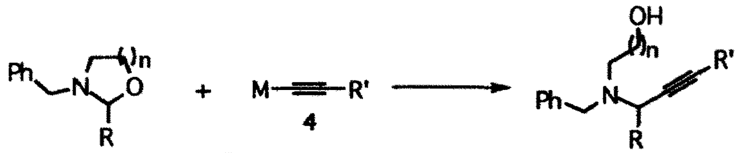
Abstract: The reaction of alkynyl boranes, generated *in situ* from lithium acetylides and boron trifluoride etherate, with 3-benzyl-tetrahydro-1,3-oxazines and 1,3-oxazolidines gave the corresponding β-aminoacetylenes in modest to good yield. By the employment of titanium acetylides to the same reaction provided comparable results.

The ring opening of tetrahydro-1,3-oxazines by nucleophilic agents, such as lithium aluminum hydride,[1] and bromozincio acetate,[2] provided a useful synthetic method to form 3-aminopropanol derivatives. In our current development of the enantioselective synthesis of (+)-meroquinine (**1**), the propargylaminopropanol **2** appeared to be an attractive synthetic intermediate for the preparation of (+)-meroquinine. Compound **2** could be formed by direct ring opening of 1,3-oxazinane **3** with metal acetylides **4** (R' = CH_2SiMe_3). This thought has stimulated us to investigate these ring opening reactions.



Since alkynyl boranes have been successfully used in the ring opening reaction of oxiranes to form β-hydroxy acetylenes,[3] and addition reaction of imines to give β-amino acetylenes,[4] we have thus investigated the reaction of 3-benzyl-1,3-oxazinanes **3**[5] with these reagents. The results were summarized in Table. Indeed, these reactions were quite rapid at 25 °C to give β-aminoacetylene **7a**-**7c** in good yield. On the other hand, titanium acetylides[6] were also employed in this study to give a comparable yield. Compound **5** and the homologous oxazolidines **6a** and **6b** were prepared. Reaction of these compounds with various alkynyl boranes and titanium acetylides gave the corresponding ring opening adduct in acceptable yield. It should be noted that the reaction of 1,3-oxazinanes **3** with lithium acetylide **4** (R' = $SiMe_3$) or the acetylides generated by adding $ZnCl_2$, $TiCl_4$, and $CeCl_3$ to lithium acetylide **4** (R' = $SiMe_3$) did not give ring-opening adduct and recovered mainly the starting materials.



3, n = 2, R = H
5, n = 2, R = Ph
6a, n = 1, R = H
6b, n = 1, R = Ph

7a, R = H, n = 2, R' = $SiMe_3$
7b, R = H, n = 2, R' = CH_2SiMe_3
7c, R = H, n = 2, R' = Ph
7d, R = Ph, n = 2, R' = $SiMe_3$
7e, R = Ph, n = 2, R' = Ph

8a, R = H, n = 1, R' = $SiMe_3$
8b, R = H, n = 1, R' = CH_2SiMe_3
8c, R = H, n = 1, R' = tBu
8d, R = H, n = 1, R' = Ph
8e, R = Ph, n = 1, R' = $SiMe_3$
8f, R = Ph, n = 1, R' = Ph

A typical procedure was described for the synthesis of 3-[N-(3-trimethylsilyl-2-propynyl)-N-benzyl]aminopropanol (**7a**): To a cold (-78 °C) solution of trimethylsilylacetylene (0.198 g, 2 mmol) in dry THF (6 mL) was added a solution of butyllithium in hexane (1.5 mL, 1.6 M) dropwise. The reaction mixture was stirred for 15 min, then boron trifluoride etherate (0.25 mL, 2 mmol) was added to stir for additional 30 min. Finally, the solution of 3-benzyl-tetrahydro-1,3-oxazine (0.354 g, 2 mmol) in dry THF (2 mL) was added. After 1 h at -78 °C, the reaction mixture was allowed to warm to room temperature and stirred for furthur 2 h, quenched with saturated ammonium chloride and extracted with ethyl acetate (10 mL x 3). The organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by flash column chromatography (15 % ethyl acetate in hexane as eluent) to give 3-[N-(3-trimethylsilyl-2-propynyl)-N-benzyl]aminopropanol (0.275 g, 50 %) as an oil.

Table. The Synthesis of β-Aminoacetylenes **7** and **8**

oxazinanes or oxazolidines	acetylides	products[c]	yield (%)[a]
5a	$F_2B-\equiv-SiMe_3$	**7a**	50
5a	$(iPrO)_3Ti-\equiv-SiMe_3$	**7a**	48
5a	$F_2B-\equiv-CH_2SiMe_3$	**7b**	54
5a	$F_2B-\equiv-Ph$	**7c**	54
6a	$F_2B-\equiv-SiMe_3$	**8a**	53
6a	$(iPrO)_3Ti-\equiv-SiMe_3$	**8a**	43
6a	$F_2B-\equiv-CH_2SiMe_3$	**8b**	51
6a	$F_2B-\equiv-tBu$	**8c**	36
6a	$F_2B-\equiv-Ph$	**8d**	44
5b	$(iPrO)_3Ti-\equiv-SiMe_3$	**7d**	15[b]
5b	$F_2B-\equiv-SiMe_3$	**7d**	60
5b	$F_2B-\equiv-Ph$	**7e**	40
6b	$F_2B-\equiv-SiMe_3$	**8e**	57
6b	$(iPrO)_3Ti-\equiv-SiMe_3$	**8e**	76
6b	$F_2B-\equiv-Ph$	**8f**	49

a) Isolated yield. b) Yield was not optimized. c) All the products gave satisfactory spectral data (NMR, IR) and elemental composition by high resolution mass spectrometry.

The ring opening reaction of tetrahydro-1,3-oxazines and 1,3-oxazolidines with boron or titanium acetylides provided a unique method to prepare β-aminoacetylenes. The remaning hydroxy group would be able to transfer to a variety of functionalities. Some of these products have been extended to the synthesis of (+)-meroquinine and pyrrolidines which will be published in due course.

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5. Compounds **3** and **5** were prepared by condensation of 3-benzylaminopropanol with aldehydes. Compound **6a** and **6b** were prepared by similar method by condensation of aldehydes with 2-benzylaminoethanol.
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