Nucleophilic addition to acetylenes in superbasic catalytic systems
12.* Vinylation of lupinine

L. A. Oparina,[a]★ R. T. Tlegenov,[b] T. G. Ermakova,[a] N. P. Kuznetsova,[a] L. V. Kanitskaya,[a] A. P. Tantsyrev,[a] and B. A. Trofimov[a]

[a]*A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 ul. Favorskogo, 664033 Irkutsk, Russian Federation. Fax: +7 (395 2) 41 93 26. E-mail: oparina@irioch.irk.ru*
[b]*Karakalpakstan State University, 1 ul. Universitetskaya, 742012 Nukus, Uzbekistan. E-mail: rust012001@yahoo.com*

The addition of a natural alkaloid lupinine to acetylene in the presence of superbasic catalytic systems (KOH—DMSO, KOBu^t—DMSO, KOH—dioxane) under elevated or atmospheric pressure affords *O*-vinyllupinine (in up to 88% yield), a promising optically active monomer and intermediate for the preparation of new quinolizidine alkaloids. The same vinyl ether was obtained (in 60% yield) by the reaction of lupinine with vinyl acetate in the presence of $Hg(OAc)_2$.

Key words: lupinine, acetylene, vinylation, superbasic catalytic systems, (1*R*,9a*R*)-1-(vinyloxymethyl)octahydroquinolizine.

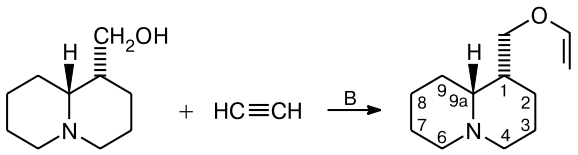
The interest in natural alkaloids containing a quinolizidine fragment is due to their high biological activities.[2] Lupinine ((1*R*,9a*R*)-1-(hydroxymethyl)octahydroquinolizine (**1**)), which is one of the major alkaloids of *Anabasis aphylla* and some species of *Lupinus*, possesses an anticholinesterase activity[3] and is used in medicine for preparing substances with local anesthetic action.[4] Due to the presence of the hydroxy group in the molecule, this compound can be converted into various derivatives, in particular, esters of carboxylic[5,6] and dicarboxylic[7] acids and phosphorylated derivatives.[3]

The present study deals with vinylation of lupinine. The combination of the quinolizidine fragment with the vinyloxy group in the reaction product opens up new potential for directed synthesis of low-toxic optically and pharmacologically active copolymers, which are of considerable interest for medicine.

Lupinine **1** reacts with acetylene in KOH—dioxane, KOH—DMSO, and KOBu^t—DMSO systems to give *O*-vinyllupinine (**2**) (Scheme 1).

The optimal conditions for the vinylation of lupinine in the KOH—dioxane system are as follows: a 10-fold molar excess of acetylene, initial acetylene pressure of 12—14 atm, 61 mol.% of the catalyst, 200 °C, 1 h. Under these conditions, the yield of the vinyl ether **2** is 68% (Table 1, entry *1*).

Scheme 1



1 **2**

B is KOH—dioxane, KOH—DMSO, KOBu^t—DMSO

As compared with aliphatic amino alcohols,[8,9] the addition of lupinine to acetylene proceeds under more drastic conditions. Thus a decrease in the reaction temperature to 180 °C results in a substantial decrease in the yield of vinyl ether **2**, and virtually no reaction occurs at lower temperature (see Table 1, entries *2*, *3*).

In the superbasic system, KOH—DMSO, which is widely used for activation of the addition of nucleophiles,[10—14] including amino alcohols,[9,15] to acetylene, vinyl ether **2** is formed in a high yield (84%) under relatively mild conditions (reaction temperature 80 °C, initial acetylene pressure 10—12 atm, twofold molar excess of KOH with respect to lupinine, reaction time 2 h) (see Table 1, entry *4*). Note that in the presence of 50 mol.% of KOH (the usual catalyst concentration in the vinylation of alcohols in superbasic systems[10—14]), virtually no reaction takes place (see Table 1, entry *5*). In these experi-

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Table 1. Vinylation of lupinine with acetylene

Entry	Catalyst (mol.%)	Solvent (volume/mL)	P_0/atm	T/°C	t/h	Yield of ether **2** (%)
1	KOH (61)	Dioxane (150)	12—14	200	1	68
2	KOH (61)	Dioxane (150)	12—14	180	3	46
3	KOH (61)	Dioxane (150)	12—14	150	1	Traces
4	KOH (200)	DMSO (50)	10—12	80—90	2	84
5	KOH (50)	DMSO (50)	10—12	85—90	2	Traces
6	$KOBu^t$ (50)	DMSO (75)	1	105—110	3	88

Note. In entries *1—3*, the amount of lupinine is 59 mmol; in entries *4—6*, this is 10 mmol; P_0 is the initial acetylene pressure, t is the reaction time.

ments, nonconsumed lupinine is recovered almost entirely after the usual workup of the reaction mixture (dilution with water and extraction with diethyl ether and chloroform).

Upon replacement of KOH by $KOBu^t$, which is a stronger base and is better soluble in DMSO, successful vinylation of lupinine in DMSO is carried out under atmospheric pressure of acetylene and at 105—110 °C. Chromatographic monitoring of the reaction shows that it proceeds efficiently and almost quantitatively, being complete in 2.5—3 h (see Table 1, entry *6*). In this case, the reaction mixture contains no reaction products of acetylene with DMSO (vinyl sulfide, divinyl sulfide).[16]

The exchange vinylation of lupinine with vinyl acetate catalyzed by mercuric acetate gives vinyl ether **2** in a yield of 60%.

The structure of vinyl ether **2** was confirmed by NMR and IR spectroscopy and mass spectrometry. The main fragmentation pathway for the $[M]^{+\bullet}$ ion is the abstraction of a vinyl alcohol molecule to give the quinolizidine ion with m/z 151 (100%). Further fragmentation of ions with m/z 150—152 follows a pathway typical of the quinolizidine nucleus in lupinine derivatives.[17]

Experimental

IR spectra were recorded in thin films on a Bruker JFS-25 spectrometer in the region of 400—4000 cm^{-1}. NMR spectra (^1H and ^{13}C) were measured at ~20 °C on a Bruker DPX-400 instrument with an operating frequency of 400.13 and 100.69 MHz, respectively, using $CDCl_3$ as the solvent and HMDS as the internal standard. Mass spectra were run with an ionizing potential of 60 eV on an LKB-2091 GC/MS instrument using the chromatographic system of sample injection (a 38 m capillary column, stationary phase SE-54, evaporator temperature 250 °C); the temperature of the ion source was 240 °C. The reaction mixtures were analyzed by GLC on an LKhM-80 instrument (heat conductivity detector, helium as the carrier gas, a 3000×3 mm column, 5% of Silicon DS-550 on Chromaton N-AW). The optical activity of the compound was determined on a Polamat A instrument.

The starting lupinine was isolated from commercial grade anabasine sulfate.[2]

Vinylation of lupinine (1) under elevated pressure. ***A.*** Lupinine (**1**) (10 g, 59 mmol), KOH (2 g, 36 mmol), and dioxane (150 mL) were charged in a rotating autoclave (V = 1 L) and acetylene was fed to the initial pressure of 12 atm. The reaction mixture was stirred for 1 h at 200 °C. After cooling, the mixture was concentrated *in vacuo*. Vacuum distillation of the residue gave 8.2 g (68%) of vinyl ether **2**.

B. Lupinine (**1**) (1.69 g, 10 mmol), KOH (1.12 g, 20 mmol), and DMSO (50 mL) were charged in a rotating autoclave (V = 0.25 L) and acetylene was fed to the initial pressure of 12 atm. The reaction mixture was stirred for 2 h at 80 °C, diluted with water (1 : 1), and extracted with Et_2O (5×20 mL). The combined extracts were washed with water, dried with Na_2CO_3, and concentrated *in vacuo*. Vacuum distillation of the residue gave 1.65 g (84%) of vinyl ether **2**.

Vinylation of lupinine (1) under atmospheric pressure. Dimethyl sulfoxide (75 mL), lupinine (1.69 g, 10 mmol), and $KOBu^t$ (0.56 g, 5 mmol) were placed in a 150-mL reaction vessel equipped by a reflux condenser, a thermometer, a magnetic stirrer, and a bubbler for acetylene inlet. The reaction mixture was heated to 110 °C and acetylene was bubbled through the mixture for 3 h at a rate of 2 L h^{-1}. The reaction was monitored by GLC. After completion of the synthesis, the reaction mixture was diluted with water (1 : 2) and worked-up as described in the previous procedure. Vacuum distillation gave 1.7 g (88%) of vinyl ether **2**.

Synthesis of vinyl ether of lupinine (2) by transvinylation. A mixture of vinyl acetate (70.07 g, 813 mmol) and $Hg(OAc)_2$ (1.2 g, 3.8 mmol) was heated to 60 °C and purged with argon for 30 min. After complete dissolution of the catalyst, concentrated H_2SO_4 (1.7 mL, 31 mmol) was added dropwise at the same temperature, and then lupinine (20 g, 102 mmol) (**1**) was added. The reaction mixture was vigorously stirred for 27 h at 60 °C. After completion of the synthesis, NaOAc (4.3 g, 54 mmol) and $NaHCO_3$ (3.2 g, 30 mmol) were added and the precipitate was filtered off. After removal of excess vinyl acetate, vacuum distillation gave 12.0 g (60%) of vinyl ether **2**.

(1*R*,9a*R*)-1-(Vinyloxymethyl)octahydroquinolizine (2). B.p. 106—107 °C (5 Torr), n_D^{20} 1.5015, d_4^{20} 0.984, $[\alpha]_D^{22}$ −17.7 (*c* 1.0, EtOH). Found (%): C, 73.88; H, 11.13; N, 7.22. $C_{12}H_{21}NO$. Calculated (%): C, 73.80; H, 10.84; N, 7.17. ^1H NMR, δ: 6.44 (dd, 1 H, OCH=, ^3J = 14.4 Hz, ^3J = 6.8 Hz); 4.18 (dd, 1 H, $=CH_{trans}$, ^3J = 14.4 Hz, ^2J = 1.8 Hz); 3.94 (dd,

1 H, $=CH_{cis}$, ^3J = 6.8 Hz, ^2J = 1.8 Hz); 3.91* (1 H); 3.79 (dd, 1 H, OCH_2, ^3J = 7.8 Hz, ^2J = 9.8 Hz); 2.74 (m, 2 H, $H_{eq}(4)$, $H_{eq}(6)$); 1.93—1.83 (m, 6 H); 1.71—1.61 (m, 3 H); 1.48—1.38 (m, 4 H); 1.18 (m, 1 H). ^{13}C NMR, δ: 21.34 (C(3)); 25.15 (C(8)); 25.64 (C(7)); 27.29 (C(9)); 29.89 (C(2)); 37.50 (C(1)); 57.55 (C(4), C(6)); 64.70 (CH_2); 66.99 (C(9a)); 86.39 (CH_2=); 151.99 (CH=). IR, ν/cm^{-1}: 3116, 3073, 3041, 1648, 1634, 1609, 1320, 1203, 957, 809 (CH_2=CHO); 2802, 2759, 2678, 2608 (quinolizidine system). MS, m/z (I_{rel} (%)): 195 $[M]^+$ (10), 152 (21), 151 (100), 150 (22), 138 (3), 136 (7), 122 (1), 98 (12), 84 (9), 69 (4), 55 (5), 41 (12), 32 (11).

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* The multiplicity and spin-spin coupling constants were not determined due to superposition of the $=CH_{cis}$ signal.

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