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PREPARATION OF A MONOTERPENE ALKALOID BY THE THERMAL REACTION OF PROPARGYL 4-(3,5-DIMETHYL)PYRIDYL ETHER

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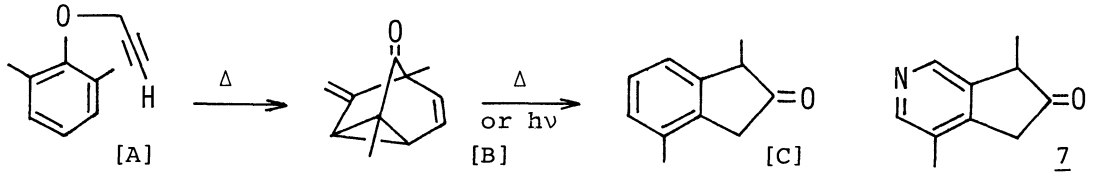
Thermal rearrangement of propargyl 4-(3,5-dimethyl)pyridyl ether afforded 3,7-dimethyl-5-azaindan-2-one which was transformed into racemic actinidine by the subsequent Huang-Minlon reduction.

Among thermal reactions of aryl propargyl ethers,[1,2] a typical example is the following: 2,6-dimethylphenyl propargyl ether [A] isomerize to 1,5-dimethyl-6-methylenetricyclo[3.2.1.$0^{2,7}$]oct-3-en-8-one [B].[2] The compound [B] is known to rearrange to 3,7-dimethylindan-2-one [C] by the thermal or photochemical reaction.[2,3] This type of reaction sequences of pyridine analogue[4] has not been elucidated so far. The interest in the synthesis and chemical behavior of a nitrogen analogue of [B] and an azaindanone such as 7 prompted us to investigate the thermal reaction of propargyl 4-(3,5-dimethyl)pyridyl ether (3). The azaindanone 7 should receive some

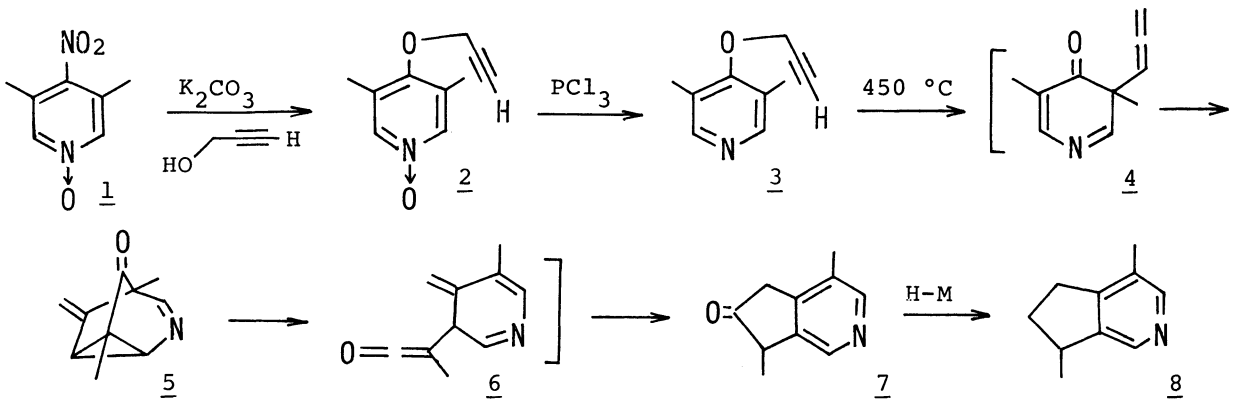


[A] [B] [C] 7

attention because it has a skeleton of monoterpene alkaloids such as actinidine,[5,6] tecomanine,[7] and other natural products.[8]

The preparation of the ether 2 was achieved in 90% yield by the reaction of easily obtained 3,5-dimethyl-4-nitropyridine oxide (1)[9] with propargyl alcohol in the presence of potassium carbonate in refluxing acetonitrile, according to the modified literature procedure.[4,10] On deoxygenation with phosphorus trichloride in dichloromethane,[9] the oxide 2 was converted to 3 in 95% yield. The ether 3 exhibited the following spectral data: IR (film) 3283, 2125, 1576, 997 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (6H, s), 2.44 (1H, t, J=2.5 Hz), 4.47 (2H, d, J=2.5 Hz), 8.08 (2H, broad s).

The thermolysis of 3 was carried out under a nitrogen atmosphere (flow rate: 20 cm^3/min) by passing the benzene solution (20 cm^3) of 3 (500 mg) through a quartz column (15 mm x 150 mm) containing glass beads (φ=2-3 mm) preheated at 450 °C. Under this condition, almost of 3 disappeared. The subsequent distillation of the pyrolysate afforded 273 mg (55%) of pure 3,7-dimethyl-5-azaindan-2-one (7), which was characterized from the following physical data: bp 100-140 °C (bath temp)/266.2



Pa; IR (film) 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (3H, d, J=7.0 Hz), 2.25 (3H, s), 3.45 (2H, s), 3.60 (1H, m), 8.37 (2H, broad s). Further supportive evidence of the structure 7 was also obtained by Huang-Minlon reduction of 7 to the racemic actinidine 8 in 63% yield, according to the literature procedure.[12] The comparison of the spectral data of 8 with the literature data[13] and mp 146-146.5 °C (reported, 146-147 °C)[14] of the picrate of 8 support the structure 8 and then 7. The formation of 7 is reasonably explained by a mechanism which is similar to that for the formation of indanone [C].[1,2] The Claisen rearrangement affording 4 and the subsequent internal Diels-Alder reaction should give 5. The intermediate 5 could not survive at this reaction temperature, so it rearranged to 7 via the ketene intermediate 6.

In the thermolysis of 3 at 400 °C, no 5 was obtained, only 3 and 7. Furthermore 3 was refluxed in 1,2-dichlorobenzene for 7 h, however, again no 5 was obtained, only 20% of 3 and tarry material. Under this condition almost of [A] could be converted to [B]. This slow reaction rate of 3 as compared to [A] should be ascribed to the presence of electron negative nitrogen atom and may correlate to the substituent effect of Claisen rearrangement: electron-withdrawing substituents decrease the reaction rate.[15]

Although the isolation of 5 could not be achieved, the present thermolysis is a convenient method for the preparation of monoterpene alkaloid skeleton. Further work concerning synthetic aspects of the thermal reaction is in progress.

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