

KINETICALLY CONTROLLED ALKYLATION AND PROTONATION OF
THE 2-OXABICYCLO[3.2.1]OCTAN-3-ONE SYSTEM

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Abstract—Alkylation and protonation of the 2-oxabicyclo[3.2.1]octan-3-one system under the kinetic conditions have been examined.

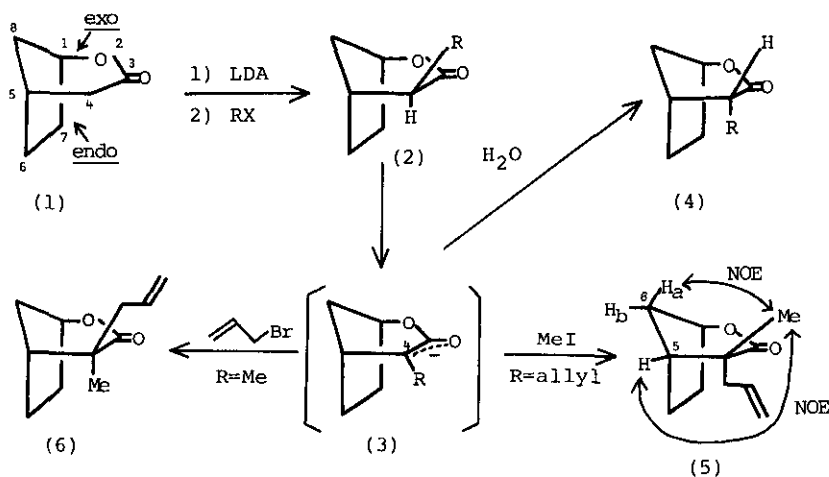
Recently, we developed a general method for the syntheses of a variety of the alkaloids bearing piperidine moiety biologically originated from secologanin using 2-oxabicyclo[3.2.1]octan-3-one (1) as a common starting material.¹ In these syntheses, one of the critical stages was stereocontrolled introduction of an appropriate group by alkylation at 4 position of the starting lactone (1) with an alkyl halide in the presence of a base catalyst. We report here a detailed examination of the stereochemical course of the alkylation reaction and the optimum conditions for controlling the stereochemistry.

Stereoselective alkylation of (1) was examined by using two alkylating agents, methyl iodide and allyl bromide, in the presence of an equimolar amount of lithium diisopropylamide(LDA) in tetrahydrofuran(THF) at low temperature(ca. -30°C). On alkylation, each gave the exo isomer (2) as a single product in a highly stereoselective fashion although the actual stereochemistry could not be determined at this stage. Addition of an equimolar amount of hexamethylphosphoramide in the reaction medium did not affect the stereochemical outcome though some acceleration of reaction rate was observed. Each alkylation product, upon treatment with saturated aqueous sodium sulfate³ under the same conditions for the alkylation, furnished cleanly the endo isomer (4) as a single product isomeric with the starting exo isomer (2), respectively. These apparently suggest that both the alkylation and the protonation were kinetically occurred.

Cross alkylation experiment also substantiated a kinetically controlled sequence. Thus, alkylation of the 4-allyl compound (2:R=allyl) with methyl iodide under the same conditions as above(LDA, -78 ~ -30°C) gave the dialkyl compound (5) as a single isomer which was isomeric with the dialkyl compound (6) obtained from the 4-methyl compound (2:R=methyl) with allyl bromide under the same conditions.

Of two isomeric dialkyl compounds, only the former exhibited NOEs between 4-methyl group and 8-Ha(5.03%) as well as the hydrogen at 5 position(3.66%) indicating its structure expressed to be (5) with

exo methyl group but not to be (6) with endo methyl group. Consequently, it was concluded that both the alkylation and the protonation of the 2-oxabicyclo[3.2.1]octan-3-one system occurred preferentially from the exo face of the molecule under kinetic conditions.⁴



Scheme

Table

substrate	RX(or H ₂ O)	product	NMR()ppm	bp(Torr)	yield
(1)	MeI	(2:R=Me)	1.33(3H, d, J=7 Hz)	134-137 ^o (20)	74%
(1)	C ₃ H ₅ Br	(2:R=C ₃ H ₅)		155-160 ^o (17)	86%
(2:R=Me)	H ₂ O	(4:R=Me)	1.25(3H, d, J=7 Hz)		100%
(2:R=C ₃ H ₅)	H ₂ O	(4:R=C ₃ H ₅)			100%
(2:R=C ₃ H ₅)	MeI	(5)	1.29(3H, s)	135-140 ^o (1.5) ^a	73%
(2:R=Me)	C ₃ H ₅ Br	(6)	1.22(3H, s)	135-140 ^o (1.5) ^a	71%

a. Kugelrohr.

GENERAL PROCEDURE

Alkylation-----To a stirred solution(ca. 0.5 Mol) of lithium diisopropylamide, prepared from diisopropylamine(1 equimol) and n-butyllithium in n-hexane(15%w/v)(1 equimol) in THF, under argon at -78°C was added (1X1 equimol) in THF. After stirring at the same temperature for 30 min, an alkyl halide(1 equimol) was added in one portion and the temperature was allowed to rise to -30°C . After stirring at the same temperature for ca. 5 h, the reaction mixture was quenched by the addition of saturated aqueous Na_2SO_4 solution and the organic layer was separated, washed (sat. NaCl), dried(Na_2SO_4), and evaporated in vacuo. The residue was distilled under vacuum to give a pure product (2).

Protonation-----To a stirred solution of an enolate (3), prepared in situ from an alkyl-lactone (2) with lithium diisopropylamide(1 equimol) in THF as above, under argon at -78°C was added an excess amount of saturated aqueous Na_2SO_4 solution all at once and the reaction temperature was allowed to rise to room temperature. The organic layer was separated, washed(sat. NaCl), dried (Na_2SO_4), and evaporated in vacuo to give pure (4).

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- Satisfactory spectral(IR, ^1H - and ^{13}C -NMR, MS) and analytical data were obtained for new compounds.
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