

REGIOSELECTIVE SYNTHESSES OF OPTICALLY ACTIVE (R)-5-METHYL- AND
(R)-7-METHYL-5,6,7,8-TETRAHYDROQUINOLINES

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Abstract — Five synthetic routes have been evaluated for the regioselective preparation of (R)-5-methyl- and (R)-7-methyl-5,6,7,8-tetrahydroquinolines from (+)-(R)-3-methylcyclohexanone.

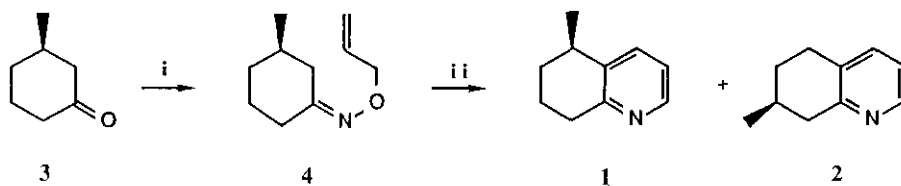
In developing synthetic approaches to 5,6,7,8-tetrahydroquinolines containing one asymmetric carbon in the alicyclic ring¹ we have devoted our attention to the synthesis of (R)-5-methyl- and (R)-7-methyl-5,6,7,8-tetrahydroquinolines (**1**) and (**2**). These compounds are the most convenient starting points for the synthesis of the corresponding optically active 2,2'-bipyridines and 1,10-phenanthrolines, whose applications receive considerable attention whether as chiral ligands for asymmetric reactions² or for the study of the chiroptical properties of the pyridine chromophore.³

A mixture of racemic (**1**) and (**2**) had been prepared by Irie *et al.* through a straightforward method of pyridoannulation starting from 3-methylcyclohexanone.⁴ However no information about the ratio of the regioisomers was reported. More recently, a mixture of **1** and **2** has been obtained, among other by-products, in the synthesis of (+)-(R)-5-methyl-8-isopropylidene-5,6-dihydro-7H-quinoline.⁵

To synthesize **1** and **2**, the largely accessible (+)-(R)-3-methylcyclohexanone⁶ (**3**) appeared a very interesting starting material. This paper is concerned with the evaluation of five synthetic routes to synthesize **1** and **2** from **3**.

Initially, trying Irie's procedure, by heating a benzene solution of (R)-3-methylcyclohexanone O-allyloxime (**4**) in a sealed tube, a 30% yield of a 24:76 mixture of **1** and **2** was obtained (Scheme 1). It was impossible to effect any separation of the two isomers and their ratio was determined on the basis of nmr data.

Scheme 1



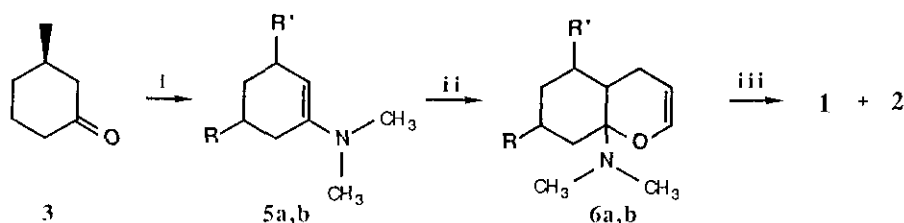
Reagents: i, $\text{CH}_2=\text{CHCH}_2\text{ONH}_3^+\text{Cl}^-$; ii, C_6H_6 , 200°C

The most direct synthesis of pyridine derivatives is by condensation of a suitable nitrogen source with appropriate δ -dicarbonyl compounds. These are easily obtained by the reaction of enamines with vinyl aldehydes or ketones.^{1,7}

Morpholine enamine of 3-methylcyclohexanone exists as ca. 1:1 mixture of two structural isomers.⁸ The reaction of this mixture with various electrophiles is known to give adducts whose composition deviates from that of the parent enamines.⁹ In some cases only one of the two possible adducts has been obtained.¹⁰ Moreover, to our knowledge no data is reported in the literature about the reaction of enamines of 3-methylcyclohexanone with Michael acceptors.¹¹

Thus, a 1:1 mixture of morpholine enamines (5a,b) was allowed to react with acrolein to give cycloaddition adducts (6a,b)¹² (Scheme 2). Treatment of crude (6) with hydroxylamine hydrochloride¹ gave a 25:75 mixture of 1 and 2 in 30% overall yield. It is reasonable to think that the composition of the isomers in 6 is the same found in the final products.

Scheme 2

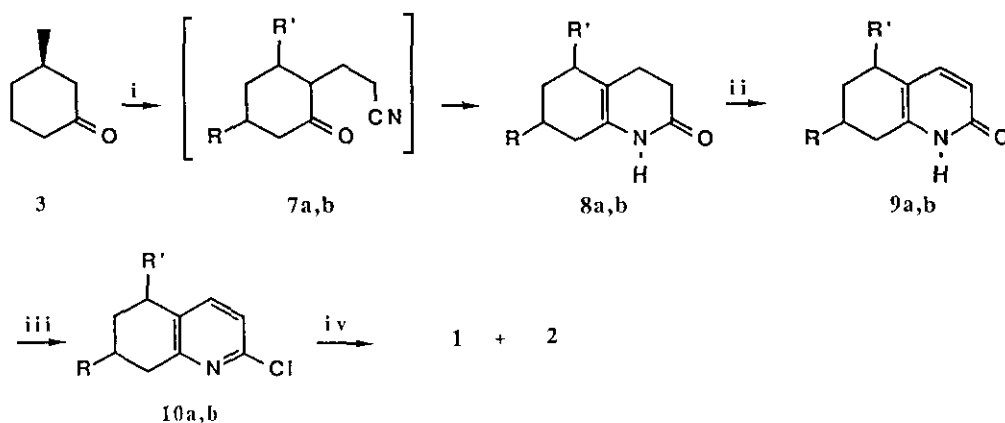


a: $\text{R}=\text{H}$, $\text{R}'=\text{CH}_3$ b: $\text{R}=\text{CH}_3$, $\text{R}'=\text{H}$

Reagents: i, morpholine, TsOH , C_6H_6 ; ii, acrolein, C_6H_6 ; iii, $\text{NH}_2\text{OH}\cdot\text{HCl}$, 78°C

Another route we have followed to obtain **1** and **2** is depicted in Scheme 3. A mixture of **8a** and **8b** was formed in one step when **3** and acrylonitrile were heated in an autoclave in the presence of 4-methylcyclohexylamine and acetic acid¹³ (53% yield). Dehydrogenation¹⁴ of crude (**8a,b**) gave a mixture of tetrahydroquinolones (**9a**) and (**9b**) in 25:75 ratio (by nmr) which was converted into the corresponding halogen-derivatives (**10a**) and (**10b**)¹⁵ (70% yield) having the same isomeric ratio. Hydrogenolysis of **10a,b** catalyzed by palladium on charcoal¹⁶ gave a 25:75 mixture of **1** and **2** in 85% yield. This ratio undoubtedly reflects the composition of the isomer mixture in **8a,b**, as confirmed by glc analysis of the mixture obtained in an experiment stopped before completion: beside the final product (**8a,b**) a 26:74 mixture of isomeric nitriles (**7a**) and (**7b**) was detected. A very similar ratio (28:72 by nmr) of nitriles (**8a**) and (**8b**) was obtained when the reaction was carried out in atmospheric pressure.

Scheme 3



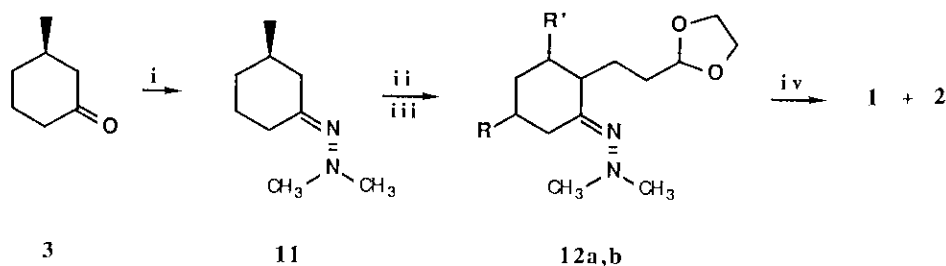
a : R = H, R' = CH₃ b : R = CH₃, R' = H

Reagents : i, CH₂=CHCN ; ii, SO₂Cl₂ ; iii, (PhO)₃PCl₂ ; iv, Pd/C, H₂

The alkylation of metallated N,N-dimethylhydrazones (DMH's) is a very efficient method for forming highly regioselective C-C bonds.¹⁷ Enders reported that the alkylation of (2S)-2-methoxymethyl-1-(3-methylcyclohexylidenamino)pyrrolidine with isopropyl iodide takes place in the 6-position to give, after hydrolysis, a menthone-isomenthone mixture.¹⁸

Moreover, we have recently described a pyridoannellation method based on the regiospecific alkylation of DMH's with 2-(2-bromoethyl)-1,3-dioxolane (BED) followed by acid catalyzed intramolecular cyclization of the iminoacetal intermediates.¹⁹ Following this synthetic strategy, a 8:92 mixture of **1** and **2** was obtained starting from **3** (48% overall yield) (Scheme 4).

Scheme 4

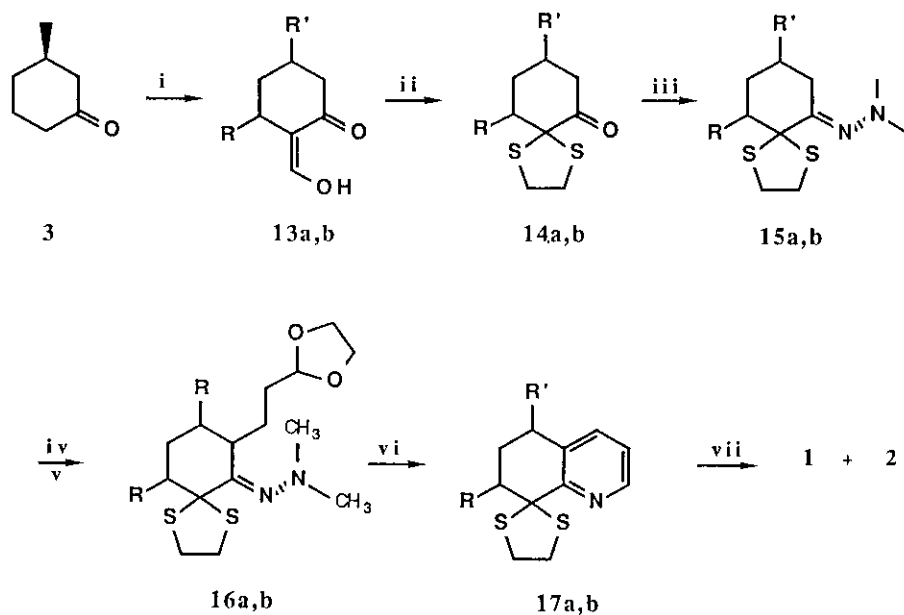


a: R=H, R'=CH₃ b: R=CH₃, R'=H

Reagents: i, H₂NN(CH₃)₂; ii, LDA; iii, BED; iv, AcOH, 115 °C

All the methods reported above give tetrahydroquinoline (**2**) as the main product. In order to obtain **1**, we attempted to block selectively the 6-position of the ketone (**3**). Base-catalyzed condensation of **3** with ethyl formate²⁰ gave a mixture of **13a** and **13b** in ca. 80:20 ratio by nmr (Scheme 5). Treatment of **13a,b** with 1,2-ethanedithiol ditosylate and potassium acetate in ethanol²¹ produced thioketal ketones (**14a**) and (**14b**) in about 90:10 ratio (62%). Chromatographic purification gave pure **14a**²² but, up to the moment, not in sufficient quantities for our needs. Therefore a mixture of **14a** and **14b** (90:10) was converted into the dithiaspirotetrahydroquinolines (**17a**) and (**17b**) according to Scheme 5. Thus **14a,b** were first transformed into N,N-dimethylhydrazones (**15a,b**) and then alkylated with BED to give **16a,b** which were used directly in the next step. Heating of crude **16a,b** in acetic acid produced **17a,b** (45% overall yield from **15**) which, by treatment with Raney-Ni in 7:3 ethanol/water,²³ gave a 90:10 mixture of **1** and **2** (95% yield). The Table summarizes the results obtained in the pyridoannellation of **3** by all the synthetic routes tested.

Scheme 5



a: R = H, R' = CH₃ b: R = CH₃, R' = H

Reagents: i, NaH, HCOOC₂H₅; ii, TsS(CH₂)₂STs; iii, H₂NN(CH₃)₂; iv, LDA; v, BED;

vi, AcOH, 115 °C; vii, Raney-Ni, H₂

Table

route	yield*	% of 1	% of 2
O-Allyloxime (4)	30	24	76
Enamine (5)	26	25	75
Quinolone (8)	36	25	75
Hydrazone (11)	48	8	92
Hydroxymethylene (13)	22	90	10

* Overall yield from 3

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- 22 Selected ^1H nmr data: (CDCl_3) δ 1.02 (d, $J = 6$ Hz, 3H); 3.23 (s, 4H). Anal. Calcd for $\text{C}_9\text{H}_{14}\text{OS}_2$: C, 53.42; H, 6.97; S, 31.69. Found: C, 53.31; H, 7.05; S, 31.75. $[\alpha]^{25}_{\text{D}} +130.3^\circ$ (c 2.70, cyclohexane).
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