REGIOSELECTIVE SYNTHESES 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.

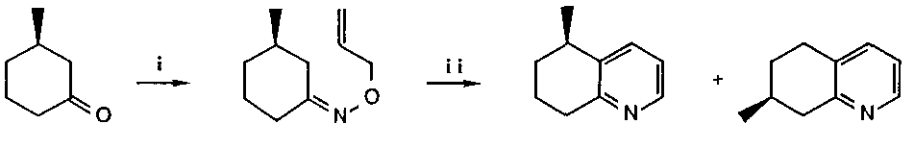
In developing synthetic approaches to 5,6,7,8-tetrahydroquinolines containing one asymmetric carbon in the alicyclic ring[1] we have devoted our attention to the synthesis of (R)-5-methyl- and (R)-7-methyl-5,6,7,8-tetrahydroquinolines (**1**) and (**2**). These compounds are the most convenient starting 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 reactions[2] or for the study of the chirooptical properties of the pyridine chromophore.[3]

A mixture of racemic (**1**) and (**2**) had been prepared by Iric et al. through a straightforward method of pyridoannelation 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-methylcyclohexanone[6] (**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 Iric'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



3 4 1 2

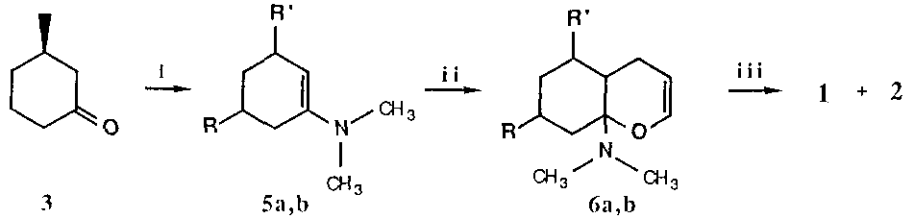
Reagents: i, CH_2=$CHCH_2ONH_3^+Cl^-$; ii, C_6H_6, 200 °C

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 hydrochloride[1] 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



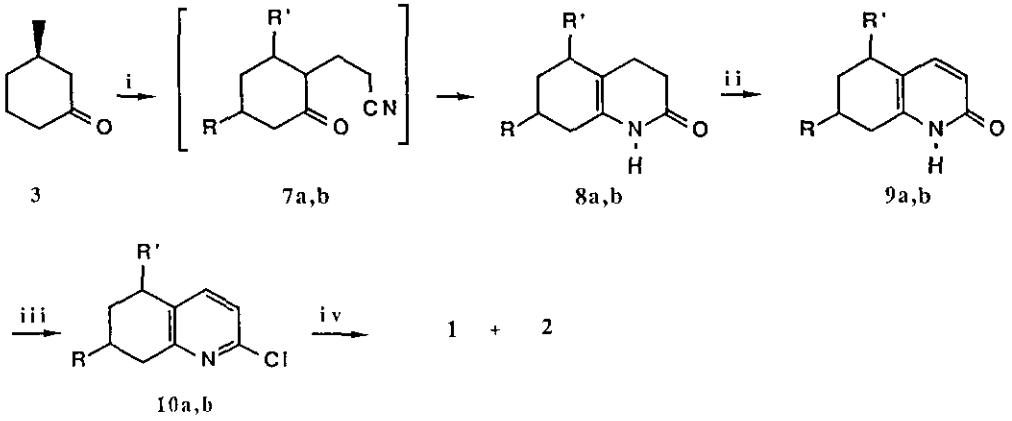
3 5a,b 6a,b

a : R=H , R'=CH_3 b: R= CH_3 , R'=H

Reagents: i, morpholine, TsOH, C_6H_6; ii, acrolein, C_6H_6; iii, $NH_2OH \cdot HCl$, 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 acid[13] (53% yield). Dehydrogenation[14] 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 charcoal[16] 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



3 7a,b 8a,b 9a,b 10a,b

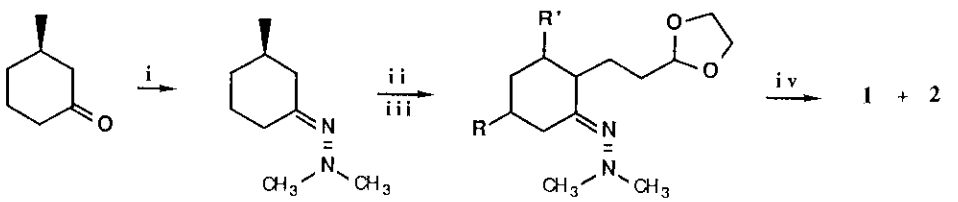
a : R = H , R' = CH_3 b : R = CH_3 , R' = H

Reagents : i, CH_2 = CHCN ; ii, SO_2Cl_2 ; iii, $(PhO)_3PCl_2$; iv, Pd/C, H_2

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 pyridoannelation 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



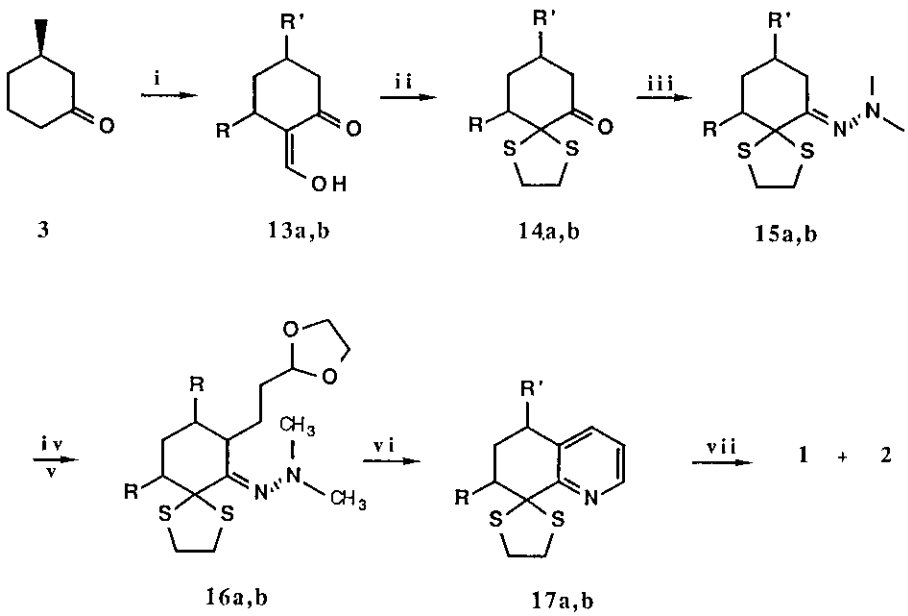
3 **11** **12a,b**

a : R=H , R'=CH_3 b: R= CH_3 , R' =H

Reagents: i, $H_2NN(CH_3)_2$; 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 formate[20] 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 ethanol[21] 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 pyridoannelation of **3** by all the synthetic routes tested.

Scheme 5



3 13a,b 14a,b 15a,b

16a,b 17a,b

a : R = H , R' = CH_3 b: R = CH_3 , R' = H

Reagents : i, NaH, $HCOOC_2H_5$; ii, TsS $(CH_2)_2$ STs ; iii, $H_2NN(CH_3)_2$; iv, LDA ; v, BED; vi , AcOH, 115 °C; vii, Raney-Ni, H_2

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 ^{1}H nmr data: ($CDCl_3$) δ 1.02 (d, J= 6 Hz, 3H); 3.23 (s, 4H). Anal. Calcd for $C_9H_{14}OS_2$: C, 53.42; H, 6.97; S, 31.69. Found: C, 53.31; H, 7.05; S, 31.75. $[\alpha]^{25}_D$ +130.3° (c 2.70, cyclohexane).

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