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AN EFFICIENT SYNTHESIS OF 1-PHENYL-1-PIPERIDINO-trans-4-METHYLCYCLOHEXANE: UNANTICIPATED TOTAL STEREOSELECTIVITY IN THE CATALYTIC HYDROGENATION OF AN OLEFIN

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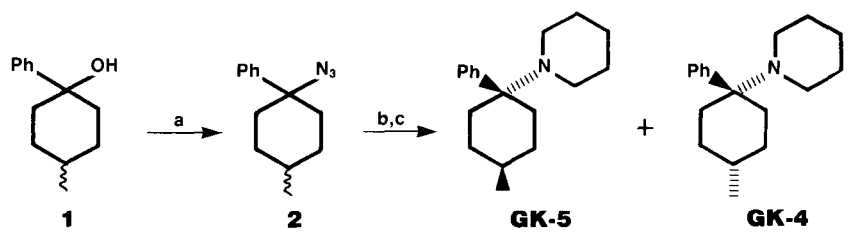
Abstract: A superior synthesis of the title compound, 1-phenyl-1-piperidino-trans-4-methylcyclohexane, is reported. The key step, the catalytic hydrogenation of 1-phenyl-1-piperidino-4-methylenecyclohexane hydrochloride, proceeds with unusual stereospecificity via addition of hydrogen trans to the axial phenyl substituent.

We recently had occasion to prepare several compounds related to the psychotomimetic drug, phencyclidine (1-phenyl-1-piperidinocyclohexane; "angel dust;" PCP), including the epimers, 1-phenyl-1-piperidino-cis-4-methylcyclohexane (**GK-4**) and 1-phenyl-1-piperidino-trans-4-methylcyclohexane (**GK-5**). These two compounds are of interest because **GK-5** exhibits pronounced PCP-like pharmacological properties, whereas the isomer, **GK-4**, is only weakly active[1,2]. Syntheses of both of these substances have been previously reported[3-5]. Although **GK-4** can be conveniently prepared by the addition of phenylmagnesium bromide to 1-cyano-1-piperidino-4-methylcyclohexane[3], an equally practical synthesis of **GK-5** was not available.

Geneste and co-workers[4,5] obtained this compound by the route shown below, in which the relative stereochemistry at C-1 and C-4 is set nonselectively in the second step, the reaction of **1** with hydrazoic acid.

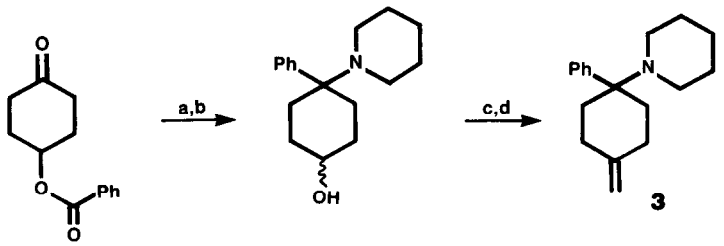


1 **2** **GK-5** **GK-4**

a) hydrazoic acid; b) LAH; c) 1,5-dibromopentane

The diastereomeric azides, **2** are obtained as a 57:43 mixture (trans:cis), which, not unexpectedly, indicates little preference for the trapping of the intermediate carbonium ion.

Consequently, a possibly stereoselective route to the trans isomer was investigated. We elected to prepare 1-phenyl-1-piperidino-4-methylenecyclohexane (**3**) in anticipation that hydrogenation of the double bond in the presence of a bulky homogeneous catalyst might afford predominant addition of hydrogen trans to the phenyl moiety. It was expected that variation of the nature of the catalyst would significantly influence the product ratio. Thus, compound **3** was synthesized according to the following sequence[6-8]:



a) KCN, piperidine hydrochloride, 33% yield; b) PhMgBr, THF, 67% yield; c) Jones reagent, acetone, then sodium citrate and mossy Zn, 46% yield; d) methyltriphenylphosphonium bromide, n-BuLi, THF, 87% yield.

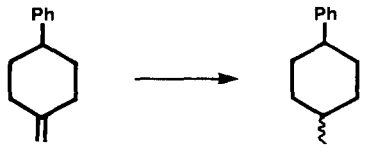
With **3** in hand, we first sought to establish what we suspected might be the most unfavorable isomer ratio by carrying out the hydrogenation in the presence of a simple, non-complex catalyst, namely Raney nickel. Much to our surprise, when **3** was hydrogenated over Raney nickel in ethanol at a pressure of 40 PSI (16 hr.; room temperature), a 96:4 ratio[9] of **GK-5:GK-4** was produced, as evident from the 300 MHz proton nmr spectrum of the unpurified reaction mixture (the epimers are easily differentiated by the chemical shifts of the C-4 methyl groups which appear as doublets (J = 6 Hz) at delta 0.72 and 0.93 for **GK-5** and **GK-4**, respectively). Pure **GK-5** was obtained as a thick colorless oil in 78% yield after chromatography of the reaction residue on silica gel with 2:1/hexane:ethyl acetate. Thus, the original goal of a convenient, stereochemically unambiguous synthesis of **GK-5** had been realized.

We attempted to investigate further this remarkably selective hydrogenation. Reduction of **3** over 5% palladium on carbon (ethanol; 40 PSI; room temperature) resulted in a less favorable isomer ratio, namely, 70:30. However, hydrogenation of the hydrochloride salt of **3** in the presence of palladium on carbon afforded only **GK-5** (no **GK-4** could be observed in either the high field proton or carbon-13 nmr spectra of the unpurified reaction mixture).

It is known[10-14] that phencyclidine itself exists almost exclusively in a conformation in which the phenyl group is axial and the piperidine equatorial. Not surprisingly, minimum energy calculations[15] for the axial and equatorial phenyl conformations of **3** (chair cyclohexane) revealed that the axial phenyl form was more stable than the equatorial by 4.89 kcal/mole (28.60 vs. 33.49 kcal/mole; >99% axial phenyl conformation)[16]. It appeared that the observed stereochemical outcome of the hydrogenation reaction was either the result of a remote hindering effect exerted by the axial phenyl group forcing the approach of catalyst from the opposite face, complexation of the catalyst with the nitrogen of the piperidine ring, or a subtle combination of both factors.

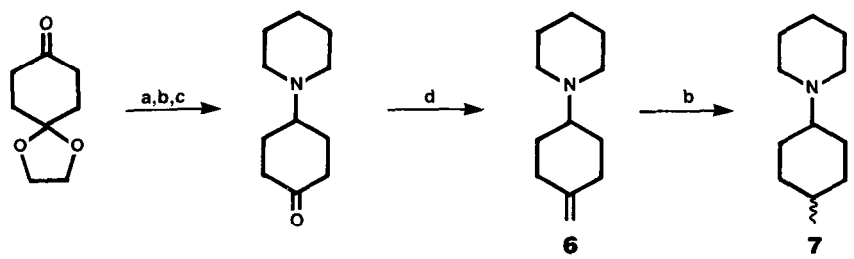
In order to gain more information, we chose to study the reduction of several model substrates. 4-Phenyl-methylenecyclohexane (**4**) was selected for study on the basis of a significant calculated energy difference (3:43

kcal/mole; >99% equatorial) between the equatorial (favored) and axial phenyl conformations. Hydrogenation of **4** under the conditions previously described for **3** afforded a 1:1 mixture of epimers (**5**), thus indicating that either shifting to an equatorial rather than axial phenyl substituent, or removal of the piperidine moiety abolishes any directing effect.



4 **5**

We wished to separate these two possibilities and therefore, 1-piperidino-4-methylenecyclohexane (**6**), the desphenyl analog of **3**, was next synthesized. The calculated energy minima for the axial and equatorial conformers of **6** were 19.79 and 19.38 kcal/mol, respectively, indicating an approximate equatorial/axial ratio of 67/33. Reduction of **6** under conditions identical to those used in the hydrogenation of **3** resulted in a 70:30 (trans:cis) mixture of diastereomers (**7**) as determined by ^{13}C-nmr[17]. It is interesting that the product ratio closely reflects the conformational equilibrium of the starting olefin, suggesting that the piperidine nitrogen could be influencing the mode of addition of hydrogen. The hydrochloride salt of **6** was also prepared. It was thought that this modification would favor an even greater percentage of the equatorial piperidine conformer, and, by analogy with the reduction of **3** hydrochloride, lead to increased stereoselectivity. Surprisingly, the reduction of **6** hydrochloride afforded a 60:40 isomer ratio (trans:cis), a somewhat less selective result than that seen with the free base as substrate.



6 **7**

a) piperidine, benzene, reflux; b) hydrogen, Pd-C, ethanol, 40 PSI; c) 4N HCl, reflux; d) methyltriphenylphosphonium bromide, n-BuLi, THF.

Thus, we speculate that the complete stereoselectivity observed in the hydrogenation of **3** is probably due to a remote directing effect exerted by the axial phenyl group and is not dependent on a catalyst interaction with the piperidine nitrogen. The slightly diminished selectivity seen in the case of the free base may reflect a small "leakage" of the starting material into the equatorial phenyl form under the hydrogenation conditions, i.e., alcohol solvent and increased pressure. Additional studies of this unusual reduction are in progress.

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