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PREPARATION AND REDUCTION OF SOME CAMPHOR IMINES

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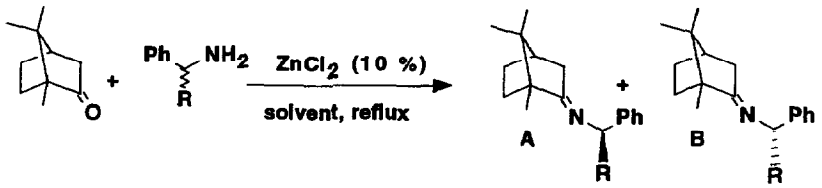
ABSTRACT:- A simple procedure for the preparation and the stereoselective reduction of some camphor based imines is reported.

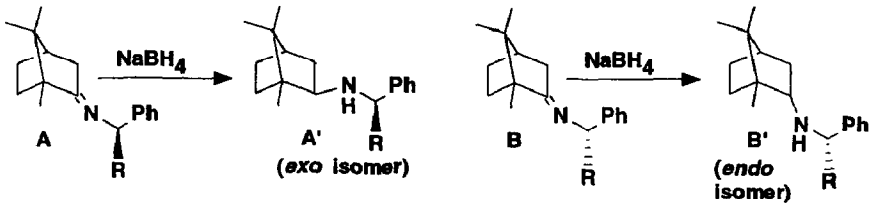
Two recent publications[1,2] describing the synthesis of sterically crowded camphor imines have prompted us to report our findings in this field. Our method allows the simple synthesis of such imines in high yield. Condensation of 1-phenyl alkylamines with (+)-camphor occurred when a solution of the two components were refluxed with 10 mol % anhydrous $ZnCl_2$. (Dean-Stark trap). The temperature required for the reaction increased with the bulk of the alkyl substituent of the amine.



Compound	R	Solvent	Time(h)	Yield(%)
1	H	toluene	4	80
2	Me	xylenes	48	77
3	Et	xylenes	72	70
4	*iso*-Pr	mesitylene	72	60
5[a]	*t*-Bu	mesitylene	120	<5

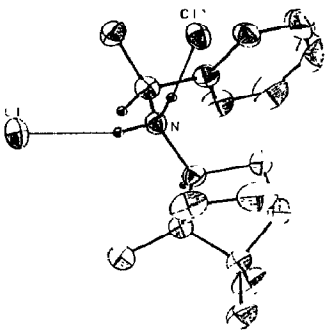
(a) Product was not formed to any extent under the conditions described, possibly due to the hindered nature of the amine.

The imines were inert to $LiAlH_4$ even after prolonged periods of reflux. However the corresponding diastereomeric amines (**A'** and **B'**) were produced by reduction of camphor imines **A** and **B** with $NaBH_4$ in methanol.



Optically pure **2A** (prepared either from (*R*)-α-methyl benzylamine or by chromatographic separation of **2A** and **2B**), on reduction ($NaBH_4$ in methanol at 0 °C) led exclusively to the *exo* product **2A'**. Reduction of **2B** under identical conditions however, led to exclusive formation of the *endo* product **2B'**. Reduction of **2A** and **2B** with $LiBH_4$ gave similar results. It has previously been noted that reduction of **2B** with $NaCNBH_3$ leads exclusively to the *endo* product **2B'**. Assignment of this stereochemistry however, was based primarily on the observation of an extra ω- coupling in

the ^{1}H n.m.r. spectrum[3]. We have now obtained an X-ray crystal structure of **2B'** (as its HCl salt) and proved beyond doubt that only the *endo* product forms.



Crystal data:
p2,2,2, -orthorhombic
Z=4, a=7.369 Å, b= 12.947Å , c=18.355 Å.
V=1754, R=0.037.

The literature reports of the reduction of camphor imines is confusing; **2** gives *iso* bornylamine with concomitant hydrogenolysis when reduced with H_2-Pd/C.[4] Under milder conditions ($NaBH_4$-$NiCl_2$-MeOH) imine **1** provides *N* -benzylbornylamine[5] while the phenylamine analogue gives *N* -phenyl-*iso* bornylamine.[6] In an attempt to rationalise the stereoselectivity of these reductions we examined the geometry around the C=N bond of the imines **2A** and **2B**. These were assigned as *E* on the basis of n.O.e. difference spectroscopy. Irradiation of the methine proton of the *R* and *S* 1-phenylethyl fragment lead to an enhancement of the signals due to protons C3 and C3' of the camphor fragment. Enhancement of the signal of the methyl group at C1 of the camphor fragment was not observed. These results indicate that the methine proton of the 1-phenylethyl fragments of **2A** and **2B** are in the proximity of the protons at C3 and C3' of the camphor residue. Examination of the molecular models of **2A** and **2B** indicates that only an *E* orientation about the C=N bond brings these protons into the required position for these observations. The difference in the products obtained from the reduction of **2A** and **3A** compared to **2B** and **3B** may be a result of steric hindrance of the reacting centres.

In each case there was a difference in the rate of reaction of the imine **A** compared to imine **B**. After 2 hours at -78 °C, 85 % of **2A'** had formed compared to 70 % of **2B'** (1.2:1). Under identical conditions 40 % of **3A'** was formed compared to 14 % of **3B'** (3:1). The remaining unreacted imines were significantly enriched in the proportion of the slower reacting component, but we were unable to hydrolyse these to yield the corresponding optically enriched amines. Attempts to reduce compound **4** under the conditions described failed to yield either the *exo* or *endo* amines. This observation is presumably due to the increased steric hindrance which results from the spacially more demanding *iso* -propyl substituent.

In conclusion this simple synthesis of hindered camphor based imine allows easy access to chiral secondary amines which are useful sources of lithium amide bases in asymmetric synthesis. The selective reduction of other chiral bicyclic imines is currently under investigation

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