3-Benzylidenecamphor derivatives and their conversion into chiral auxiliaries and organocatalysts

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Camphor-based chiral auxiliaries

The rigid camphor system with its well defined geometry potentially possesses all the key features required for a highly effective chiral auxiliary. This has been realized by Oppolzer, who developed three general exo-substituted camphor derivatives for use in a wide variety of reactions. Helimchen has also developed endo-substituted camphor-base alcohols.

In earlier work, we demonstrated that the electronical- ly complementary aromatic rings of 3-benzylidenecamphor derivatives from which the 2-endocamphor stage can so easily be halted at benzylidenecamphor stage.

Reactions of benzylcamphor with nitrogen nucleophiles

We had expected that the condensation of the benzylcamphor with nitrogen nucleophiles would proceed straightforwardly, but this has not proved to be the case. Despite the fact that camphor itself yields a semicarbazone, a phenylhydrazone and a simple hydrazone, the 3-endobenzylcamphor \((X = H \text{ or } \text{OMe})\) failed to provide any of these derivatives in isolatble yield. This may have been precluded by the fact that the sodium borohydride reduction of the benzylidenecamphor can so easily be halted at the benzylcamphor stage.

Reactions of benzylidenecamphor with nucleophiles

As an alternative to condensing the benzylcamphor itself with a nitrogen nucleophile, we tested the possibility that we could form the desired compounds from the benzylidenecamphor.

The reaction with phenylhydrazine initially gave us the expected product as a mixture of 2 and 3 isomers, but the reaction proved to be very irreproducible. The HNMR spectrum showed that the olefinic proton was retained in the product, so the final product was not the \(N\)-phenylpyrazoline, as might be expected from a mechanism involving conjugate addition followed by condensation with the carboxyl group.

The reaction with hydrazine gave neither the hydrazone, nor the azine nor the pyrazoline. In addition, the possibility that the Knoevenagel cyclopropane might have been formed was investigated. None of these products was obtained, and the staring enone was the only compound recovered.

Camphor-based chiral organocatalysts: Initial approaches to targets

In our earlier work, we had shown that the Bouveault-Blanc reduction of \(E\)-3-arylmethylenecamphors gave a mixture of the corresponding saturated alcohols as a mixture of the 2-exo-3-exo, 2-endo-3-endo and 2-endo-3-exo diastereoisomers from which the 2-exo-3-exo isomer could be obtained by fractional crystallization of the mixed \(p\)-nitrobenzoate esters.

By analogy with that earlier work, we expected that the Bouveault-Blanc reduction of a similar imine derivative should permit us to obtain a \(p\)-nitrobenzamide derivative with similar crystallizing properties.

To obtain the required imine derivatives, it was necessary to form the 3-exo-endo benzyl ketone first. This was accomplished straightforwardly by catalytic hydrogenation over palladium, which gave a mixture containing predominately the 3-exo isomer; equilibration with potassium carbonate in methanol resulted in almost complete epimerization to the 3-endo ketone.

The same overall result could be obtained by direct reduction of the enone with sodium borohydride in ethanol. In this reaction, which gives the 3-exo-endo-bomeol, excess reducing agent only slowly attacks the carbonyl group after the reduction of the double bond.

Orbitals of benzylidenecamphor

Examination of the corresponding orbitals of benzylidenecamphor suggested that the \(ji\) position is sufficiently free of hindrance to allow the formation of an adduct.

Future directions

With the almost uniform failure of our current approaches, we are now investigating the alklylation of imine anions with an appropriate benzyl halide as a means to obtain the desired imine precursor to a secondary amine. At this stage, we have completed the synthesis of both the tert-butyl and 2-phenylethyl imines from camphor.

We have also demonstrated that we can reduce the imine in situ with zinc borohydride to give a mixture of the \(\text{N-alkyl\hspace{0.16em}borylamine}\) and the \(\text{N-alkylisoborylamine}\). It is reasonable to expect that the isoborylamine will be the major diastereoisomer, but the stereochemistry has not yet been assigned.