Asymmetric 1,4-Reduction of Alkylidene-cyanoacetic Esters and Alkylidene-malononitriles

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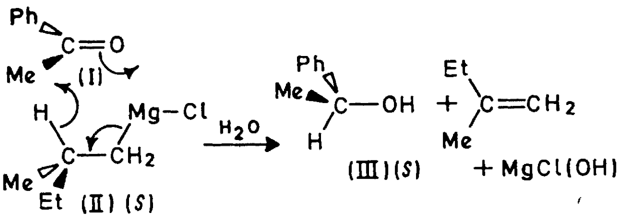
Summary The stereochemical result of the reduction of the ethyl 2-cyano-3-phenylbutenoate by (*S*)-2-methylbutylmagnesium chloride is opposite to that of the reduction of acetophenone by the same reagent.

ONE of the best pieces of evidence for Whitemore's cyclic mechanism[1] for the reduction of carbonyl compounds by Grignard reagents is Mosher's stereochemical results in the reduction of acetophenone (I) by optically active organomagnesium halides, such as the *S*-2-methylbutylmagnesium chloride (II).[2] (Scheme 1.)

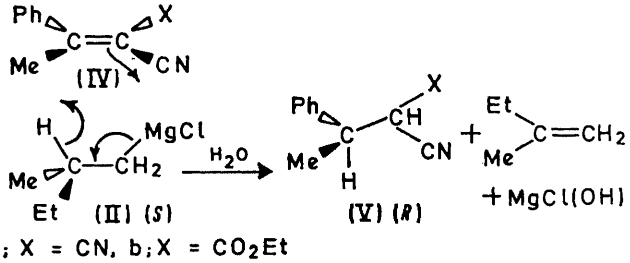


SCHEME 1

(—)-*S*-1-Phenylethanol (III) (4% optical purity) is formed during this reduction. This and other similar results[3] are in good agreement with the cyclic transition state of Scheme 1 in which the magnesium halide is *obligatorily* pointed towards the oxygen atom of the ketone, the ring being formed in such a way as to minimize steric repulsion between the two large groups, phenyl and ethyl.[2]

Similar results can be used also for a better understanding of the Grignard reduction of compounds having electrophilic C=C double bonds, such as alkylidene-cyanoacetic esters and alkylidene-malonic esters or -malononitriles.[4-7]

So in the reduction of compounds (IV) by the Grignard reagent that Mosher used, one would expect, if a similar cyclic mechanism operates, to get the (V) *R*-compound (Scheme 2).

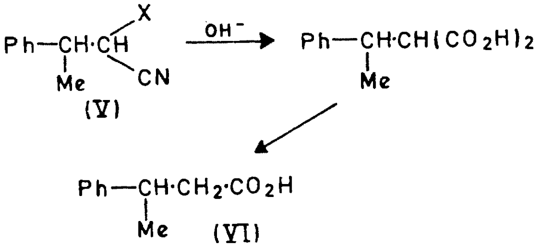


SCHEME 2

We treated the (*S*)-2-methylbutylmagnesium chloride (II) with the *β*-methylbenzylidenemalonitrile (IVa) and also with a mixture (39% *cis* and 61% *trans*) of the two stereoisomeric ethyl cyanoacetates (IVb). It is known that these compounds may be reduced by the usual Grignard reagents.[5]

Using Grignard reagent (II) (91% purity†) the reaction with compound (IVa) gives a reduction product (Va) (42%). This compound after t.l.c. purification (Kieselgel G, solvent ether–cyclohexane 2 : 8) has a rotation $[\alpha]^{25}_{D}$ — 4·69° (pure liquid). The mixture of the two diastereoisomeric compounds (Vb) obtained in the same way has a rotation $[\alpha]^{25}_{D}$ +0·90° (pure liquid). Under these conditions there is no separation of the diastereoisomers (Vb), so the optical purity of the compound (V) *R* was not increased by this procedure.

For the determination of the configuration of the benzylic carbon atom of compounds (Va) and (Vb), we correlated these compounds with the *β*-phenylbutyric acid (VI) of known configuration and known optical purity[9] by the following reactions:



This correlation has shown that acids (VI) resulting from compounds (Va) or (Vb) have the *S*-configuration. The intermediate malonic acid was not purified by crystallisation, so as to avoid enrichment of the optically pure material. But a possible partial racemisation of the benzylic carbon atom during the saponification was not ruled out. The optical purity of compound (VI) thus obtained from (Va) is 32% {$[\alpha]^{25}_{D}$ 17·6° (*c* 6·14%, benzene)} and from (Vb) 18% {$[\alpha]^{25}_{D}$ 10·1° (*c* 7·89%, benzene). So compounds (Va) and (Vb) also have the *S*-configuration with at least 32% and 18% optical purities, respectively.

The comparison of these results with the results of the acetophenone reduction[2] permits us to comment on the following points:

(1) The stereochemistry of the reduction of compounds (IVa) and (IVb) is opposite to that of the acetophenone reduction. Consequently, the reduction of these compounds may involve the previously suggested acyclic transition state.[6,10]

The known importance of polar and steric effects[11] in the determination of the relative stabilities of diastereoisomeric transition states suggests the following explanation of the observed stereochemical results: from the three pairs of diastereoisomeric transition states resulting from the both-side attack of electrophilic double bond, and from the free rotation about the C–H bond, the most stable ones are (A) and (B), in which the negatively charged Mg · · · · $CH_2^{\delta-}$

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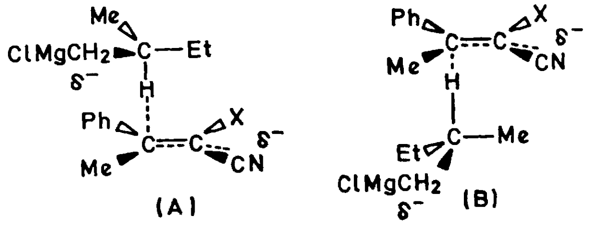
† It is known that the optically pure (*S*)-2-methylbutanol contains some isopentyl alcohol, too.[8]

moiety of the Grignard reagent is far away from the developing high-electron-density enolate centre and from the electronegative phenyl group of the electrophilic reagent. So for steric reasons, transition state (A), in which the two large groups, phenyl and ethyl, are remote is more stable than transition state (B) in which these groups are close to each other (Scheme 3).

(2) Taking into account the various arguments based on stereochemical[12] and other considerations,[10] the most favoured hydrogen transfer must be linear in a cyclic as well as in an acyclic transition state. So the higher stereospecificity of the reduction of compounds (IV) as compared with the acetophenone reduction can be understood either on the basis of the strong orientation of dipolar effects, or, as suggested by the previous isotope-effect study,[10] the smaller distance between the hydride-donating and hydride-accepting reagent in the reduction of the C=C double bond of compounds (IV) than in the reduction of the C=O double bond of compound (I). The reason for the different optical yield in the reduction of compounds (IVa) and (IVb) is not yet clear.



SCHEME 3

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