Mechanism of the Grignard Addition Reaction. XVI. Homolytic and Concerted Mechanisms in the Reaction of α,β-Unsaturated Carbonyl Compounds with Grignard Reagents

Torkil Holm

The Technical University of Denmark, Department of Organic Chemistry, Building 201, DK-2800 Lyngby, Denmark

Holm, T., 1991. Mechanism of the Grignard Addition Reaction. XVI. Homolytic and Concerted Mechanisms in the Reaction of α,β-Unsaturated Carbonyl Compounds with Grignard Reagents. – Acta Chem. Scand. 45: 925–929.

Kinetic measurements have shown that the addition of Grignard reagents to α,β-unsaturated carbonyl compounds takes place either by a concerted mechanism or by a homolytic mechanism. Phenylmagnesium bromide, which is incapable of homolysis, reacts rapidly in a 1,4-fashion if an s-*cis* conformation exists between the C=C and the C=O bonds, but only 1,2-addition takes place if the conformation is s-*trans*. *tert*-Butylmagnesium bromide is unsuited to the concerted reaction, but 1,4-addition takes place via homolysis. Primary and secondary Grignard reagents, like phenyl, react rapidly in a concerted manner with s-*cis* substrates, but unlike phenyl, these Grignard reagents may, with s-*trans* substrates, produce some 1,4-adduct via the homolytic mechanism.

Though the Grignard reagent is usually considered as being highly polar and is thought to react by polar reaction mechanisms, it has been known since the time of its discovery that certain 'abnormal' reaction products, especially dimers, were explainable only by accepting that homolysis of the C–Mg bond took place so that free radicals were produced.[1] Although the abnormal products can only be produced by homolysis, the normal addition products could result either from concerted or from homolytic reaction mechanisms. Recently it has been shown that the elusive problem of homolytic versus concerted mechanisms may be dealt with by studying the reactivity series of various Grignard reagents in their reaction with a given substrate.[2]

The assignment of a homolytic reaction mechanism to a reaction of a Grignard reagent in this way is usually simple, since the reactivity is the same, or almost the same, from one substrate to the other. Qualitatively, and often also quantitatively, the rate is correlated to the strength of the carbon–magnesium bond of the reagents. Steric effects are of little importance and *tert*-butylmagnesium halide, which has the weakest C–Mg bond is highly reactive, while methyl- and phenyl-magnesium halide, which have strong C–Mg bonds, are of low reactivity.

It has been assumed for some time that the rate-determining step in the homolytic reactions is the transfer of a single electron (SET). However, closer investigation shows that electron transfer must be concerted with transfer of magnesium, so that the slow step of the reactions is an induced homolysis.[3]

Substrates which induce homolysis of Grignard reagents usually have resonance-stabilized radical anions, which form stable magnesium salts so that the process of eqn. (1)

$$R\text{–}MgX + S \rightarrow R^{\bullet} + {}^{\bullet}S\text{–}MgX \qquad (1)$$

is only weakly endothermic.[3] Typical examples are benzophenone, azobenzene, pyridazine, di-*tert*-butyl peroxide, etc. In Table 1 is shown the reactivity series for benzophenone (**1**) which reacts by a typical homolytic mechanism.

If homolysis is unfavorable, a concerted reaction may take over. Thus saturated esters and ketones have less stabilized ketyls than, *e.g.*, aromatic ketones, and an effective reaction mechanism requires that C–C and especially O–Mg bond formation is concerted with C–Mg and π C=O breakage.

The concerted mechanism requires the close approach of the α-carbon to magnesium and the carbonyl carbon. Since the planar phenyl group may approach the planar C–CO–C system, phenylmagnesium halide is highly reactive (Fig. 1). Similarly, primary reagents and methylmagnesium halide are also unhindered and effective, while secondary and tertiary reagents react very slowly. The reactivity series for acetone (**2**) is shown in Table 1.

If the carbonyl is α,β-unsaturated, another mode of reaction, namely 1,4-addition, is possible. Like the 1,2-addition, the 1,4-addition may take place either concertedly or

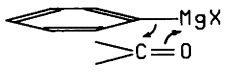

Fig. 1.

Table 1. Pseudo-first-order rate constants, in s^{-1}, for in the reaction of 0.05 M ketones (**1–12**) (Fig. 1) with 0.5 M alkylmagnesium bromides in ether at 20 °C. For the α,β-unsaturated ketones **3–12**, the ratio, in per cent, of 1,4-addition relative to the sum of 1,4- and 1,2-addition is given in parentheses.

Substrate	Alkyl in RMgBr					
	Methyl	Ethyl	Isopropyl	Butyl	*t*-Butyl	Phenyl
1	0.3	7.2	21	3.2	27	0.3
2	3.8	7.5	1.6	2.2	0.01	42
3	6 (0)	72 (60)	21 (67)	36 (65)	0.1 (65)	164 (42)
4	1.4 (0)	4.1 (0)	2.0 (0)	1.4 (0)	0.01 (25)	6.3 (0)
5	2.0 (0)	7.5 (20)	1.9 (66)[a]	1.9 (4)	0.25 (92)	70 (0)
6	9 (16)	700 (75)	800 (87)	120 (75)	46 (51)	210 (28)
7				125		
8	4 (85)	5 000 (100)	2 500 (100)	1 250 (100)	22 (100)	1 100 (100)
9	20 (66)	21 000 (96)	28 000 (67)	11 000 (98)	14 000 (49)	1 100 (95)
10		0.07		0.02	0.00007	0.6
11				0.0005		
12	500 (100)	45 000 (100)[b]	42 000 (100)[c]	22 000 (100)[d]	600[e]	8 000 (100)

Superscripts indicate the presence of reduction product: [a]25 %. [b]5 %. [c]35 %. [d]20 %. [e]100 %. If not stated, the amount of reduction product or other by-products was not determined. The absolute yield of addition and reduction product is normally > 80 %, most of the remainder being starting material recovered after enolisation. Details may found in Ref. 1.

by homolysis depending on the redox and steric properties of the substrate and the reagents. A concerted 1,4-addition requires a six-centered transition state and a *cisoid* conformation of the substrate. This mechanism was suggested by Lutz and Reveley,[4] but its existence has been questioned by several authors[5,6] on the grounds that substrates with *transoid* conformation such as 2-cyclohexenone may still undergo 1,4-addition with some Grignard reagents, The problem is discussed in modern textbooks,[7] although Kharasch in 1954 stated (Ref. 1, page 228) that... 'One careful quantitative study of a series of organomagnesium compounds with a series of twelve or fifteen intelligently selected ketones would contribute more to understanding of the subject than have all the reported observations of the past half century.'

In an attempt to follow this suggestion the present investigation presents kinetic information and product distributions for the reaction of several saturated and α,β-unsaturated esters and ketones (**1–12**, Fig. 2) with simple aliphatic and aromatic Grignard reagents.

The rate measurements were obtained by the thermographic procedure, which gives the rate of consumption of the substrate, and, by the use of a tenfold excess of Grignard reagent, pseudo-first-order kinetics for the reactions were obtained. The method allows the study of even very fast reactions since nearly quantitative mixing of the ether solutions could be obtained within 50 μs owing to the low viscosity of ether. It was a problem that regular first-order kinetic schemes for the reactions were usually obtained only with rate constants in the range 100–200 s^{-1}. Fast reactions often showed extreme initial rates and relatively slow consumption of the last 20–30 % of the substrate. Since a large spectrum of reaction rates and reaction types was needed, the detailed kinetics of the individual reaction were not studied. For the fastest reactions with rate constants above 10 000 s^{-1} only one point was obtained on the time–temperature plot, and on this basis a first-order rate constant was found using the expression given in eqn. (2).

$$k = 1/t \ln a/a-x \qquad (2)$$

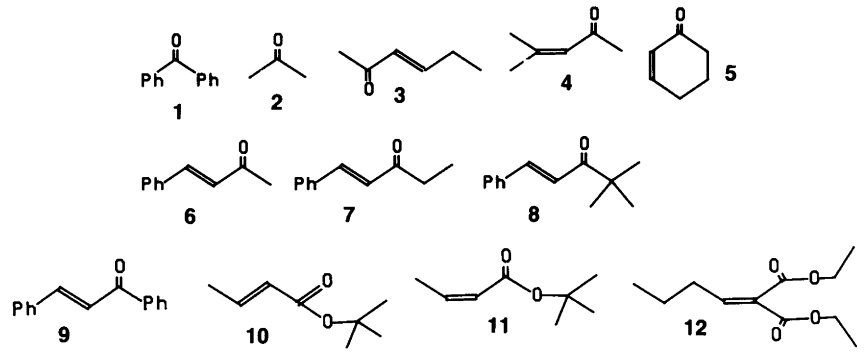

Fig. 2.

Some of the rate constants given in Table 1 should therefore be considered as being only semi-quantitative. While rate constants in the range 1–100 s^{-1} were reproducible to within ± 10 %, very fast and very slow reactions may be uncertain, to within ± 50 %.

No attempts were made to find the reaction order with respect to Grignard reagent or to analyse the relative contributions to the reaction from the components of the Schlenk equilibrium.

The analyses of the product distributions were performed by the use of GLC–MS and NMR spectroscopy, and since pseudo-first-order conditions were used, the partial rate constants for the formation of the specific products could be estimated.

Results and discussion

A direct indication of a cyclic reaction mechanism is obtained from the fact that isocrotonic acid *t*-butyl ester (**11**) which has the *Z* configuration is 40 times less reactive towards butylmagnesium bromide than is the *E*-ester (**10**), Table 1. In a *cisoid* cyclic transition state (Fig. 3) the β methyl group will be a hindrance to the approaching alkyl group in the case of **11**, while it does not interfere with the reaction of **10**. The silylated enolate **13** formed in the reaction of the *E*-ester with pentylmagnesium bromide, when analysed by means of the NOE technique, showed 100 % *Z* configuration as expected.

The enolates originally obtained by Lutz and Reveley[4] likewise had a stereochemistry which was the result of the operation of the six-center mechanism.

Mesityl oxide (4-methyl-3-penten-2-one, **4**) has two methyl groups at the conjugated double bond, one of which is *cisoid*. Just as in the case of the crotonic esters, the 1,4-addition is therefore hindered. The reaction of mesityl oxide with Grignard reagents consequently leads to 1,2-addition exclusively in a slow reaction compared with the rather facile 1,2- and 1,4-addition of Grignard reagents to the isomeric (*E*)-3-hexen-2-one (**3**), Table 1. Thus unhindered hexenone reacts 25 times faster than mesityl oxide with butylmagnesium bromide, producing a 2:1 mixture of 1,4- and 1,2-adduct.

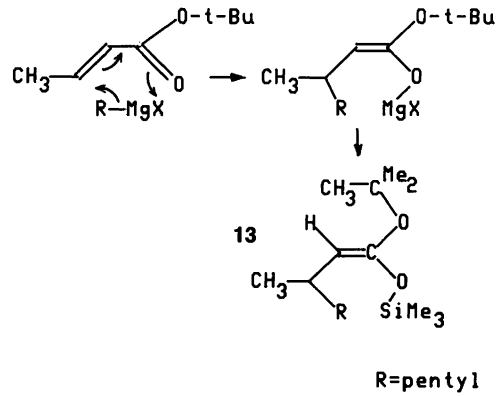

Fig. 3.

In contrast with butylmagnesium bromide, methylmagnesium bromide does not react in the 1,4-fashion with **3**. The reason for this might be that the CH_3–Mg bond is strong, but even though C_6H_5–Mg is a stronger bond, phenylmagnesium bromide is extremely reactive towards 3-hexen-2-one and produces 1,4- and 1,2-products in equal amounts. The reason why methylmagnesium bromide is much less able to react 1,4 than is the phenyl reagent therefore remains obscure.

With 2-cyclohexenone (**5**), in which C=C and C=O have a *transoid* conformation, phenylmagnesium bromide does not react in a 1,4-fashion at all. The operation of a fast six-center reaction mechanism thus seems to be unequivocally established for this reagent, since only substrates which have or which may assume the *cisoid* conformation, may react in a 1,4-fashion. House[6] similarly reported that phenylmagnesium bromide would react 1,4 with an octalone, which had a *cisoid* conformation, but not with an isomeric octalone which had a *transoid* arrangement of C=C and C=O.

While homolytic mechanisms are unlikely in unconjugated aliphatic substrates, an α,β-conjugated ketone has a much more stable ketyl and a homolytic mechanism may compete effectively. As usual this mechanism is most apt to take place with *tert*-butylmagnesium halide. Mesityl oxide, with its two methyl groups in the β-position, is not capable of adding Grignard reagents 1,4 by the concerted mechanism as explained above. With *tert*-butylmagnesium bromide, however, a slow reaction takes place and the product is 75 % 1,2-adduct and 25 % 1,4-adduct.[8] The obvious explanation is that this is produced by a homolytic mechanism. Radical combination is less demanding sterically than normal 1,4-addition and allows the production of the overcrowded 4,4,5,5-tetramethyl-2-hexanone from the initially formed magnesium mesityl oxide ketyl and *tert*-butyl radical (Fig. 4).

The observation of 1,4-addition to cyclohexenone can therefore also be explained by homolysis. This is the reason why the ratio of 1,4- to 1,2-adduct is correlated to the ease of homolytic fission of the Grignard reagent (*tert*-butyl > isopropyl > ethyl > butyl) while methyl and phenyl show no 1,4-addition at all (Table 1).

If a comparison is made between the results obtained with cyclohexenone (**5**) and with 3-hexen-2-one (**3**) it can be seen that the open-chain compound is more reactive for two reasons. (1) The double bond makes the carbonyl group more electron deficient so that **3** reacts three times faster with methylmagnesium bromide in the 1,2-fashion than **5** and (2) **3** is able to adopt a *cisoid* conformation which therefore allows a competing, cyclic 1,4-addition to take place, so that the overall rate increases by up to a factor of 20 for a primary Grignard reagent.

While the very high reaction rates of most Grignard reagents toward open-chain 3-hexen-2-one are mainly the result of the operation of the fast six-center mechanism, it seems probable that most, if not all, of the 1,4-product produced in the reaction of 3-hexen-2-one with *tert*-butyl-

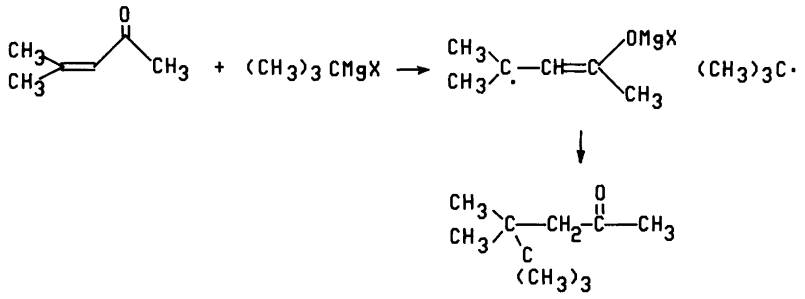

Fig. 4.

magnesium bromide is formed by the homolytic mechanism, since the tertiary reagent is the only reagent that is less reactive toward the open-chain ketone than toward the cyclic. Analysis of the reaction mixture showed that 92 % of the 1,4-adduct had been formed.

The importance of the *cisoid* conformation in the 1,4-addition is also demonstrated in a convincing way by comparing the rates of reaction for a series of chalcones, Table 1. 4-Phenyl-3-buten-2-one (**6**), 4,4-dimethyl-5-phenyl-1-penten-3-one (**8**), and 1,3-diphenol-2-buten-1-one (**9**) react with butylmagnesium bromide with the rate constants 120, 1250 and 11 000 s^{-1} respectively, while the rate constants for *tert*-butylmagnesium bromide are 46, 22 and 14 000 s^{-1} respectively. The *tert*-butylmagnesium reagent reacts by homolysis. The first and rate-determining step in this mechanism is transfer of magnesium from the Grignard reagent to the ketone, which corresponds to a reduction and the rates therefore correlate with the polarographic half-wave reduction potentials for **6**, **8** and **9**, which are −1.590, −1.603 and −1.361 V respectively in DMF, relative to a saturated calomel electrode.[9] Compound **8** is a little more difficult to reduce than is **6** and is a little less reactive toward the *tert*-butyl reagent. Compound **9** is very easily reduced and reacts extremely fast with *tert*-butylmagnesium bromide. In contrast with these results butylmagnesium bromide reacts 10 times faster with **8** than with **6**. Since Grignard reagents are usually very succeptible to steric hindrance it is astonishing that the introduction of the bulky *tert*-butyl group increases the reaction rate very substantially. The explanation is that, while the *transoid* conformation predominates to the extent of 3:1 over the *cisoid* conformation in **6**, and in its homolog **7**, compound **8** is forced to adopt a *cisoid* conformation because of the interaction between the *tert*-butyl group and the distant vinylic hydrogen. The phenomenon is well known from IR and UV spectroscopic observations.[10] Very direct proof was obtained in the present investigation by the observation of a very strong NOE between the *tert*-butyl signal and the vinyl proton at the carbon α to the carbonyl group.[11]

Rate measurements performed with butylidenemalonic ester (**12**), Table 1, showed extreme rates for primary reagents and a faster rate for phenyl than for *tert*-butyl. Since one carbonyl is s-*cis* to the double bond a cyclic concerted mechanism is indicated for primary reagents and phenyl. For *tert*-butylmagnesium bromide a homolytic mechanism is the most probable since with this reagent the reduction product is formed in a relatively slow reaction, and no 1,4-addition takes place.

From the results obtained one may conclude that the six-center concerted mechanism for the 1,4-addition of Grignard reagents to α,β-unsaturated carbonyl compounds is extremely important, for aromatic, primary, or secondary Grignard reagents, when a *cisoid* conformation is possible. The cyclic mechanism is ineffective for methylmagnesium halide and for *tert*-butylmagnesium halide. The last-mentioned reagent is, however, capable of producing a 1,4-addition product by a homolytic mechanism, as are secondary and primary reagents, to a limited extent.

When Grignard reagents react by homolysis it is often possible to isolate radical-type by-products. This happens if the radicals formed escape from the cage before recombination can take place. In one experiment, involving the reaction of *tert*-butylmagnesium bromide with 3-hexen-2-one, in which atmospheric oxygen was, accidentally, not completely excluded, a by-product was isolated, which according to NMR spectroscopy and GC–MS was the hydroperoxide **14** (Fig. 5). Experiments showed that this product could only form if oxygen was present during the reaction and did not form by exposing the reacting mixture to oxygen. Apparently escaped radicals formed by the attack of *tert*-butyl radicals on the substrate reacted with oxygen to form a peroxy radical, which, in a chain reaction, abstracted magnesium from a molecule of Grignard reagent.

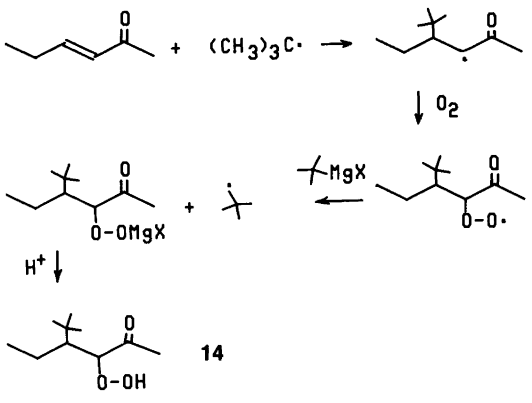

Fig. 5.

The suggestions about the homolytic versus concerted mechanisms given above are supported by observations of the intensity of the yellow to brownish coloration of the reaction mixture of the Grignard reagents and the α,β-unsaturated ketones. While quantitative measurments have not been made, it seems that the higher the homolytic/heterolytic mechanism ratio, the more intense the coloration of the reaction mixture, while the reaction is in progress. Reactions that take place by a concerted mechanism show no color, since no intermediates are formed.

Experimental

Starting materials. 2-Cyclohexenone was obtained from Fluka AG.Chalcones were prepared according to the literature.[12] 3-Hexen-2-one was prepared from chloroacetone and propionaldehyde via the Wittig reagent.[13] Crotonic acid was prepared according to Rappe.[14] Grignard reagents were prepared from commercially available alkyl bromides and reagent-grade magnesium.

Kinetics. The thermographic procedure was used as described.[15] Mixing of the reagents took place in a T made by drilling 1 mm holes in a piece of polyethylene. Polyethylene tubes were inserted into the holes. The liquid speed in the reaction tube was normally 3000 mm s^{-1}. For very fast reactions a mixing T and reaction tube were used made from two pieces of 0.22 mm glass capillary, which were precision ground and cemented with epoxy cement. In the glass capillary a liquid speed of 14000 mm s^{-1} was obtained. The thermocouple was placed 1 mm after the mixing point ≈ 70 μs. The mixing of butanol (0.02 M in ether) and butylmagnesium bromide (0.2 M in ether) was found to be 90 % complete after 0.5 mm ≈ 35 μs. Slow reactions were run in a small Dewar vessel as described.[16]

Standard concentrations were 0.5 M Grignard reagents and 0.05 M substrate in ether.

For analysis of the product distributions 1 mM of substrate in 10 ml of ether was mixed with 5 ml of 1 M Grignard reagent. The mixture was quenched with ammonium chloride solution and the ether layer was dried and concentrated under vacuum.

The products were analysed by NMR spectroscopy and GLC–MS. When necessary, separations were made by preparative TLC.

4-tert-Butyl-3-hydroperoxyhexan-2-one (**14**). 1 mM 3-hexen-2-one was added to *tert*-butylmagnesium bromide as above. After work-up the product was separated by TLC using 10 % ethyl acetate in pentane as the eluent. Development of the plate with iodine vapor showed a white, iodine-consuming zone, R_f = 0.5. The NMR spectrum showed a mixture of two diastereomeric hydroperoxides. GLC–MS using chemical ionisation gave *m/z* = 188. MS 57 (100), 43 (93), 72 (34), 41 (33), 55 (12), 58 (8), 99 (3), 84 (3), 127 (2.5). NMR (250 MHz, $CDCl_3$): a-Isomer: δ 9.32 (s, 1 H), 4,68 (d, 1 H, *J* = 1.5 Hz), 2.25 (s, 3 H), 1.5–1.3 (m, 2 H), 1.02 (s, 9 H), 0.82 (t, *J* = 7.3 Hz). b-Isomer: δ 9.45 (s, 1 H), 4.49 (d, 1 H, *J* = 3.2 Hz), 2.3 = (s, 3 H), 1.7–1.6 (m, 2 H), 0.91 (s, 9 H), 0.82 (t, 3 H, *J* = 7.3 Hz).

Repetition of the above experiment under completely anaerobic conditions produced no **14** even if oxygen was bubbled through the reaction mixture before work-up. Compound **14** was, however, produced if the ether solution of 3-hexen-2-one was exposed to oxygen before the addition of the Grignard reagent.

(Z)-1-tert-Butoxy-3-methyl-1-trimethylsilyloxyoct-1-ene (**13**). A solution of 1 g of crotonic acid *tert*-butyl ester in 5 ml of ether was added over 4 min to 20 ml of 0.8 M ethereal pentylmagnesium bromide at 20 °C. After 5 min, were added 2 ml of triethylamine and 2 ml of trimethylsilyl chloride and, finally and very slowly, 6 ml of HMPT (**caution:** carcinogenic!). The mixture was left at room temperature overnight. After the reaction mixture had been cooled in dry ice–acetone, water was added with stirring. The organic layer was washed three times with water, dried over potassium carbonate and distilled, b.p. 95 °C at 0.5 mmHg. Yield 60 %. NMR (270 MHz, $CDCl_3$): δ 3.79 (d, 1 H, *J* = 9.8 Hz), 1.44 (s, 9 H), 1.33–1.16 (m, 9 H), 0.95–0.84 (m, 6 H), 0.20 (s, 9 H). In an NOE experiment irradiation of the *t*-butyl signal at δ 1.44 gave an NOE effect on the signal for the vinylic hydrogen. Irradiation of the silyl methyl signal at δ 0.2 had no effect.[10]

References

1. Kharasch, M. S. and Reimuth, O. *Grignard Reactions of Nonmetallic Substances,* Prentice-Hall, New York 1954.
2. Holm, T. *Acta Chem. Scand., Ser. B 37* (1983) 567 and references therein.
3. Holm, T. *Acta Chem. Scand., Ser. B 42* (1988) 685.
4. Lutz, R. I. and Reveley, W. G. *J. Am. Chem. Soc. 63* (1941) 3184.
5. Alexander, E. R. and Coraor, G. R. *J. Am. Chem. Soc. 73* (1951) 2721.
6. House, H. O. and Thompson, H. W. *J. Org. Chem. 28* (1963) 360.
7. March, J. *Advanced Organic Chemistry,* Wiley, New York 1985.
8. Whitmore, F. C., Goldsmith, D. P. J., Cook, N. C., Yarze, J. C. and Ecke, G. C. *J. Am. Chem. Soc. 72* (1950) 53.
9. Lund, H. *Personal communication.*
10. Tisnes, P. and Perry, M. *J. Chem. Educ. 62* (1985) 903.
11. NOE determinations were kindly performed by Professor Klaus Bock, Carlsberg Research Laboratory, Copenhagen, Denmark.
12. *Org. Synth., Coll. Vol. I,* p. 77.
13. Ramirez, F. and Dershowitz, D. *J. Org. Chem. 22* (1957) 44.
14. Rappe, C. *Acta Chem. Scand. 17* (1963) 2766.
15. Holm, A., Holm, T. and Huge-Jensen, E. *Acta. Chem. Scand., Ser. B 28* (1974) 784.
16. Holm, T. *Acta Chem. Scand. 20* (1966) 2821.

Received December 12, 1990.