ortho Conjugate Addition of Benzyl Grignards—a Remarkable Copper Effect

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Summary *ortho*-1,4-Addition is the predominant reaction between *m*-methoxybenzyl Grignard reagent and methyl vinyl ketone but it is sharply reduced in the presence of copper(I) chloride.

The reaction of a benzyl organometallic reagent such as (Ia); (X = OMe) with (II) methyl vinyl ketone might, in principle produce monoalkylated products (IIIa), (IVa), (Va), and (VIa) *via* (a) α-1,4-addition, (b) α-1,2-addition, (c) *ortho*-1,4-addition,[1a–d] and (d) *ortho*-1,2-addition, respectively. The formation of ring alkylated products (1,2 or 1,4) at the *para* or *ortho′* position relative to the Grignard is also a formal, but less likely possibility. We report (i) the first instance of process (c), (ii) the apparent requirement of a suitably placed electron donating group for its realization, and, (iii) the dramatic effect of copper(I) chloride in favouring process (a) relative to (c).

Reaction of (Ia) with methyl vinyl ketone in tetrahydrofuran at −10° in the presence of 8 mole % of copper(I) chloride (standard conditions for 1,4-addition) affords a 46% yield[†] of a mixture of (IIIa)[‡] (2,4-dinitrophenylhydrazone m.p. 171—172°) (IVa) and (Va) (2,4-dinitrophenylhydrazone m.p. 162—164°) in a ratio 15 : 1 : 3. When the reaction was conducted under identical conditions except for the omission of copper(I) chloride, the ratio of these products was 2 : 1 : 8 in a yield of 34%.[†] Product stability studies have not been conducted with the tertiary, allylic, benzylic carbinol (IVa), and its relative abundance as a

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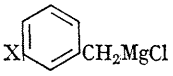
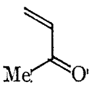
[†] The remainder of the reaction products were 1,2-di-*m*-methoxyphenylethane methyl vinyl ketone polymer and a small amount of product whose mass spectrum corresponds to its being derived from two moles of methyl vinyl ketone and one mole of Grignard reagent. Its genesis is well precedented in the work of Benkeser. The yields are based on distillation fractions comprising these compounds and are minimal in that small amounts of this mixture was present in higher distillation cuts. The difference between the yields in the presence or absence of copper(I) chloride in the case of (Ia) is due to a greater amount of diaddition product in the latter case. Since this almost certainly arises from prior *ortho* attack, the actual effect of the cuprous catalysis on the *ortho*: α ratio is even greater than is apparent from analysis of the monoalkylated products.

function of copper(I) catalysis must be viewed with considerable reserve. However, the dramatic (twenty-fold variation)† effect of this catalysis on the ratio of α-1,4: *ortho*-1,4 products is unprecedented as is, indeed, the *ortho*-1,4-addition reaction itself.

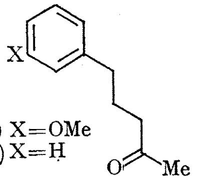
Reaction of (Ib) with (II), in the presence or absence of copper(I) chloride gave no recognizable product corresponding to *ortho*-1,4-addition. The two products were, in each case (IIIb)[2] (semicarbazone m.p. 126—127°) and (IVb)‡ in 45% yield. An unexceptional effect of copper(I) chloride on the ratio of these products (4 : 1 in its absence, 8 : 1 in its presence) was noted.



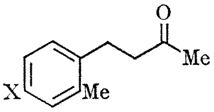
(Ia) X=OMe
(Ib) X=H



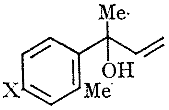
(II)



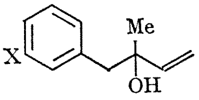
(IIIa) X=OMe
(IIIb) X=H



(Va) X=OMe
(Vb) X=H



(VIa) X=OMe
(VIb) X=H



(VIa) X=OMe
(VIb) X=H

Intuitively, one would not expect that the effect of a neutral methoxy-group on the distribution of negative charge of a benzyl anion would be such as to account for the drastic difference between (Ia) and (Ib). Thus, on the basis of these preliminary findings, *ortho*-1,4-addition is more readily viewed as an electrophilic attack on a relatively covalent system. The presence of the methoxy-group, presumably in conjunction with a developing benzylic anion, is required to render the vulnerability to substitution (involving a disruption of aromaticity) competitive (in this case, predominant) with α-attack. The substitution is directed to the least hindered position *ortho* to the Grignard possibly by a transfer of a halogenomagnesium species to the emerging enolate.

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‡ The ratios were determined gas chromatographically. The individual compounds were purified by preparative g.l.c. The assigned structures are in complete agreement with the spectral properties and combustion analysis of the purified samples.

[1] The phenomenon of *ortho* attack has recently been investigated by R. A. Benkeser and co-workers: (a) R. A. Benkeser and T. E. Johnston, *J. Amer. Chem. Soc.*, 1966, **88**, 2220, (b) R. A. Benkeser and W. DeTalvo, *ibid.*, 1967, **89**, 2141, and (c) R. A. Benkeser, T. E. Johnston, and W. Hong Tong, 1968, *J. Org. Chem.*, 1968, **33**, 2203. For *ortho* 1,2-addition with αβ-unsaturated aldehydes see (d) R. Miravelles and A. J. Guillarmod, *Helv. Chim. Acta*, 1968, **49**, 2313.

[2] J. Levy and M. Sifras, *Compt. rend.*, 1927, **184**, 1337.