The Stereochemistry of Condensation Reactions of (±)-3-Phenylbutan-2-one with Phenylmetallic Compounds as a Function of the Reagent Nucleophilicity

Odón Arjona, Rafael Pérez-Ossorio,* Alfredo Pérez-Rubalcaba, and María L. Quiroga

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Complutense, Ciudad Universitaria, Madrid-3, Spain

The influence of changing the metal and adding electrophilic catalysts or iron(III) and copper(I) salts on the stereochemical path of the nucleophilic addition of organometallics to (±)-3-phenylbutan-2-one is discussed.

We have previously[1] reported a linear free-energy relationship between the stereoselectivity observed in the reaction of PhMgBr with (±)-3-phenylbutan-2-one and the $E_{\mathrm{T}}(30)$ parameter of the solvent. To account for the stereochemical pathway of this reaction two transition states (I)‡ (*RS*) and (II)‡ (*SS*) (Figure 1) were selected. A third one (III)‡ (*SS*) was neglected on account of overcrowding.

In (I)‡ (*RS*) a slight rotation in the sense indicated would bring the phenyl group opposite to the direction of attack by the reagent. This would relieve the torsional strain developed by this attack with the C(3)–H bond. Moreover, a stabilization, of orbital origin, due to the antiperiplanar arrangement of Ph with respect to the attacking PhMgBr may extensively modify the stereoselectivity in favour of the (*RS*)-tertiary alcohol. In this case, Felkin's model accounts for the stereochemical course of nucleophilic additions to the carbonyl group.[2,3]

A similar conformational change in (II)‡ (*SS*) that brings the methyl group antiperiplanar to the entrance of the nucleophile would not be favoured as the bulkiest group at the chiral centre, Ph, would cause some steric restriction of the nucleophilic attack. In the absence of stereoelectronic stabilization of (I)‡ (*RS*) in the sense described above it is expected that (II)‡ (*SS*) would play a more important role in determining the stereochemical route of the process.[1]

Induction in favour of the (*SS*)-tertiary alcohol has been observed in the condensation of PhMgBr with (±)-3-phenylbutan-2-one in diethyl ether at 30 °C. This is exceptional behaviour for this ketone in nucleophilic additions;[1,2,4] other carbonyl compounds with the same chiral centre react with organometallics, yielding, as a major product, the alcohol formed by the direction of attack opposite to that giving the (2*S*,3*S*)-2,3-diphenylbutan-2-ol.[1,5,6]

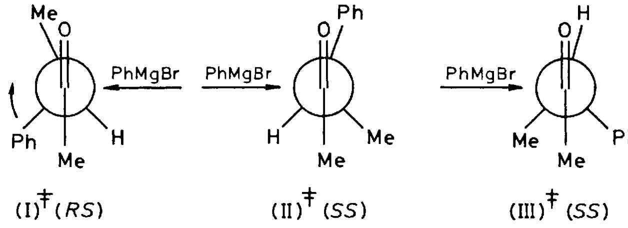

Figure 1

Thus 3-phenylbutan-2-one seems to be a good model substrate for the study of the factors controlling stereoselectivity in nucleophilic additions to the carbonyl group. We report here the effect of changes in reagent and reaction conditions on the stereochemical path of the condensation reactions of (±)-3-phenylbutan-2-one with various phenylmetallic compounds. The results are gathered in Table 1.

It was observed that changing the metal causes an important change in stereoselectivity (entries 1, 6, 10, and 14), the hardest metal (Li> Mg> Al) yielding the larger percentage of (*RS*)-tertiary alcohol. Tests with phenyl derivatives of softer metals (Zn, Cd) failed giving practically no conversion.

Addition of electrophilic $\mathrm{LiClO_4}$ gives rise to small increases in stereoselectivity in favour of the (*RS*)-alcohol (entries 1, 4, 5, 10, and 12). Similar effects were observed on increasing the polarity of the solvent in the reactions of both PhMgBr[1] and $\mathrm{Ph_2Mg}$ (entries 6—9). These changes may be related to an increase in the dielectric constant of the medium which would stabilize the transition state *via* larger anisotropy of the π-cloud [orbital interaction[3] $(\mathrm{Ph{-}Nu})_{1\cdot2\,anti}$ developed from (I)‡ (*RS*)].

Addition of an excess of $\mathrm{MgBr_2}$ to the solution of PhMgBr (entry 3) does not modify the result observed with PhMgBr (entry 1). Since addition of $\mathrm{MgBr_2}$ changes the Schlenck equilibrium this result should mean that in entry 1 the mixed species is the reactive one. Moreover, when the symmetric species $\mathrm{Ph_2Mg}$ (produced by precipitation of $\mathrm{MgBr_2}$ with 1,4-dioxan) is used a different stereoselectivity is observed in the same solvent (entries 1 and 6).

Addition of iron(III) and copper(I) salts in catalytic amounts decreases the percentage of the (*RS*)-alcohol pointing to a partially radical mechanism.[8] In this case, the stereoelectronic

Table 1. Observed stereoselectivity [% of (*RS*)-alcohol] in the condensation of (±)-3-phenylbutan-2-one with phenylmetallic compounds at 30 °C.

Entry	Nu:	Salt	Ketone/Nu:/salt	Solvent[a]	%(*RS*)-Alcohol[b] (±3%)
1	PhMgBr	—	1/5/–	Et_2O	36
2	PhMgBr	—	1/5/–	DME	73[c]
3[d]	PhMgBr	$MgBr_2$	1/5/50	Et_2O	36
4[e]	PhMgBr	$LiClO_4$	1/5/1	Et_2O	42
5[e]	PhMgBr	$LiClO_4$	1/5/5	Et_2O	46
6	Ph_2Mg	—	1/5/–	Et_2O	53
7	Ph_2Mg	—	1/5/–	THF	76
8	Ph_2Mg	—	1/5/–	1,4-dioxan	63
9	Ph_2Mg	—	1/5/–	DME	83
10	PhLi	—	1/5/–	Et_2O	94
11	PhLi	—	1/5/–	DME	96
12[e]	PhLi	$LiClO_4$	1/5/1	Et_2O	96
13[f]	PhMgBr	CuI	1/5/0.25	Et_2O	26
14[f]	PhMgBr	$FeCl_3$	1/5/0.25	Et_2O	26
15[g]	Ph_3Al	—	1/10/–	PhH	30[h]

[a] DME = 1,2-dimethoxyethane, THF = tetrahydrofuran. [b] Conversions >95% in all experiments except 3(70%) and 15(30%). Evaluated by g.l.c., UCC-3 m-150°. [c] Ref. 1. [d] A 0.25 M solution of PhMgBr in Et_2O was added over a solution of Mg_2Br in diethyl ether prepared from 1,2-dibromoethane and Mg before adding the ketone. [e] $LiClO_4$ was added to either the ketone or the Grignard solution before the reaction. The method of addition does not alter the stereoselectivity. [f] Salts were added to the Grignard solution before the reaction. [g] A 1 M solution of Ph_3Al in benzene was prepared from PhMgBr and $AlCl_3$ (ref. 7). [h] Reflux for 1 h.

requirements of the ketone should differ from those controlling the attack by the harder nucleophilic species. This stereochemical result is in line with those observed for the reactions of phenyl-lithium, -magnesium, and -aluminium derivatives.

It appears that the relationship between the stereoselectivity and the hardness of the metal or the nucleophilicity of the reactive species can be accounted for by a competition between transition states $(I)^‡$ (*RS*) and $(II)^‡$ (*SS*) (Figure 1). The changing value of the $(Ph\text{–}Nu)_{1.2anti}$ interaction may cause the stereo-differentiating effect found.

Other factors may also modify this interaction and contribute to the stereoselective synthesis of similar tertiary alcohols.

Received, 22nd January 1982; Com. 068

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