

Stereoselectivity in the Condensation Reactions of 1-Phenylethyl Alkyl and Phenyl Ketones with Organometallic Reagents

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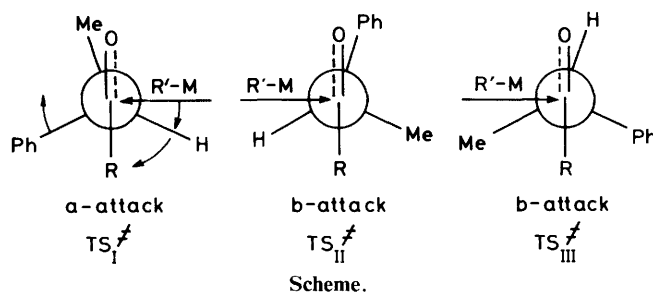
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Stereochemical results of the condensation reactions of a series of ketones, PhCHMeCOR (R = Me, Et, Prⁱ, Bu^t, Ph), with various organomagnesium and organolithium derivatives in ethers as solvents are reported. Results are accounted for on the basis of competition between two transition states which may adopt either Karabatsos- or Felkin-type conformations according to the nature of R, the reagent nucleophilicity, and the polarity of solvent. Polar and steric analysis of this reaction allows highly stereoselective syntheses of diastereoisomeric α -phenylalkanol to be devised.

In a previous paper,¹ we proposed that both steric and polar factors should be considered to account for the observed asymmetric induction in condensation reactions in solvents of different polarity of phenyl- and methyl-magnesium bromides with (\pm)-2-phenylpropanal (1) and (\pm)-3-phenylbutan-2-one (2). In the case of condensation reactions of (2) the transition states TS_I[‡] and TS_{II}[‡] (Scheme; R = Me) have been postulated; both have a Karabatsos-type geometry² and yield, respectively, the *SR*- and *RR*-alcohols. The experimental results are consistent with the assumption of a selective stabilization of TS_I[‡], whereby the phenyl group adopts an *anti*-arrangement to the nucleophilic attack (attack *a*, Scheme) upon increasing the solvent $E_T(30)$ parameter. This proposal is consistent with an increased inductive anisotropic effect of the phenyl group inducing the preferential entrance of the nucleophile on the face of the carbonyl group opposed to it.³ For the reactions of (1) with phenyl- and methyl-magnesium bromides a transition state TS_{III}[‡] (Scheme; R = H), characterized by a phenyl-nucleophile arrangement identical to TS_I[‡] but yielding the diastereoisomeric alcohol, should be taken into account. This can be concluded from the lack of stereo-differentiating effect of the solvent.

Lately, we have found new evidence for the contribution of polar effects to condensation processes of (2) with arylmetal reagents. The stereoselectivity increases upon increasing the nucleophilicity of the reacting species (PhLi > Ph₂Mg > PhMgBr > Ph₃Al > PhMgBr-Cu^I). Thus, reaction with PhLi is highly stereoselective (96% of the *RS*-diastereoisomer). The effect of an interaction (Ph-Nu)_{1,2-anti}, present in TS_I[‡] but not in TS_{II}[‡] and directly dependent from the polar parameters of the whole process (reagent nucleophilicity and solvent polarity), accounts for these results.⁴ In addition, the stereoselectivity observed in the condensation of (2) with various X-ArMgBr species (X = H, *m*-Me, *p*-Me, *m*-MeO, *m*-F, *p*-F, and *p*-CF₃) is also consistent with this interpretation.⁵

In this paper we report the stereochemistry of the condensation processes of various carbonyl derivatives, PhCHMeCOR, having a common chiral centre. The effect of changing the R group [R = Me (2), Et (3), Prⁱ (4), Bu^t (5), and Ph (6)], the organic residue of the organometallic reagent, R'X (R' = Me, Et, Prⁱ, Bu^t, Ph), the metal (Li, Mg), and the ether solvent [Et₂O, tetrahydrofuran (THF), and dimethoxyethane (DME)] are examined. The aim of this work is to generalize the hypothesis made for the condensation reactions of ketone (2). We try to gain a deeper insight into the polar influences affecting these processes and to devise highly stereoselective syntheses of α -phenylalkanol by suitable



selection of the prochirality of the carbonyl group and of the experimental conditions.

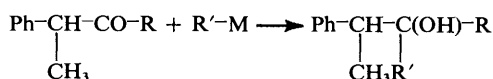
Results and Discussion

In the Table are gathered the stereochemical results observed for the condensation reactions of the α -phenylketones PhCHMeCOR [R = Me (2), Et (3), Prⁱ (4), Bu^t (5), and Ph (6)] with alkyl- and phenyl-metal compounds in various ether solvents and in the presence or absence of added copper(I) salts.

From these results a number of remarks follow. (1) In the reactions of the Grignard reagents an increase in solvent polarity (Et₂O < THF < DME) favours attack *a* (Scheme) (entries 1, 7, 11, 13, 15, and 21). This holds also in the condensation reactions with organolithium derivatives (entries 8 and 12). (2) Increasing the hardness of the reactive species (RMgBr-Cu^I < RMgBr < RLi) † causes, for all substrates, an increase in the stereoselectivity in the sense defined by attack *a* (among others see entries 1 and 2, 7 and 8, 11 and 12, 21 and 22, 23 and 24). Whatever the group R in the substrate, this stereoselectivity is higher than 90% when using alkyl- or aryl-lithium as reagents. (3) An increase in the bulk of R (Me < Et < Prⁱ < Bu^t) leads in general to an increase in the stereoselectivity in favour of *a*-attack (Scheme) for each reagent and in each solvent (see, for instance, entries 7, 11, 15, and 19). Similar results are observed upon changing the nucleophile (R' = Me < Et < Prⁱ < Bu^t) (see, among others, entries 1, 3, and 5). The reactions of ketones (2) and (3) with

† An increase in the concentration of added copper(I) salt decreases the total conversion but without modification of the stereochemical result. The intervention of a radical reaction may possibly contribute to softening of the nucleophile.⁴

Observed stereoselectivity (% of *a*-attack, see Scheme) in the condensation of α -phenylketones with organometallic reagents at 30 °C



Entry	R	R'-M	% <i>a</i> -attack ^a			
			Cu ^I -Et ₂ O	Et ₂ O	THF	DME
1	Me	EtMgBr	85	88	91	93
2	Me	EtLi		93		
3	Me	Pr ^t MgBr		91		94
4	Me	Pr ^t Li		96		95
5	Me	Bu ^t MgBr		96		
6	Me	Bu ^t Li		97 (83) ^b		
7	Me	PhMgBr	26	36	61	73
8	Me	PhLi		94		96
9	Et	MeMgBr	86	86	89	89
10	Et	MeLi		94		96
11	Et	PhMgBr	62	66	70	77
12	Et	PhLi		85	90	91
13	Pr ^t	MeMgBr	90	90	94	96
14	Pr ^t	MeLi		96 (95.5) ^b		96
15	Pr ^t	PhMgBr	93	95	96	96
16	Pr ^t	PhLi		96 (92.5) ^b		
17	Bu ^t	MeMgBr	95	96 (97) ^b	96	96
18	Bu ^t	MeLi		97 (98) ^b		
19	Bu ^t	PhMgBr		98		
20	Bu ^t	PhLi		98		
21	Ph	MeMgBr	80	87	87	92
22	Ph	MeLi		97		
23	Ph	EtMgBr	80	82	89	86
24	Ph	EtLi		96		97
25	Ph	Pr ^t MgBr		93		95
26	Ph	Pr ^t Li		93		93
27	Ph	Bu ^t MgBr		96		
28	Ph	Bu ^t Li		97 (79) ^b		

^a Yields were higher than 90% except for branched Grignard reagents where conversions into condensation products of ca. 50% were obtained. ^b Data in parentheses are from Karabatsos *et al.*⁸ In our case each reaction was repeated three times to test reproducibility.

PhMgBr and PhMgBr-Cu^I lead to the highest proportion of *b*-attack (Scheme) that has been obtained (entries 7 and 11).

It follows from points (1) and (2) that every one of the α -phenylketones studied behaves qualitatively like (\pm)-3-phenylbutan-2-one. Consequently, the observed stereochemical results may be explained as a consequence of the competition between transition states TS_I[‡] and TS_{II}[‡] (Scheme) such as was done for (2). An increase in reagent nucleophilicity and/or solvent polarity favours TS_I[‡], where the nucleophile enters *anti* to the phenyl group attached to the chiral centre. This differential stabilization of TS_I[‡] should be associated with an increase of the stabilizing interaction (Ph-Nu)_{1,2-anti}. This interaction has its origin in the -I effect of the phenyl group and should be strengthened by an intensification of the polar parameters of the reacting system.

An additional conclusion can be drawn from point (3). In the Karabatsos-type reacting conformations (Scheme; TS_I[‡] and TS_{II}[‡] with R \neq H) the torsional strain developed between the incipient C(1)-R' bond and the C(2)-H bond which is flanking the side of attack is large ($\theta < 30^\circ$) and increases upon increasing the effective bulk of the reacting species. This interaction may be relieved by modification of the transition state in the Felkin sense⁶ (as indicated by curved arrows in the Scheme). But this modification would be strongly limited for TS_{II}[‡] since it is accompanied by an increase in the steric strain between the phenyl group, the bulkiest substituent at the chiral centre, and the approaching nucleophile. This strain is practically negligible for a Karabatsos-type geometry ($\theta > 90^\circ$). According to this an increase

in the bulk of the reacting species should comparatively disfavour TS_I[‡] to a lesser degree. As a consequence a higher stereoselectivity in favour of the *a*-attack should be obtained for the same remaining polar parameters. This is in agreement with experimental results.*

The influence of the effective bulk increase of the R group, directly attached to the carbonyl group, on the stereoselectivity may be accounted for in the same manner. A geometrical modification of TS_I[‡] and TS_{II}[‡] in the Felkin sense may decrease the interactions (Ph-R) and (Me-R) which are, for each transition state, the most sensitive to the variation of the steric requirements of R. As stated before, this modification being limited for TS_{II}[‡] should stabilize differentially TS_I[‡] and give increased stereoselectivity.

Thus, TS_I[‡] is favoured by an increase in the steric requirements of R and R' as well as by increasing the polarity parameters of the system. Only the softest species (R'MgBr and R'MgBr-Cu^I) allow the participation of TS_{II}[‡] in a higher or lesser degree depending of the effective bulk of R'. Such stereoselectivity change cannot be observed with harder species, such as the organolithium derivatives, which select TS_I[‡] right away.

* It should be pointed out that PhMgBr seems to have lower steric requirements than MeMgBr and EtMgBr in the condensation reactions with (2) and (3) (compare entries 1 and 7 and 9 and 11, Table). This result may be related to the reported possibility⁷ that the planar phenyl group modifies its steric requirements by rotation more easily than groups with a tetrahedral arrangement of ligands.

In conclusion, the stereodifferentiating effects due to solvent polarity and to reagent nucleophilicity operate whatever the nature of R and R'. Polar and steric analysis allows rationalization of the stereochemical results obtained in these processes. From here, as a practical application, follows the highly stereoselective synthesis of diastereoisomeric α -phenyl-alkanols. Thus, permutation of R and R' and exaltation of the polar parameters (using organolithium derivatives and DME) yield, in every case, percentages of α -attack higher than 90%.

Experimental

I.r. spectra were measured on a Perkin-Elmer 257 spectrophotometer. N.m.r. spectra were recorded on a Varian T-60 spectrometer; carbon tetrachloride was used as solvent and tetramethylsilane as internal reference. G.l.c. was carried out on a Perkin-Elmer Sigma-3 instrument with a Sigma-10 data collector. Microanalysis were performed at the Instituto Nacional de Química Orgánica, C.S.I.C., Madrid.

Syntheses.—Ketones (1)—(5) were prepared from 2-phenylpropanal* (0.020 mol) and the corresponding Grignard reagent in Et₂O. This was prepared from magnesium (0.10 mol) and the alkyl or phenyl halide (0.10 mol) (methyl bromide, ethyl bromide, isopropyl bromide, t-butyl bromide, and bromobenzene) twice distilled over P₂O₅. After 6 h the mixture was hydrolysed with a saturated solution (80 ml) of NH₄Cl. The organic layer was dried (MgSO₄) and after removal of the solvent the alcohols were purified by fractional distillation. They were identified by i.r. and n.m.r. The oxidation procedure described by Ratcliffe⁹ led to the ketones (1)—(5), which were purified by silica gel chromatography using light petroleum—Et₂O (97 : 3) as eluant. The purity was tested by g.l.c. (10% UCC on a Chromosorb GW-AW-DMCS column; length 3 m; 150 °C).

3-Phenylbutanone (2) had v_{\max} . (neat) 1 710 cm⁻¹; δ 1.45 (d, 3 H), 1.95 (s, 3 H), 3.65 (q, 1 H), and 7.25 (s, 5 H) (Found: C, 80.95; H, 8.05. Calc. for C₁₀H₁₂O: C, 81.1; H, 8.1%).

2-Phenylpentan-3-one (3) had v_{\max} . (neat) 1 715 cm⁻¹; δ 0.85 (t, 3 H), 1.30 (d, 3 H), 2.20 (q, 2 H), 3.55 (q, 1 H), and 6.90 (s, 5 H) (Found: C, 81.35; H, 8.6. Calc. for C₁₁H₁₄O: C, 81.5; H, 8.65%).

2-Phenyl-4-methylpentan-3-one (4) had v_{\max} . (neat) 1 710 cm⁻¹; δ 0.80 (d, 3 H), 0.95 (d, 3 H), 1.30 (d, 3 H), 2.50 (m, 1 H), 3.50 (q, 1 H), and 7.00 (s, 5 H) (Found: C, 81.75; H, 9.0. Calc. for C₁₂H₁₆O: C, 81.8; H, 9.1%).

2-Phenyl-4,4-dimethylpentan-3-one (5) had v_{\max} . (neat) 1 705 cm⁻¹; δ 1.00 (s, 9 H), 1.30 (d, 3 H), 4.25 (q, 1 H), and 6.90 (s, 5 H) (Found: C, 82.2; H, 9.4. Calc. for C₁₃H₁₈O: C, 82.1; H, 9.45%).

1,2-Diphenylpropanone (6) had v_{\max} . (neat) 1 680 cm⁻¹; δ 1.40 (d, 3 H), 4.40 (q, 1 H), and 7.20 (m, 1 H) (Found: C, 85.6; H, 6.6. Calc. for C₁₅H₁₄O: C, 85.7; H, 6.65%).

Preparation of Organometallic Reagents.—Grignard reagent solutions were prepared from magnesium, previously heated and dried *in vacuo* (0.1 Torr), and the alkyl bromide (ethyl, isopropyl, and t-butyl) or bromobenzene twice distilled over P₂O₅ except in the case of the methyl † which was bubbled into the reaction vessel. Solvents Et₂O, THF, and DME were distilled over lithium aluminium hydride. The reactions were carried out under a continuous flow of dry nitrogen. Magnesium was titrated complexometrically with EDTA and bromine by the Volhard method.¹

Organolithium compounds were prepared by addition of the corresponding halide, methyl iodide, ethyl iodide, isopropyl bromide, t-butyl bromide, and bromobenzene, into lithium shot under nitrogen. The addition was made at -30 °C for the branched alkyl halides and at 0 °C for methyl iodide and bromobenzene. The molarity of the organolithium solutions was determined by titration.¹⁰

Condensation Reactions.—Condensation reactions of organometallic reagents with ketones (2)—(6) were carried out by the following procedure. A four-necked flask provided with magnetic stirrer and nitrogen inlet and outlet was used. Air was evacuated (0.1 Torr) and a dry nitrogen current passed through. An excess of organometallic reagent (5 : 1) was added and the solution was thermostatted at 30 °C. Then, the carbonyl compound (10⁻³ mol) dissolved in the minimum amount of solvent was introduced through a septum and stirring was continued for 2 h at 30 °C. Finally the mixture was hydrolysed with a stoichiometric volume of water followed by addition of a saturated (50 ml) solution of NaCl. The organic layer was decanted and the aqueous layer extracted with several portions of ether. The ethereal extracts were dried (MgSO₄) and after removal of the solvent *in vacuo* the residue was analysed by chromatography, i.r., and n.m.r. The stereochemistry of the products was investigated by the method described below.

Estimation of Mixtures of Diastereoisomeric α - and β -Alcohols (7)—(13).—The estimation of mixtures of diastereoisomeric α - and β -alcohols was followed by g.l.c. The results are gathered in the Table.

α - and β -2,3-diphenylbutan-2-ol (7). G.l.c. conditions: 10% UCC on Chromosorb GW-AW-DMCS; length 3 m; internal diam. $\frac{1}{8}$ in; column temperature 150 °C; gas flow (N₂) 65 ml min⁻¹. Retention times: α -alcohol 30 min; β -alcohol 28 min.

α - and β -2-phenyl-3-methylpentan-3-ol (8). G.l.c. conditions: 10% Carbowax 20M (5%) on Chromosorb GW-AW-DMCS; length 2 m; internal diam. $\frac{1}{8}$ in; column temperature 100 °C, gas flow (N₂) 65 ml min⁻¹. Retention times: α -alcohol 78 min; β -alcohol 71 min.

α - and β -2-phenyl-3,4-dimethylpentan-3-ol (9). G.l.c.: the conditions described above for (8) were used. Retention times: α -alcohol 112 min; β -alcohol 104 min.

α - and β -2-phenyl-3,4,4-trimethylpentan-3-ol (10). G.l.c. conditions: 10% Carbowax 20M (5%) on Chromosorb GW-AW-DMCS; length 2 m; internal diam. $\frac{1}{8}$ in; column temperature 140 °C; gas flow (N₂) 65 ml min⁻¹. Retention times: α -alcohol 22 min; β -alcohol 19 min.

α - and β -2,3-diphenylpentan-3-ol (11). G.l.c.: the conditions described above for (7) were used. Retention times: α -alcohol 36 min; β -alcohol 32 min.

α - and β -2,3-diphenyl-4-methylpentan-3-ol (12). G.l.c.: the conditions described above for (7) were used. Retention times: α -alcohol 62 min; β -alcohol 59 min.

α - and β -2,3-diphenyl-4,4-dimethylpentan-3-ol (13). G.l.c.: the conditions described above for (7) were used. Retention times: α -alcohol 87 min; β -alcohol 73 min.

Configurational assignments. Assignments of relative configurations (*RR,SS* and *RS,SR*) for alcohols (7)—(13) gave the assignment: α -alcohol = *RS,SR*; β -alcohol = *RR,SS*. For alcohols (7), (9), (10), (12), and (13) this assignment had previously been reported.^{8,11} We have found that the β -alcohols have shorter retention times on UCC or Carbowax columns. We have also found that the ¹H chemical shifts of the alkyl groups of β -alcohols appear at higher field than those of the α -alcohols. These observations were used to establish the configuration of alcohols (8) and (11).

* 2-Phenylpropanal was purchased from Merck.

† Methyl bromide was purchased from Fluka.

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