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REGIOSELECTIVITY IN THE CROSS CONDENSATION OF α,β-UNSATURATED ALDEHYDES AND METHYL KETONES PROMOTED BY MAGNESIUM PHENOXIDES

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Abstract: "Kinetic selectivity" in the cross condensation of α,β-unsaturated aldehydes and methyl ketones are obtained using 2,4,6-trimethylphenoxymagnesium bromide (2,4,6-TMPOMgBr) in benzene as catalyst.

Recent observations made by several authors that organic reactions are subjected to a fundamental cation and solvent effect,[1] encouraged us to continue our work on ion-pair effects on the condensation of carbonyl compounds.[2,3]

The major aim of this work is to find conditions for selective reactions exploiting the systematic variation of solvent, cation, and anion in processes wich are usually catalyzed by acids and/or bases.

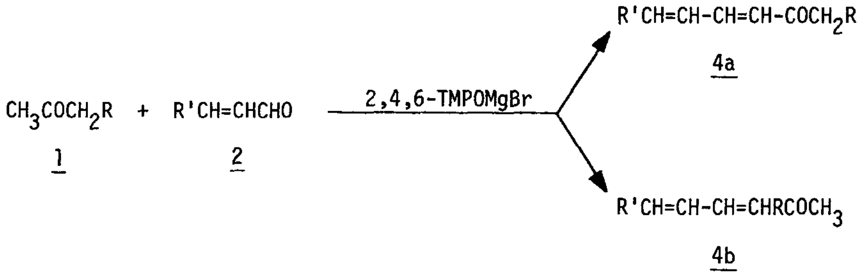
We have recently shown that 2,4,6-trimethylphenoxymagnesium bromide (2,4,6-TMPOMgBr) in benzene is an efficient catalyst for the self-condensation of linear aliphatic[2] and α,β-unsaturated[3] aldehydes.

In this paper we report the results obtained in the cross condensation of α,β-unsaturated aldehydes and methyl ketones induced by this salt. The reactions are performed by slowly adding (3 hrs) the aldehyde to a refluxing benzene solution (0.2 M) of the ketone and 2,4,6-TMPOMgBr in equimolar ratio.

Cross condensation products (4a + 4b) are obtained in good yields (see Table). Interestingly the reaction occurs mainly ($R = CH_3$) or exclusively ($R \geq C_2H_5$) on the less hindered position of the ketone giving products (4a) which formally derive from the attack of a "kinetic" ketone enolate on the aldehyde carbonyl followed by dehydration.

The selectivity obtained resembles that recently observed in cross aldol reactions by several authors, who isolated regioselective β-ketols using lithium salts of hindered bases at low temperature.[4-6] In these conditions the base deprotonates the methyl group of the ketone

Table. Cross Condensation of α,β-Unsaturated Aldehydes and Methyl Ketones[a]



R	R'	Cross condensation products, yield %[b] 4a	 4b
CH_3	CH_3	37	13
CH_3	C_6H_5	41	14
C_2H_5	C_6H_5	57	-
nC_4H_9	CH_3	40	-
nC_4H_9	CH_3	25[c]	-
nC_4H_9	C_6H_5	62	-

[a] In refluxing benzene for 5 hrs. [b] By glc; all products gave satisfactory nmr, ir, and elemental analysis data. [c] This reaction was performed simultaneously adding aldehyde and ketone to the catalyst.

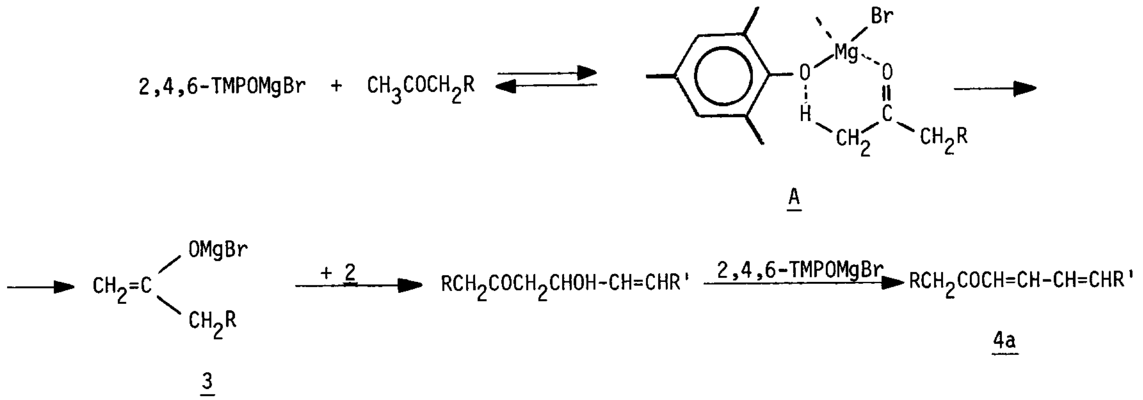
even in the presence of enolizable aldehydes,[5] and condensation occurs before the equilibration of the two enolates can take place.

2,4,6-TMPOMgBr in benzene is able to discriminate methyl toward α-methylene of ketones but not α-methylene of aldehydes. The cross condensation between linear aliphatic aldehydes and methyl ketones, in fact, occurs with very poor overall yields and 2,3-dialkylacrylaldehydes (aldehyde self-condensation products) are mainly obtained (see also footnote c to Table).

Our results can be better explained assuming that 2,4,6-TMPOMgBr in benzene behaves as a bifunctional mild acid-base catalyst as we already observed.[2,3] The enolization at the less hindered position of unsimmetrical ketones occurs after their complexation to the catalyst through a magnesium bridge (see Scheme).

The subsequent fast condensation of the α,β-unsaturated aldehydes (2) on the magnesium enolate (3) produces 4a after an irreversible dehydration catalyzed by 2,4,6-TMPOMgBr.

Scheme



Kinetic primary isotope effect ($K_H/K_D \simeq 6$) observed in the condensation of cinnamaldehyde and 2-heptanone-d[5] agrees with this reaction Scheme. Aldehydes, which strongly complex 2,4,6-TMPOMgBr in low polarity media,[7] compete with ketones to from the adduct A which generates the magnesium enolate and this could explained the observed great tendency of these substrates to self-condense even in the presence of ketones.

Our results show that an alternative way to achieve "kinetic selectivity" in the cross condensation of methyl ketones and α,β-unsaturated aldehydes is the use of a simple acid-base catalyst formed by a highly coordinating cation (MgX^+) paired with a mild base in a low polarity solvent in which the catalyst-reagent interaction[8] is enhanced.

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