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CHROMIUM (II) CHLORIDE : A NEW REAGENT FOR CROSS-ALDOL REACTIONS

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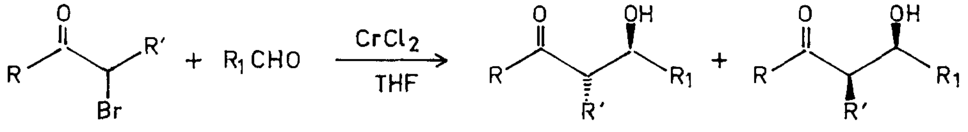
ABSTRACT.- *The proposed cross aldolization of α-bromoketones with aldehydes in presence of Chromium (II) chloride is an excellent stereospecific reaction. One exception to the stereospecific orientation is reported.*

The importance of cross-aldol reactions in the construction of carbon-carbon bonds has now been largely demonstrated. A number of metal enolates or silicon enol ethers have been employed successfully for this purpose[1].

Scattered reports are known dealing with the use of Cr(II) salts in the construction of carbon-carbon bonds. They have been reported to reduce organic halides to dimeric products[2], while, more recently, the reductive cyclization of acetylenic halides[3] and the reduction of γ-bromoacetylenic acetals[4] have been performed using Chromium(II) chloride. It has been reported, finally, that alkenyl[5] and alkyl[6] halides lead to alcohols by a Grignard type carbonyl addition with good stereoselectivity. These results, and particularly the latter ones in connection with our previous work on the aldolization of α-bromoketone 1 with magnesium[7], prompted us to examine the reaction of 1 with aldehydes in the presence of Chromium (II) chloride. Condensation of ketone 1 to an aldehyde leads theoretically to the two diastereoisomers E (erythro) and T (threo) of a β-hydroxyketone:



1 (T) (E)

A typical experiment involves adding, under nitrogen, one equivalent of 1 in dried THF to a stirred mixture of one equivalent of aldehyde and three equivalents of Chromium (II) chloride in THF at room temperature. The reaction is allowed to proceed for about 24 hours and is then quenched with cold water, extracted with ether, dried over magnesium sulfate and analyzed. The results obtained are listed in the table.

TABLE : Reaction of α-bromoketone 1 with aldehydes in the presence of Chromium (II) chloride[a]

Entry	R	R'	R_1	Yield %	T[d]	E[d]
1	tBu	Me	Me	50[b]	0	100
2	tBu	Me	Et	81[b]	0	100
3	tBu	Me	i-Pr	70[b]	0	100
4	tBu	Me	Pr	83[b]	0	100
5	tBu	Me	Ph	75[c]	0	100
6	tBu	Me	tBu	87[b]	0	100
7	Ph	Me	Ph	68[c]	50	50
8	———$(CH_2)_4$———		Ph	75[c]	100	0

a) Commercially available ; b) Estimated yield (GLC) ; c) Yield on isolated pure products (Thin Layer Chromatography on silica gel) ; d) Stereochemistry determined by 100 MHz ^1H NMR spectroscopy and by comparison of GLC retention times with those of authentic samples (see ref.8).

As can be seen from the table, Chromium (II) chloride is an excellent new reagent for cross aldol reactions, leading to β-hydroxyketones with good yields.

Preliminary stereochemical considerations indicate that in agreement with our previous observations[1b], the reaction is totally erythro selective with bulky substituents on the "enolate" counterion, independently of the bulkiness of the aldehyde substituent (entries 1-6). Nevertheless, a phenyl substituent (entry 7) is stereorandom as previously observed[1b] while the opposite selectivity is obtained with α-bromocyclohexanone (entry 8). This striking reversal of selectivity in the case of cyclic ketones has already been mentioned in similar cases[9].

No real attempt has yet been made to determine if the reacting entity is a C or O metallated species and, it is consequently, too early to propose a mechanism for the high selectivities observed. It is nevertheless probable that the reaction does not proceed via a stable chromium enolate. This hypothesis is based on the following observations. First, we observed no reaction when the aldehyde was added to a mixture of 1 and Chromium (II) chloride in THF ; second, Nozaki et Coll.[2] failed to couple a presumed chromium enolate of α-bromocyclododecanone with methyl iodide or trimethylsilyl chloride. Spectroscopic studies of the mechanism of this reaction are in progress in our laboratory.

In conclusion, we have shown in this preliminary communication that Chromium (II) chloride finds good applicability for selective carbon-carbon bond formation and successfully complements the many existing methods.

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