Stereoselective Control of the Reduction of Aryl-β-ketoesters by *ortho* Aromatic Substituents

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Reduction of 2-allyl-3-phenyl-β-ketoesters (**1**) with complex metal hydrides ($LiBH_4$) gave mainly *erythro* glycols (**2**) when an *ortho* substituent larger than fluorine was present, but with 2,6-disubstitution (**1i**) the *threo* glycol (**3i**) was the main product.

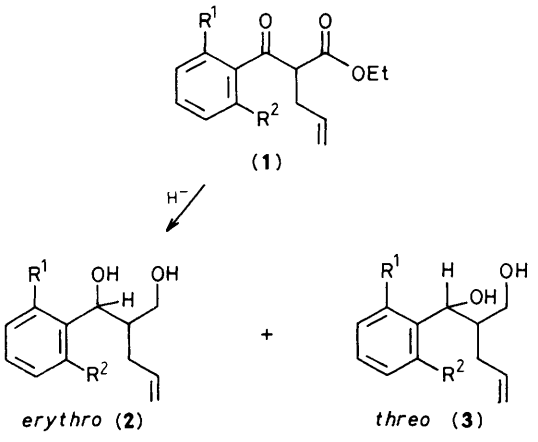
Recently there has been considerable interest in the stereoselective synthesis of compounds with oxygen atoms in a vicinal- or 1,3-stereorelationship, because these features are key constituents of natural products such as the polyether and macrolide antibiotics. Steric control of aldol condensations has been the most useful basis for synthetic approaches to these natural products,[1] but the stereoselective reduction of ketoesters has also been suggested as an alternative basis.[2] Studies of the stereoselective reduction of ketoesters are also of more general interest in relation to the continuing debate[3] concerning the steric control of carbonyl group reduction. We describe the reduction by excess of complex metal hydrides in tetrahydrofuran (THF) of aryl-β-ketoesters in which variation of the *ortho* aromatic substitutent led selectively to both *erythro* and *threo* products.

The reduction of phenyl-β-ketoesters, without aromatic ring substituents has been reported[4] to afford predominately *erythro* glycols with $LiAlH_4$ in Et_2O and *threo* glycols with KBH_4 in MeOH. In contrast we report that reduction of the unsubstituted derivative (**1a**) with $LiBH_4$ in THF did not proceed selectively and inclusion of an *ortho* fluorine atom (**1b**) did not affect *erythro* and *threo* product ratios (Table 1). When a ketoester with a single *ortho* substituent was reduced by $LiBH_4$, *erythro* selectivity increased as the steric bulk of the *ortho* group increased, with the exception of the methoxy derivative (**1h**), which was more selective than would have been expected from its size. This increased selectivity found for (**1h**) may be due to chelation of the methoxy group oxygen atom to the reducing lithium species, thereby strengthening the chelation control of the reduction, (A). Reduction of (**1h**) with the more polar $Zn(BH_4)_2$ was, as reported[2] for other ketoesters, very selective for *erythro* product (**2h**). Here the ester group was reduced in a subsequent step with $Na(MeOCH_2CH_2O)_2AlH_2$. In a similar two-step reduction of (**1h**) starting with KBH_4 in MeOH, the *threo* diastereoisomer (**3h**) was the main product. This reversal of steric control may

Table 1. Reduction of β-ketoesters.

(1)	Reagent[a]	(2):(3)	% Yield
a	$LiBH_4$, THF	1:1	93
b	$LiBH_4$, THF	1:1	90
c	$LiBH_4$, THF	1.2:1	63
d	$LiBH_4$, THF	1.6:1	80
e	$LiBH_4$, THF	3.4:1	64
f	$LiBH_4$. THF	3.6:1	49
g	$LiBH_4$, THF	4:1	50
h	$LiBH_4$, THF	3:1	69
h	$Zn(BH_4)_2$, THF[b]	17:1	90
h	KBH_4, MeOH[b]	1:5	75
i	$LiBH_4$, THF	1:4	80
i	$NaBH_4$, EtOH	1:4	76
i	$LiAlH_4$, THF	1:4	78
i	$LiAlH_4$, THF (−70 °C)[b]	All *threo*	90
i	$Zn(BH_4)_2$, THF[b]	All *erythro*	33

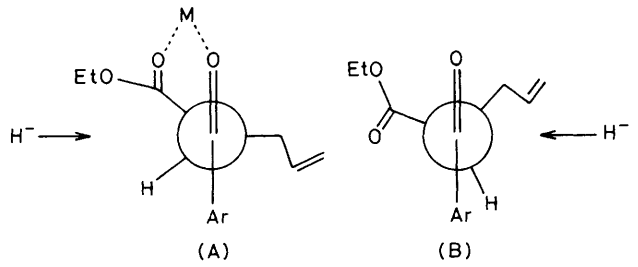
[a] Reactions at 25 °C for 18 h unless otherwise stated. [b] Reaction time 30 min. Intermediate hydroxyester reduced in a subsequent step with $Na(MeOCH_2CH_2O)_2AlH_2$ in toluene.



a; $R^1 = R^2 = H$
b; $R^1 = F$, $R^2 = H$
c; $R^1 = Cl$, $R^2 = H$
d; $R^1 = Me$, $R^2 = H$
e; $R^1 = Et$, $R^2 = H$
f; $R^1 = Pr^i$, $R^2 = H$
g; $R^1 = CF_3$, $R^2 = H$
h; $R^1 = OMe$, $R^2 = H$
i; $R^1 = R^2 = F$

be explained in terms of the absence of chelation control by K^+ ions in MeOH allowing the ester group to assume a preferred conformation (B) where the ester carbonyl group was close to the electron deficient carbon of the ketone carbonyl group. In this way, approach by hydride ion would be less hindered from the opposite face of the ketone carbonyl group giving mainly *threo* product.

Although a single fluorine atom (**1b**) did not confer any selectivity on $LiBH_4$ reductions, an additional fluorine (**1i**) led mainly to *threo* product in contrast to the monosubstituted ketoesters (**1,c—h**). Selectivity for *threo* glycol (**3i**) was maintained with $NaBH_4$ in EtOH and $LiAlH_4$ in THF. With $LiAlH_4$ at −70 °C, selectivity improved to give only (**3i**). In (**1i**) the fluorine atoms will not lie close to the proton on the carbon between the ester and allyl groups or the ketone carbonyl. The aryl ring must thereby adopt a position orthogonal to the plane of the ketone carbonyl group. Examination of Dreiding stereomodels suggests that one of the fluorine atoms would be close to the allyl group unless steric interactions were resolved by the ester group moving out of chelation with the reagent and towards the ketone carbonyl, (B). This would hinder approach of the reducing species and



account for the *threo* product, an explanation which is consistent with the same selectivity being found for $LiBH_4$ and $NaBH_4$. In a reduction of (**1i**) with $Zn(BH_4)_2$ the greater chelation strength of zinc led only to *erythro* glycol (**2i**). Attempts to show generality of this unexpected reversal of stereochemical control by reducing another disubstituted ketoester (**1**; $R^1 = R^2 = Me$) with $LiAlH_4$ or $Zn(BH_4)_2$, were unsuccessful. Complex mixtures of products were obtained and diol products would not ring close to 1,3-dioxanes, so that stereochemical ratios could be ascertained. The effect of temperature on the degree of selectivity of reduction was examined for (**1h**). The ratio of *erythro* to *threo* product from $LiBH_4$ reductions of (**1h**) at −70 °C fell, compared to room temperature, to 1.4 : 1.0 whereas at 67 °C the 3 : 1 ratio was maintained.

Structures of the ketoesters and their reduction products were supported by ^1H n.m.r. spectra and microanalyses. Assignment of the stereochemistry of the diastereoisomers was based on ^1H n.m.r. spectra of 1,3-dioxanes derived from the diols (**2**), (**3**) by reaction with 2,2-dimethoxypropane. The diastereoisomer ratios were determined by isolation of the respective 1,3-dioxanes by column chromatography, which gave results identical to those obtained by examination of the ^1H n.m.r. spectra of the crude mixture of 1,3-dioxanes.

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