Zn Mediated Chemoselective Allylation of Keto Esters with Allylic Halides in Aqueous Medium

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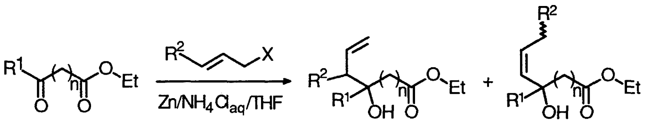
The Zn mediated reactions of allyl, crotyl and cinnamyl halides with β- and γ-keto esters in THF–NH_4Cl(aq) give — by completely selective keto allylation and with good yields — β- and γ-hydroxy esters, respectively. The γ-hydroxy esters were easily and quantitatively converted to γ-allyl substituted γ-butyrolactones in a one-pot reaction.

Zn mediated addition of allylic halides to aldehydes and ketones in aqueous media was introduced by Luche and co-workers some years ago,[1,2] and has become a well established method for the synthesis of homoallylic alcohols.[3] The reaction is particularly attractive for the allylation of aldehydes and ketones containing acidic hydrogens or less reactive carbonyl groups like those of esters and amides. Several examples on the Zn mediated allylation in aqueous media of aldehydes and ketones containing other functional groups have been reported.[3,4] However, no studies of the reactions of keto esters have, to our knowledge, been published.

We reacted some keto esters with allyl, crotyl and cinnamyl halides in a saturated water solution of ammonium chloride containing some THF in the presence of Zn powder according to the previously reported procedure.[5]

The reactions were performed with a 2.5 : 1 excess of the allylic halide (and Zn) to the ester. The reaction mixtures were acidified (dil. H_2SO_4) prior to extraction of the products in order to break the complexes formed between Zn salts and the allylation products. The reaction mixtures were analysed and the reaction products identified by GC/MS and ^1H NMR spectroscopy.[6] Our aim was to find out the degree of chemoselectivity (*ie.* ketone *vs.* ester group allylation) as well as to elucidate the stereochemical course of the reactions. The reactions gave mixtures of homoallylic alcohols **1-4** (Scheme 1 and Table 1) by completely chemoselective additions to the keto group. Propenes and propene dimers formed from the allylic halides were also detected in the reaction mixtures. These by-products have been described previously.[5]



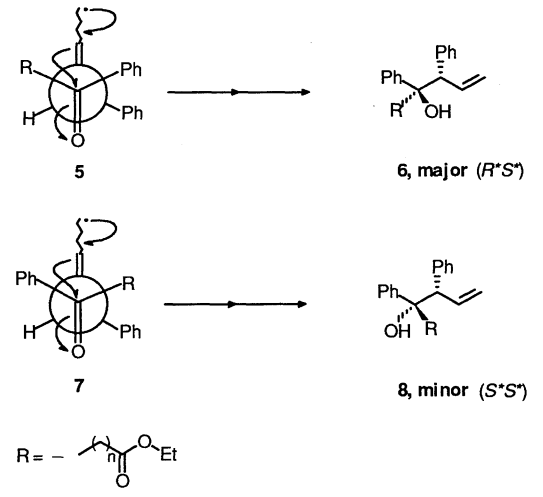
Scheme 1.

The crotyl and cinnamyl groups added almost exclusively *via* an allylic rearrangement giving mixtures of diastereomeric γ-adducts (**1** and **2**). However, small amounts (2-4 % with crotyl and <1 % with cinnamyl halides, respectively) of *Z*- and *E*-, α-adducts (**3** and **4**, Scheme 1) were detected in the reaction mixtures by GC/MS. The yields of homoallylic alcohols (non- and <1 % with cinnamyl halides, respectively) of *Z*- and *E*-, α-adducts (**3** and **4**, Scheme 1) were detected in the reaction mixtures by GC/MS. The yields of homoallylic alcohols (non-optimized yields determined by GC and ^1H NMR and excluding

Table 1. Normalised and total yields of homoallylic alcohols (γ-adducts) in the Zn mediated reactions of allylic halides with keto esters in THF-NH_4Cl(aq). Yields were determined by gas chromatography and ^1H NMR spectroscopy

Entry	R^1	R^2	n	X	1,2		Yield
					major	minor	%
1	H	Me	1	Br		-	76
2	Me	Me	1	Br	54	46	73
3	Ph	Me	1	Cl	64	36	77
4	H	Ph	1	Br		-	81
5	Me	Ph	1	Br	60	40	69
6	Ph	Ph	1	Cl	93 [a]	7	63
7	H	Me	2	Br		-	80
8	Me	Me	2	Br	52	48	73
9	Ph	Me	2	Cl	76	24	84
10	H	Ph	2	Br		-	74
11	Me	Ph	2	Br	73	27	73
12	Ph	Ph	2	Cl	87 [a]	13	82

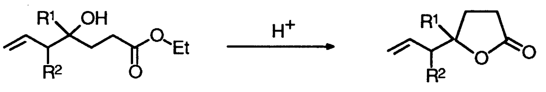
[a] *R* * *S* * relative configuration tentatively assigned to the major isomer.



Scheme 2.

the α-adducts) ranged between 63 and 84 %. The yields did not increase significantly when the excess of halide was increased from 2.5:1 to 6:1. However, the amounts of propenes and propene dimers formed by radical coupling reactions increased (*cf* ref. 5). The diastereoselectivities were moderate in most cases, but generally higher with the benzoyl acetic and benzoyl propanoic acid esters (entries 3,6,9 and 12) than with the corresponding acetyl compounds. The highest diastereoselectivities were displayed by the reactions of the benzoyl compounds with cinnamyl chloride (entries 6 and 12, de = 86 and 74 %, respectively). Assuming that a radical addition takes place *via* a non-cyclic transition state with an antiperiplanar arrangement of the C=C bond of the halide and the C=O bond of the keto group of the ester (**5** and **7**, Scheme 2), as suggested previously,[5] the high selectivity could be due to a favourable π - π interaction between the phenyl groups in the transition state leading to the major isomer (Scheme 2).

Based on the arguments presented in Ref. 5 the major and minor diastereomers formed in the reactions of the benzoyl acetic and benzoyl propanoic acid esters (entries 6 and 12) would then have *R*S** and *S*S** relative configurations, respectively (**6** and **8**, Scheme 2). These assignments of configurations are of course only tentative.



9, 10

Scheme 3.

The hydroxy esters formed from the γ-keto esters (entries 7 - 12) were quantitatively (by GC and ^{1}H NMR spectroscopy) transformed to mixtures of diastereomeric γ-allyl substituted γ-lactones (**9** and **10**) within 1 h when dilute H_2SO_4 was added to the reaction mixtures after completed allylation (Scheme 3).

In conclusion, β- and γ-keto esters react smoothly with allylic halides in THF/NH_4Cl(aq) in the presence of Zn powder to give good yields of homoallylic alcohols containing a carboxylic acid ester functionality. The reactions are completely chemoselective and no addition to the ester group is observed. Crotyl and cinnamyl halides give almost exclusively γ-adducts. Moreover, the reactions with γ-keto esters give good yields of 5-allyl substituted butyrolactones in a one-pot reaction.

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References and Notes

1 C. Pe´trier and J-L. Luche, *J. Org. Chem.*, **50**, 910 (1985).
2 C. Einhorn and J-L. Luche, *J. Organomet. Chem.*, **322**, 177 (1987).
3 Reviews: a) Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993); b) C. J. Li, *Chem. Rev.*, **93**, 2023 (1993); c) T. H. Chan, C. J. Li, M. C. Lee and Z. Y. Wei, *Can. J. Chem.*, **72**, 1181 (1994).
4 T. Kuntz and H- U. Reißig, *Liebigs Ann. Chem.*, **1989**, 891.
5 R. Sjöholm, R. Rairama and M. Ahonen, *J. Chem. Soc., Chem. Commun.*, **1994**, 1217 and references therein.
6 The reaction products gave mass and ^{1}H NMR spectra consistent with the structures. The relative stereochemistries of the major and minor isomers were not obvious from the NMR spectra and were not determined at this stage. It should also be noted that some of the hydroxy esters, and especially those with R^1=R^2=Ph, were prone to loose water when analysed by GC. Therefore the quantitative analyses were also made by ^{1}H NMR spectroscopy.