

1,4-Addition of Dialkylaluminium Chlorides to α,β -Unsaturated Carboxylic Acid Derivatives: a New Synthesis of β -Branched Carboxylic Acids

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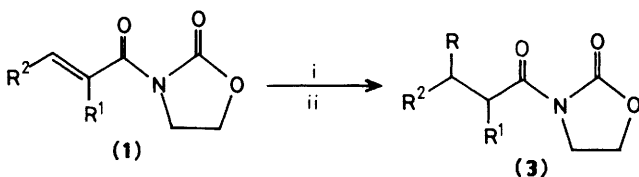
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A new synthesis of β -branched carboxylic acid derivatives by the 1,4-addition of dialkylaluminium chlorides to α,β -unsaturated *N*-acyl amides, the oxazolidones (**1**) and the oxazinone (**4**), is described.

The introduction of branching into carbon-carbon chains is a basic problem in organic synthesis. Branching at the β -position to a carbonyl function is usually introduced by Michael addition¹ (or one of its modern variants²) of carbon nucleophiles, activated by carbonyl or other acidifying groups, to enone systems; the 1,4-addition of alkyl groups is achieved regioselectively using alkyl cuprates generated from alkyllithium derivatives.³

We here report a new route to β -branched carboxylic acids by the 1,4-addition of dialkylaluminium chlorides to α,β -unsaturated carboxylic acid derivatives. The 1,4-addition of organoaluminium compounds⁴ has been described for the transfer of the cyano group to α,β -unsaturated ketones and esters,⁵ of alkynyl⁶ and alkenyl groups^{6,7} to enones, and also of the methyl group in the nickel-catalysed reaction of trimethylaluminium with enones.⁸ However, analogous reactions of higher aluminium alkyls with α,β -unsaturated carboxylic acid derivatives are hitherto unreported.

In this paper we describe the use of α,β -unsaturated *N*-acyl urethanes, in particular α,β -unsaturated *N*-acyl oxazolidones† (**1**), as the electrophilic acceptors. They are easily obtained from 2-oxazolidone by deprotonation with butyl-lithium and subsequent reaction with α,β -unsaturated acyl chlorides. Addition of dialkylaluminium chlorides (**2**) (2 equiv. 1 M solution in hexane or heptane) to the amides (**1**) in dichloromethane at -40°C and allowing to warm to 0°C , gave the almost pure branched *N*-acyloxazolidones (**3**) (Scheme 1, Table).



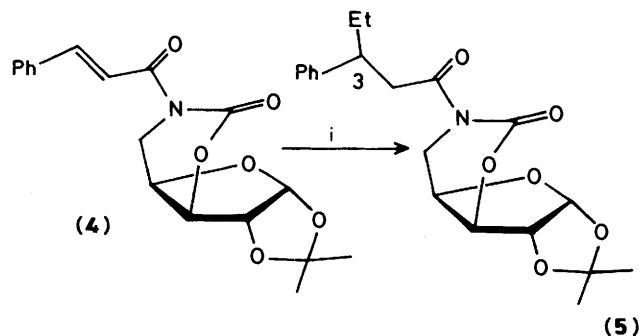
Scheme 1. Reagents: i, R₂'AlCl (**2a**), CH₂Cl₂, -40°C ; ii, R₂AlCl (**2b**), CH₂Cl₂, $-40 \rightarrow 0^\circ\text{C}$

The reaction is strongly dependent upon both the quantity and type of alkylaluminium reagent used. Addition of 1 equiv. of diethylaluminium chloride to the cinnamoyloxazolidone (**1c**) led to rapid complex formation (orange colour), but t.l.c. analysis of the hydrolysed reaction mixture after 2 h showed that no reaction had occurred. On addition of a further 1 equiv. of diethylaluminium chloride [*ie.* (**2a**) = (**2b**), R = R' = Et], however, reaction did occur to give 1-(3-phenylpentanoyl)-2-oxazolidone (**3e**) within 18 h. In contrast, under identical

conditions, neither two equivalents of dimethylaluminium chloride nor of di-isobutylaluminium chloride reacted with the electrophiles (**1**). However, treatment with an equimolar mixture of dimethyl- and di-isobutyl-aluminium chloride [(**2a**), R' = Me; (**2b**), R = Buⁱ] resulted in the transfer of the isobutyl group to the acceptor (**1c**) to give 1-(5-methyl-3-phenylhexanoyl)-2-oxazolidone (**3f**). This series of reactions is summarized in the Table.

It was found that aliphatic, branched chain, aromatic, and alicyclic α,β -unsaturated acyl oxazolidones (**1a–e**) underwent 1,4-addition on treatment with dialkylaluminium chlorides. Although methylaluminium chloride alone formed complexes with compounds (**1**), it failed to bring about transfer of a methyl group to the acceptor; however, it was found to catalyse the nucleophilic transfer of higher alkyl groups. Side reactions, such as 1,2-additions, were not observed. The moderate yields obtained in some cases were due partly to incomplete conversion (Table entries 1, 4, 5, 9, and 10) and partly to hydrolysis of the products (**3**) during work up and chromatography (entries 1, 2, 5, and 6). The reactivity of the electrophiles (**1**) was influenced by steric and electronic factors as expected—in particular, the cyclohexenecarboxylic acid derivative (**1e**) reacted slowly even at room temperature. It should also be noted that *N,N*-diethylcinnamamide does not react with dialkylaluminium chlorides under identical conditions.

The 1,4-addition of alkylcuprates to α,β -unsaturated esters of chiral camphor derivatives has been achieved in high diastereoselectivity.¹⁰ Preliminary experiments show that the addition of dialkylaluminium chlorides can also be performed diastereoselectively by the use of carbohydrate auxiliaries.¹¹ Thus reaction of the *N*-cinnamoyl xylofuranose-oxazinone derivative (**4**) with diethylaluminium chloride gave the β -branched product (**5**) in high yield, due to its relative stability to hydrolysis, and with a diastereoisomeric ratio of 87:13 (by 400 MHz ¹H n.m.r.) (Scheme 2). Hydrolysis of (**5**) with hydrochloric



Scheme 2. Reagents: i, 2 × Et₂AlCl, CH₂Cl₂, -80°C ; yield > 90% (3S):(3R) = 87:13

† α,β -Unsaturated *N*-acyl derivatives of chiral 2-oxazolidones have been successfully used in Diels-Alder reactions with catalysis by diethylaluminium chloride.⁹

Table. Synthesis of β -branched *N*-acyl-2-oxazolidones (**3**) from α,β -unsaturated *N*-acyloxazolidones (**1**) and dialkylaluminium chlorides (**2**) at $-40^\circ\text{C} \rightarrow 0^\circ\text{C}$

Entry	Substrate (1)		Reagents (2a) and (2b)		Reaction time (h)	Product (3) ^a	Yield (%) ^b	M.p. ($^\circ\text{C}$)
	R ¹	R ²	R'	R				
1	(1a)	H Me	Et Et		4	(3a)	75	5–8
2	(1a)	H Me	Me	CH ₂ CHMe ₂	1.5	(3b)	26 ^c	oil
3	(1b)	H CH ₂ CHMe ₂	Me Et		18	(3c)	81	oil
4	(1b)	H CH ₂ CHMe ₂	Me	CH ₂ CHMe ₂	27	(3d)	33 ^c	oil
5	(1c)	H C ₆ H ₅	Et Et		2.5	(3e)	35 ^c	66
6	(1c)	H C ₆ H ₅	Me Et		18	(3e)	49	65–66
7	(1c)	H C ₆ H ₅	Me	CH ₂ CHMe ₂	18	(3f)	55	77
8	(1d)	H <i>o</i> -MeOC ₆ H ₄	Et Et		17	(3g)	91	65–67
9	(1d)	H <i>o</i> -MeOC ₆ H ₄	Me	CH ₂ CHMe ₂	27	(3h)	45 ^c	oil
10	(1e)	-(CH ₂) ₄ -	Me Et		48 ^d	(3i)	48 ^c	oil

^a All products had correct elemental analyses. ^b After flash chromatography with ethyl acetate–light petroleum as eluant. ^c Incomplete conversion by t.l.c. ^d Reaction was allowed to warm to room temperature.

acid gave free 3-phenylpentanoic acid which showed a positive optical rotation, and consequently consisted predominantly of the (3*S*)-diastereoisomer.¹²

The 1,4-addition of alkyl groups from dialkylaluminium chlorides to α,β -unsaturated *N*-acylamides, such as (**1**) or (**4**), offers a new access to β -branched carboxylic acids, including sterically demanding structures such as compounds (**3b–d**) and (**3f–h**). Furthermore, the reaction conditions are completely different and complementary to those of alkylcuprate additions, which require use of alkyl-lithium reagents and exclusion of oxygen.

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