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Conjugate Addition of Organolithium Reagents to α,β-Unsaturated Carboxylic Acids.

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Abstract

Conjugate addition of primary, secondary, tertiary alkyl and phenyl lithium reagents to 2-alkenoic acids affords good yields of branched saturated carboxylic acids. Substitution by methyl groups at the α-carbon strongly decreases reactivity, whereas deprotonation of the starting acid occurs almost exclusively with methyl substitution at the β-carbon of the 2-alkenoic acid.

Keywords: Conjugate Addition; Carboxylic Acids; Organolithium

Conjugate additions of carbon centred nucleophilic reagents to the C-C double bonds of unsaturated aldehydes, ketones, esters and amides, are of utmost importance in synthetic methodology [1]. Organolithium reagents usually afford 1,2-addition products on reaction with these compounds [2] and organocuprates are usually acknowledged instead as the reagents of choice for 1,4-addition [3-5]. On the other hand, organocuprates fail to afford 1,4-addition products on reaction with unsaturated carboxylic acids, although this addition may be attained with primary alkyl organocuprous-boron trifluoride complexes [6,7], as long as restricted to primary alkyl reagents. Inversion of the trend usually found for organolithium reagents would certainly provide an important simplification in synthetic methodology. Conjugate addition of organolithium reagents has been researched by a number of authors and found to be favoured when steric congestion [2, 8], or conjugation of the carbonyl group to an anionic carbon or nitrogen atom prevents 1,2-addition [2, 9].

Addition of organolithium reagents to carboxylic acids is usually acknowledged as a general procedure for the synthesis of ketones [10-13], but poor yields are usually reported for α,β-unsaturated carboxylic acids, which lead to mixtures of the expected ketones along with the acids resulting from the double deprotonation of the starting acid and from 1,4-addition [10, 14]. However, a charge directed conjugate addition to unsaturated carboxylic acids might be attainable, as deprotonation of the carboxylic group at low temperature should occur much

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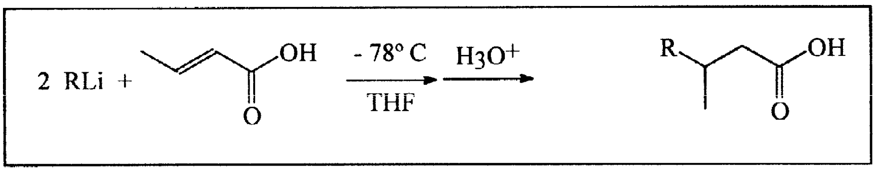
more rapidly than any 1,2- or 1,4-addition [15]. Conjugate addition of organolithium reagents to naphthoic acids [16], or to cinnamic acid [17] have been reported recently, but as far as we know, the synthetic applicability of the conjugate addition of organolithium reagents to unsaturated carboxylic acids has not been described as a general feature.

We wish to show here that the conjugate addition of commercially available organolithium reagents to simple 1,2-unsaturated carboxylic acids, namely acrylic acid and 2-alkenoic acids is, within some constrains, a convenient synthesis of saturated carboxylic acids otherwise difficult to obtain (Scheme 1).



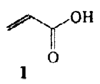
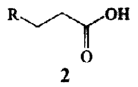
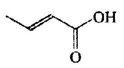
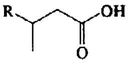
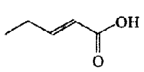
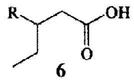
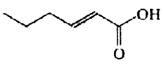
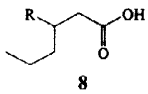
Scheme1

A solution of 2.25 mmols of the unsaturated carboxylic acid in 20 ml of THF was added slowly to 2.2 equivalents (4.5 to 5 mmols) of the organolithium reagent in about 10 ml of hydrocarbon /THF at -70° C and the resulting solution allowed to react for 1 or 2 h at the same temperature. Inverted addition, i.e. addition of the commercial hydrocarbon solution of the organolithium reagent to 10 ml of the acid in THF at - 70° C was occasionally used. Acidic products were isolated and characterized, but neutral products were not studied as they consisted of complex mixtures.

Conjugate additions to acrylic acid **1** are frequently accompanied by polymerisation [18]. However, addition of *n*-butyl-, *tert*-butyl- and phenyl-lithium to acrylic acid afforded moderate yields of the acids **2** which were obtained in spectroscopically and analytically pure form by bulb to bulb distillation of the crude mixtures (Table 1). Yields for addition of *tert*-butyllithium were better with diluted solutions of the reagent.

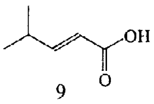
For but-2-enoic acid **3**, higher homologues and for alkyl substituted acids, deprotonation at C-4 can compete with addition. This deprotonation would lead to dienediolates which would be protonated at C-2 on quenching [19], and thus acidic fractions of the reaction mixtures may contain the 1,4 addition product together with unreacted starting acid and the deconjugated isomer of the latter. In practice moderate to good yields of the conjugate addition products **4**, **6** and **8** (Table 1) were obtained on addition of either *n*-, *sec*-, or *tert*- butyllithium reagents or phenyllithium to unsubstituted 2-alkenoic acids **3**, **5** and **7**. However deprotonation was observed to compete with addition for the longer chain hex-2-enoic acid **7** (^{1}H NMR of the crude mixtures). and yields for adducts **8** were less satisfactory.

Table 2.
Addition of organolithium reagents to 2-alkenoic acids.

2-Alkenoic Acid	R	Method [a]	Product	Yield [b] (%)
 **1**	*n*-Bu	A	 **2**	43
	tert-Bu	B		42
	tert-Bu	A [c]		58
 **3**	Me	A	 **4**	0
	n-Bu	A		65
	sec-Bu	A		63 [d]
	tert-Bu	B		69
	Ph	A		77
 **5**	*n*-Bu	A	 **6**	55
	sec-Bu	A		56 [d]
	tert-Bu	B		67
	Ph	A		60
 **7**	*sec*-Bu	A	 **8**	44 [d]
	tert-Bu	A		59

a.- Method A: Addition of the starting acid to stirred RLi. Method B: Addition of RLi to stirred starting acid.
b.- Purified by bulb to bulb distillation, spectroscopically (^{1}H and ^{13}C NMR) and analytically pure samples.
c.- Acrylic acid in 30 ml of THF was added slowly to *tert*-BuLi in 20 ml of THF/hexane.
d.- Isolated as a diastereoisomeric mixture.

Surprisingly, methyllithium, either dissolved in THF/cumene, or in the form of its complex with LiBr in ethyl ether, fails to add to but-2-enoic acid **3**. Best results for the additions were obtained for *tert*-butyllithium and phenyllithium, as observed through the yields of pure compounds **4** and yields and ^{1}H NMR spectra of the crude mixtures.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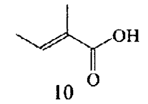
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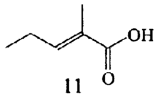
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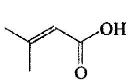
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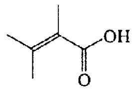
13

Branched chain 4-methylpent-2-enoic, 2-methylbut-2-enoic and 2-methylpent-2-enoic acids **9** to **11** react sluggishly and, although the deconjugated acid was not always observed, yields of the adducts were poor and their isolation was not attempted. The effect of substitution at the α-carbon in reducing reactivity is not unique, as it has been observed for conjugate addition of organocopper to 2-methylbut-2-enoic acid **10** [7] and for addition of organolithium reagents to related unsaturated compounds [20]. On methyl substitution at the β-ethylenic carbon, as is the case for 3-methyl- and 2,3-dimethyl-buten-2-oic acids **12** and **13**, no conjugate addition was observed: deprotonation was preferred and mixtures of deconjugated and starting acids were obtained on quenching. The ready deprotonation of the latter acids has some precedents in similar additions [7,9] and most probably occurs through an eight-membered cyclic transition state which involves the carboxyl and the *cis* β-methyl groups, similar to that postulated by Weiler for the kinetically controlled deprotonation of 3-methylbut-2-enoic acid **12** or its esters by lithium amides [21, 22].

In conclusion, we have shown that both primary, secondary and tertiary alkyl- and phenyllithium reagents add conveniently to unsubstituted 2-alkenoic acids to afford conjugate addition products. Improvement of conditions for 2-alkyl substituted 2-alkenoic acids and the study of the more complex conjugated additions to cinnamic acids is under way.

Acknowledgements

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