

Directed conjugate addition of organolithium reagents to α,β -unsaturated carboxylic acids

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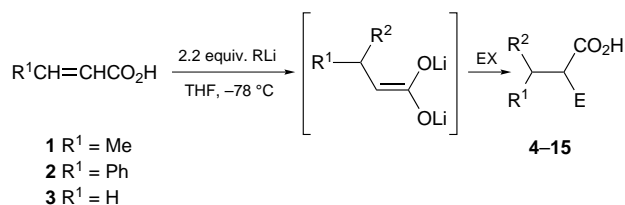
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α,β -Unsaturated carboxylic acids undergo predominantly conjugate addition with organolithium reagents at low temperature ($-78\text{ }^\circ\text{C}$) in THF and lead to various substituted alkanolic acids after quenching with electrophiles; with (*E*)-3-phenylpropenoic acid, this tandem alkylation sequence also affords significant amounts of isomeric 1,3-addition products.

1,4-Additions of organolithium reagents to α,β -unsaturated carbonyl compounds are usually promoted by steric interference of the 1,2-addition process.¹ Literature furnishes little information regarding the conjugate addition of *unprotected* α,β -unsaturated acids to organolithiums^{2,3} and the data, scarce as they are, even appear to be inconsistent at first sight. Majewski and Snieckus described in 1984 the reaction in THF at $0\text{ }^\circ\text{C}$ between senecioic acid [(*E*)-3-methylbut-2-enoic acid] and 2-lithiodithiane which afforded the 1,4-addition product in 65% yield.⁴ Reaction of (*E*)-3-trimethylsilylpropenoic acid with *n*-butyllithium in THF-hexane at $-70\text{ }^\circ\text{C}$ was reported to give a mixture of 1,2-(55%) and 1,4-(45%) addition products.⁵ The conjugate addition of α -silylated α,β -unsaturated acids to organolithiums appears to be a particular case.⁶ Indeed the 1,2-addition is suppressed by the placement of a unit of negative charge adjacent to the carbonyl group. Furthermore the enolate dianions resulting from such additions are not efficiently intercepted with alkylating agents.

We have recently described the efficient addition of organolithium reagents to naphthalene-1- and -2-carboxylic acids followed by electrophilic trapping.⁷ The diastereoisomeric ratios of 1,1,2- and 1,2,2-trisubstituted-1,2-dihydronaphthalenes were found to contain only *trans* addition products. The *trans* addition was verified in each system by single X-ray determination. Thus, in either case, the electrophile approached the naphthalene nucleus from the side opposite to the organolithium. We now describe results which demonstrate that the process can be expanded to simple α,β -unsaturated carboxylic acids.

Typical unsaturated carboxylic acids **1–3** underwent 1,4-addition reactions with lithium reagents in THF at low temperature ($-78\text{ }^\circ\text{C}$) over the course of several minutes



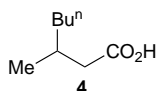
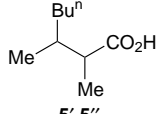
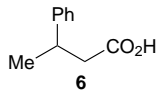
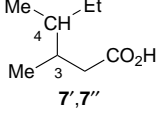
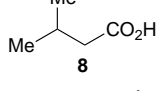
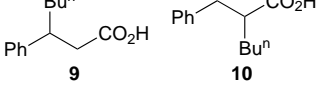
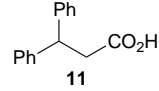
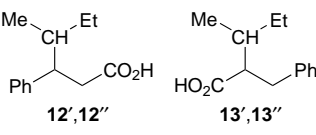
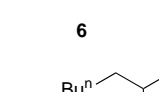
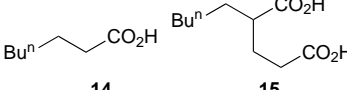
giving carboxylic acid dilithium enolates which, when quenched with a proton source ($\text{CF}_3\text{CO}_2\text{H}$) or an alkyl

halide (MeI),⁸ gave moderate to good yields of substituted alkanolic acids **4–15**. These reactions almost certainly involve deprotonation of the acid first, which reduces but does not suppress the reactivity of the carbonyl towards 1,2-addition.⁹ At $-78\text{ }^\circ\text{C}$, *n*-butyllithium and *sec*-butyllithium added efficiently to the carboxylic acid derivatives **1–3**. The use of phenyllithium, however, proceeded very sluggishly to **1** and **2** and after trapping with trifluoroacetic acid gave only **6** and **11** in 40 and 20% purified yields, respectively (Table 1, entries 3 and 7). Methylithium failed to react (entries 5 and 9) and gave mainly products resulting from carbonyl addition at higher temperatures.

Reaction of *n*-butyllithium with (*E*)-3-methylpropenoic acid **1**, followed by quenching with trifluoroacetic acid, provided the 1,4-adduct **4** in good yield (entry 1). A 1:1 mixture of the diastereoisomers **5'** and **5''** was obtained when the enolate was trapped with methyl iodide (entry 2). When **1** was treated with *sec*-butyllithium, proton quench with trifluoroacetic acid afforded the conjugate 1,4-addition product in moderate yield as a mixture of diastereoisomers (**7'** and **7''**) differing in their configuration at C-3 and C-4 (7:3 ratio, entry 4). Reactions of (*E*)-3-phenylpropenoic acid **2** with *n*-butyllithium and *sec*-butyllithium gave mixtures of the conjugate 1,4-addition products **9** and **12'**, **12''** as well as the isomeric products **10** and **13'**, **13''**, respectively. Structures of types **9**, **10** and **12**, **13** were easily distinguished by their ^{13}C NMR spectra by the multiplicity and the order of the chemical shift of the carbon in α -position of the carboxylic acid. 1,3-Addition reactions of Grignard and organolithium reagents to cinnamate derivatives, involving the addition of a free radical produced by a single electron transfer from the organometallic reagent to the alkene, are precedented.^{2a,5,10} Turning to acrylic acid **3**, it was found that *n*-butyllithium with **3** in THF at $-78\text{ }^\circ\text{C}$ followed by hydrolysis, gave **14** and **15** (5:3) which were isolated in 50% yield (entry 10). Compound **15** resulted presumably from the double conjugate addition of the organolithium reagent to the lithium acrylate.

The following procedure for the synthesis of 3-methylheptanoic acid **4** is representative. In a 250 ml flask maintained under argon, were placed 40 ml of dry THF and 20 ml of *n*-butyllithium (1.6 M in hexanes, 33 mmol). The mixture was then cooled to $-78\text{ }^\circ\text{C}$ and (*E*)-methylpropenoic acid **1** (1.29 g, 15 mmol) in THF (40 ml) was slowly added. After the mixture was stirred for 1 h at $-78\text{ }^\circ\text{C}$, a THF solution (20 ml) of an excess of trifluoroacetic acid (4.62 ml, 60 mmol) was added. The solution was allowed to warm slowly to room temperature with stirring, then treated with water, washed with diethyl ether, and shaken. The aqueous layer was acidified with 2 M HCl, diluted with diethyl ether, and the organic layer was separated, washed with aq. NaHCO_3 and water, and dried with MgSO_4 . Filtration and concentration *in vacuo* afforded **4** which was purified by distillation (bp $75\text{--}80\text{ }^\circ\text{C}/1\text{ mmHg}$, 1.72 g, 80%).

Table 1 Additions of organolithium reagents to acyclic α,β -unsaturated carboxylic acids^a

Entry	Acceptor	R ³ Li ^b	Product(s)	Ratio ^c	Yield (%) ^d
1	1	Bu ⁿ Li		—	80 (90)
2	1	Bu ⁿ Li		1 : 1	76 (85)
3	1	PhLi		—	40 (70)
4	1	Bu ^s Li		7 : 3	46 (62)
5	1	MeLi		—	0
6	2	Bu ⁿ Li		7 : 3	60 (73)
7	2	PhLi		—	20 (32)
8	2	Bu ^s Li		42 : 22 : 23 : 13	70 (78)
9	2	MeLi		—	0
10	3	Bu ⁿ Li		5 : 3	50 (64)

^a All structures are supported by spectral and analytical data. ^b BuⁿLi in hexane; Bu^sLi in cyclohexane–hexane; MeLi and PhLi in diethyl ether; 2.2 equiv. of RLi is used. ^c Determined by ¹H NMR spectroscopy. ^d Yields refer to purified isolated compounds. Yields in parenthesis are based on the consumed starting material.

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Footnote and References

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- Other electrophiles such as PhSSPh, ClCO₂Me, CO₂ were also effective.
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