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CONJUGATE ADDITION OF ORGANOLITHIUM REAGENTS TO ACRYLANILIDE ANIONS

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Summary: Phenyllithium, n-butyllithium, and t-butyllithium were found to add to substituted acrylanilide anions to give the 1,4-addition products in fair to good yields.

Examples of 1,4-addition of Grignard reagents to α,β-unsaturated tertiary amides have been known since shortly after the discovery of Grignard reagents.[1] One case of 1,4-addition of an organolithium reagent to a hindered α,β-unsaturated tertiary amide has also been reported.[2] Recently the conjugate addition of both Grignard and organolithium reagents to α,β-unsaturated tertiary thioamides was shown to be quite general.[3] When acrylanilide was treated with two equivalents of n-butyllithium, followed with quenching with benzaldehyde, the alcohol 1 was isolated. Further investigation showed that the conjugate addition of organolithium reagents to α,β-unsaturated anilides was a general reaction as shown in Table 1.

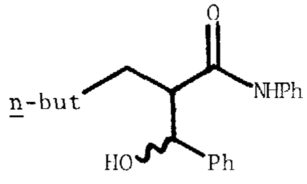

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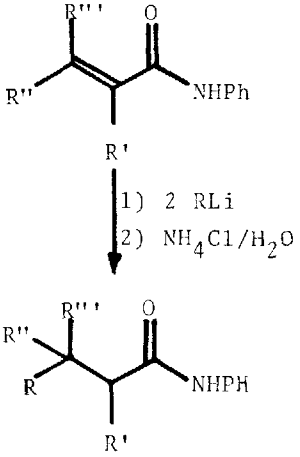
TABLE 1

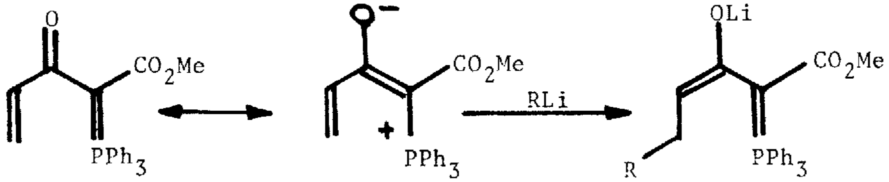
Entry	R	R'	R"	R"'	Yield[a] %
1	Ph	H	H	H	39
2	n-Bu	H	H	H	90
3	t-Bu	H	H	H	94
4	Ph	H	Me	H	48
5	t-Bu	H	Me	H	82
6	Ph	Me	H	H	46
7	Ph	H	Ph	H	32
8	Ph	H	Me	Me	0

[a] refers to isolated and recrystallized products



Methyllithium gave poor yields of the 1,4-addition product. The major product was usually polymer. Ethoxyvinyllithium, lithium phenylacetylide, lithium dimethylcuprate and phenylmagnesium bromide failed to add in a 1,4-manner under the conditions employed. It was also found that the sodium salt of the anilide, formed by treatment with sodium hydride, reacted with one equivalent of an organolithium reagent to give comparable yields of the 1,4-addition product.

The failure of β,β-dimethylacrylanilide (Entry 8) was due to enolization since a mixture of starting material and the deconjugated isomer was recovered.[3,4] This appears to be an example of charge directed conjugate addition analogous to the 1,4-addition of organolithium reagents to ylids 2 discovered by Cooke.[5]



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General method for conjugate addition

A solution of 22 to 25 mmol of the organolithium reagent was added to a mixture of 5 ml of THF and 5 ml of tetramethylethylenediamine at -65°. It was warmed to 0° and recooled. A solution of 10 mmol of the anilide in 25 ml of THF was slowly added. It was warmed to room temperature for two hours and then quenched with saturated aqueous ammonium chloride solution. The product was extracted with ether, washed sequentially with 6N HCl, saturated aqueous $NaHCO_3$ solution and saturated NaCl solution, and dried over Na_2SO_4. Filtration, and evaporation gave the crude product. Recrystallization gave the pure products which were identified by their physical and spectroscopic properties.

Acknowledgments

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