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DILITHIATED N-ALLYLCARBOXAMIDES. A SYNTHESIS OF ENAMIDES

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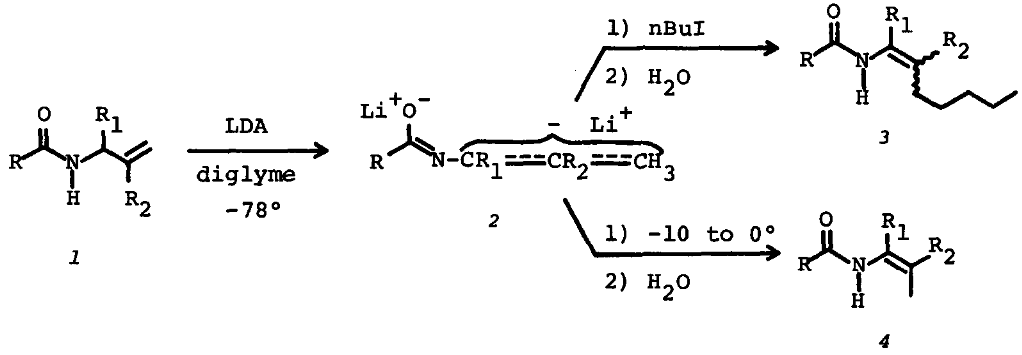
There has been considerable interest in recent years in investigating the alpha-metalation and subsequent reactions of amine derivatives. Secondary amine derivatives that have been alpha-metalated include nitrosamines,[1] amides,[2] and thioamides.[3] Isocyanides,[4] and to a lesser extent, imines,[5] are representative of alpha-metalated primary amine derivatives.

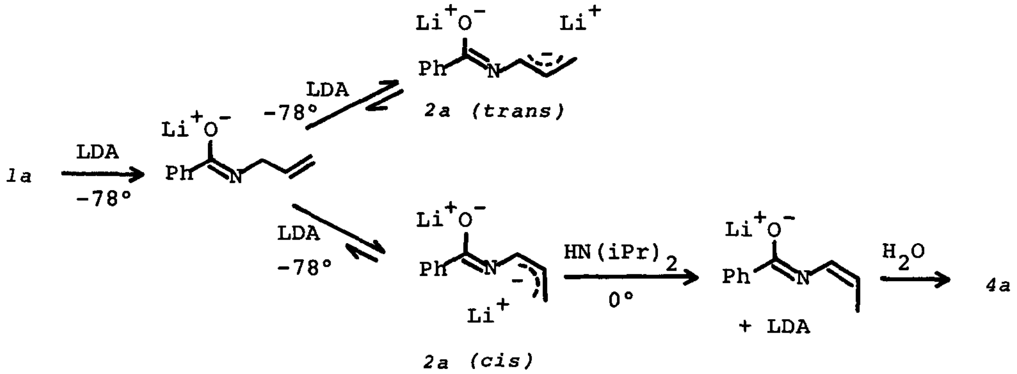
Recently, we reported the first example of a dimetalated monosubstituted amide in which the carbon alpha to nitrogen is metalated, dilithiated N-benzylbenzamide.[6] We wish to report at this time an extension of this reaction type to N-allylamides. These amides are readily dilithiated with either lithium diisopropylamide (LDA) or n-butyllithium in diglyme at -78°. Subsequent reaction with alkyl halides, as exemplified here by n-butyl iodide, occurs exclusively at the gamma position yielding alkylated enamides as products. Warming of the dilithiated amides from -78° to -10° results in an irreversible isomerization of allylamides to enamides when LDA is used.



	Amide *1*[15]			Yield (%)[16]		NMR Chemical Shift of *4* (δ)		
	R	R_1	R_2	*3*	*4*	α	β	γ
1a	Ph	H	H	91	83	6.8	4.8	1.7
1b	Ph	H	Me	77	90	6.6	--	1.7
1c	Ph	H	Ph	75	70	7.3	--	2.1
1d	Ph	Ph	H	99	99	--	6.1	1.7
1e	t-Bu	H	H	88	78[17]	6.7	4.8	1.6

The dilithiated allylbenzamides *2* are formed instantaneously upon the addition of the second equivalent of base, and are intensely colored; *2a* and *2b* are purple, while *2c* and *2d* are brown. The dilithiated trimethylacetamide *2e* is not colored. All of the dilithiated allylamides react rapidly with butyl iodide and other primary halides at -78°. The N-heptenylamide products *3* were isolated by ether extraction of the neutralized reaction mixture. NMR and IR[7,8] analysis indicate the *cis*-enamides as the predominant isomer. The observation that N-allyltrimethylacetamide *1e* reacts similarly to the allylbenzamides indicates that extended conjugation of the allyl anions is not required.

Warming of the dilithiated benzamides *2* to -10° to 0° prior to neutralization results in the propenamides, *4*. The overall reactions, *1* to *4*, amount to the isomerization of allylamides to enamides.[8] These isomerizations appear to be highly stereoselective, with the *cis*-enamides *4* formed preferentially, if not exclusively. We have made a preliminary study of the isomerization of N-allylbenzamide *1a* to N-propenylbenzamide *4a*. In this case only the *cis* isomer[7] is obtained. We propose the following scheme to account for the reaction.



Several observations, in addition to the stereoselectivity, support this scheme. Upon warming, the intense purple color associated with *2a* goes to a much less intense red-orange. Addition of n-butyl iodide to the red-orange solution does not result in alkylation under these conditions. When n-butyllithium is used instead of LDA to form *2a*, no color change is observed upon warming, and the addition of butyl iodide at this point results in alkylation. Consistent with the scheme as proposed, it was found that the reaction can be catalyzed by LDA. The use of only 1.10 equivalent of LDA, which produces *2a* to the extent of only 10%, resulted in a slower but complete conversion upon warming. After 30 minutes at 0°, the color change is complete and *4a* is obtained in 78% yield. No isomerization of *trans* to *cis*-propenamides was observed when a mixture of *cis* and *trans*-propenamides (4:6), prepared via a different route,[7] was subjected to the isomerization conditions. When *2a* is reacted with water or sec-butanol at -78°, the resulting product is a mixture of enamide (*cis* and *trans*) and the starting allylamide in a ratio of approximately 2:1.

Presumably, the stronger acids, water and sec-butanol, can protonate both *2a(trans)* and *2a(cis)* at the α or γ position to give the observed mixture of products, while the much weaker acid, diisopropylamine reacts irreversibly with *2a(cis)* at the γ position at 0°. Alkyl halides such as n-butyl iodide react with either *2a(cis)* or *2a(trans)* at the γ position exclusively.

We believe that the reaction type described here will prove to be of general synthetic applicability. In addition to providing an excellent route to enamides themselves, the enamides may in turn be versatile synthetic intermediates. Hydrolysis of enamides *3* and *4* should yield aldehydes (R_1 = H) and ketones.[9] Toward this end we have recently found that enamides *4b* and *3a* are cleanly converted to isobutyraldehyde and heptaldehyde respectively upon heating to 100° in 50% acetic acid (v/v) containing 2% ascorbic acid. Thus the dilithiated allylamides, *2*, can be used as homoenolate synthons. There are also precedents for electrophilic and nucleophilic reactions,[7,10] as well as oxidation[9] and hydrogenation[7] reactions of the enamide double bond. There has been considerable interest in enamides as monomers.[11]

Allyl lithiation has also been reported for two tertiary allylamines, N-methyl-N-allylaniline,[12a] and N-allylpyrrolidine.[12b] Base-induced isomerization was reported for the allylaniline in the absence of electrophiles.[13]

We are currently investigating the scope and mechanism of dimetalated allylamides with a range of electrophiles under varied solvent, cation, and temperature parameters.

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13. In contrast to the isomerization of this 3° amine, we have observed no isomerization of a 3° allylamide, N-phenyl-N-allylbenzamide, with LDA in diglyme at 0°.
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15. All of the allylamides *1* were prepared by reaction of the appropriate acid chloride and allylamine. The acid chlorides, allylamine and methallylamine were purchased. The phenylallylamines were prepared as previously described.
    (a) 2-Phenylallylamine: H. L. Panzik and J. E. Mulvaney, *J. Polym. Sci., Polym. Chem.*, **10(12)**, 3469 (1972).
    (b) 1-Phenylallylamine: L. E. Overman, *J. Am. Chem. Soc.*, **98(10)**, 2901 (1976).
16. The reported yields represent the amount of actual product contained in the isolated crude product as determined by NMR. The conversions were generally above 90%.
17. *Cis* and *trans* obtained, 6:4.

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