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REMOTE LITHIATION OF *N*-METHALLYL AMIDES

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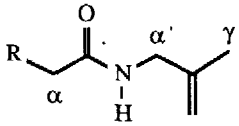
Abstract: Metalation of *N*-methallyl amides occurs at nitrogen and at the remote methyl group. The dilithiated intermediates can be trapped with electrophiles to give substituted derivatives.

Metalations of remote positions which are directed by chelating functionality are of considerable theoretical and synthetic interest.[1] In our continuing interest in directed metalations of allylic systems[2] we had the occasion to examine the dilithiation of *N*-methallyl secondary amides **1**. Structure **1** contains a number of potential sites for a second metalation to occur: deprotonation at the α-carbon would lead to the amide enolate; metalation at the α'-position would give an α-aza-allyllithium; while removal of a vinylic or γ'-proton would produce a remotely substituted carbanion. We speculated that the presence of a negative charge on the nitrogen might disfavor the two former processes while the strong directing ability of the lithiated secondary amide function[3] would serve to activate a remote process.[4] γ'-Metalation would provide a synthetic equivalent for the 2-aminomethyl allylic carbanion **2**, a species of considerable synthetic potential.[5]



1a, R = CH_3
1b, R = H

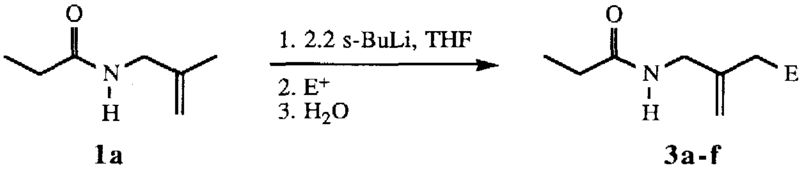
2

Treatment of **1a** with 2.2 equivalents of *sec*-butyllithium in tetrahydrofuran at -78°C followed by addition of an electrophile leads to the remotely substituted amides **3** (Scheme I). Yields for representative electrophiles are given in Table I. Reaction with both carbonyl compounds and alkyl halides proceeds in synthetically useful yields, reflecting the high reactivity of allylic nucleophiles. Bromination is best achieved by initial treatment with trimethylborate followed by quenching the intermediate "ate" complex with bromine.[2a]

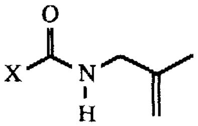
Table I. Remote Metalation and Electrophilic Substitution of **1a**.

Electrophile	Product	Yield
CH_3OD	**3a**, E = D	77% (95% d_1)
PhCHO	**3b**, E = PhCHOH	73%
Cycloheptanone	**3c**, E = $(CH_2)_6CHOH$	64%
$PhCH_2Br$	**3d**, E = CH_2Ph	55%
$CH_3(CH_2)_3I$	**3e**, E = $(CH_2)_3CH_3$	71%
$(MeO)_3B$; Br_2	**3f**, E = Br	66%

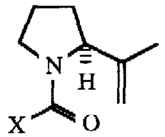
Scheme I



The remote metalation of **1a** is presumably a result of factors which both promote γ'-metalation and disfavor kinetic deprotonation at either the α or α'-carbons. Subjection of **1b**, which lacks the anion destabilizing alkyl group,[6] to the same conditions gives rise to a mixture of products, apparently a result of competing α and γ'-proton removal. Moreover, both benzamide **4**[7] and carbamate **5**[8] undergo exclusive α'-lithiation as do the tertiary systems **6**[9] and **7**,[8,9] which lack the destabilizing negative charge on nitrogen. Apparently, this charge in **4** and **5** is sufficiently delocalized by the electron withdrawing functionality on the amide that removal of the α'-proton becomes more facile. Indeed, small amounts (<10%) of products of α'-metalation are formed in the reactions of **1a** as well. Simple destabilization of the α'-position does not provide an adequate explanation for the facile remote metalation of **1a**, however. Lithiation of allylic methyl groups in systems which lack strong directing functionality generally proceed under much more vigorous conditions.[1a] Moreover, ortho-metalation of the aromatic ring in *N*-phenylpivalamide[10] is significantly more rapid than that of the corresponding *t*-butyl carbamate,[11] illustrating the superior directing ability of the amide function. It is thus likely that the monolithiated secondary amide of **1a** enhances the rate of remote metalation through a preequilibrium complex with the alkyllithium base.[1b,12] The more electron deficient groups X in **4** and **5** would be expected to be less efficient in this process.



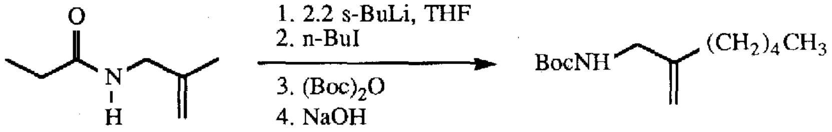
4, X = Ph
5, X = t-BuO



6, X = *t*-Bu
7, X = *t*-BuO

For **1a** to provide a synthetic equivalent for primary amine **2**, mild conditions for the hydrolysis of the propionyl group must be available. Application of the procedure of Grieco[13] (Boc$_2$O, DMAP; LiOH) is effective; however, a more straightforward approach, shown in Scheme II, involves sequential addition of an electrophile to the dianion of **1a** followed by di-*tert*-butyldicarbonate to produce the *N*-Boc derivative. Hydrolysis of the crude reaction mixture at ambient temperature gives the protected amine **8** in 61% overall yield. Application of this method to the synthesis of systems of biological interest will be reported in due course.

Scheme II



1 a 61% **8**

The preparation of **8** describes a typical experimental procedure. Anhydrous tetrahydrofuran (8 mL) was cooled under inert atmosphere to -78°C and treated with 5.1 mL (5.6 mmol) of *sec*-butyllithium in cyclohexane followed by a solution of 323 mg (2.53 mmol) of *N*-methallyl propionamide in 2 mL of tetrahydrofuran. The solution was stirred for 1 h, treated with 0.31 mL (2.8 mmol) of 1-iodobutane, and stirred at -78°C for an additional hour. After being allowed to warm to ambient temperature, the solution was treated with 1.11 g (5.1 mmol) of di-*tert*-butyldicarbonate and stirred for 3.5 h. The resulting solution was treated cautiously with 3 N NaOH, extracted with ether, dried over MgSO$_4$, and concentrated. The crude product was taken up in 15 mL of dioxane, treated with 7.5 mL of 1 N NaOH, and stirred at ambient temperature for 7 h. Extractive workup and flash chromatography with ethyl acetate/hexane mixtures gave 351 mg (61%) of **8** as a colorless oil. ^{1}H NMR (CDCl$_3$) δ 0.88 (t, J = 7 Hz, 3 H), 1.30 (m, 4 H), 1.45 (s, 9 H), 1.47 (m, 2 H), 2.01 (t, J = 8 Hz, 2 H), 3.68 (d, J = 6 Hz, 2 H), 4.10 (br, 1 H), 4.32 (br s, 1 H), 4.37 (br s, 1 H). CIMS, *m* / *e* 228 (M + H).

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1. (a) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. (b) Beak, P.; Meyers, A. I. *Acc. Chem Res.* **1986**, *19*, 356.

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4. The factors which influence vinylic vs allylic metalation in systems where both compete are not well understood (references 2,5). We have observed only the latter.

5. *N,N*-Dimethylmethallylamine and *N*-phenylmethallylamine undergo remote allylic metalation: (a) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1981**, *46*, 3349; (b) Barluenga, J., Fananas, F. J., Foubelo, F., Yus, M. *Tetrahedron Lett.* **1988**, *29*, 4859.

6. The presence of only one alkyl group at the α-position of secondary amides is sufficient to prohibit enolization. For other remote allylic metalations which are favored over enolate formation, see Beak, P.; Hunter, J. E.; Jun, Y. M.; Wallin, A. P. *J. Am. Chem. Soc.* **1987**, *109*, 5403.

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8. *tert*-Butyllithium was used instead of *sec*-butyllithium as the metalating agent.

9. Prepared from L-proline methyl ester by *N*-acylation, addition of methyllithium, and dehydration with thionyl chloride/triethylamine.

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