

Direct Regio- and Stereo-selective Lithiation of Secondary Allyl and Methylallyl Amines: Reaction with Electrophiles

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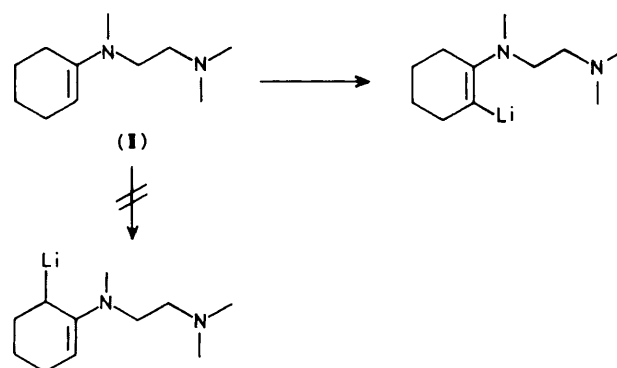
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Several secondary allyl and methylallyl amines (**1**) have been regio- and stereo-selectively lithiated with *t*-butyl-lithium, giving the corresponding sp^2 γ -aminated organolithium intermediates (**2**), which by reaction with electrophiles (D_2O , Me_2S_2 , Pr^iCHO , $PhCHO$, Me_2CO , or Ph_2CO) give the products (**3**) expected from S_E reaction with retention of configuration; in the case of methylallylaniline (**1f**), the corresponding intermediate (**2f**) and products (**3f**) were obtained, under similar reaction conditions.

Recently¹ the first direct lithiation of chelating tertiary vinylic amines, by *t*-butyl-lithium, was described. Thus, in the amine (**I**) the vinylic proton was replaced instead of the expected allylic one (Scheme 1). The existence of a chelating amino function seems essential for lithiation, since metallation of the pyrrolidine enamine of cyclohexanone failed under the same reaction conditions, even in the presence of hexamethylphosphoric amide;¹ furthermore, lithiation of dimethyl (methylallyl)amine gives the corresponding species metallated at the allylic position.^{2†} In the present communication we report the regio- and stereo-selective lithiation of allyl and methylallyl secondary amines and their subsequent functionalization with various electrophilic reagents.

Successive treatment of various allylic or methylallylic secondary amines (**1a–e**) with *n*-butyl-lithium and *t*-butyl-lithium at temperatures ranging between -50 and $20^\circ C$ led to the vinylic lithiated dianions (**2**) in a regio- and stereo-selective manner. Further reaction of these d^3 reagents⁵ with several

electrophilic reagents (deuterium oxide, dimethyl disulphide, or carbonyl compounds) occurred with retention of configuration⁶ yielding, after hydrolysis, the corresponding functional-



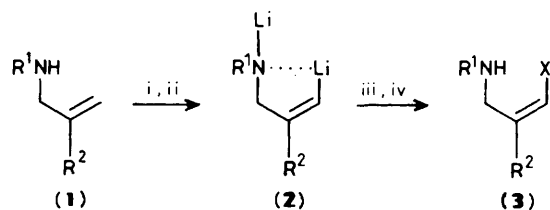
Scheme 1

† The lithiation of allyl alcohols leads to different results, depending on the reaction conditions.^{3,4}

Table 1. Preparation of intermediates (2) from amines (1) and reaction with electrophiles to give products (3).

Starting amine	Intermediate	Electrophile	Product (3) ^a	% Yield ^b	B.p./°C [mmHg]
(1a)	(2a)	D ₂ O	(3a; X = D)	82	76–77 [760]
(1b)	(2b)	D ₂ O	(3b; X = D)	93	43–45 [0.1]
(1b)	(2b)	Me ₂ S ₂	(3b; X = MeS)	85	80–81 [0.1]
(1b)	(2b)	PhCHO	(3b; X = PhCHOH)	73	120–122 [0.1]
(1b)	(2b)	Me ₂ CO	(3b; X = Me ₂ COH)	78	96–98 [0.1]
(1c)	(2c)	D ₂ O	(3c; X = D)	91	51–53 [0.1]
(1c)	(2c)	Me ₂ S ₂	(3c; X = MeS)	88	91–93 [0.1]
(1d)	(2d)	D ₂ O	(3d; X = D)	91	89–91 [760]
(1e)	(2e)	D ₂ O	(3e; X = D)	94	56–58 [0.1]
(1e)	(2e)	Me ₂ S ₂	(3e; X = MeS)	88	91–93 [0.1]
(1e)	(2e)	PhCHO	(3e; X = PhCHOH)	79	132–133 [0.1]
(1e)	(2e)	Me ₂ CO	(3e; X = Me ₂ COH)	81	106–107 [0.1]
(1f)	(2f)	D ₂ O	(3f; X = D)	85	66–68 [0.1]
(1f)	(2f)	Me ₂ S ₂	(3f; X = MeS)	79	110–112 [0.1]
(1f)	(2f)	Pr ⁱ CHO	(3f; X = Pr ⁱ CHOH)	71	84–86 [0.001]
(1f)	(2f)	PhCHO	(3f; X = PhCHOH)	73	142–144 [0.001]
(1f)	(2f)	Me ₂ CO	(3f; X = Me ₂ COH)	71	71–73 [0.001]
(1f)	(2f)	Ph ₂ CO	(3f; X = Ph ₂ COH)	69	(Oil)

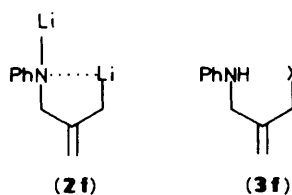
^a All products (3) were fully characterised by spectroscopic methods (i.r., ¹H and ¹³C n.m.r., and mass spectra). ^b Isolated yield based on the starting amine (1).



Cy = cyclohexyl

- a; R¹ = Prⁱ, R² = H
 b; R¹ = Cy, R² = H
 c; R¹ = Ph, R² = H
 d; R¹ = Prⁱ, R² = Me
 e; R¹ = Cy, R² = Me

Scheme 2. Reagents and conditions: i, BuⁿLi, –50 to –30 °C; ii, Bu^tLi, –30 to 20 °C; iii, electrophile = D₂O, Me₂S₂, PrⁱCHO, PhCHO, Me₂CO, or Ph₂CO, –78 to 20 °C; iv, H₂O.



ized allylic or methylallylic amines (3)[‡] (Scheme 2 and Table 1). With *N*-(methylallyl)aniline (1f; R¹ = Ph, R² = Me) under the same reaction conditions, allylic rather than vinylic lithiation took place exclusively, leading to the dianionic

[‡] The stereochemistry of compounds (3) was confirmed by n.m.r. experiments [*J*_{CH=CH} (ca. 10 Hz) and/or nuclear Overhauser enhancement determinations].

intermediate (2f), which by reaction with the same electrophiles gave, after hydrolysis, the expected products (3f) (Table 1).

In a typical reaction, to a solution of the amine (1) (5 mmol) in diethyl ether (25 ml) at –50 °C under argon was added an ethereal solution of *n*-butyl-lithium (5 mmol), and stirring was continued for 20 min at temperatures ranging between –50 and –30 °C. To the resulting mixture at –30 °C was added a solution of *t*-butyl-lithium (5 mmol) in pentane, and the mixture was stirred for 2 h, while the temperature was allowed to rise to 20 °C. The mixture was then cooled to –78 °C, the electrophile (5 mmol)[§] was added, and the resulting mixture was stirred overnight while the temperature was allowed to rise to 20 °C. The mixture was then hydrolysed with water and extracted with diethyl ether. The organic layer was dried (Na₂SO₄), the solvents were removed (15 or 760 mmHg), and the residue was purified by distillation (see Table 1).

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- See, for instance, J. Barluenga, J. R. Fernández, and M. Yus, *J. Chem. Soc., Chem. Commun.*, 1986, 183, and references cited therein.

[§] When D₂O was used as electrophile a large excess (ca. 100 mmol) was added.