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REACTIONS OF ORGANOLITHIUM REAGENTS WITH AMINES; SYNTHESES OF KETONES AND α-SUBSTITUTED AMINES FROM PRIMARY AMINES[1]

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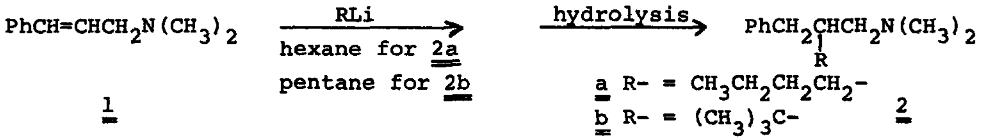
Reactions under mild conditions of primary amines with an excess of an organolithium reagent furnish (after hydrolysis) unexpected products: α-substituted amines and ketones.

In an adjoining communication, we reported that the allyl Grignard reagent added readily to the double bonds of N,N-dimethylcinnamylamine (**1**) and cinnamylamine.[2] In extending this work to organolithium reagents, we observed additions to the tertiary amine **1** to form addition products, **2a** (52%) and **2b** (56%).[3] It

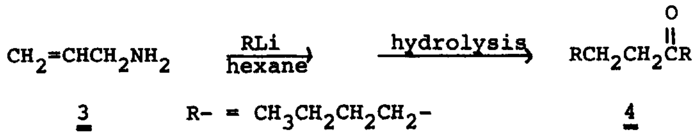


$$\underset{\mathbf{1}}{PhCH{=}CHCH_2N(CH_3)_2} \xrightarrow[\text{hexane for } \mathbf{2a}\text{; pentane for } \mathbf{2b}]{RLi} \xrightarrow{\text{hydrolysis}} PhCH_2\underset{R}{\underset{|}{C}}HCH_2N(CH_3)_2 \quad \mathbf{2}$$

$$\mathbf{a}\ R- = CH_3CH_2CH_2CH_2- \qquad \mathbf{b}\ R- = (CH_3)_3C-$$

is not certain that the tertiary amine function promoted these additions, since significant addition of *n*-butyllithium to 1-phenyl-1-propene occurred under similar conditions.

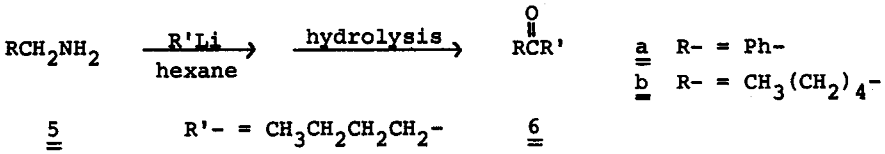
Reactions of primary allylamines and lithium reagents (3 equivalents) took an unexpected course. For example, hydrolysis of a reaction mixture obtained by refluxing a hexane solution of allylamine (**3**) and *n*-butyllithium furnished



$$CH_2{=}CHCH_2NH_2 \xrightarrow[\text{hexane}]{RLi} \xrightarrow{\text{hydrolysis}} RCH_2CH_2\overset{O}{\overset{\|}{C}}R$$

3 R- = $CH_3CH_2CH_2CH_2$- 4

ketone 4 (30%). Similar reactions seem to be general for primary amines in which the alkyl group is primary; under similar conditions, benzylamine (5a) and *n*-hexylamine (5b) furnished ketones 6a (20%) and 6b (32%).[3] Primary amines in which the alkyl group is secondary undergo related reactions. Under similar



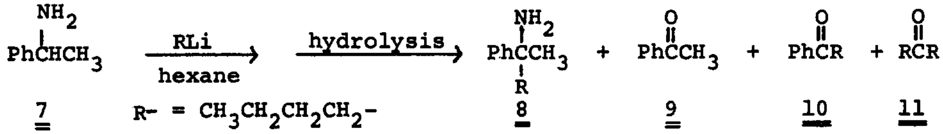
$$RCH_2NH_2 \xrightarrow[\text{hexane}]{R'Li} \xrightarrow{\text{hydrolysis}} R\overset{O}{\overset{\|}{C}}R'$$

a R- = Ph-

b R- = $CH_3(CH_2)_4$-

5 R'- = $CH_3CH_2CH_2CH_2$- 6

conditions, 7 furnished a mixture of 8 (25%), 9 (6%), 10 (6%), and 11 (30%).[3] The observation that 8 (43%) and 9 (6%) but only minor amounts of 10 and 11 were



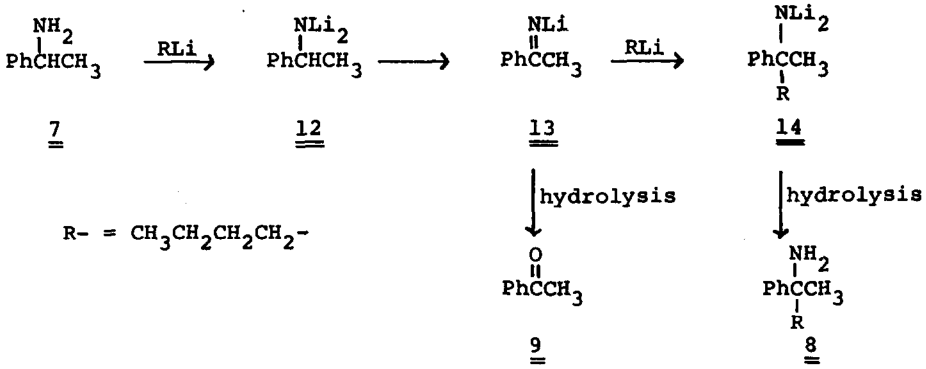
$$Ph\overset{NH_2}{\overset{|}{C}}HCH_3 \xrightarrow[\text{hexane}]{RLi} \xrightarrow{\text{hydrolysis}} Ph\underset{\underset{R}{|}}{\overset{NH_2}{\overset{|}{C}}}CH_3 + Ph\overset{O}{\overset{\|}{C}}CH_3 + Ph\overset{O}{\overset{\|}{C}}R + R\overset{O}{\overset{\|}{C}}R$$

7 R- = $CH_3CH_2CH_2CH_2$- 8 9 10 11

obtained when instead the reaction was carried out at room temperature suggested that the lithiated amine that (upon hydrolysis) furnished 8 underwent transformations under more vigorous reaction conditions that resulted in production of 10 and 11. This suggestion that a lithiated primary amine with even a tertiary alkyl group may undergo reactions that furnish ketones was confirmed when a reaction of 8 with *n*-butyllithium in refluxing hexane led to formation of some 10 and 11.

A primary amino function seems necessary for these reactions. A secondary amine, $PhCH_2NHCH_3$, and several tertiary amines were isolated unchanged from similar reaction solutions.

The formation from primary amines of the products reported above can be rationalized by reaction sequences in which eliminations of lithium hydride or of organolithium compounds from lithiated amines alternate with additions of organolithium compounds to the elimination products. For example, formation of the products (8 and 9) obtained from 7 under mild conditions could be due to a sequence in which a critical step is loss of lithium hydride from 12 to form 13. Because related reactions of monolithiated amines are not generally observed,[4]



it is assumed that dilithiation is required for rapid elimination. Though PhCLi(CH_3)NHLi rather than 12 might be responsible for the reactions of 7, lithiation at the α-carbon could not be involved in the reaction of primary amines (such as 8) in which that carbon lacks a hydrogen. Formation of the ketones obtained from 3, 5a, and 5b could be explained by similar reaction sequences.[5,6,7] Formation of the products (10 and 11) obtained from 7 with more vigorous conditions could be rationalized by a further reaction sequence (beginning with 14) that involves successive loss and addition of organolithium compounds.

These reactions may find application not only for the synthesis of ketones and for the introduction of α-substituents into primary amines, but also for syntheses of products that might result from interception of the postulated intermediate species. Moreover, to the extent that the reaction scheme suggested above approaches reality, the ready elimination of lithium hydride, the slower but still remarkably facile elimination of organolithium reagents,[8] and the ready addition to lithiated imines (such as 13) of organolithium reagents are noteworthy and merit further study.

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REFERENCES

1. Part of this material is taken from the M.S. Thesis of A. S. Heyn, The Pennsylvania State University, 1970.
2. H. G. Richey, Jr., W. F. Erickson, and A. S. Heyn, *Tetrahedron Lett.*, (1971).
3. The yield figures generally are based on the quantities of product mixtures isolated by distillation (corrected for the composition of the distillates determined by glc analyses). Losses in work-up and distillation were significant since only a few g of amine were used for each reaction, so the amounts of products formed were greater than the yields that are indicated.
4. Lithium hydride is eliminated from the monolithiated amines that results from 1,2-additions of organolithium reagents to pyridines; however, the eliminations are slow even though they produce aromatic systems [for example, see K. Zeigler and H. Zeiser, *Chem. Ber.*, **63**, 1847 (1930)].
5. Loss of two molecules of lithium hydride to form a nitrile might occur in the reactions of amines with primary alkyl groups.
6. The isolation in some reactions of higher-boiling products, probably N-alkylimines, suggests that this scheme is incomplete.
7. The addition of the organolithium reagent to the carbon-carbon double bond during the formation of **4** presumably is facilitated by conjugation of the carbon-carbon double bond with a carbon-nitrogen multiple bond.
8. Compare to the loss of alkyl groups from lithium alkoxides [for example, see H. D. Zook, J. March, and D. F. Smith, *J. Amer. Chem. Soc.*, **81**, 1617 (1959); D. J. Cram, A. Langemann, W. Lwowski, and K. R. Kopecky, *ibid.*, **81**, 5760 (1959); D. J. Cram, F. Hauck, K. R. Kopecky, and W. D. Nielsen, *ibid.*, **81**, 5767 (1959); D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielsen, and J. Allinger, *ibid.*, **81**, 5774 (1959); D. J. Cram and W. D. Nielsen, *ibid.*, **83**, 2174 (1961); D. J. Cram, L. K. Gaston, and H. Jäger, *ibid.*, **83**, 2183 (1961)].