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BASE-CATALYZED FORMATION OF SECONDARY AMINES FROM PRIMARY AMINES

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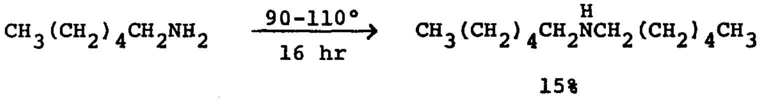
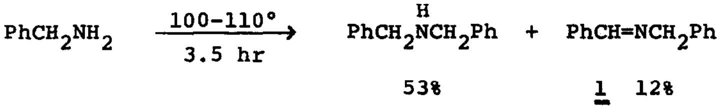
Many primary amines when heated with a <u>catalytic amount</u> of a strong base are converted into secondary amines. Sodium hydride (0.2-0.3 mole per mole of amine)



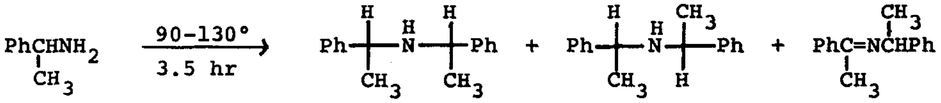
$$CH_3(CH_2)_4CH_2NH_2 \xrightarrow[16\ hr]{90-110°} CH_3(CH_2)_4CH_2\overset{H}{N}CH_2(CH_2)_4CH_3$$

15%

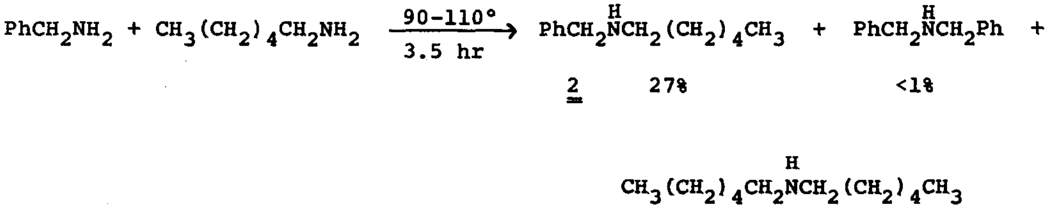


$$PhCH_2NH_2 \xrightarrow[3.5\ hr]{100-110°} PhCH_2\overset{H}{N}CH_2Ph + PhCH{=}NCH_2Ph$$

53% **1** 12%



15%[2] and 22%[2] 14%



$$PhCH_2NH_2 + CH_3(CH_2)_4CH_2NH_2 \xrightarrow[3.5\ hr]{90-110°} PhCH_2\overset{H}{N}CH_2(CH_2)_4CH_3 + PhCH_2\overset{H}{N}CH_2Ph + CH_3(CH_2)_4CH_2\overset{H}{N}CH_2(CH_2)_4CH_3$$

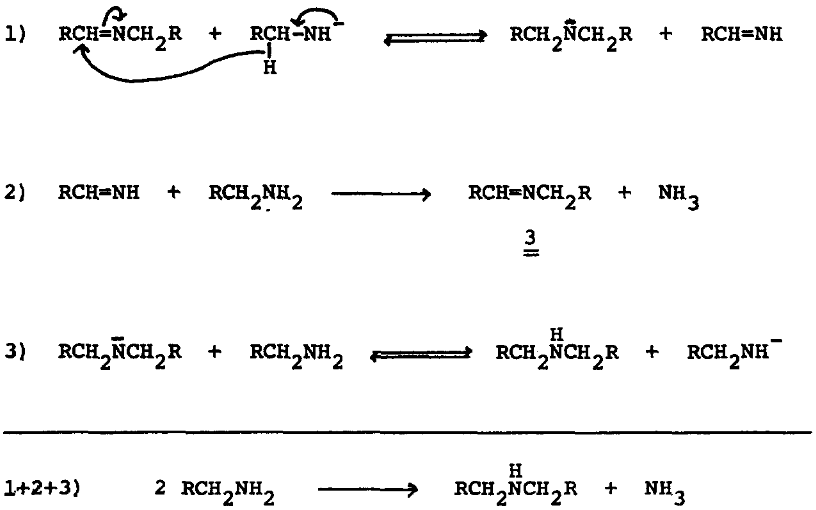
2 27% <1% <1%

was the base in the examples of this reaction that are shown.[1]

A report[3] of the conversion of benzylamine to dibenzylamine on heating with sodium hydride (the additional product 1 was not observed) is the only closely related work that we have found. The suggestion made in that report that the

$$PhCH_2NH^- + H_2N{-}CH_2Ph \longrightarrow PhCH_2\overset{H}{N}CH_2Ph + {}^-NH_2$$

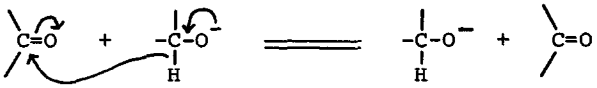
reaction involves displacement of amide ion seems improbable. We suggest tentatively that the following reaction scheme is involved:



$$\begin{array}{ll}
1) & RCH{=}NCH_2R + R\underset{H}{C}H{-}\bar{N}H^- \rightleftharpoons RCH_2\bar{N}CH_2R + RCH{=}NH \\
2) & RCH{=}NH + RCH_2NH_2 \longrightarrow \underset{\mathbf{3}}{RCH{=}NCH_2R} + NH_3 \\
3) & RCH_2\bar{N}CH_2R + RCH_2NH_2 \rightleftharpoons RCH_2\overset{H}{N}CH_2R + RCH_2NH^- \\
\hline
1{+}2{+}3) & 2\ RCH_2NH_2 \longrightarrow RCH_2\overset{H}{N}CH_2R + NH_3
\end{array}$$

This scheme is in accord with (a) the need for only catalytic amounts of base, (b) the isolation from some of the reactions of the N-alkylimines (3) proposed as intermediates, and (c) the failure in preliminary experiments to observe related reactions with primary amines that have tertiary alkyl groups or with primary aryl amines.[4]

Step 1 postulates a hydride transfer from an anion of an amine to an imine. Though donation of hydride by amines and reduction of imines by hydride are known, we have not found a prior example of a base-catalyzed amine-imine hydride transfer.[6] However, the reaction is isoelectronic with the hydride transfer between ketones and anions of alcohols that is involved in the Oppenauer oxidation and



the Meerwein-Ponndorf-Verley reduction.[7] Steps 2 and 3 of the proposed mechanism are unexceptional - the condensation in step 2 of an imine and an amine to produce an N-alkylimine and ammonia is well-known,[8] and step 3 is a proton transfer that should be rapid.

This reaction may prove to be useful for the synthesis of a variety of amines. By the use of two reactant amines, unsymmetrical secondary amines can be produced - formation of only the mixed secondary amine **2** from such a reaction indicates that the different roles played by two amine molecules in the reaction process may impose considerable selectivity on product formation. In fact, according to the proposed mechanism, an amine need not have an α-hydrogen to enter into step 2, so that primary amines with aryl or tertiary alkyl groups might be incorporated into unsymmetrical secondary amines.

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References

1. The reactions were run without a solvent; product mixtures were isolated by distillation and their compositions determined by glc analysis.
2. Assignments of configuration have not been made.
3. R. Baltzly and S. W. Blackman, J. Org. Chem., **28**, 1158 (1963).
4. An alternate scheme in which step 1 is replaced by the steps of (1a) elimination[5] of sodium hydride from the anion of the amine and (1b) reduction of the imine by sodium hydride seems less likely. In a control experiment, heating **1** with sodium hydride did not produce dibenzylamine. However, this control experiment is not definitive - the sodium hydride added externally in the

control experiment may be less reactive than that generated *in situ*.

5. It has been reported [C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Amer. Chem. Soc.*, **78**, 1653 (1956)] that the corresponding imine is formed in good yield from 9-aminofluorene (and in low yield from benzhydrylamine and benzylamine) on treatment with potassium amide in liquid ammonia.
6. A close analogy, however, is donation of hydride by an amine to a protonated imine, a significant step in some mechanisms that have been proposed for the Sommelet reaction [S. J. Angyal, *Org. Reactions*, **8**, 197 (1954); P. Le Hénaff, *Ann. Chim. (Paris)*, [13] **7**, 367 (1962)].
7. The overall reaction postulated in steps 1-3 resembles in some respects the condensation of benzyl alcohol with aniline in the presence of potassium benzylate and nickel to give N-benzylaniline [E. F. Pratt and E. J. Frazza, *J. Amer. Chem. Soc.*, **76**, 6174 (1954)] and the base-catalyzed condensation of alcohols known as the Guerbet reaction [S. Veibel and J. I. Nielson, *Tetrahedron*, **23**, 1723 (1967), and references cited therein; see also E. F. Pratt and D. G. Kubler, *J. Amer. Chem. Soc.*, **76**, 52 (1954)].
8. R. W. Layer, *Chem. Rev.*, **63**, 489 (1963); P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," v. 1, W. A. Benjamin, New York, 1965, Chapter 7; S. Dayagi and Y. Degani in "The Chemistry of the Carbon-Nitrogen Double Bond," S. Patai, Ed., Interscience, London, 1970, Chapter 2.