This is to certify that the

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The Synthesis and Hydrogenation of
Sterically Hindered Secondary Amines

presented by

IHOR ELIAS KOPKA

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Michael Lakka
Major professor

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THE SYNTHESIS AND HYDROGENATION OF STERICALLY HINDERED SECONDARY AMINES

By

Ihor Elias Kopka

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ABSTRACT

THE SYNTHESIS AND HYDROGENATION OF STERICALLY HINDERED SECONDARY AMINES

By

Ihor Elias Kopka

Tertiary propargylic chlorides react with primary propargylic amines giving hindered bispropargylic secondary amines in good yield. Thus 1,1,1',1'-tetraethyl-di-2-propynylamine $\underset{\sim}{1}$ was synthesized using a 1:2 molar ratio of 1-chloro-3-ethyl-1-pentyne $\underset{\sim}{2}$ with 3-amino-3-ethyl-1-pentyne $\underset{\sim}{3}$ for three days at 4°C in a DMF solution containing catalytic amounts of Cu_2Cl_2 and copper bronze powder. Hydrogenation of $\underset{\sim}{1}$ to the diallyl secondary amine 1,1,1',1' tetraethyl-di-1-propenylamine $\underset{\sim}{7}$ and the saturated secondary amine 1,1,1,1',1',1' hexaethyl-di-methylamine $\underset{\sim}{10}$ was investigated. Platinum dioxide hydrogenolyzed $\underset{\sim}{1}$ completely upon low pressure hydrogenation in ethanol. Hydrogenation of $\underset{\sim}{1}$ with 10% palladium on charcoal gave two heterocyclic amines; 3,4-dimethyl-2,2,5,5-tetraethyl-3-pyrroline $\underset{\sim}{8}$ and 3-methylene-4-methyl-2,2,5,5-tetraethyl-3-pyrrolidine $\underset{\sim}{9}$. Semihydrogenation of $\underset{\sim}{1}$ with 10% Pd/C in ligroine gave $\underset{\sim}{7}$ in fair yield. Different Raney nickel catalysts were tried in hydrogenating $\underset{\sim}{1}$. The best yield of $\underset{\sim}{10}$ was obtained when $\underset{\sim}{1}$ was hydrogenated in ethanol containing W2 Raney nickel and a 2:1 ratio of potassium hydroxide to $\underset{\sim}{1}$.

To

My Parents, without whose guidance and support

I would not be the man I am today

ACKNOWLEDGEMENTS

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INTRODUCTION

Organic bases which are efficient proton abstractors but poor nucleophiles are generally valuable in synthetic organic chemistry. Metal salts of sterically hindered 2° amines, particularly the lithio derivatives of di-tert-butylamine, 2,2,6,6-tetramethylpiperidine and other compounds of the general structure $LiNR_2$, where R is a bulky aliphatic group, are good non-nucleophilic bases. The most hindered secondary amines are reagents with the nitrogen atom attached to two tertiary carbons. They are also the most difficult amine bases to synthesize in a convenient and efficient manner. There are very few viable general synthetic routes for making secondary amines which are more hindered than di-tert-butylamine. Therefore, efforts are still being made to find convenient synthetic methods for preparing secondary amines more hindered than di-tert-butylamine.

In this thesis we will present a very simple and general method for the synthesis of saturated secondary amines of unprecedented steric bulk from tertiary acetylenic chlorides and the corresponding primary acetylenic amines. Also discussed is a method for greatly reducing hydrogenolysis of the bulky secondary acetylenic amines, precursors

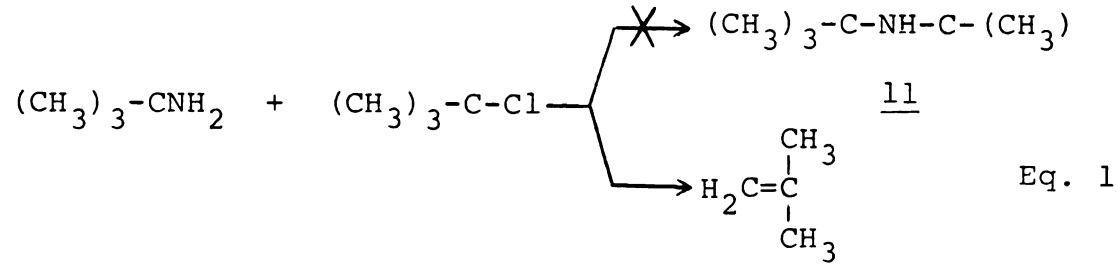
to the saturated secondary amines, by catalytically hydrogenating them in alkaline alcoholic suspension of Raney nickel.

Since less hindered secondary amines have been made previously by coupling propargylic chlorides with saturated primary amines, experiments were performed with saturated and unsaturated primary amines to determine what effect the degree of unsaturation of the amines had on the formation of hindered secondary amines.

LITERATURE REVIEW

A. The Synthesis of Hindered Secondary Amines

There have been many reactions developed for synthesizing secondary amines but only a handful are amenable to the synthesis of amines containing two tertiary carbon atoms attached to a secondary nitrogen center as, for example, di-tert-butylamine 11. Primary amines, when reacted with tertiary alkyl halides, give the elimination product almost exclusively rather than the coupled amine.



Eq. 1

A generally useful method for the synthesis of amines is treatment of an aldehyde or ketone with ammonia or a primary or a secondary amine to form an intermediate imine which may be subsequently reduced to an amine by a number of reducing agents. By carefully choosing the starting aldehyde or ketone and amine, one can obtain good yields of secondary amine. In general, secondary amines cannot

be usefully prepared with aldehydes of less than five carbon atoms. The best yields are reported for aromatic aldehydes, presumably because of the greater ease of imine (Schiff base) formation. Secondary amines can be prepared by two possible procedures: 2 moles of ammonia and 1 mole of aldehyde or ketone (Eq. 2), or 1 mole of primary amine and 1 mole of carbonyl compound (Eq. 3), the latter method being better for all but aromatic aldehydes.

$$NH_3 + O{=}CR_2 \ (R{=}H,alkyl) \rightleftharpoons NH_2\text{-}\underset{\underset{OH}{|}}{CR_2} \rightleftharpoons NH{=}CR_2 \xrightarrow{Red} NH_2\text{-}CHR_2$$

Eq. 2

$$NH_2\text{-}CHR_2 + O{=}CR_2 \rightleftharpoons NH(CR_2)\underset{\underset{OH}{|}}{(CR_2)} \rightleftharpoons \overset{\overset{CR_2}{|}}{N{=}CR_2} \xrightarrow{Red} NH(CR_2)_2$$

$$RNH_2 + O{=}CR_2 \ (R{=}H,alkyl) \rightleftharpoons RNH\text{-}\underset{\underset{OH}{|}}{CR_2} \rightleftharpoons RN{=}CR_2 \xrightarrow{Red}$$

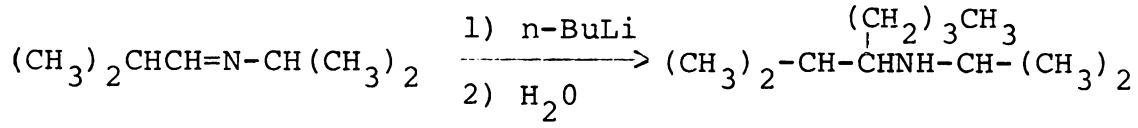
Eq. 3

$$\longrightarrow RNHCR_2$$

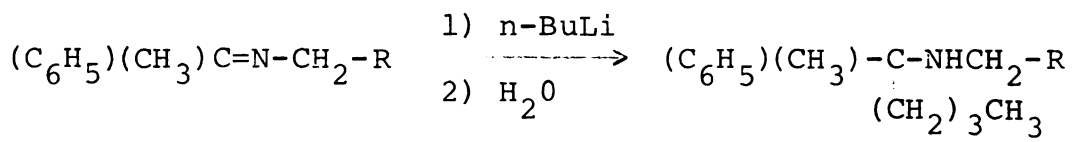
Many of these general observations were taken from two reviews of the chemistry of the amine group.[26] The formation of secondary amines works well only for long chain aldehydes, aromatic aldehydes and ketones, and aliphatic ketones that are not hindered about the carbonyl carbon. The intermediate imine rapidly decomposes or disproportionates with hindered ketones to give polymers when there is not at least one phenyl group attached to the

nitrogen atom. Aromatic imines are much more stable than purely aliphatic imines because conjugation increases the thermodynamic stability of the azomethine linkage.

Imines derived from aliphatic primary amines and enolizable or non-enolizable ketones and aldehydes will add organolithium compound across the azomethine linkage to give hindered secondary amines.[1,5]



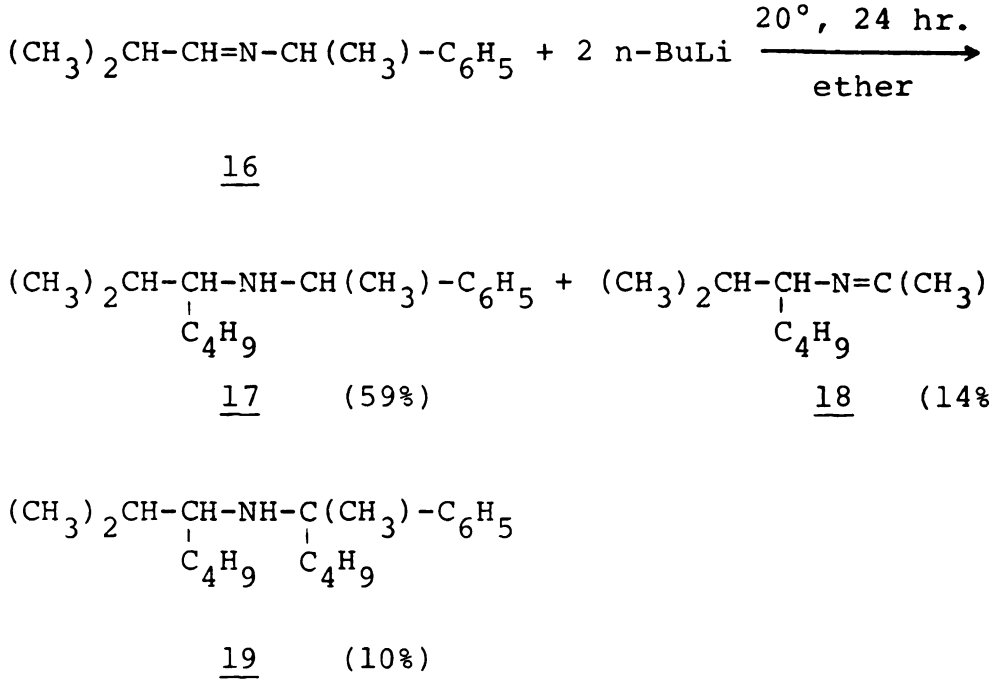
12 13 (60%) Eq. 4



Eq. 5

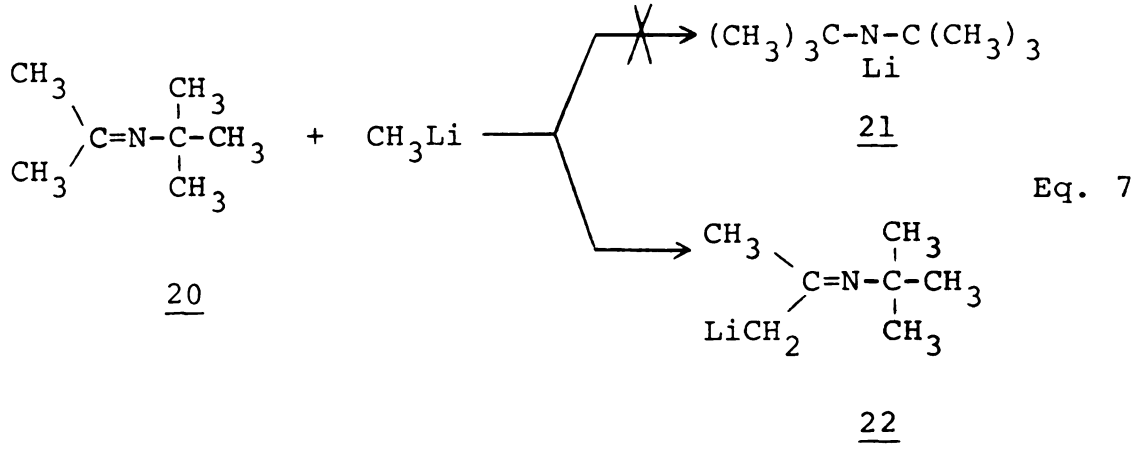
14a	R=(C_6H_5)	15a	R=(C_6H_5)	(34%)
14b	R=i-propyl	15b	R=i-propyl	(0%)

However, if an aliphatic R group is substituted for an aromatic substituent in Eq. 5, there is no addition across the (> C=N-) bond.[2] Another complication arising from the reaction of organolithium compounds with aldimines and ketimines is LiH elimination of the aminolithium compounds; the imines react with organolithium compounds to give secondary amines with branched alkyl groups.[2]



Eq. 6

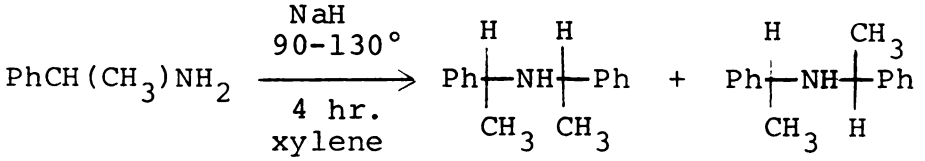
The Schiff bases of some α-substituted aldehydes and ketones, in addition to being difficult to make, tend to metalate at the former α-carbonyl carbon position giving an imine enolate[3] rather than adding the organolithium reagent across the carbon-nitrogen double bond.



Eq. 7

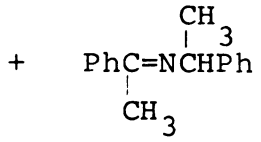
In many cases, heating 1° amines with catalytic amounts of strong base forms the corresponding secondary amines.[4]

Refluxing primary amines and NaH gives mixtures of 2° amines as well as unreduced imines.



23 24 (15%) 25 (22%)

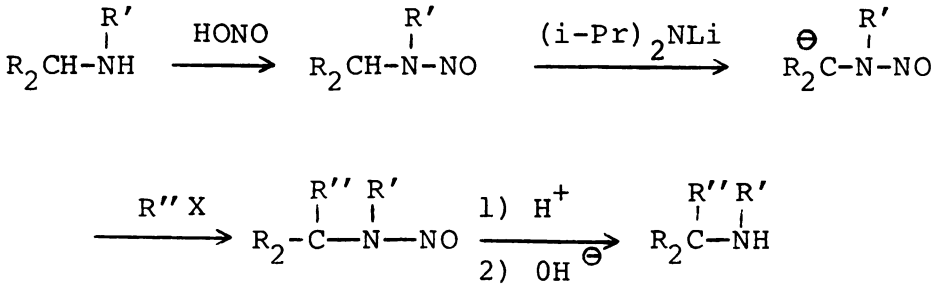
Eq. 8



26 (14%)

This procedure suffers from the limitations that yields are generally low, significant quantities of unreduced imine remain in the reaction mixture and attempted coupling of two different primary amines generally give mixtures of all possible cross-coupled secondary amines.

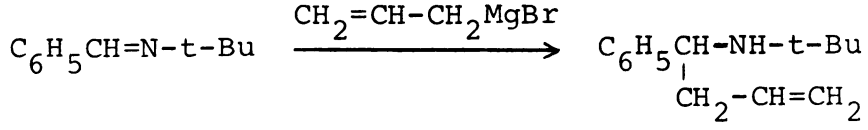
Another useful technique for chain extension at the α-carbon of secondary amines is to convert the amine to its N-nitroso derivative. The α-alkylated N-nitroso product is easily hydrolyzed to the product amine.[6]



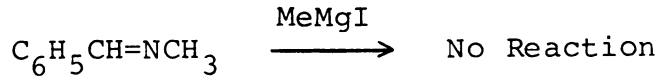
Eq. 9

Though fairly hindered amines can be made in good yield by this method, there is an obvious safety hazard when handling carcinogenic nitrosamines.

Grignard reagents react with imines to form addition products which on hydrolysis give hindered secondary amines. The reaction is usually applied to Schiff bases prepared from aryl halides. The reactions with Grignard reagents provide a general synthetic method for secondary amines of the type RR'CHNHR'' where R is an aryl group. Sterically hindered reactions of Grignard reagents with Schiff bases have been studied.[8] N-Benzylidene-t-butylamine 27 reacts with allyl-magnesium bromide; however, methylmagnesium iodide does not react with 29, even under forcing conditions.

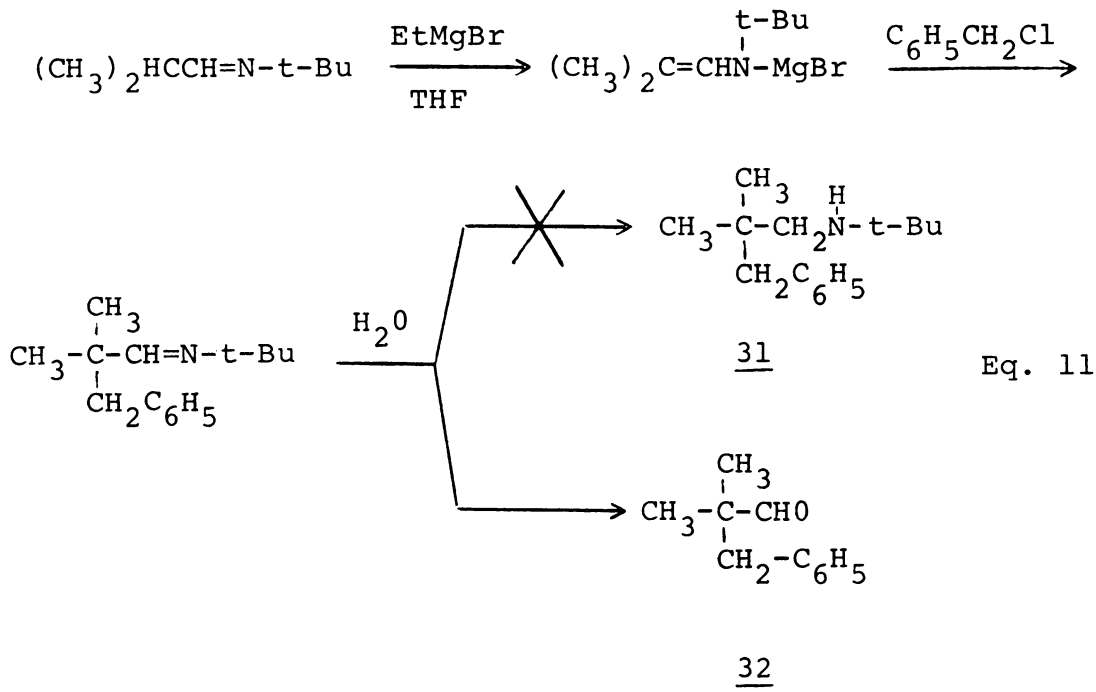


27 28 Eq. 10



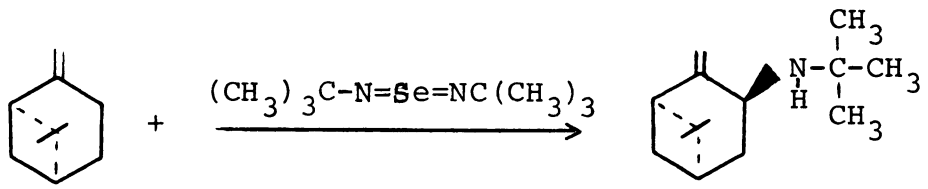
29

Various imines derived from aliphatic primary amines and enolizable aldehydes or ketones undergo complete enolization with one equivalent of alkylmagnesium compound in THF.[8] The resulting enamines react with alkyl halides giving addition products which hydrolyze to α-substituted aldehydes or ketones rather than the hindered secondary amine (Eq. 11a).



Eq. 11a

Sharpless et al[9] found that aza analogues of selenium dioxide effect allylic amination of reactive olefins. Unfortunately, amination of less reactive olefins gave poor yields of hindered allylic amines.



33 34 (62%) Eq. 11b

The nitrogen insertion reaction is similar to the allylic insertion of oxygen into olefins by selenium dioxide. These aminations probably occur via the same sequence of -ene and [2,3]-sigmatropic reactions proposed for the analogous oxo-process.[10]

Alkyl boranes R'_3B react with organic azides, RN_3, in benzene or xylene to give $R'RNBR'_2$ which is readily converted by alkaline hydrolysis to the corresponding secondary amine R'NHR.[11] The reaction becomes quite slow with sterically hindered azides. It fails completely when both sterically hindered azides and sterically hindered organoboranes are used. These results are interpreted by a mechanism involving reversible coordination of the azide with the trialkyl borane. This step is followed by loss of nitrogen from the intermediate with migration of the alkyl group from boron to nitrogen (Eq. 12).

$$R'\overset{+}{N}N\equiv N + R_3B \rightleftharpoons R'N\overset{-}{B}R_3 \overset{+}{N}\equiv N \longrightarrow R'RNBR_2 + N_2 \xrightarrow[H_2O]{NaOH} RR'NH$$

Eq. 12

A number of dialkylchloroboranes[12] and alkyldichloroboranes[13] were prepared[14] and treated with organic azides.

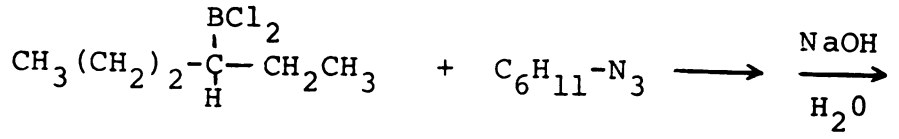
$$BHCl_2{:}0Et_2 + R\text{-}CH{=}CH_2 + BCl_3 \longrightarrow RCH_2CH_2BCl_2 + BCl_3{:}0Et_2$$

Eq. 13a

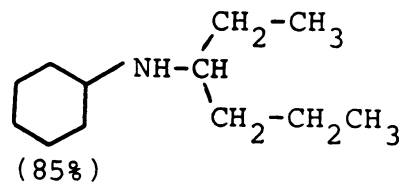
$$BH_2Cl{:}0Et_2 + 2R\text{-}CH{=}CH_2 \longrightarrow (RCH_2CH_2)BCl + 0Et_2$$

Eq. 13b

These chloroboranes proved to be quite reactive relative to the trialkylborane, even when the alkyl group(s) on the boron derivative and the organic azide were both secondary. This increased reactivity of the dialkylchloro and alkyldichloroboranes may be attributed to decreasing steric interference of the alkyl groups on the boron atom as well as to an increase in Lewis acidity of the organohaloboranes, facilitating the coordination of the azide with the boron derivative. The most hindered amine synthesized by this procedure is N-3-hexylcyclohexylamine (Eq. 14).



35 36 Eq. 14

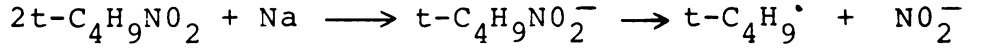


(85%)

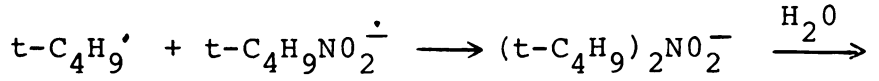
37

The use of alkyldichloroboranes provides a highly useful synthesis of fairly hindered secondary amines. This has some synthetic potential since a simple general synthesis of alkyldichloroboranes has been developed.[14]

The first efficient synthesis of an amine with two tertiary carbon centers bonded to nitrogen was that of di-tert-butylamine 11. This was achieved by the reaction of 2-methyl-2-nitropropane 38 with sodium metal to generate the presumed unstable intermediate 39 which was hydrolyzed to di-tert-butylnitroxide 40.[15] Subsequent mechanistic study established that 40 is formed by the hydrolysis of a compound formulated as sodium di-t-butylhydroxylamine oxide 41.[16] 41 is considered to arise by a combination of the tert-butyl radical with t-nitro butyl anion radical (Eq. 15 and 16).

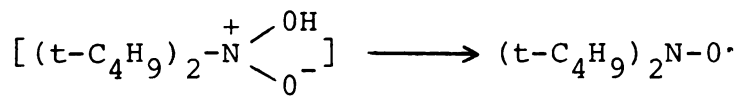


38 Eq. 15



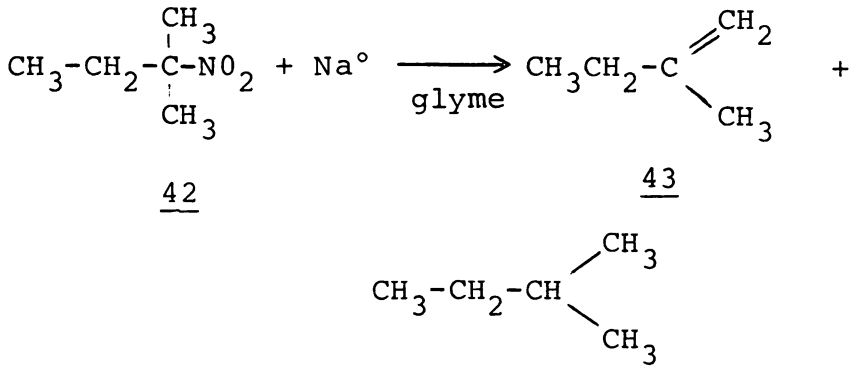
39

Eq. 16



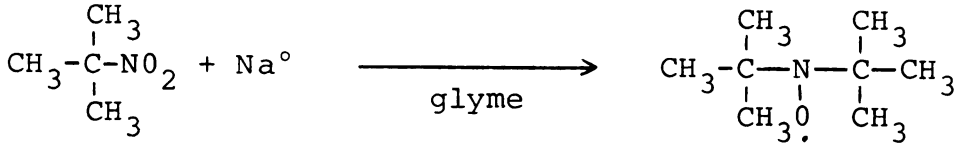
41 40

Nitroxide 40 then may be converted to 11 by a reducing mixture of sodium sulfide nonahydrate, elemental sulfur and N,N,dimethylformamide in the presence of light.[17] Direct reduction of the intermediate 39 by this procedure gives di-tert-butylamine in improved yield.[18] However, there is a major limitation in the application of nitro compounds as precursors in the synthesis of hindered secondary amines. Subsequent work designed to define the scope of the transformation of nitro compounds to secondary amines showed that the reductive conversion of nitro compounds to the corresponding nitroxides is not general. The formation of nitroxide in substantial yields was successful only with 38 among the large number of nitro compounds studied.[19]



42 43 44

Eq. 17



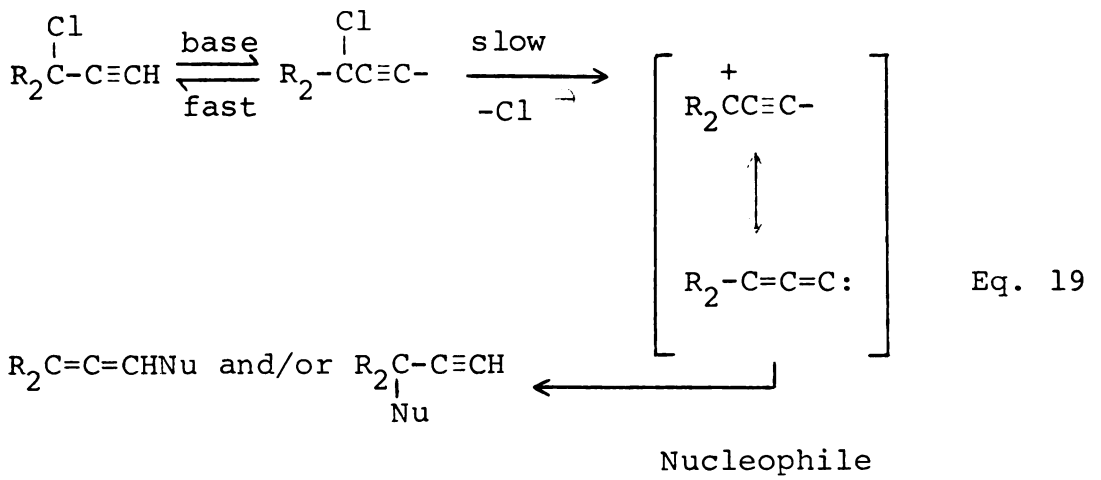
38 40

Eq. 18

This result severely restricts the usefulness of this reaction as a general method for the synthesis of sterically hindered secondary amines.

Probably the most thorough investigation of a generally applicable method for the synthesis of sterically hindered amines was initiated by Hennion in the 1950's. He and his co-workers discovered that aliphatic tertiary propargyl chlorides and bromides successfully alkylate alcohols and amines of virtually all classes to produce propargylic ethers and amines, respectively.[20] These reactions proceed under very mild conditions in alkaline, partially aqueous solution and generally give good yields of product. The utility of these reactions is that they

achieve nucleophilic substitution at tertiary aliphatic carbon centers, a reaction which is ordinarily difficult. It is generally accepted that the t-propargylic halide reaction involves an intermediate zwitterion-allene-carbene which is stable to proton elimination and quite electrophilic at the tertiary carbon.[21]



Eq. 19

It is obvious that the zwitterion-allenecarbene should be an ambident electrophile capable of yielding both propargylic and allenic products; both products have been seen in a number of cases.[21d] Good evidence for the above mechanism comes not only from kinetic and product studies[20g,21] but also from the fact that the allenecarbene has been trapped by a stereospecific reaction with olefins, a reaction typical of ordinary carbenes.[22]

There are a number of observations however, not readily reconcilable with the zwitterion-allenecarbene mechanism. Methanol and ethanol give good yields of propargylic ethers

whereas alkaline aqueous alcohol solutions containing 50 mole % water produce much more of the propargylic ether than the carbinol. These reactions follow second order kinetics, first order each in t-propargyl halide and base. tert-Butyl alcohol, however, does not give any ether product despite the fact that steric inhibition of tert-butyl allenyl ether should not be serious.[20e] This is in sharp contrast to reactions with t-alkyl and other sterically hindered amines which give N-tert-propargylic amines in reasonably good yields.[20d,20f,23] It was later discovered that some primary and secondary saturated aliphatic amines could be used in place of strong base to give hindered secondary acetylenic amines.[20c,20d,23] It is not clear why all reactions with amines are markedly catalyzed by trace amounts of cuprous salts.[20d] Some good nucleophiles give no substitution products, even though steric effects cannot explain the failure. Thus, the reaction of 45 with excess KCN in aqueous methanol yields only the solvent derived methyl ether 46 and no nitrile (Eq. 20).

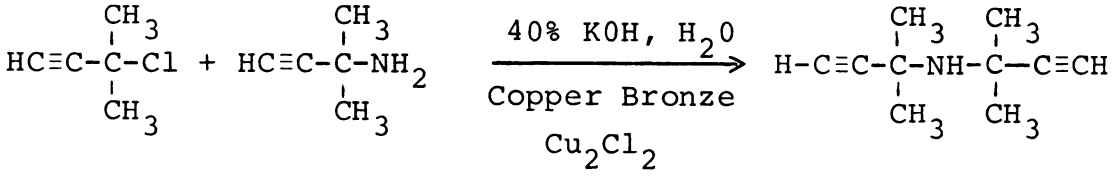
$$(CH_3)_2\text{-}C(Cl)\text{-}C{\equiv}CH \quad + \quad KCN \xrightarrow[H_2O]{MeOH} (CH_3)_2\text{-}C(OCH_3)\text{-}C{\equiv}CH$$

45 46 Eq. 20

Presently, no satisfactory correlation exists between steric features of the nucleophilic reagent, its basicity, nucleophilicity, polarizability, solvent employed and the

outcome of the substitution reaction.

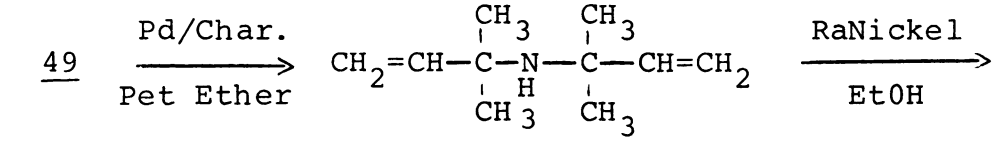
Hennion synthesized the following compound 49 based on the observation that hindered primary amines react with tert-propargylic chlorides to give hindered N-tert-propargylic secondary amines.



47 48 8 days, 30°C 49 (47%)

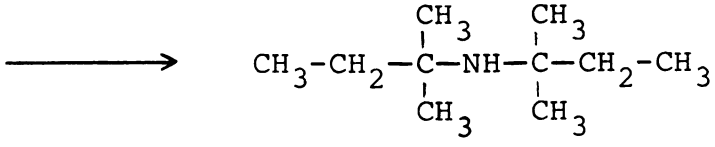
Eq. 21

Compound 49 was semihydrogenated to 50 using 10% palladium on charcoal catalyst and then hydrogenated to the saturated amine 51 using Raney nickel in ethanol. Compound 51 appears to be the most hindered 2° amine obtained by any method reported to date.



50

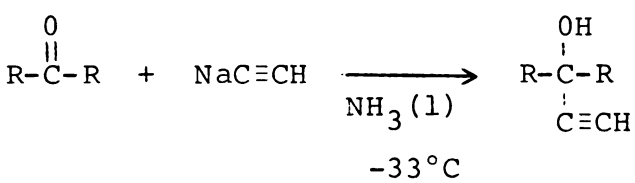
Eq. 22



51

RESULTS

Tertiary propargylic chlorides were synthesized from the corresponding propargylic alcohols: 3-Methyl-1-butyne-3-ol 52, 3-ethyl-1-pentyne-3-ol 53 and 4-methyl-3-isopropyl-1-pentyne-3-ol 54. The alcohols were made from acetone, 3-pentanone and 2,5-dimethyl-3-pentanone, respectively, by reacting the ketones with sodium acetylide in anhydrous liquid ammonia (Eq. 23).



Eq. 23

52; R = Methyl (55%)

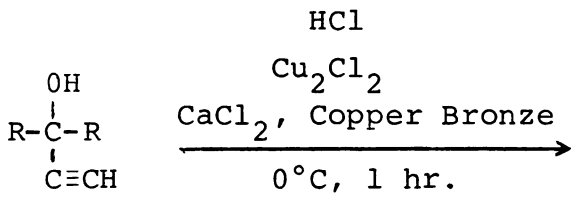
53; R = Ethyl (93%)

54; R = Isopropyl (89%)

Bubbling acetylene gas slowly through the ammonia solution for several hours once NaC≡CH was formed,[35] then adding the ketone to the solution, increased the carbinol yields substantially over reported literature values.[24]

The alcohols were worked up and then purified by vacuum distillation.

The tertiary acetylenic chlorides were prepared from the corresponding propargylic alcohols by reacting the alcohols with excess cold hydrochloric acid containing copper bronze powder, calcium chloride and cuprous chloride.[25] When R is methyl or ethyl, the chloride may be prepared with concentrated HCl and $CaCl_2$ alone. When R is isopropyl, rearrangement products are obtained at the expense of the desired tert-propargylic chloride (Eq. 24).



Eq. 24

47; R = Methyl (65%)

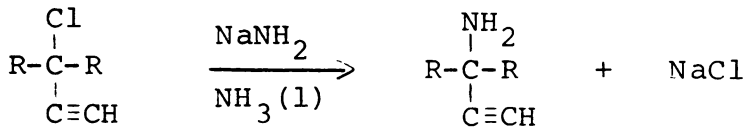
2; R = Ethyl (73%)

56; R = Isopropyl (70%)

All of the propargylic chlorides are sensitive to heat and were used without further purification. The proportion of chloride in each reaction mixture was determined by GLC and the value calculated was used in determining the yield of propargylic amine.

Tertiary propargylic chlorides 2, 47 and 56 were converted to the corresponding primary propargylic amines

by dropwise addition of the chloride to a liquid ammonia suspension of sodamide, prepared *in situ* (Eq. 25).



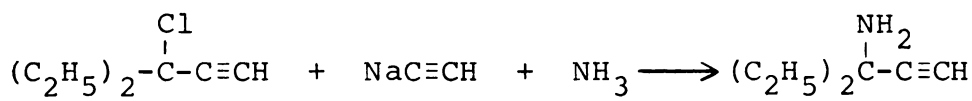
Eq. 25

48; R = Methyl (20%)

3; R = Ethyl (73%)

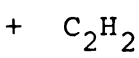
58; R = Isopropyl (40%)

Ordinarily, sodamide in liquid ammonia reacts with aliphatic halides by eliminating HX.[29] Sodium acetylide may be substituted for sodamide in the propargylic amine synthesis with no difference seen in the results.[24]

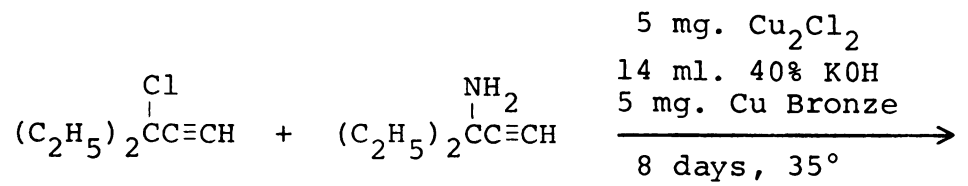


2 3

Eq. 26



An attempt was made to synthesize 1 by applying Hennion's procedure (Eq. 21) for synthesizing 1,1,1',1'-tetramethyl-di-2-propynyl amine 49.



$(C_2H_5)_2\overset{Cl}{\underset{|}{C}}C\equiv CH$ + $(C_2H_5)_2\overset{NH_2}{\underset{|}{C}}C\equiv CH$

2 3

Eq. 27

$(C_2H_5)_2\overset{OH}{\underset{|}{C}}C\equiv CH$

53

No coupled amine was seen by GLC, only the solvolysis product 53 and low boiling impurities. The experiment was repeated with the di-isopropyl propargylamine and chloride, 56 and 58, with similar results. Low boiling impurities and the carbinol 54 were the only products seen after reaction for two weeks at 30°.

Another approach was used to prevent solvolysis of the chloride. Conversion of the propargylic chloride to the acetylide with the strong base NaH (oil dispersion) should be complete. The reaction's progress could be followed by monitoring H_2 evolution with a gas buret. Thus the chloride 2 was added to 1 mmole of 3 and 1 mmole of NaH in 2 ml of tetrahydrofuran (THF) (Eq. 28).

$$\underline{2} + NaH \underset{\text{THF}}{\overset{}{\rightleftharpoons}} (C_2H_5)_2\text{-}\overset{Cl}{\overset{|}{C}}\text{-}C{\equiv}C^- + H_2 \longrightarrow (C_2H_5)_2\text{-}C{=}C{=}C: \quad (22°)$$

Eq. 28

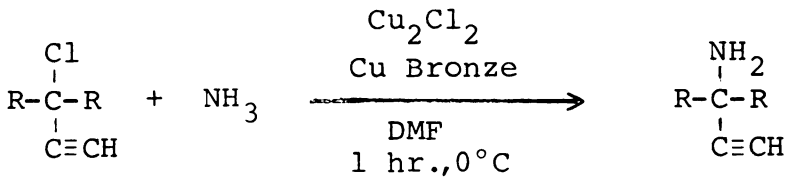
$$+ \quad (C_2H_5)_2\overset{NH_2}{\overset{|}{C}}\text{-}C{\equiv}CH \longrightarrow \underline{1}$$

Only 0.8 mmole of H_2 was evolved over a 5 hour period. The solution was quenched with H_20 and the brown mixture was analyzed by GLC. No coupled amine 1 was detected. Analysis for recovered starting material was impossible, since the starting amine and chloride were inseparable by GLC. The same slow, incomplete H_2 evolution was observed (0.55 m mole) with KH (mineral oil suspension) when 1 mmole of the base was used with 2 and 3 under identical experimental conditions. Again, no coupled amine 1 was detected by GLC analysis.

The above experiment with KH as base was repeated, but this time a catalytic quantity of Cu_2Cl_2 and copper bronze was added. Evolution of H_2 was very slow (1 mmole in 21 hrs.) and GLC analysis of the mixture showed no coupled amine 1.

The same experiment was repeated using 2 m moles each of 2 and 3 in THF along with 10 mg. of copper bronze, Cu_2Cl_2 and 4 mmoles of potassium tert-butoxide as base. A thick black tar was the only material obtained.

Easton [23] in his investigation of hindered amines noted that dimethylformamide, when used as a solvent, gave much better yields of hindered secondary propargylic amines than either ethyl ether or THF. We thought that it might be possible to synthesize primary propargylic amines directly from an ammonia saturated dimethylformamide solution of Cu_2Cl_2 and copper bronze by adding the propargylic chlorides directly to the mixture. The experiment was performed by adding 2, 47 and 56 dropwise to a well stirred DMF solution of ammonia, Cu_2Cl_2 and copper bronze at 0°C. The DMF solution was kept saturated with ammonia by rapidly bubbling the gas through the solution. In every case we obtained the corresponding primary propargylic amine in only fair yield (Eq. 29).



Eq. 29

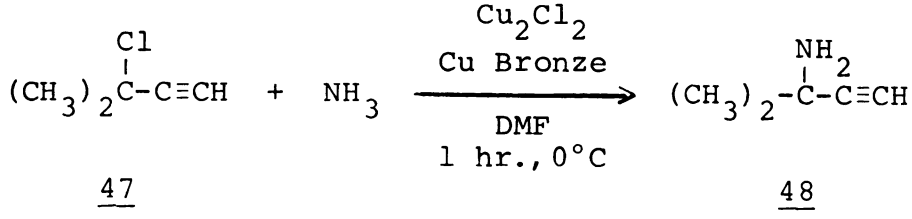
47; R = Methyl — 48; R = Methyl (-)

2 ; R = Ethyl — 3 ; R = Ethyl (40%)

56; R = Isopropyl — 58; R = Isopropyl (36%)

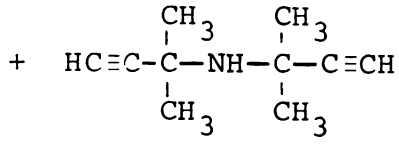
No attempt was made to determine the yield of 48 because on closer investigation by GLC, two products were seen; the primary amine 48 and an unidentified high boiling product.

Upon isolation of the high boiling component by GLC, we identified it as 1,1,1',1' tetramethyl-di-2-propynylamine 49, the same amine which Hennion synthesized (Eq. 21) only after reacting 47 and 48 for 8 days in a 40% aqueous solution of KOH.



47 48

Eq. 30



49

The amine 49 was identified by its physical and spectral properties; NMR ($CDCl_3$) δ 1.23 (S, 1H), 1.5 (S, 12H), 2.23 (S, 2H), m.p. 34-35°, Lit.[20f] 32-35°. This is the first method reported for preparing primary propargylic amines directly from ammonia. Hennion attempted to prepare 3 by reacting the chloride 2 with aqueous ammonia at 100°C in an autoclave.[20c] The only products obtained were 3-ethyl-3-pentyne (30%), produced by HCl elimination, and the hydrolysis product 53.

Based on the observation that DMF greatly increases the reaction rate between propargylic chlorides and propargylic

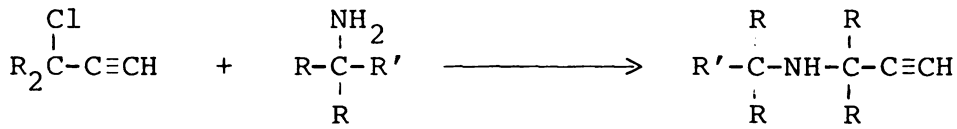
amines, a number of experiments were performed to determine the limits of this method for obtaining hindered secondary amines. Table I lists the results of a number of these experiments. Amine 1 was isolated by quenching the reaction mixture containing amine hydrochloride with NaOH. DMF was removed by extracting the solution with water. The remaining solution was steam distilled to remove the primary and secondary amine, and the two amines were then separated by distillation.

A minimum 2:1 ratio of propargylic amine to chloride was maintained so that the extra equivalent of amine would act as an HCl acceptor. Adding either triethylamine or di-isopropylamine as an HCl acceptor greatly reduces the yield of 1 (< 7%). Compound 1 was identified by its spectral properties; NMR ($CDCl_3$) δ 0.9 (t, 13H, J=6Hz), 1.72 (q, 8H, J=6Hz), 2.25 (S, 2H); mass spec (parent peak m/e 205).

Several interesting trends appear in Table I. As the temperature of the reaction mixture increases, the overall yield of coupled amine decreases. The ratio of amine to chloride has a greater influence on the yield of coupled amine formed at higher temperatures than it does for amines formed at lower temperatures. As the size of the alkyl groups on the chloride and amine increase, the yield of coupled amine decreases. Finally, as the degree of unsaturation of the primary amine decreases, the yield of coupled amine decreases drastically.

TABLE I

Yields of 2° Propargylic Amines Under Various Reaction Conditions



R	R′	m moles Amine	m moles Chloride	Amine / Chloride	Solvent[a]	Temp.	Time	Yield[b]
Methyl	Ethyne	34	97	2.9	DMF	0°	1 hr.	83
Ethyl	Ethyne	50	14	3.6	DMF	24°	1 day	40
Ethyl	Ethyne	5	1.4	3.6	$HCONH_2$	24°	1 day	42
Ethyl	Ethyne	5	1.4	3.6	DMF	24°	3 days	43
Ethyl	Ethyne	5	1.4	3.6	DMF	75°	1 day	20
Ethyl	Ethyne	1.4	1.4	1.0	DMF	24°	1 day	12
Ethyl	Ethyne	2.8	1.4	2.0	DMF	24°	1 day	33

TABLE I (cont.)

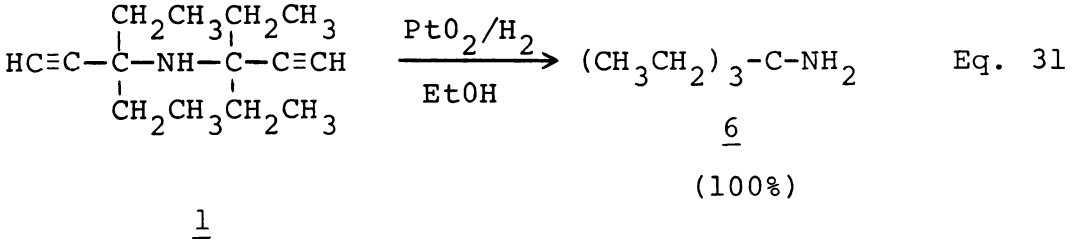
R	R′	m moles Amine	m moles Chloride	Amine / Chloride	Solvent[a]	Temp.	Time	Yield[b]
Ethyl	Ethyne	5	1.4	3.6	DMF	4°	3 days	61(48)
Ethyl	Ethyne	10	5	2.0	DMF	4°	3 days	63
Ethyl	Ethene	15	4.5	3.3	DMF	4°	3 days	17
Ethyl	Ethyl	15	4.5	3.3	DMF	4°	3 days	0
Isopropyl	Ethyne	50	14	3.6	DMF	4°	2 wks.	0
Isopropyl	Ethene	50	14	3.6	DMF	-33°	2 wks.	0

[a]All experiments contained 1 mg each of Cu_2Cl_2 and copper bronze per 0.8 m moles chloride

[b]All yields are GLC yields. Isolated yields are in parentheses.

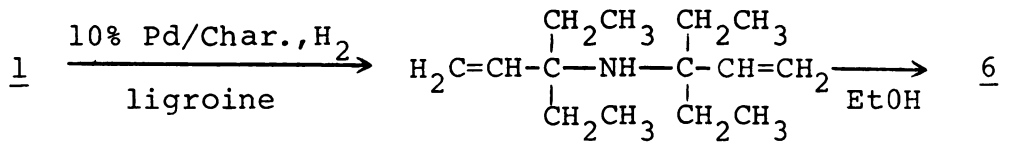
For every experiment in Table I where R is either a methyl or ethyl group and R' is an ethyne or ethene group, the coupled 2° unsaturated amine is the only reaction product seen by GLC. When R is an isopropyl group, a trace amount of high boiling product is formed. This product can not be the coupled amine: neither a C-H acetylenic bond stretch (IR, 3270-3330 cm^{-1}) nor a C-H acetylenic proton signal (NMR, δ 2.0-3.1) was observed when the sample was characterized.

Hydrogenation of 1 to either the semihydrogenated diallyl amine 7 or the completely hydrogenated secondary amine 10 was not as straightforward as originally anticipated. Hydrogenation of 1 to the diallyl amine 7 or to the saturated amine 10 with palladium on charcoal or platinum oxide (Adam's Catalyst) proved unsuccessful. Hydrogenation of 1 to 10 over PtO_2 in absolute ethanol gave the hydrogenolysis product 6, exclusively (Eq. 31). The same results were observed with the hydrochloride of 1 under identical conditions. It has been reported that hindered secondary amine hydrochlorides undergo hydrogenolysis less readily than the free amines.[23]



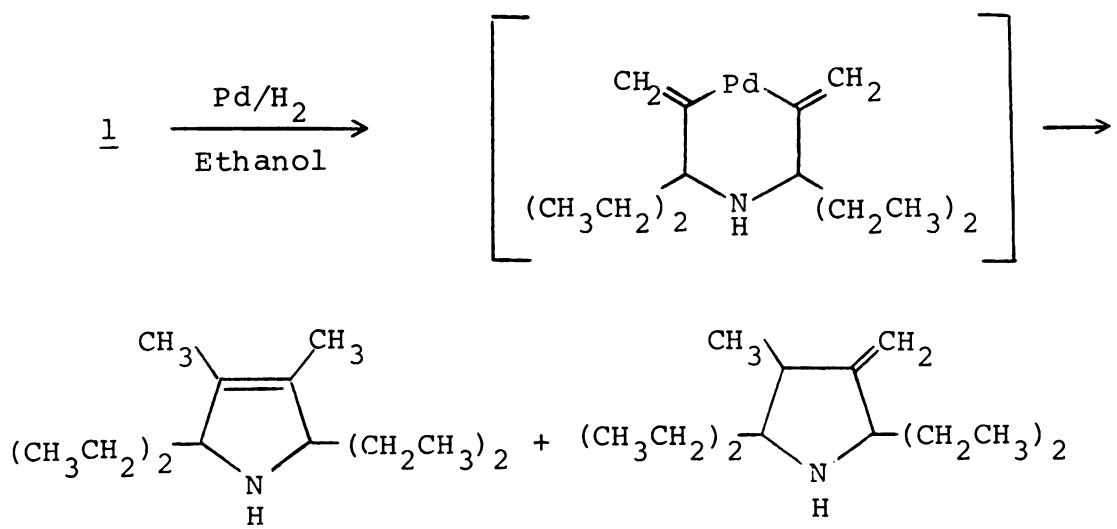
1 6 (100%) Eq. 31

Attempted semihydrogenation of 1 to 7 using 10% palladium on charcoal in the aprotic solvent ligroine gave fair yield of 7 along with some hydrogenolysis. However, when ethanol was added to the solution and the hydrogenation continued, 7 was hydrogenolyzed almost immediately to 6.



7 (55%) Eq. 32

The same sequence of reactions attempted with 1 and 10% palladium on charcoal in ethanol gave two unusual cyclization products; 3,4 dimethyl-2,2,5,5-tetraethyl-3-pyrroline, 8 and 3-methylene-4-methyl-2,2,5,5-tetraethyl-3-pyrrolidine 9 in about a 3:1 molar ratio, respectively.



8 9 Eq. 33

Spectral data confirm the structures of 8 and 9; compound 8, ^{13}C NMR 20 MHz ($CDCl_3$) δ 7.2, 8.7, 29.8, 70.7, 134.2; ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 13, J=6Hz) 1.42 (broad multiplet, 8H) 1.45 (S, 6H); mass spectrum (parent peak m/e 209). Compound 9, ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 13H J=6Hz), 1.41 m, 11H), 2.4 (m, 1H), 4.63 (t, 2H, J=3Hz); mass spectrum (parent peak m/e 209).

The reaction of 1 with 10% palladium on charcoal in ethanol appears to be the first catalytic cyclization reaction forming substituted pyrrolines and pyrrolidines from bispropargylic secondary amines.

Attempts to reduce 1 to either 7 or 10 with a number of stochiometric reducing agents proved equally fruitless. Reduction of the bisalkynyl amine by hydroboration with borane[30] prepared *in situ* gave a number of low boiling products, none of which corresponded to either the bisallyl amine 7 or the saturated amine 10 (Eq. 34)).

$$\mathrm{HN\text{-}(C(CH_2CH_3)_2\text{-}C{\equiv}CH)_2} + 3\ \mathrm{NaBH_4} + 4\ \mathrm{BF_3{:}0Et_2} \xrightarrow[\text{diglyme}]{\underline{1}} \xrightarrow[\text{1) propionic acid, 100° 4 hrs. 2) NaOH}]{} \text{No Product} \qquad \text{Eq. 34}$$

Attempts to reduce 1 with nickel boride, a reactive olefin hydrogenation catalyst, gave similar results.[31]

The saturated amine 10 was finally synthesized in about 20% yield by low pressure catalytic hydrogenation of 1 in ethanol with W2 grade Raney nickel. The hydrogenation took about 12 hours to complete at 22° and 30 psi H_2 pressure. When more reactive grades of Raney nickel were used for hydrogenating 1 in ethanol, (W4 and W6 grades),[33] hydrogenolysis was more extensive. Also, the hydrogenation generally fails to go to completion with the more active grades of Raney nickel. One can stop the hydrogenation at the diallylamine stage by monitoring the reaction by GLC. Hydrogenation of the diallylamine 7 to the saturated amine 10 was much slower than hydrogenation of 1 to the diallylamine 7.

If the hydrogenolysis of 1 occurs at the diallylamine stage through a carbonium ion mechanism, a presumption supported by results of other investigators,[28,32] perhaps hydrogenolysis could be minimized by hydrogenating in a strongly basic ethanolic solution of W2 Raney nickel. This hypothesis was tested and proved correct. A 71% yield of 10 was obtained by hydrogenating 1 under the same conditions with W2 Raney nickel, except that a 2:1 molar excess of KOH was added to the ethanolic solution of 1. Amine 10 is the most hindered secondary amine ever synthesized. The spectral data confirm its structure; ^1H NMR ($CDCl_3$) δ 0.78 (t, 19, J=7Hz) 1.32 (q, 12, J=7Hz); mass spec (parent peak m/e 213).

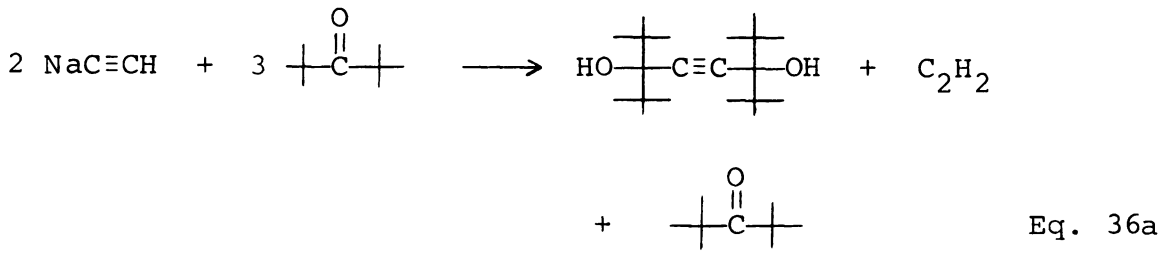
DISCUSSION

The reaction of metal acetylides with ketones and aldehydes has been thoroughly studied by a number of investigators. The most satisfactory general procedure for the synthesis of propargylic carbinols involves the condensation of sodium acetylide with aldehydes and ketones in anhydrous liquid ammonia.[24] Comparatively small amounts of the glycols, formed by the condensation of two molecules of the carbonyl compound with one of acetylene, are obtained.

The yields of the acetylenic carbinols 52, 53 and 54 are increased and that of the glycols decreased by passing acetylene gas into the mixture during the entire course of the reaction. Passing acetylene gas through the ammonia solution during the course of the reaction presumably suppresses the disproportionation of sodium acetylide to disodium acetylide and acetylene (Eq. 35).

$$2\ NaC{\equiv}CH \longrightarrow NaC{\equiv}CNa + HC{\equiv}CH \qquad \text{Eq. 35}$$

Attempted acetylation of di-tert-butylketone with sodium acetylide in liquid ammonia gave rapid evolution of acetylene and, upon workup, starting ketone and glycol (Eq. 36a).

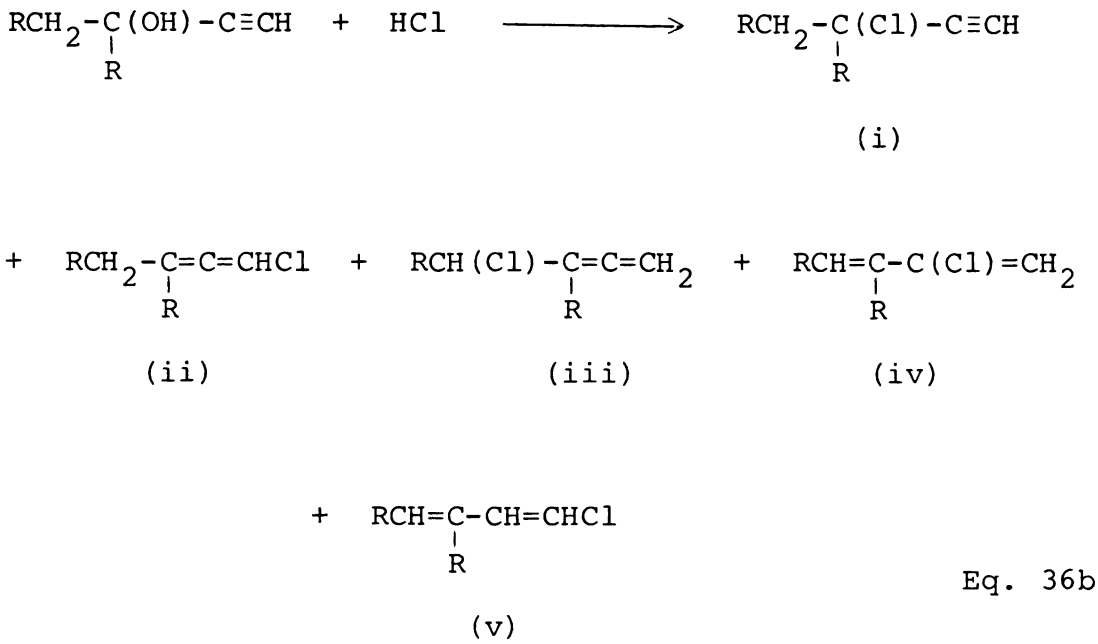


Eq. 36a

Successful acetylation of very hindered ketones was reportedly achieved by adding n-butyl lithium to acetylene in tetrahydrofuran at -78°C. Addition of di-tert-butylketone at -78°C, followed by warming to room temperature, gave good yield of di-tert-butylpropargyl alcohol.[24] The monolithium acetylide is stable when maintained at low temperatures. Warming the solution of monolithium acetylide to 0° results in the irreversible formation of a white solid, presumably dilithium acetylide. In cases where sodium acetylide in liquid ammonia fails to monoacetylate hindered ketones, acetylation with lithium acetylide in tetrahydrofuran at -78°C appears to be the method of choice.

The tertiary acetylenic chlorides were prepared from the corresponding propargylic alcohols. When R is either methyl or ethyl (water and acid soluble tert-propargylic carbinols), the chlorides 47 and 2 were prepared in good yield and acceptable purity from concentrated hydrochloric acid and calcium chloride. When R is isopropyl, a number of products, including the propargylic chloride 56, were obtained. These rearrangement products were obtained along with the desired tert-propargylic chloride, in accord with

published observations[25] (Eq. 36b).



Eq. 36b

The carbonium ion ($R_2\overset{+}{C}-C\equiv CH \longleftrightarrow R_2C=C=\overset{+}{C}H$) derived from the alcohol could lead directly to i and ii. Dehydration of the alcohol would yield the conjugate eneyne hydrocarbon which is converted to iii and iv by 1,4 and 1,2 addition of hydrogen chloride, respectively. Prototropic rearrangement of ii yields v. It has long been recognized in individual cases that mixtures of products are encountered when tert-propargylic carbinols are converted to tert-propargylic halides.[36]

The most successful general procedure for converting tert-propargylic carbinols to tert-propargylic chlorides is by treatment with excess hydrochloric acid containing calcium chloride, cuprous chloride and copper bronze

powder.[25] The combination of these reagents in cold concentrated hydrochloric acid seem to give higher yields and purer products than any other procedure reported to date. The choice of these reagents in the synthesis of tert-propargylic chlorides was arrived at empirically.

The formation of the propargylic amines 3, 48 and 58 from the corresponding propargylic chlorides 2, 47 and 56, respectively, in a sodamide-liquid ammonia solution is a solvolysis reaction by ammonia and not a simple nucleophilic displacement by the amide anion. This conclusion is based on the observation that sodium acetylide may be substituted for sodamide in the amine synthesis (Eq. 26).[20b] This is good evidence for the mechanism involving the propargyl zwitterion-allenecarbene species (Eq. 19), where a consequence of the suggested mechanism is that the reaction of tertiary propargylic chlorides with base in a suitable solvent should likewise produce the solvolytic product.

In 1962 Shiner et. al.[21a,21b] offered conclusive kinetic evidence for the intermediacy of the species 60 in the solvolysis of the propargylic halide 47 in basic aqueous ethanol (Figure 1).[21c]

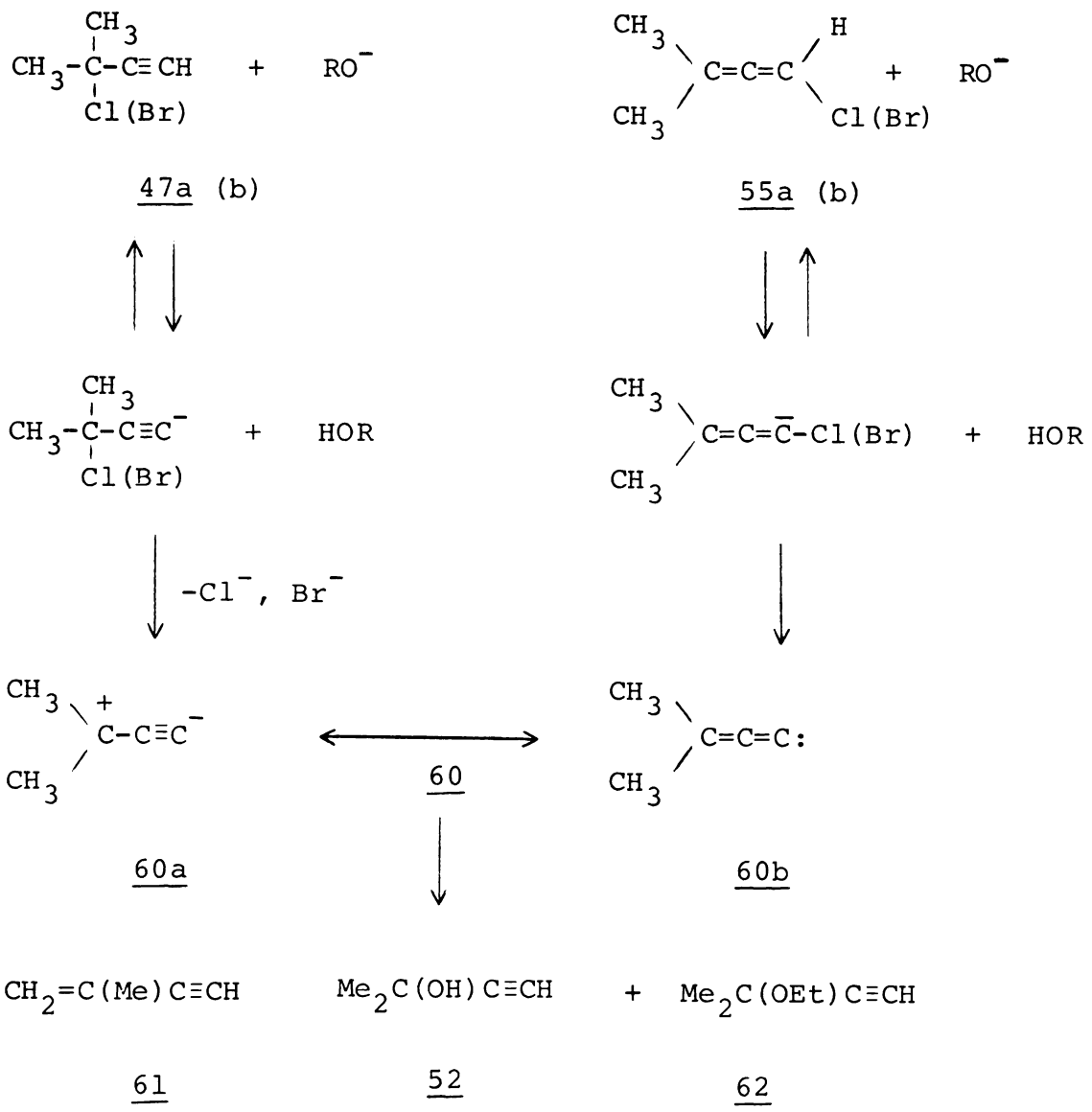


Figure 1. Reaction scheme for the base promoted solvolysis of isomeric allenyl and tertiary propargylic halides.

He showed that 47b exchanged the acetylenic hydrogen in basic 80% ethanol-d-deuterium oxide solution much faster than it solvolyzed and that the rate of the second-order solvolysis in the non-deuterated medium was depressed by adding sodium salts in the order: $Br^- > Cl^- > NO_3^- \sim ClO_4^-$.

These results are consistent with Hennion's mechanism only if the rate determining step is the ionization of the halide from the conjugate base of 47b in Figure 1.

Gas chromatographic analysis of products from the reaction mixture of 47b in basic ethanol indicated that the propargylic ether 62 was the predominant product (90% relative yield) accompanied by small amounts of the propargylic alcohol 52 (7%) and olefin 61 (3%).[21a] In comparison, the first order, initially neutral, solvolysis of 1b, characterized as an S_N1 process,[21a,21b] gave an entirely different distribution of these same propargylic products: 62, (43%); 52, (22%), and 61 (35%). Shiner concluded that "The difference in product proportions is apparently dictated by the different reactivity, and therefore selectivity, of the two intermediates, the carbonium ion and the zwitterion-carbene. The latter is more stable and more selective because the allene-carbene resonance contribution form [60b] contains no formal charges and therefore contributes more importantly to the structure [60] than the allene carbonium ion VIIb does to the structure VII."[21a]

$$[Me_2\overset{+}{C}\text{-}C{\equiv}CH \longleftrightarrow Me_2C{=}C{=}\overset{+}{C}H]$$

VIIa VII VIIb

With the zwitterion-allene carbene species in Figure 1. identified as the reactive intermediate in what is

essentially a base catalyzed solvolysis reaction with ammonia and alcohols, tertiary propargylic chlorides were shown to undergo alkylation with primary and secondary amines to give the coupled secondary and tertiary propargylic amines, respectively.[20d] Experimental results confirm that the coupling reaction of 47 with primary amines is notably insensitive to steric features of the amine, except for rate (Eq. 37).

$$(CH_3)_2\overset{Cl}{\overset{|}{C}}-C\equiv CH \quad + \quad 2\ R^1R^2NH \longrightarrow (CH_3)_2C(NR^1R^2)C\equiv CH \quad + \quad R^1R^2NH\cdot HCl$$

47 — Eq. 37

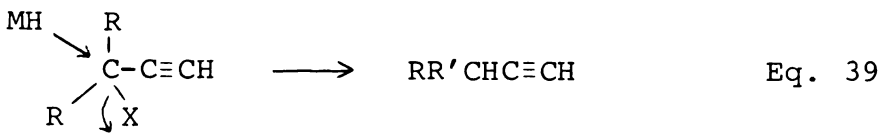
Thus tert-butylamine reacts with 47 essentially as well as ethylamine to give coupled secondary propargylic amine in 52% and 44% yield, respectively, in aqueous solution within one day.[20d] The same reaction is catalyzed by copper and by cuprous salts. When the amine subjected to alkylation is a strong base, catalysis is not necessary. With weakly basic compounds (aromatic and propargylic amines) cuprous salt catalysis is necessary in order to obtain the products in good yield within a reasonable reaction time. Thus the sterically crowded secondary amine 49, 1,1,1',1'-tetramethyl-di-2-propynylamine is prepared (Eq. 21) from the corresponding propargylic chloride 47 and propargylic amine 48 in 47% yield in 8 days by using cuprous chloride as a catalyst.

An attempt to synthesize 1,1,1',1'-tetraethyl-di-2-propynylamine 1 using the same conditions as in Eq. 21 failed to give the desired product. Only the propargylic carbinol 53 and starting propargylic amine 3 were recovered. Apparently, solvolysis of the propargylic chloride 2 is more facile than coupling with the propargylic amine 3. This is probably due to the severe steric crowding between the reactive allenecarbene intermediate and the primary amine 3. It appears that when both the propargylic amine and chloride are crowded about the reaction centers, solvolysis by the aqueous solution is faster than the coupling reaction.

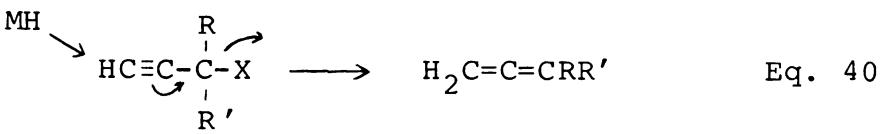
Attempts to couple the propargylic amine 3 with the propargylic chloride 4 in the polar aprotic solvent dimethylformamide by using KH or NaH as the base with a cuprous chloride catalyst were equally unsuccessful. The slow, incomplete H_2 evolution seems to indicate that the propargylic chloride 2 is not being converted to the acetylide. This observation is not unexpected. Jacobs et al.[37] reported that lithium aluminum hydride dehalogenates tertiary propargylic halides to give allenic hydrocarbons mixed in most instances with some of the corresponding acetylenic hydrocarbon (Eq. 38).

$$RR'CXC{\equiv}CH \xrightarrow{LiAlH_4} RR'C{=}C{=}CH_2 + RR'CHC{\equiv}CH \qquad \text{Eq. 38}$$

The results can be explained by a combination of S_N2 and S_N2' attack by hydride ion as pictured in equations 39 and 40, suggested by Wotiz.[38]



Eq. 39



Eq. 40

This seems to be a reasonable explanation for the lack of H_2 evolution, though no attempt was made to actually identify the low boiling products of the reactions with the metal hydride bases.

Amination of the propargylic chlorides 2, 47 and 56 to the amines 3, 48 and 58, respectively, by adding the propargylic chlorides to an ammonia saturated solution of dimethylformamide and cuprous chloride was somewhat unexpected. Ammonia is not a particularly strong base and it seems unlikely that any appreciable amount of acetylide could be present. Detailed examination[39a] of reactions of terminal alkynes with cuprous salts have shown that cuprous alkyne derivatives are the reactive intermediates in coupling reactions with 1-haloalkynes (Eq. 41), known as the

Cadiot-Chodkiewicz coupling.[38a]

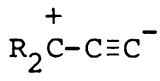
$$R\text{-}C{\equiv}CH \xrightarrow{Cu^{+}} RC{\equiv}CCu + H^{+}$$

Eq. 41

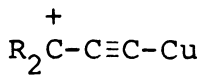
$$RC{\equiv}CCu + BrC{\equiv}CR' \longrightarrow RC{\equiv}C\text{-}C{\equiv}CR' + Cu^{+} + Br^{-}$$

A number of observations by Cadiot et al. pertaining to the unsymmetrical coupling reactions of alkynes seem applicable to coupling of ammonia and primary propargylic amines with propargylic chlorides.[38a,38b] Firstly, ammonia facilitates greatly the formation of very reactive cuprous derivatives. Secondly, solvents like dimethylformamide and n-methyl phosphoramide are generally the best solvents for coupling cuprous acetylides with terminal acetylenes.[38b] Hennion was unable to couple tertiary propargylic chlorides with an aqueous ammonia solution to form primary propargylic amines. This is not unexpected, since the Cu^{+} ion lifetime in water is generally very short and it readily disproportionates to Cu^{o} and Cu^{+2}.[40] Thirdly, ammonia facilitates the oxidation of Cu^{+} to Cu^{2+} in aqueous solution to form ammine complexes of the form $[Cu(H_2O)_{6-n}(NH_3)_n]^{+2}$ n = 1 to 5, depending on the relative ammonia concentration.[40]

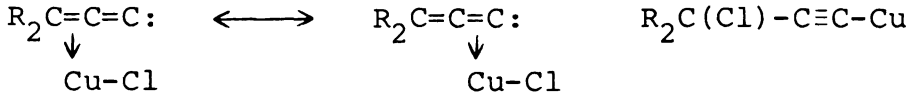
It may be that in dimethylformamide, the dipolar intermediate A is made more reactive in the form of the acetylide structure B or C. Alternatively, the t-acetylenic chloride used may form the acetylide D, subsequently leading to A, B or C as the species responsible for alkylation.[20d]



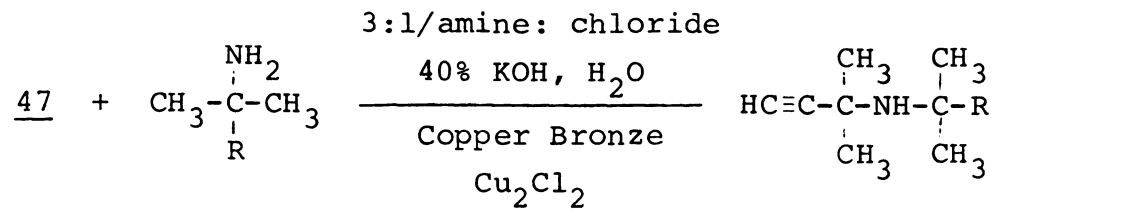
A



B

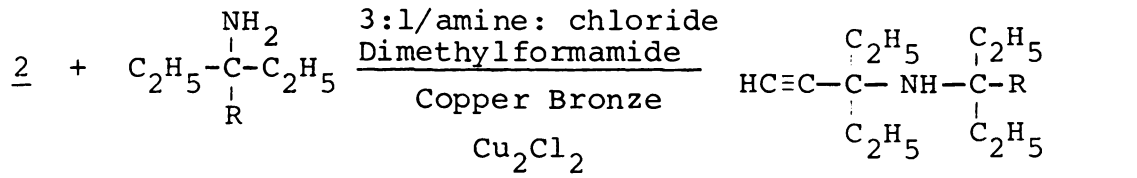


C D



Eq. 42

48;	R = Ethynyl	49;	R = Ethynyl (47%)
57;	R = Ethenyl	64;	R = Ethenyl (47%)
63;	R = Ethyl	65;	R = Ethyl (-)



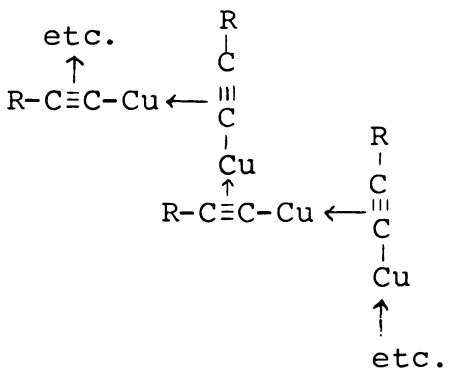
Eq. 43

3;	R = Ethynyl	1;	R = Ethynyl (63%)
4;	R = Ethenyl	5;	R = Ethenyl (17%)
6;	R = Ethyl	66;	R = Ethyl (0%)

It seems unlikely that a cuprous salt derived from the saturated and unsaturated amines is the active agent in the coupling reaction with the cuprous acetylides derived from the propargylic chlorides. The terminal hydrogens on the ethenyl and ethyl groups of the secondary amines are not sufficiently acidic to form the cuprous salt under the relatively mild reaction conditions used in the experiments.[40] It seems that all of these coupling reactions

would involve formation of similar intermediary copper derivatives (in particular, cuprous acetylide). This common factor, which is very little examined as yet, seems of primary importance for understanding why the hindered secondary amines are formed so easily.

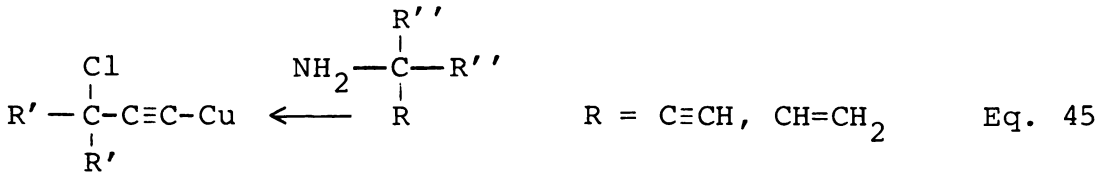
A polymeric structure has been proposed for cuprous derivatives of alkynes.[41] A trimethyl phosphine cuprous



Eq. 44

derivative of phenylacetylene has been isolated as a crystallized product and its structure has been determined by an X-ray study.[42] Though it is hazardous to extrapolate from a solid phosphinous derivative to amino complexes formed in the reaction media, experimental evidence does not preclude the possibility of the formation of amino cuprous complexes where copper valence variation and the existence of two (or more) different copper species could be used for the coupling reaction to occur.

A number of experimental observations may be rationalized by some kind of copper stabilized complex for cuprous derivatives of propargylic chlorides and unsaturated amines (Eq. 45).

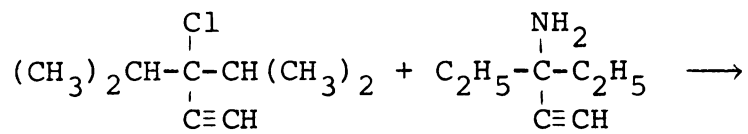


Eq. 45

As the reaction mixture temperature increases for a given ratio of propargylic chloride to unsaturated amine in the dimethylformamide solution, the yield of coupled amine decreases. This result is in accord with the proposal that at higher temperatures, an unsaturated amine-propargylic chloride complex would tend to dissociate and destroy the reactive intermediate which is responsible for the coupling reaction. This proposal is reinforced by the observation that the temperature, rather than the ratio of propargylic chloride to unsaturated amine (provided that the ratio is at least 1:2, respectively), is the most important factor in maximizing yield. Reaction of propargylic chloride 2 with alkynyl amine 3 in a 1:2 and 1:3.6 ratio at 24° for 1 day gave a 33% and 43% yield, respectively, of 1. Repeating the same two experiments at 4°C for 3 days gave a 61% and 63% yield, respectively, of 1 (Table 1). For the relatively unhindered propargylic chloride 47 ($R'=CH_3$) and propargylic amine 48 ($R''=CH_3$) in Eq. 45, the Cu←R complex formation is strong enough to overcome the repulsive forces of steric crowding between the chloride and amine alkyl groups. This would explain why R= C≡CH and $CH=CH_2$ both appear equally

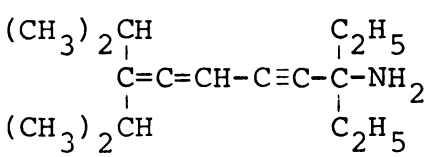
effective in forming the coupled secondary amine. But as the steric repulsion increases (R'=C_2H_5 and R''=C_2H_5), R= ethyne appears to give substantially better yield (63%) of coupled secondary amine than R= ethene (17%). This may be because the ethynyl group has a pair of perpendicular empty π^* orbitals which may back bond with a suitable filled hybrid orbitals on the copper in a manner which orients the intermediate complex to facilitate formation of coupled secondary amine. With R= ethenyl, the steric repulsion of the alkyl groups may be great enough to overcome any stabilizing effect achieved between a copper-olefin complex.

Preliminary results indicate that the bulkiness of alkyl groups on the propargylic amine and the tertiary propargylic chloride influence greatly the final reaction products. When we attempted to couple the propargyl chloride 56 with the propargylic amine 3, using copper bronze and Cu_2Cl_2 in dimethylformamide, we obtained 67 (Eq. 46) as the major product.



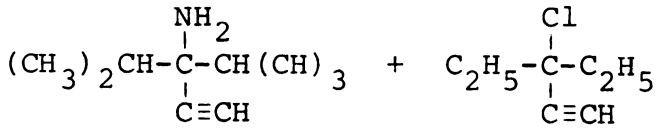
56 3

Eq. 46



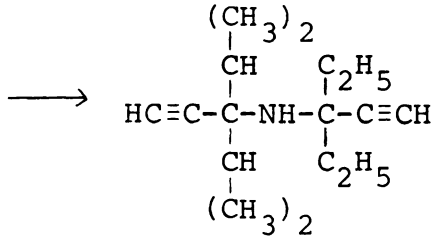
67

When we used the propargylic amine 58 with the propargylic chloride 2 under the same conditions, we obtained the coupled secondary amine 68 in poor yield with none of 67 seen (Eq. 47).



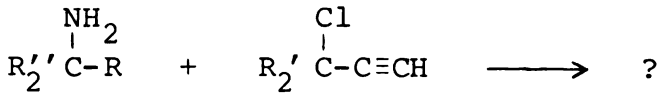
58 2

Eq. 47



68

Presently, it is unclear what role propargylic and allylic amines play in forming coupled secondary amines. A novel approach for investigating the influence of unsaturated primary amines on the coupling reaction would be to progressively shift the center of unsaturation away from the amino group by one carbon units and observe what effect this has on product formation (Eq. 48).



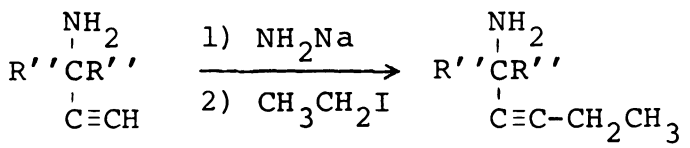
R = $CH_2C{\equiv}CH$, Eq. 48

$CH_2CH_2C{\equiv}CH$,

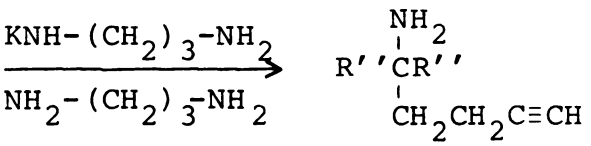
$CH_2CH_2CH_2C{\equiv}CH$,

etc.

The terminal acetylenic amines could be synthesized by treating the propargylic amine with sodamide and the appropriate alkyl halide[32] and then isomerizing the internal alkyne with potassium-3-aminopropylamide[43] to the terminal alkyne (Eq. 49a).



Eq. 49a



This approach would be especially interesting for investigating the product distribution of the coupling reaction when either the propargylic chloride (Eq. 46) or the

propargylic amine (Eq. 47) has very bulky alkyl groups. In this manner, a better understanding might be gained into the nature of the reactive intermediate involved in the coupling reaction.

When triethylamine is used as an HCl acceptor in the coupling reaction of 2 and 3 in dimethylformamide, Cu_2Cl_2 and copper bronze, the yield of the coupled amine 1 is reduced greatly. Adding triethylamine to a reaction mixture of 2 and 3 in dimethylformamide causes a heavy white precipitate to form immediately. Addition of aqueous sodium hydroxide to the solution mixture causes the precipitate to disappear. Analysis by GLC shows that an extremely small amount of 1 is formed and the triethylamine is recovered. Hennion studied the reaction of trimethylamine with tertiary propargylic chlorides in acetone.[20g,27] He found that the reaction produces quaternary ammonium chlorides that have the propargylic structure when R or R′ is CH_3. When R and R′ are larger than CH_3, the products are allenic (Eq. 49b). He also found that trace amounts of copper bronze or cuprous chloride catalyze both reactions, as in the case of primary and secondary amine alkylations.

$$RR'C(Cl)-C\equiv CH + (CH_3)_3N \begin{cases} \xrightarrow{a} RR'C(NMe_3)-C\equiv CH(Cl^-) \\ \quad (R \text{ or } R' \text{ small}) \\ \xrightarrow{b} RR'C=C=CH-NMe_3(Cl^-) \\ \quad (R=R'=C_2H_5 \text{ or larger}) \end{cases} \qquad \text{Eq. 49b}$$

It may be that the propargylic chloride reacts preferentially with the tertiary amine rather than with the propargylic amines. This would explain the low yield of coupled secondary amine 1. However, since no attempt was made to identify the precipitate, any conclusions are speculation.

Hydrogenation of 1 in ethanol with platinum oxide gave the hydrogenolysis product 6 almost exclusively (Eq. 31). The same result was observed with the hydrochloride of 1 under identical conditions. There are many examples in the literature[28,32] illustrating that hindered allyl amines, intermediates in the hydrogenation of propargylic amines, undergo hydrogenolysis readily with heterogeneous catalysts in polar protic solvents.[43] It appears that hindered amine hydrochlorides are susceptible to solvolysis as well as hydrogenolysis. This is illustrated by the fact that two tertiary amine hydrochlorides, prepared from N,N-diallyl-isobutylamine 69 and N-allyl-N-benzyl-t-butylamine 70, suffer rapid loss of an allyl group when recrystallization was attempted from mixed solvents containing ethanol.[28] The products are allyl-isobutylamine hydrochloride 71 and benzyl-t-butylamine hydrochloride 72, respectively. The latter case is particularly interesting, since 70 has three different groups presumably liable to cleavage as carbonium ions (Eq. 50,51).[28,32]

$$(CH_2{=}CH{-}CH_2)_2\overset{+}{\underset{HCl}{N}}{-}CH_2CH(CH_3)_2 \xrightarrow{EtOH} CH_2{=}CHCH_2\overset{+}{\underset{H_2Cl^-}{N}}{-}CH_2CH(CH_3)_2$$

69 71 Eq. 50

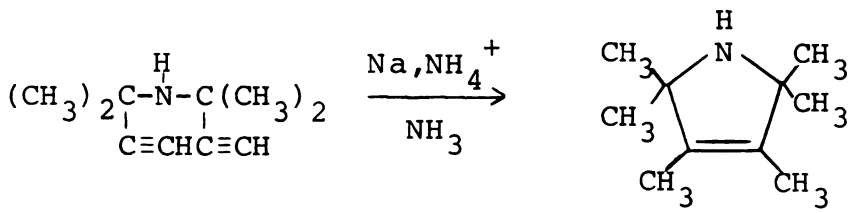
$$CH_2{=}CHCH_2\overset{+}{\underset{HCl^-}{N}}(C(CH_3)_3){-}CH_2C_6H_5 \xrightarrow{EtOH} (CH_3)_3C\overset{+}{\underset{H_2Cl^-}{N}}{-}CH_2C_6H_5$$

70 72 Eq. 51

The susceptibility of hindered allyl amines towards hydrogenolytic and solvolytic cleavage in protic solvents might explain why the bisdiallyl amine 7 in Eq. 32 was hydrogenolyzed to 6 when ethanol was added to the ligroine solution containing palladium on charcoal as the hydrogenation catalyst.

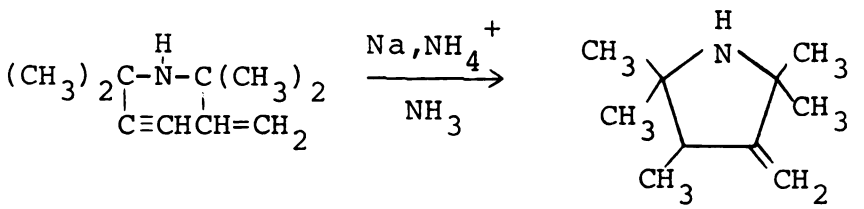
When 1 was hydrogenated with 10% palladium on charcoal in ethanol, the unsaturated heterocycles 8 and 9 were obtained in good yield (Eq. 33). The formation of substituted pyrrolines and pyrrolidines from unsaturated alicyclic amines is not unprecidented. Hennion synthesized 3,4-dimethyl-2,2,5,5-tetramethyl-3 pyrroline 73 and 3-methylene-4-methyl-2,2,5,5-tetramethyl-3-pyrrolidine 75 from the corresponding bispropargylic and propargylic-allylic amines 49 and 74, respectively, with sodium in liquid

ammonia (Eq. 52, 53).[20f]



Eq. 52

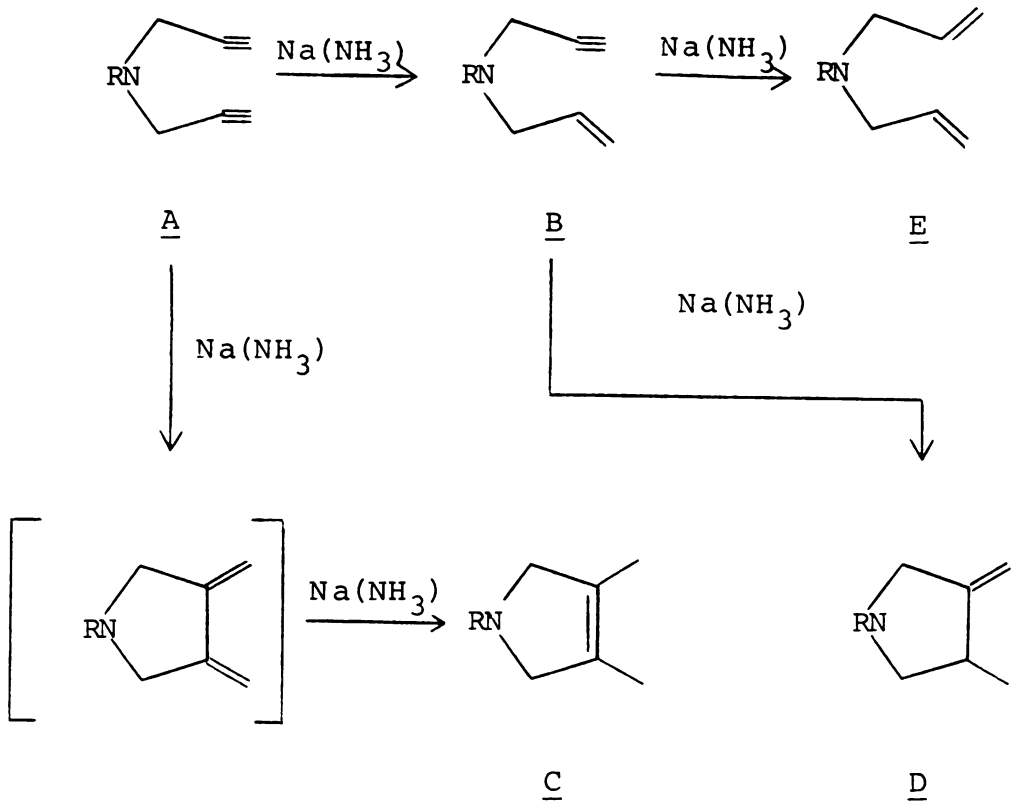
49 73



Eq. 53

74 75

Hennion investigated the steric and conformational effects of the sodium-ammonia reduction of bispropargylic and propargylallyl amines.[28] From the data, he concluded that cyclization occurs as the major reaction only when the unsaturated centers are conformationally restrained to close proximity. Below is a scheme drawn up by Hennion[28] showing the possible reaction pathways.



He determined that for the unhindered bispropargylic amine A (R=CH_3), the reaction product proceeded almost exclusively by the pathway A⟶B⟶E. If bispropargylic amine A was more hindered (R=$C(CH_3)_3$), the product mixture contained a 2:1 ratio of D to E. And in instances where there were alkyl groups α to the nitrogen, as in 49 , the product mixture consisted predominantly of substituted pyrrolines analogous to C. Apparently, considerable steric assistance is required for such reactions to occur in good yield and reactions B⟶D and A⟶B⟶D require less steric crowding than does the reaction A⟶C.

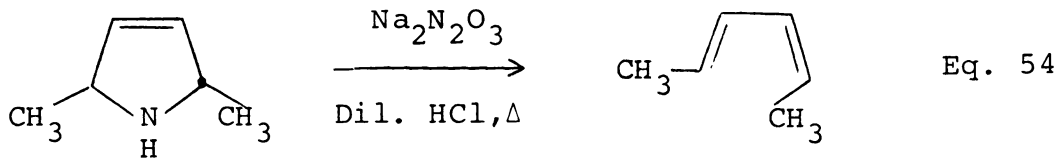
The catalytic cyclization reaction of 1 using palladium on charcoal in ethanol gives us the substituted pyrroline 8 and the substituted pyrrolidine 9 in good yield. It appears, at least qualitatively, that the products formed by catalytic cyclization of 1 with palladium on charcoal seem to follow the same general scheme as the cyclization reaction achieved with sodium in liquid ammonia.

Mechanistically, cyclizations induced by sodium-ammonia probably involve the union of a radical center derived from one ethynyl group with the appropriate allylic or propargylic carbon atom in the other unsaturated group.[28] Mechanistically, little can be said about the catalytic cyclization reaction of 1, except that it is probably an oxidative addition-reductive elimination oligomerization reaction involving some change in the oxidation state of palladium. It may be a heterogeneous oligomerization reaction involving Pd(0) or it may be a homogeneous catalysis reaction involving traces of $PdCl_2$ left unreduced when palladium metal was deposited on charcoal by reduction of a $PdCl_2$-charcoal solution with hydrogen gas.

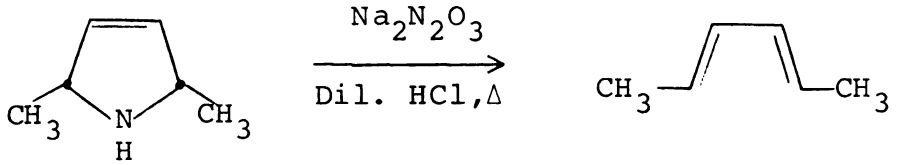
Whatever the active agent is, amine 1 must have the unsaturated centers restrained much closer to one another than in the case of 49, since 49 may be reduced to 50 with palladium on charcoal in ethanol with no traces of the heterocyclic amines 73 or 75 seen.[20f] This is in contrast with results obtained with 1 under identical experimental conditions, where we obtained the diallyl amine 7 along with

substantial amounts of the heterocyclic compounds 8 and 9.

An interesting and potentially useful application of substituted 3-pyrrolines, formed from the sodium-ammonia reduction of bispropargylic secondary amines, might be in their use as synthons for substituted dienes. Lemal and McGregor[44] reported that dienes are generated in high yield from 3-pyrrolines by treatment with nitrohydroxylamine. The availability of 3-pyrrolines from substituted bispropargylic amines makes this reaction potentially useful from a synthetic viewpoint, particularly since it proceeds with complete stereospecificity via a disrotatory thermolytic cleavage (Eq. 54, 55).[44]



Eq. 54



Eq. 55

One might start with the appropriate aldehyde or ketone and form the propargylic chloride and propargylic amine, then couple them to form the substituted bispropargylic secondary amine. Cyclization of the bispropargylic amine

and resolution of the cis-trans isomers (if any) should give the substituted 3-pyrroline, a potential source of the desired diene.

The saturated amine 10 was successfully synthesized by low pressure catalytic hydrogenation of 1 in ethanol with W2 grade Raney nickel. More reactive grades of Raney nickel generally failed to completely hydrogenate 1. One explanation for the apparent lack of reactivity of the more active grades of Raney nickel might be that amines are effective catalyst poisons for many platinum, palladium and nickel catalysts.[33] As the activity of the Raney nickel became greater, the amount of hydrogenolysis increased. Since the hydrogenolyzed amine was less hindered than the starting secondary amine, it might act as a more effective poison than the unhydrogenolyzed amine. This would tend to explain why increased hydrogenolysis seemed to go hand in hand with the catalysts' failure to completely hydrogenate 1.

Hydrogenation of 1 with W2 Raney nickel in a strongly basic ethanolic solution reduced considerably the competing hydrogenolysis reaction. This observation tends to support the observation that hydrogenolysis of hindered unsaturated amines occurs via a carbonium ion mechanism and that strongly basic reaction media suppress this undesired sidereaction.

EXPERIMENTAL

I. Materials

Propargylic Alcohols

3-Methyl-1-butyne-3-ol was commercially available (Aldrich). All other propargylic alcohols were synthesized from the corresponding ketones.

Propargylic Chlorides

All propargylic chlorides were prepared from the corresponding alcohols and used without further purification. All were stored over anhydrous potassium carbonate.

Propargylic Amines

The propargylic amines were made from the corresponding chlorides. All were distilled under reduced pressure and stored over molecular sieve.

Solvents

Tetrahydrofuran was dried over sodium benzophenone ketyl, distilled and stored under argon over molecular sieve. Anhydrous diethyl ether was used without purification. Dimethylformamide was dried over calcium hydride, distilled under vacuum and stored over molecular sieve. U.S.P. grade absolute ethanol was used for all hydrogenations.

Inorganic Chemicals

Commercially available Cu_2Cl_2 (Alpha Co. 95%) was used for preparing the propargylic chlorides. Freshly prepared Cu_2Cl_2 was used in catalytic coupling reactions.[45] Copper bronze powder and all other inorganic reagents were obtained commercially and used without further purification.

II. Preparation of Tertiary Propargylic Alcohols

A. General Procedure

3-Ethyl-1-pentyne-3-ol 53 is a representative example for the preparation of tertiary propargylic alcohols. GLC analyses used a 1/4" by 6' stainless steel column packed with 10% Carbowax 20-M liquid phase on Chromasorb G support.

A 5-liter three-neck round bottom flask was fitted with an efficient mechanical stirrer mounted through a short glass bushing and two gas inlet tubes for acetylene and ammonia which dipped below the surface of the liquid ammonia. The third neck of the flask was fitted with a large Dry Ice condenser which was connected to a KOH drying tower by rubber tubing.

The flask was charged with about 4 l. of anhydrous liquid ammonia (Matheson Gas Co.), the stirrer started, and a rapid stream of acetylene gas was passed in for about 30 minutes to saturate the solution. Welding grade acetylene was sufficiently purified by passage through two sulfuric acid gas wash bottles. Additional ammonia gas was condensed from time to time to keep the solution level at

about 4 l. Sodium (115 g., 5 g. atoms) was cut into strips so that they could be inserted through the side neck of the flask. The Dry Ice condenser was removed and replaced with a short piece of 12-15 mm. wide glass tubing through which was passed a long piece of flexible iron wire. The lower end of the wire was bent into a hook. One of the pieces of sodium was attached to the wire hook and was gradually lowered into the liquid ammonia while a rapid stream of acetylene was bubbled in. The sodium was added at such a rate that the entire solution did not turn blue. If it did, the sodium was raised above the level of the ammonia until the color was discharged. The rest of the sodium was added in a similar manner. The addition required about one hour, depending on the rate of passage of the acetylene. After the sodium was added, stirring was continued for 1 hour while still bubbling acetylene through the solution.

The acetylene was then shut off. The gas inlet tubes and the glass tube with the iron wire were removed and replaced with a large addition funnel and the Dry Ice condenser. Then 430.6 g. of 3-pentanone (4.95 moles, 98% pure) was added dropwise over an hour period to the ammonia solution. After the addition, the dropping funnel was removed and the neck stopped up. The flask was insulated with a 5 l. heating mantle and glass wool. The solution was allowed to stir overnight. The heating mantle was removed, the stirring stopped and the reaction mixture was allowed

to stand until all the ammonia had evaporated. The solid residue was decomposed by adding about 1.5 l. of ice and water, and the mixture was carefully acidified with 50% sulfuric acid (300 to 350 ml.). The organic layer was dissolved in 400 ml. of ether and washed with 200 ml. of brine. The original aqueous phase and the brine wash were then extracted with the 200 ml. portions of ether. The combined ethereal solutions were dried over anhydrous magnesium sulfate, filtered, and the ether removed by vacuum distillation. The product was then distilled under reduced pressure through a 15 cm. Vigreux column. The yield of 3-ethyl-1-pentyne-3-ol 53 was 520 g. (93% yield), b.p. 135-136°, $n^{25}D$ 1.4351.

B. Product Analysis

3-Methyl-1-butyne-3-ol 52

NMR ($CDCl_3$): δ 1.68 (S, 1H), δ 1.83 (S, 6H), δ 2.38 (S, 1H). IR (neat): 3413 cm^{-1} (O-H), 3300 cm^{-1} (C≡C-H). $n^{25}D$ 1.4207. Yield: 55%.

3-Ethyl-1-pentyne-3-ol 53

NMR ($CDCl_3$): δ 1.0 (t, 6H, J=7Hz), δ 1.65 (q, 4H, J=7Hz), δ 2.3 (S, 1H), δ 2.38 (S, 1H). IR (neat): 3410 cm^{-1} (O-H), 3300 cm^{-1} (C≡C-H). $n^{25}D$ 1.4351. Yield: 93%.

4-Methyl-3-isopropyl-1-pentyne-3-ol 54

NMR ($CDCl_3$): δ 0.98 (dd, 12H, J=7Hz), δ 1.92 (m, 3H, J=7Hz), δ 2.35 (S, 1H). IR (neat): 3495 cm^{-1} (O-H), 3315 cm^{-1} (C≡C-H). $n^{25}D$ 1.4435. Yield: 89%.

III. Preparation of Tertiary Propargylic Chlorides.

A. General Procedure

The following procedure for the conversion of 3-ethyl-1-pentyne-3-ol 53 to 3-chloro-3-ethyl-1-pentyne 2 is representative for preparing the chlorides. A 1 l. 3-neck flask provided with a magnetic stirrer, thermometer and dropping funnel was charged with 56 g. (0.5 mole) calcium chloride, 40 g. (0.4 mole) Cu_2Cl_2 chloride (95% brown powder), 400 mg. copper bronze powder (Illinois Bronze Powder Co.) and 430 ml. (5 moles) of cold concentrated hydrochloric acid. The mixture was flushed with argon and cooled (ice bath) with stirring. One mole of 3-ethyl-1-pentyne-3-ol 53 (112.2 g.) was added dropwise within 30 minutes. Stirring was continued for 1 hour. (0-5° solution temperature). The upper organic layer was separated and washed immediately with three 100 ml. portions of cold concentrated hydrochloric acid, then with two 100 ml. portions of water and once with 100 ml. of saturated aqueous sodium carbonate. The colorless product was dried superficially with anhydrous potassium carbonate and then thoroughly with fresh potassium carbonate. Analysis of the sample by GLC with a 10% Carbowax 20-M on Chromasorb-G column showed the sample to be 96% pure. The chloride was used without further purification. Total isolated yield of pure chloride was 73%, $n^{25}D$ 1.4387.

B. Product Analysis

3-Chloro-3-methyl-1-butyne 47

NMR ($CDCl_3$): δ 1.82 (S, 6H), δ 2.57 (S, 1H). IR (neat): 3390 cm^{-1} (C≡C-H), 2110 cm^{-1} (-C≡C-). $n^{25}D$ 1.4156. Yield: 65%.

3-Chloro-3-ethyl-1-pentyne 2

NMR ($CDCl_3$): δ 1.47 (t, 6H, J=7Hz), δ 1.92 (q, 4H, J=7Hz), δ 2.58 (S, 1H). IR (neat): 3390 cm^{-1} (C≡C-H), 2115 cm^{-1} (-C≡C-). $n^{25}D$ 1.4387. Yield: 73%.

3-Chloro-4-methyl-3-isopropyl-1-pentyne 56

NMR ($CDCl_3$): δ 1.10 (d, 12H, J=6Hz), δ 2.13 (m, 2H, J=6Hz), δ 2.55 (S, 1H). IR (neat): 3395 cm^{-1} (C≡C-H), 1390-1375 cm^{-1} (isopropyl doublet). $n^{25}D$ = 1.4560. Yield: 70%.

IV. Preparation of Primary Propargylic Amines

A. General Procedure (Hennion's Sodamide Method)

The following procedure for the conversion of 3-chloro-3-ethyl-1-pentyne 2 to 3-amino-3-ethyl-1-pentyne 3 is representative. Twenty four grams of sodium (1.04 g. atom) was converted to the amide in 1 l. of anhydrous liquid ammonia within a 3 l. three neck round bottom flask provided with a mechanical stirrer, Dry Ice condenser and a long stem gas inlet tube for introducing ammonia into the flask. To the mechanically stirred ammonia solution was added 0.3 g. of finely powdered anhydrous ferric (III)

chloride and 1 g. of sodium. Dry air was bubbled through the solution until the blue color was discharged. The remaining 23 g. of sodium was then added in small chunks. A reaction set in immediately and within 30 minutes the blue color was replaced by grey, indicating the end of the conversion to sodamide. Then 130.6 g. of 96% pure 3-chloro-3-ethyl-1-pentyne 2 (0.96 mole), diluted with about four volumes of anhydrous ether, was added dropwise during a period of 90 minutes with continuous stirring. The flask was insulated with a 3 l. heating mantle, glass wool and allowed to stir overnight. The insulation was removed, the stirring discontinued and the ammonia allowed to evaporate. Chopped ice (500 g.) and ether (150 ml.) were then added. The ether layer was separated and the aqueous layer extracted once with 100 ml. ether. The combined ethereal extract was washed with cold water and filtered. The solution was chilled in an ice bath and 60 g. of chopped ice was added with stirring. The solution was titrated with concentrated HCl to about pH 2 (litmus) (58 ml. acid). The ether layer was discarded and the solution was extracted once with 50 ml. of ether to remove non-basic impurities. The aqueous solution was then treated with 29 g. of sodium hydroxide in 30 ml. of water to release the amine, recovered by extraction with ether. Distillation gave 81.2 g. (73% yield) of pure amine, b.p. 36-38°/2mm, $n^{25}D$ 1.4392.

B. General Procedure (DMF With Ammonia Method)

To a 100 ml. round bottom flask with an 8 mm. O.D. septum sidearm and containing a magnetic stir bar was added 56 ml. of dimethylformamide, 111 mg. of freshly prepared Cu_2Cl_2 and 111 mg. of copper bronze. A small gas dispersion tube fitted through a rubber stopper was inserted through the ground glass joint so that the tube was immersed in the dimethylformamide solution. Anhydrous ammonia gas was slowly bubbled through the rapidly stirring solution for 30 minutes to saturate the solution with ammonia. Then 12.8 g. of 88% pure 3-chloro-4-methyl-3-isopropyl-1-pentyne 56 (75 mmole) was added dropwise with a syringe through the open sidearm. After one hour, ammonia bubbling was discontinued, the sidearm capped, and the solution stirred overnight. Then 100 mmoles 20% NaOH (20 ml.) was added to the solution. The solution was extracted with three 25 ml. portions of ether and the ether was washed with three 10 ml. portions of water to remove the dimethylformamide. The ether was then added to 20 ml. water and cooled to 0°. Eight ml. of concentrated HCl was added dropwise until the solution became acidic (litmus). The ether layer was discarded. Another 25 ml. portion of ether was added to the solution and the solution basified with saturated aqueous NaOH to free the propargylic amine. The ether layer was decanted and the solution was extracted with two 25 ml. portions of ether. The ether solutions were combined and dried over potassium carbonate. The solvent was evaporated and

the remaining amine was distilled (bulb to bulb) under reduced pressure. Isolated 3.0 g. (36%) of 3-amino-4-methyl-3-isopropyl-1-pentyne 58, b.p. 51-52°/7 mm. $n^{25}D$ 1.4501.

C. Product Analysis

3-Amino-3-methyl-1-butyne 48

NMR ($CDCl_3$) δ 1.4 (S, 6H), δ 1.67 (S (b), 2H), δ 2.25 (S, 1H). IR (neat): 3370, 3210 cm^{-1} (N-H stretch), 3290 cm^{-1} (C≡C-H), 1620 cm^{-1} (N-H bend). $n^{25}D$ 1.4180, Yield: 20%.

3-Amino-3-ethyl-1-pentyne 3

NMR ($CDCl_3$): δ 1.0 (t, 6H, J=7Hz), δ 1.53 (m, 6H), δ 2.27 (S, 1H). IR (neat): 3360, 3280 cm^{-1} (N-H stretch), 3290 cm^{-1} (C≡C-H) 2080 cm^{-1} (C≡C). $n^{25}D$ 1.4392, Yield: 73%.

3-Amino-4-methyl-3-isopropyl-1-pentyne 58

NMR ($CDCl_3$): δ 0.98 (d, 12H, J=6Hz), δ 1.27 (S (b), 2H), δ 1.85 (m, 2H, J=6Hz), δ 2.2 (S, 1H). IR (neat): 3370, 3250 cm^{-1} (N-H stretch), 3290 cm^{-1} (C≡C-H). $n^{25}D$ 1.4501, Yield: 40%.

V. Preparation of Primary Allylic Amines

A. General Procedure

The following procedure for the conversion of 3-amino-3-ethyl-1-pentyne 3 to 3-amino-3-ethyl-1-pentene 4 is representative. Sodium metal (2.3 g.) was added in small

pieces with stirring to a solution of 22.2 g. (0.2 moles) of 3-amino-3-ethyl-1-pentyne 3 in a 500 ml. 3 neck round bottom flask containing 0.2 l. of liquid ammonia. Ammonium chloride (0.1 mole, 5.4 g.) was then added slowly. Alternate additions of sodium and ammonium chloride were repeated until a total of 11.3 g. (0.5 g. atom) of sodium and 27.0 g. (0.5 moles) of ammonium chloride had been added. The total volume was maintained at 0.2 l. by periodic addition of liquid ammonia. Ether (50 ml.) was added and the liquid ammonia was allowed to evaporate overnight. The mixture was filtered and the solid was washed with two 50 ml. portions of ether which were combined with the filtrate. The combined ether solutions were dried over anhydrous potassium carbonate. Distillation gave 9.44 g. (42% yield) of 3-amino-3-ethyl-1-pentene 4, b.p. 128-129°/760 mm.

B. Product Analysis

3-Amino-3-ethyl-1-pentene 4

NMR ($CDCl_3$): δ 0.88 (q, 8H, J=7Hz), δ 1.42 (q, 4H, J=7Hz), δ 4.8-5.9 (m, 3H). IR (neat): 3350, 3290 cm^{-1} (N-H stretch), 3075 cm^{-1} (C=C-H stretch), 1685 cm^{-1} (C=C stretch). Yield: 42%.

3-Amino-4-methyl-3-isopropyl-1-pentene 59

NMR ($CDCl_3$): δ 0.82 (dd, 14H, J=7Hz), δ 1.8 (m, 2H, J=7Hz), δ 4.83-5.9 (m, 3H). IR (neat): 3375, 3290 cm^{-1} (N-H stretch), 3065 cm^{-1} (C=C-H stretch), 1375, 1345 cm^{-1} (isopropyl bend). $n^{25}D$ 1.4490. Yield: 65%.

VI. Preparation of Hindered Bispropargylic Secondary Amines.

A. General Procedure

The following procedure for the coupling of 3-amino-3-ethyl-1-pentyne 3 with 3-chloro-3-ethyl-1-pentyne 2 to form 1,1,'1,'1-tetraethyl-di-2-propynylamine 1 is representative. A 500 ml. round bottom flask, equipped with a magnetic stir bar, septum inlet and gas inlet valve, was flame dried under a stream of argon. The gas inlet value was removed and 220 mg. of copper bronze powder and 220 mg. of freshly prepared Cu_2Cl_2 was added to the flask. Then 109 ml. of dimethylformamide (dried and distilled over calcium hydride) and 260 mmoles of 3-amino-3-ethyl-1-pentyne 3 (29.8 g.) were added to the flask. The gas inlet valve was replaced and the flask flushed with argon for 10 minutes. The flask was placed in a cold room and the solution allowed to cool to 4°C. Then 18.3 g. (133 mmole) of 95% 3-chloro-3-ethyl-1-pentyne 2, also at 4°C., was added dropwise over a ten minute period via syringe to the vigorously stirring solution. The gas inlet valve was closed and the solution stirred for 3 days at 4°C. The solution was then quenched with 30 ml. of 20% aqueous NaOH (150 mmoles) and stirred for 10 minutes. One hundred ml. of water and 100 ml. of ether were added to the solution. The solution was transferred to a separatory funnel and the water-dimethylformamide layer decanted. The ether layer was washed with three 75 ml. portions of water and then dried over anhydrous

potassium carbonate. The ether was evaporated and the primary amine removed at 30-35°/1 mm. by vacuum distillation. The coupled bispropargylic amine was removed at 61-65°/ 0.5 mm. by vacuum distillation through a 20 cm. Vigreux column. About 12.9 g. (48% yield) of the coupled amine 1 was recovered, based on the starting chloride.

The procedure for preparing the corresponding hindered primary allylpropargylic amine 5 was identical to the procedure for preparation of the primary bispropargylic amine, except that 3-amino-3-ethyl-1-pentene 4 was substituted for 3-amino-3-ethyl-1-pentyne 3.

B. Product Analysis

1,1,1',1'-Tetramethyl-di-2-propynylamine 49

NMR ($CDCl_3$): δ 1.28 (S, 1H), δ 1.48 (S, 12H), δ 2.23 (S, 2H). IR (KBr pellet): 3390 cm^{-1} (C≡C-H), 2080 cm^{-1} (C≡C). Mass Spec: parent peak m/e 149. Yield: 83%.

1,1,1',1'-Tetraethyl-di-2-propynylamine 1

NMR ($CDCl_3$): δ 0.93 (t, 13H, J=7Hz), δ 1.73 (q, 8H, J=7Hz), δ 2.25 (S, 2H). IR (neat): 3390 cm^{-1} (C≡C-H), 2080 cm^{-1} (C≡C). $n^{25}D$ 1.4701. Mass Spec: parent peak m/e 205. Yield: 48%.

N-(1,1-Diethylallyl)-1,1-diethyl-2-propynylamine 5

NMR ($CDCl_3$): δ 0.88 (q, 13H, J=7Hz), δ 1.4 (q, 8H, J=7Hz), δ 2.18 (S, 1H), δ 4.73-6.18, (m, 3H). IR (neat) 3280 cm^{-1} (C≡C-H), 3045 cm^{-1} (C=C-H stretch). Mass Spec: parent peak m/e 207. Yield: 17%.

VII. Hydrogenation of 1,1,1',1'-Tetraethyl-di-2-propynylamine 1 in Absolute Ethanol With 10% Palladium on Charcoal

A. General Procedure

A 50 ml. round bottom flask, equipped with a magnetic stir bar, septum inlet and gas inlet valve, was attached with rubber tubing to a mineral oil filled gas buret. Ten mg. of 10% palladium on charcoal (Engelhard Ind. Inc.) and 5 ml. absolute ethanol (Gold Shield U.S.P.) were added. Hydrogen gas (Matheson 99.9%) was flushed through the system and the gas buret was charged with the same. The solution was cooled to 0°C with an ice bath. Then 1 mmole (0.23 ml.) of the bispropargylic amine 1 was added to the rapidly stirring solution. Hydrogen uptake was monitored with the gas buret and product formation determined by GLC with a 10% Carbowax-20M on Chromasorb-G column at 160°C. Hydrogen uptake (74 ml., 2.9 mmole) ceased within 55 minutes. The GLC trace showed two distinct high boiling products and a low boiling product eluting with the solvent. Preparative GLC and subsequent spectroscopic analysis identified the high boiling components as 3,4-dimethyl-2,2,5,5-tetraethyl-3-pyrroline 8 and 3-methylene-4-methyl-2,2,5,5-tetraethyl-3-pyrrolidine 9. Repeating the experiment using tridecane as an internal standard established the yields of 8 and 9 as 48% and 15%, respectively.

B. Product Analysis

3,4-Dimethyl-2,2,5,5-tetraethyl-3-pyrroline 8

NMR ($CDCl_3$): δ 0.80 (t, 13H, J=6Hz), δ 1.43 (singlet superimposed on a multiplet, 14H). NMR ^{13}C ($CDCl_3$): δ 134.2, 70.69, 29.79, 8.69, 7.15. IR (neat): no characteristic bands. Mass Spec: parent peak m/e 209. Reduction of 1,1,'1,'1-tetraethyl-di-2-propynylamine 1 with sodium in liquid ammonia gave a product with physical and spectral properties identical to 8.[20f]

3-Methylene-4-methyl-2,2,5,5-tetraethyl-3-pyrrolidine 9

NMR ($CDCl_3$): δ 0.85 (t, 13H, J=6Hz), δ 1.1-1.6 (m, 11H)), δ 2.2-2.5 (m, 1H), δ 4.6 (t, 2H, J=3Hz). IR (neat): 3055 cm^{-1} (C=C-H_2 stretch), 1660 cm^{-1} (C=C stretch). Mass Spec: parent peak m/e 209. Reduction of N(1,1-diethylallyl)-1,1-diethyl-2-propynylamine 5 with sodium in liquid ammonia gave a product with physical and spectral properties identical to 9.[20f]

VIII. Hydrogenation of 1,1,1',1'-Tetraethyl-di-2-propynylamine 1 in Absolute Ethanol With Platinum Oxide.

A. General Procedure

The same experimental conditions as in section VII A. were used, except that 10 mg. of PtO_2 was substituted for 10 mg. of 10% palladium on charcoal. A total of 93 ml. (3.8 mmoles) of hydrogen was taken up. By GLC, only trace amounts of products having the same retention times as 8

and 9 were seen, the rest of the starting material having been hydrogenolyzed to 1,1-diethyl-1-aminopropane 6 , the saturated primary amine.

IX. Hydrogenation of 1,1,1',1'-Tetraethyl-di-2-propynylamine 1 to Bis (1,1-diethylallyl)amine 7 in Ligroine With 10% Palladium on Charcoal.

A. General Procedure

Ten mmoles of 1,1,1',1'-tetraethyl-di-2-propynylamine (2.05 g.) was dissolved in 30 ml. of ligroine in a 250 ml. centrifuge bottle. Then 20 mg. of 10% palladium on charcoal was added to the solution. The bottle was placed in a Parr hydrogenation apparatus and hydrogenated for 10 hours at an initial pressure of 50 psi hydrogen. The pressure dropped 37 psi. GLC analysis of the sample showed 3 peaks. The first component was analyzed and identified as bis-(1,1-diethylallyl) amine 7. Its spectral properties were identical with those from the product obtained by semi-hydrogenating 1,1,'1,'1-tetraethyl-di-2-propynylamine with Raney Nickel in ethanol. The two higher boiling components had spectral properties identical with the hetercyclic unsaturated amines 8 and 9 (see section VII B). Adding 10 ml. of ethanol to the ligroine solution and continuing the hydrogenation completely hydrogenolyzed the bis(1,1-diethylallyl)amine 7.

B. Product Analysis

Bis(1,1-diethylallyl)amine 7

NMR ($CDCl_3$): δ 0.75 (t, 13H, J=7Hz), δ 1.43 (8, 8H, J=7Hz), δ 4.67-6.0 (m, 6H). IR (neat): 3380 cm^{-1} (C≡C-H), 3045 cm^{-1} (olefin H stretch), 1630 cm^{-1} (C=C stretch). Mass Spec: parent ion peak m/e 209. Yield: not determined.

X. Hydrogenation of 1,1,1',1'-Tetraethyl-di-2-propynylamine in Absolute Ethanol with Raney Nickel Catalyst.

A. Preparation of Raney Nickel Catalysts.

W2 Raney Nickel

Raney nickel alloy (150 g. Alpha Chemical Co.) was added in small portions to a solution of 190 g. of sodium hydroxide in 800 ml. of distilled water contained in a 2 liter beaker and cooled to 10°C. with an ice bath. The basic solution was stirred rapidly with a mechanical stirrer while alloy was added at a rate where the temperature of the mixture remained below 25°C. After all the alloy was added, the solution was allowed to reach room temperature. After hydrogen evolution subsided, the solution was digested for 6-10 hours on a steam bath until hardly any more hydrogen was given off. Distilled water was added periodically to keep the volume of the solution constant. After digestion was completed, the beaker was removed from the steam bath, the nickel was allowed to settle and the liquid decanted. The catalyst was washed by decantation with two 1 l. portions of water after which it was

transferred to a 1 l. beaker using distilled water. The water was poured off and replaced with a solution of 27 g. sodium hydroxide in 300 ml. of water. The nickel was suspended in the base, allowed to settle and the basic solution was decanted. The catalyst was washed with 300 ml. portions of distilled water until the solution was neutral to litmus, and then an additional ten to fifteen times to remove all traces of base. Washing was continued with three 100 ml. portions of 95% ethanol and then three 100 ml. portions of absolute ethanol. The inflammable catalyst was stored in a tightly closed wide mouth jar kept completely full of ethanol at all times. The catalyst may be stored up to 6 months without appreciable loss of activity if kept cold. About 75 g. of catalyst was obtained. Raney nickel weighs about 4 grams per teaspoonful.

W4 Raney Nickel

Raney nickel alloy (100 g.) was added in small portions to a solution of 130 g. of sodium hydroxide in 500 ml. of distilled water in a 2 l. beaker at such a rate as to maintain the temperature of the mixture between 48° and 52°C. After the addition was completed, the mixture was heated at 50°C. for another 55 minutes with gentle stirring. After washing the catalyst three times by decantation, the catalyst was transferred to a 500 ml. graduated cylinder by rinsing the beaker with distilled water.

The cylinder was fitted with a mechanical stirrer and was placed in a sink from which the wash water overflow

could be easily removed. Distilled wash water was added from a reservoir through a glass tube extending to the bottom of the cylinder. The stirrer was started and set at a rate where the catalyst was suspended to a depth 2/3 the height of the graduated cylinder. The flow rate of water was adjusted to about 5 l. per hour, where a total of 15 l. was added over a 3 hour period. The rinsing was discontinued when the wash water was neutral to litmus. The catalyst was allowed to settle and the water decanted. The nickel was transferred to a 250 ml. Erlenmyer flask and washed with three 150 ml. portions of 95% ethanol. The suspension, in order to minimize contact of catalyst with air, was stirred and not shaken. The process was repeated with three 150 ml. portions of absolute ethanol and the catalyst was stored out of air contact under absolute ethanol. The catalyst remains fresh for about 1 month. Yield was about 45 grams.

W6 Raney Nickel

W6 Raney nickel was prepared by bubbling hydrogen through the water in the cylinder (in the hood) during the continuous wash process used in the W4 Raney nickel preparation. This catalyst should be stored in the same manner as W4 Raney nickel and used within two weeks of its preparation.

B. General Procedure

One half teaspoon (~2 g.) of W2 Raney nickel was added to a solution of 50 ml. absolute ethanol and 10 mmoles

(2.05 g.) of 1,1,1',1'-tetraethyl-di-2-propynylamine 1 in a 500 ml. centrifuge bottle. The bottle was placed in a Parr hydrogenation apparatus and purged with hydrogen 5 or 6 times. The bottle was pressurized to 40 psi and the shaker turned on. The pressure dropped 32 psi in 18 hours. The ethanolic solution was filtered to remove the catalyst and the ethanol evaporated under reduced pressure. Bulb to bulb distillation (62-64°/0.2 mm) gave 0.43 g. (20%) of the saturated amine 1,1,1,1',1',1' hexaethyl-di-methylamine 10. Analysis of the sample of 10 by GLC showed it to be >95% pure. Determination of the amount of hydrogenolysis product by GLC was not possible, since the hydrogenolyzed amine eluted with the solvent.

The same experiment was performed using W2, W4 and W6 Raney nickel under identical conditions. Tridecane was added as an internal standard in each case. Analysis of the products of each experiment by GLC showed that as the reactivity of the catalyst increased, the degree of hydrogenation of the bispropargylic secondary amine decreased. Thus W2 Raney nickel was the most satisfactory catalyst for the hydrogenation of 1 to the saturated secondary amine.

The same experiment was performed under identical conditions, except that 20 mmoles (1.12 g.) of potassium hydroxide was dissolved in the ethanolic solution of the bispropargylic secondary amine before adding the W2 Raney nickel catalyst. The catalyst was filtered after the hydrogenation and the ethanol was removed under reduced pressure.

Twenty ml. each of water and ether were added to the viscous residue. The solution was transferred to a small separatory funnel, the ether layer removed and the aqueous layer extracted with two 20 ml. portions of ether. The ether layers were pooled, dried over anhydrous potassium carbonate and then evaporated under reduced pressure. The remaining amine was distilled (bulb to bulb) under reduced pressure. About 1.52 g. (71%) of the saturated amine 10 was isolated, $n^{24}D$ 1.4653.

C. Product Analysis

1,1,1,1',1',1'-Hexaethyl-di-methylamine 10

NMR ($CDCl_3$): δ 0.78 (t, 19H, J=6Hz), δ 1.4 (q, 12H, J=6Hz). IR (neat): no distinguishing bands. Mass Spec: parent ion m/e 213. Yield: 71%.

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