The Sodium–Ammonia Reduction of Bispropargyl- and Propargylallylamines. Steric and Conformational Effects[1]

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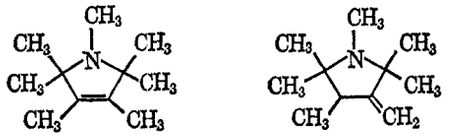
The reduction of sterically crowded N,N-bis(1,1-dimethylpropargyl)methylamine with sodium in liquid ammonia produced heptamethyl-3-pyrroline (a) in 72% yield while the same reaction applied to N-(1,1-dimethylpropargyl)-N-(1,1-dimethylallyl)methylamine

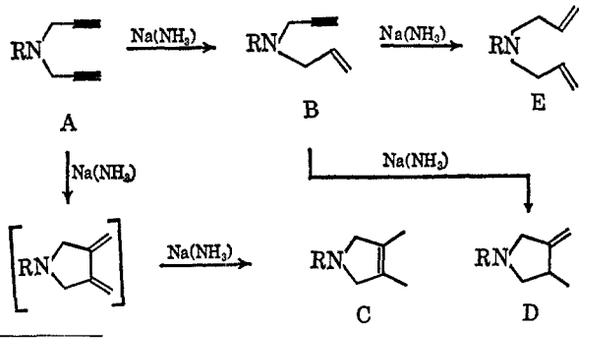


a

b

gave the isomeric hexamethyl-3-methylenepyrrolidine (b) in 61% yield.[3] The corresponding N-demethylamines, conformationally less restrained with N–H in place of N–CH_3, also gave good yields of cyclized products except that the product purities were not so high owing to some competitive reduction without cyclization. Since this new[4] cyclization reaction seemed to hold promise for the facile synthesis of substituted pyrrolines and pyrrolidines, we have studied the reduction outcome as related to steric and conformational effects in the substrate. As clearly revealed by the data of Table I, cyclization occurs as the major reaction only when the unsaturated centers are conformationally restrained to close proximity. Thus the sodium–ammonia reduction of N,N-dipropargylmethylamine (A, R = Me; not sterically crowded) gave a 72% yield of product which was found to be 95% diallylmethylamine (E), independently synthesized from allyl bromide and methylamine. The same result was had with N,N-dipropargylethylamine (A, R = Et) which yielded mostly diallylethylamine (92% of the product). On the other hand, N,N-dipropargyl-*t*-butylamine (A, R = CMe_3) was reduced in 68% yield to a product (bp 58–68° at 18 mm) which was composed of 64% 1-*t*-butyl-3-methylene-4-methylpyrrolidine (D, R = CMe_3), hydrochloride mp 183–185°, and 36% diallyl-*t*-butylamine (E, R = CMe_3), bp 62–64° at 15 mm., hydrochloride mp 124–126°. That ring closure followed the path A → B → D was established by the fact that N-allyl-N-propargyl-*t*-butylamine (B, R = CMe_3), prepared independently from *t*-butylallylamine and propargyl bromide, gave the same products in the same ratio (see Scheme I).

SCHEME I



The product composition data of Table I were obtained by glpc. When the amount of cyclized product was small, as in Table I, entries 3, 4, 6 and 7, separation for purposes of characterization was achieved by preparative glpc using a 20-ft Carbowax 20 M column (*cf.* Table II, V and XI). Compounds XIV and XV, obtained in the ratio 36:64 as stated above, were separable as their hydrochloride salts by fractional crystallization from a mixture of ethyl acetate and absolute ethanol.

That one of the reduction products was N,N-diallylalkylamine was easily established in all cases by independent synthesis from alkylamine and allyl bromide. That the other product was the isomeric 3-methylenepyrrolidine was shown by pmr and infrared examination. Thus the pmr spectrum of 1-*t*-butyl-3-methylene-4-methylpyrrolidine hydrochloride (XV · HCl) in chloroform-*d* showed a doublet at τ 8.61 (3 H) assigned to the C-4 methyl group, a singlet at τ 8.55 (9 H) for the *t*-butyl group, two doublets at τ 4.73 (2 H) assigned to the olefinic protons, and a multiplet from τ 5.5 to 7.5 (6H) assigned to the methylene protons (4), the proton at C-4 (1), and the nitrogen proton (1). Also the infrared spectrum showed peaks near 6.0 and 11.0 μ characteristic of $R_2C{=}CH_2$. Furthermore, hydrogenation of XV · HCl gave a saturated product (XVI · HCl) whose pmr spectrum showed two sets of doublets and a singlet at τ 9.13, 8.85, and 9.0, respectively (15 H), assigned to the C-3 and C-4 methyl groups and the *t*-butyl, plus two multiplets centered at τ 7.75 (3H) and 7.0 (3 H) for the single protons at C-3 and C-4 and the two methylenes bonded to nitrogen.

The sodium–ammonia reduction of N-propargyl-N-benzyl-*t*-butylamine (Table I, entry 10) was included to ascertain if ring closure of the ethynyl group with aromatic carbon could be achieved in this seemingly favorable instance. Cyclization did not occur, however, and the product proved to be entirely N-allyl-N-benzyl-*t*-butylamine.

Mechanistically, cyclizations induced by sodium–ammonia likely proceed essentially as suggested by Stork, *et al.*,[4a] for cyclization of γ-ethynyl ketones. As applied to our substrates, however, the reaction is believed to involve the union of a radical center (rather than a carbanion[4a]) derived from one ethynyl group with the appropriate allylic or propargylic carbon atom in the other unsaturated group. Clearly, 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[3] A → C.

It is also worthy of note that two tertiary amine hydrochlorides, those prepared from N,N-diallylisobutylamine and from N-allyl-N-benzyl-*t*-butylamine,

(1) Paper no. 83 on substituted acetylenes. Previous paper: G. F Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **31**, 970 (1966).

(2) Eli Lilly Co, Fellow, 1964–1965.

(3) G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **30**, 2645 (1965).

(4) For recently reported related cyclizations also achieved *via* reductions with sodium, see (a) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Am. Chem. Soc.*, **87**, 1148 (1965); (b) M. Eakin, J. Martin, and W. Parker, *Chemical Commun.*, **No. 11**, 206 (1965).

TABLE I

SODIUM–AMMONIA REDUCTIONS OF BISPROPARGYL- AND PROPARGYLALLYLAMINES

$R^1R^2NCH_2C{\equiv}CH$

			Reduction products[a]			
					Composition, %	
Entry	R^1	R^2	Bp, °C (mm)	Yield, %	Acyclic E	Cyclic D
1	Propargyl	Methyl	108–112 (atm)	72	95	5
2	Propargyl	Ethyl	71–74 (105)	70	92	8
3	Propargyl	*n*-Propyl	79–83 (75)	71	88	12
4	Allyl	*n*-Propyl	76–82 (74)	79	84	16
5	Propargyl	Isopropyl	57–61 (18)	64	82	18
6	Propargyl	Isobutyl	74–81 (50)	79	86	14
7	Allyl	Isobutyl	74–85 (47)	82	83	17
8	Propargyl	*t*-Butyl	58–68 (18)	68	36	64
9	Allyl	*t*-Butyl	63–68 (18)	73	38	61
10	Benzyl	*t*-Butyl	40–51 (0.1)	82	100[b]	0

[a] E = N,N-diallylalkylamine and D = 1-alkyl-3-methylene-4-methylpyrrolidine. [b] Product is N-allyl-N-benzyl-*t*-butylamine, bp 63–65° (0.5 mm).

TABLE II

AMINES AND PYRROLIDINES

$R^1R^2R^3N$

							Hydrochloride or oxalate salt					
					Bp,			Mp,	% C		% H	
Compd	R^1	R^2	R^3	Method	°C (mm)	Yield, %	Formula	°C	Calcd	Found	Calcd	Found
I	C_2H_5	$HC{\equiv}CCH_2$	$HC{\equiv}CCH_2$	B	84–86 (65)	55	$C_8H_{12}ClN$	142–144	60.95	61.12	7.68	7.90
II	*n*-C_3H_7	$HC{\equiv}CCH_2$	$HC{\equiv}CCH_2$	A	90–92 (55)	32	$C_9H_{14}ClN$	142–144	62.97	63.00	8.22	8.45
III	*n*-C_3H_7	$HC{\equiv}CCH_2$	$CH_2{=}CHCH_2$	C	76–78 (47)	28	$C_9H_{16}ClN$	134–136	62.23	62.20	9.29	9.45
IV	*n*-C_3H_7	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	A[a]	78–79 (73)	15	$C_{11}H_{19}NO_4$	119–121	57.62	57.77	8.35	8.57
V	*n*-C_3H_7	$-CH_2CH(CH_3)C(=CH_2)CH_2-$		See Table I, entries 3 and 4			$C_{11}H_{19}NO_4$	191–192	57.62	57.82	8.35	8.44
VI	*i*-C_3H_7	$HC{\equiv}CCH_2$	$HC{\equiv}CCH_2$	A	72–74 (18)	32	$C_9H_{14}ClN$	160–161	62.96	62.95	8.22	8.30
VII	*i*-C_3H_7	$CH_2{=}CH{-}CH_2$	$CH_2{=}CHCH_2$	A[a]	55–57 (23)	30	$C_9H_{18}ClN$	125–127	61.52	61.48	10.32	10.53
VIII	*i*-C_4H_9	$HC{\equiv}CCH_2$	$HC{\equiv}CCH_2$	B	77–80 (30)	57	$C_{10}H_{16}ClN$	168–169	64.68	64.89	8.69	8.79
IX	*i*-C_4H_9	$HC{\equiv}CCH_2$	$CH_2{=}CHCH_2$	C	78–84 (50)	41	$C_{10}H_{18}ClN$	135–137	63.98	63.95	9.66	9.65
X	*i*-C_4H_9	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	B[a]	67–71 (50)	21						
XI	*i*-C_4H_9	$-CH_2CH(CH_3)C(=CH_2)CH_2-$		See Table I, entries 6 and 7			$C_{12}H_{21}NO_4$	168–169	59.24	59.44	8.70	8.88
XII	*t*-C_4H_9	$HC{\equiv}CCH_2$	$HC{\equiv}CCH_2$	C	74–76 (18)	41	$C_{10}H_{16}ClN$	204–206	64.68	64.53	8.69	8.60
XIII	*t*-C_4H_9	$HC{\equiv}CCH_2$	$CH_2{=}CHCH_2$	C	63–64 (20)	45	$C_{10}H_{18}ClN$	186–187	63.98	64.02	9.66	9.68
XIV	*t*-C_4H_9	$CH_2{=}CHCH_2$	$CH_2{=}CHCH_2$	A[a]	62–64 (15)	3	$C_{10}H_{20}ClN$	124–126	63.30	63.47	10.63	10.58
XV	*t*-C_4H_9	$-CH_2CH(CH_3)C(=CH_2)CH_2-$		See Table I, entries 8 and 9			$C_{10}H_{20}ClN$	183–185	63.30	63.18	10.63	10.77
XVI	*t*-C_4H_9	$-CH_2CH(CH_3)CH(CH_3)CH_2-$		[b]		89	$C_{10}H_{22}ClN$	181–183	62.64	62.79	11.57	11.81
XVII	*t*-C_4H_9	$HC{\equiv}CCH_2$	$C_6H_5CH_2$	C	61–64 (0.3)	53	$C_{14}H_{20}ClN$	201–203	70.72	70.67	8.48	8.60

[a] See also Table I. [b] By hydrogenation of XV as previously described.[3]

suffered rapid loss of an allyl group when crystallization was attempted from mixed solvents containing ethanol. The products were allylisobutylamine hydrochloride and benzyl-*t*-butylamine hydrochloride,[5] respectively. The latter case is particularly noteworthy since N-allyl-N-benzyl-*t*-butylamine hydrochloride has three different groups presumably liable to cleavage as carbonium ions.

Experimental Section

New compounds prepared as starting materials are included in Table I. No attempt was made to produce these in optimum yields. The methods used were as follows.

Method A.—A mixture of 0.5 mole of alkylamine (RNH_2), 1.2 moles of anhydrous powdered potassium carbonate, and 250 ml of ether was stirred mechanically, and 1.2 moles of allyl or propargyl bromide was added dropwise. The mixture was boiled, with stirring, for 6 to 18 hr. Water was added to dissolve the salts. The ethereal layer was extracted with 100 ml of 6 *N* hydrochloric acid with cooling. The acidic aqueous solution was extracted with two 50-ml portions of ether (discarded) and then treated with 100 ml of 6.5 *N* sodium hydroxide solution. The layers were separated and the aqueous portion was extracted with three 50-ml portions of ether. The amine layer and ether extracts were combined, dried over anhydrous potassium carbonate, and then distilled.

Method B.—Propargyl or allyl bromide (0.75 mole) was added dropwise with stirring to 1 mole of aqueous primary amine (*e.g.*, 70% ethylamine) while maintaining the temperature at 35–45°. After slow cooling to room temperature, 1.1 moles of sodium hydroxide solution was added dropwise with stirring over a period of 1 hr. The layers were separated, the aqueous portion was extracted with ether, and the extract was combined with the amine layer. The ethereal solution was dried over anhydrous potassium carbonate and fractionally distilled.

Method C.—The general procedure of method A was used in two steps with isolation of the intermediate secondary amine followed by realkylation to introduce the third group. For the first step 3–5 moles of primary amine was employed with 1.5 moles of potassium carbonate and 1.5 moles of allyl or propargyl bromide. The isolated product (distillation) was further alkylated using 0.5 mole with 0.55 mole of potassium carbonate and 0.5 mole of allyl or propargyl bromide. The yields listed in Table II are for the second step only and are corrected for recovered starting material.

N-Benzyl-*t*-butylamine was prepared by a method previously described.[6]

Sodium–ammonia reductions were carried out by alternate additions of metallic sodium and ammonium chloride to substrates dissolved in liquid ammonia as reported earlier.[3]

Hydrochloride or oxalate salts were precipitated from ethereal solutions and usually crystallized from mixtures of ethyl acetate and absolute ethanol. Oxalate salts were prepared when the hydrochlorides were found to be very hygroscopic.

(5) B. L. Emling, R. Horvath, A. Saraceno, E. Ellermeyer, L. Haile, and L. Hudac, *J. Org. Chem.*, **24**, 657 (1959).

(6) N. Bortnick, L. Luskin, M. Hurwitz, W. Craig, L. Exner, and J. Mirza, *J. Am. Chem. Soc.*, **78**, 4039 (1956).

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Quaternary Salts from the Alkylation of Tertiary Amines with *t*-Propargylic Chlorides[1]

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Recently we reported[3] that *t*-propargylic chlorides, $R^1R^2C(Cl)-C\equiv CH$, alkylate trimethylamine to produce either propargylic or allenic quaternary salts depending on the size of R^1 and R^2, allenic products being produced when both are larger than CH_3. Further study of this reaction, employing a wide variety of tertiary amines as well as assorted *t*-propargylic chlorides, has revealed that it may take three courses which are shown in Scheme I. The particular

SCHEME I

$$R^1R^2C(Cl)-C\equiv CH + R^3R^4R^5N \longrightarrow \begin{cases} R^3R^4R^5N\cdot HCl + \text{enyne} \\ R^1R^2C(\overset{+}{N}R^3R^4R^5)-C\equiv CH(Cl^-) \\ R^1R^2C=C=CH-NR^3R^4R^5(Cl^-) \end{cases}$$

outcome in any one case depends not only on steric factors but also on the basicity and nucleophilicity of the particular tertiary amine employed. Quaternary salts, propargylic and/or allenic, appear to be the favored products from amines $R^3R^4NCH_3$ having pK_b in the range *ca.* 3.5–7.5. While weaker bases react very slowly, if at all, and stronger ones seemingly favor elimination, other factors certainly are involved.

Although it is not possible at this stage to disentangle and assess the solvation, basicity, nucleophilicity, and steric factors which favor quaternary salt formation over elimination, or determine whether the product will be propargylic or allenic, the following observations must be significant. The three reactions pictured above always proceed competitively; in most instances one, sometimes two, reactions are favored. Triethylamine, cyclohexyldimethylamine, dodecyldimethylamine, and 3-dimethylamino-3-methyl-1-butyne reacted chiefly by elimination and thus produced their own hydrochlorides as the only isolable products. Methyldiethylamine gave viscous oils which could not be crystallized; infrared examination indicated that the oils were mixtures of amine hydrochloride and both quaternary salts. N-methylpyrrolidine gave the propargylic quaternaries by reaction with 3-chloro-3-methyl-1-butyne and with 1-ethynylcyclohexyl chloride, but an oil, mostly the hydrochloride, by treatment with 3-chloro-3-ethyl-1-pentyne. N-methylpiperidine gave allenic quaternaries except again with 3-chloro-3-ethyl-1-pentyne which produced an oily mixture of hydrochloride and both quaternaries.

Dimethylpropyl-, dimethylallyl-, and dimethylpropargylamine, differing but little in steric features but significantly in basicity, gave good yields of quaternaries. Dimethylpropargylamine, the least basic of these three, uniquely produced the allenic and propargylic salts in about equal amounts, readily separated by selective extraction and recrystallization (see Experimental Section).

While no crystalline products were isolated from the treatment of pyridine with *t*-propargyl chlorides, the reaction of 2,4,6-collidine with 3-chloro-3-methyl-1-butyne gave a 35% yield of a brown salt, mp 203–204°, for which C,H,N analysis and infrared examination indicated a propargylic structure.

Propargylic and allenic quaternary ammonium salts [20 new] are described in Table I. It should be noted that all are hygroscopic and melt with decomposition; each one is a methochloride and hence was prepared from an amine $CH_3NR^3R^4$. Structures were established by infrared and pmr examination as previously reported.[3]

The pmr spectrum of 3-(N-propargylmethylamino)-3-methyl-1-butyne methochloride (Table I, compound II) showed a singlet at τ 5.4 assigned to methylene protons of the propargyl group, a singlet at τ 6.5 for the N-methyl protons, and a singlet at τ 7.9 for the C-methyl protons. The allenic isomer (Table I, compound XIV) showed a multiplet at τ 3.4 (allenic proton), a singlet at τ 5.6 assigned to the methylene protons of the propargyl group, a singlet at τ 6.7 (N-methyl protons), and a doublet with J = 2 cps at τ 8.1 assigned to the remaining methyl protons (both spectra in D_2O with water as internal standard).

Finally it should be stated that the various reaction products are believed to arise *via* zwitterion carbenes ($R^1R^2{}^+C-C\equiv C^- \longleftrightarrow R^1R^2C=C=C:$) as previously discussed.[3]

Experimental Section

Infrared spectra were obtained for chloroform solutions; pmr spectra with chloroform-*d* solutions with TMS as the internal standard or with D_2O solutions having water as the internal standard.

The *t*-propargylic chlorides were prepared as previously described.[4] Tertiary amines were purchased or prepared by methods given in the literature.

Quaternary chlorides were prepared by the procedure described earlier[3] except that the reactions were allowed to proceed for 24–72 hr depending on the rate of crystallization of product. In most instances the product was recovered by filtration; in some experiments the solvent (usually acetone) was removed by evaporation or distillation *in vacuo*. Crystallization usually was achieved using acetone, acetonitrile, ethyl acetate, absolute ethanol, chloroform, or an appropriate binary mixture of these.

Reaction of N,N-Dimethylpropargylamine with 3-Chloro-3-methyl-1-butyne.—A 0.1-mole scale experiment gave 11 g (60% yield) of crude product after 72 hr. Approximately half of this material dissolved by boiling with a mixture of acetonitrile and chloroform. Several crystallizations of the material so extracted (same solvent mixture) gave 1-(N-propargylmethylamino)-3-methyl-1,2-butadiene methochloride (XIV), mp 119–120°. The residue from the original extraction was crystallized from a mixture of ethyl acetate and isopropyl alcohol to give 3-(N-propargylmethylamino)3-methyl-1-butyne methochloride

(1) Paper no. 84 on substituted acetylenes. Previous paper: G. F. Hennion and R. H. Ode, *J. Org. Chem.*, **31**, 1975 (1966).

(2) Eli Lilly Co. Fellow, 1962–1965.

(3) G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **30**, 3696 (1965).

(4) G. F. Hennion and A. P. Boisselle, *ibid.*, **26**, 725 (1961).