Ring-Opening Nucleophilic Alkylations by Tertiary Azetidines

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N-Alkylazetidines were cleaved by nucleophilic reagents under moderate conditions to give the corresponding 3-substituted-propylamines. The additions were subject to acid catalysis and also proceeded slowly under alkaline S_N2 conditions.

The effects of ring strain and substituents on the reactivity of small heterocycles are of continuing interest. Although the four-membered nitrogen heterocycles had generally been considered to lack entirely the well-established alkylating activities of aziridines and aziridinium salts (1), several groups of workers have recently demonstrated the alkylation of nucleophiles by various azetidinium cations (2). The reactions were slower or required more vigorous conditions as would be predicted from a smaller ring-strain energy for the four-membered ring. However, these ring cleavages were not different in kind from those involving the three-membered cycles. We now report unequivocal examples of similar reactions of tertiary azetidines (3).

The buffered acetolysis of 1-*t*-butyl-3-chloroazetidine appeared to occur in part *via* 1-*t*-butyl-3-acetoxyazetidine (**1a**) (4), which was opened to form *t*-butyl-2,3-diacetoxy-propylamine (**2**). This unexpectedly facile cleavage of a tertiary azetidine by a weak nucleophile under relatively

mild conditions was confirmed by direct conversion of **1a** to **2** in excellent yield (Table, Run 1). The product was characterized by spectral methods, including nmr, and synthesized from *t*-butylglycidylamine (5) by usual methods (see Experimental). These observations suggested that alkylations by azetidines generally were feasible.

However, failure met attempts to open 1-*t*-butyl-3-azetidinol (**1b**) (6) at 100-125° with typical nucleophiles (sodium methoxide in methanol, diethylamine) which added smoothly to related quaternary azetidinium salts (2c). The implication seemed clear that acetic acid was providing both the nucleophile and an acidic catalyst, as indicated in 1 (3,7).
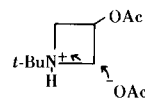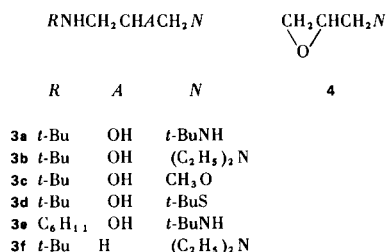

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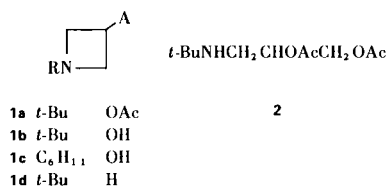
Evidence supporting this interpretation included successful alkylations in which the acid catalyst and the nucleophile were distinct entities. Thus, the strongly acidic trifluoroacetic acid, which ionizes to a poorly nucleophilic anion, was an efficient catalyst for good

t-BuNHCH₂CHOAcCH₂OAc

1a *t*-Bu	OAc	**2**
1b *t*-Bu	OH	
1c C₆H₁₁	OH	
1d *t*-Bu	H	

TABLE I

Alkylations by Tertiary Azetidines

Run	Azetidine	Nucleophile-Catalyst	°C - Days	Conversion, %	Product	B.p., °C/1 mm.	n_D^{25}	Formula	Analyses, Calcd. Found			
									C	H	N	S
1	1a	KOAc - HOAc	100 - 4	87	2	88-89	1.4366	$C_{11}H_{21}NO_4$	57.11 56.98	10.12 10.38		7.40 6.93
2	1b	t-BuNH$_2$ - TFA (a)	120 - 3	63	3a	(m.p. 58-60)		(5)				
3	1b	Et$_2$NH - TFA	120 - 3	91	3b	77	1.4469	$C_{11}H_{26}N_2O$	65.29 65.37	12.95 12.88	13.85 13.84	
4	1b	MeOH - TFA	120 - 1	4 (b)	3c	(m.p. 29-31)	1.4406 (c)	$C_8H_{19}NO_2$	59.59 59.85	11.88 12.19	8.69 8.92	
5	1b	Et$_2$NH - BF$_3$	120 - 0.3	82	3b	(see Run 3)						
6	1c	t-BuNH$_2$ - BF$_3$	120 - 0.8	57	3e	(m.p. 65-66)		$C_{13}H_{28}N_2O$	68.37 68.55	12.36 12.38	12.27 12.14	
7	1b	t-BuSNa - MeOH	110 - 0.9	34	3d	(m.p. 47-49)		$C_{11}H_{25}NOS$	60.22 60.28	11.49 11.50	6.39 6.60	14.61 14.71
8	1b	Et$_2$NH - -	150 - 10	21 (b)	3b	(see Run 3)						
9	1d	Et$_2$NH - BF$_3$	100 - 3	74	3f	44-45	1.4334	$C_{11}H_{26}N_2$	70.90 70.93	14.06 14.11	15.04 14.73	
10	1d	Et$_2$NH - TFA	100 - 1	61	3f	(see Run 9)						
11	1d	Et$_2$NH - -	130 - 2	16	3f	(see Run 9)						

(a) Trifluoroacetic acid. (b) Determined by g. c. (c) Supercooled liquid.

nonionic nucleophiles (NH).   t-Butylamine or diethyl-amine opened the azetidinol **1b** to yield the expected diamines, **3a** (5) and **3b**, (Runs 2 and 3) respectively. Even methanol, a relatively weak nucleophile which slowly opened the azetidinium ring at 60° (2c), added with tri-fluoroacetic acid catalysis to give **3c** (Run 4). The structures **3** were confirmed by independent synthesis: t-butylamine added at the terminal epoxide carbon atom of the appro-priate glycidyl derivatives, **4**.

$$RNHCH_2CHACH_2N \qquad \underset{O}{CH_2CHCH_2N}$$

	R	A	N	4
3a	t-Bu	OH	t-BuNH	
3b	t-Bu	OH	(C$_2$H$_5$)$_2$N	
3c	t-Bu	OH	CH$_3$O	
3d	t-Bu	OH	t-BuS	
3e	C$_6$H$_{11}$	OH	t-BuNH	
3f	t-Bu	H	(C$_2$H$_5$)$_2$N	

Lewis acid catalysis was also demonstrated using boron trifluoride.   Thus, diethylamine added smoothly to t-butylazetidinol (Run 5) and t-butylamine to 1-cyclo-hexylazetidinol (**1c**), (6) (Run 6).

However, acid catalysis was not mandatory for reaction with strong nucleophiles. Sodium t-butylmercaptide in methanol converted **1a** to the expected sulfide, **3d** (Run 7). Indeed, at 150° **1a** slowly added uncatalyzed diethylamine in 21% yield, 14% of **1a** remaining unchanged (Run 8). Thus, simple S_N2 conditions were less efficient than acid catalysis.

The hydroxyl or acetate substituent at the 3-position in the above azetidines is not required for successful ring opening.   1-t-Butylazetidine (**1d**) (8) added diethylamine with either boron trifluoride or trifluoroacetic acid catalysis to give **3f** (Runs 9 and 10) or without catalysis in poor yield at 130° (Run 11). Hindering N-alkyl groups served mainly to suppress secondary reactions of the initial products. It should be added that the above "uncatalyzed" reactions may involve catalytic traces of adventitious acidic impurities.

Acid-catalyzed competitive reactions of t-butylazeti-dinol and 1,1-diethyl-3-hydroxyazetidinium perchlorate (2c) with equimolar diethylamine and boron trifluoride were carried out to study the relative reactivities of these tertiary and quaternary heterocycles. In acetonitrile or methanol, none of the product (**3b**) from the azetidinol and diethylamine was detected. In both solvents, 1,3-bis(diethylamino)-2-propanol (9) was the only competitive product (43% and 24% yields, respectively). Somewhat surprisingly, methanol present in excess gave 49% yield of 1-diethylamino-3-methoxy-2-propanol (10) and 43% of **3c** from the azetidinium salt and azetidinol, respectively.

Clearly, relative reactivities varied markedly with the nucleophile-solvent. Further, a knowledge of the complex equilibria involving the acid catalyst would be necessary for an exact analysis of such results.

The evidence to date (1,2, and this work) suggests the following decreasing order of ease of ring-opening alkyla-tion for small nitrogen heterocycles: aziridinium cations, aziridinium acid salts, aziridines, azetidinium quaternary cations, azetidinium acid salts, azetidines. This order implies that ring strain is the most important factor and that inductive weakening of the N-C bond determines reactivity within a given ring size.

EXPERIMENTAL (11)

Alkylations and Alternative Syntheses.

The tabulated data include some composite results.

Run 1.

A typical reaction mixture was 5.1 g. of **1a** (6) and 5.9 g. of anhydrous potassium acetate in 30 g. of glacial acetic acid. After being heated in a small stainless steel bomb, the iced mixture was treated cautiously with excess aqueous sodium carbonate and ether. The extracted oil was distilled to give pure **2**; n.m.r. τ (CH$_3$)$_3$C, 8.93, OCOCH$_3$, 7.94, 7.97, CH$_2$OAc, 7.26, d, NCH$_2$, 5.6-5.8, 4 lines, CHOAc, 4.8-5.1, m.; infrared, 3.37, 5.76, 6.94, 7.32, 8.1-8.2 (b), 9.25 (s), 9.56, 9.76 (s), 10.46 μ (b).

An identical sample was prepared from 6.5 g. t-butylglycidyl-amine (5) in 25 ml. ether containing 1.0 g. pyridine, treated in a 20° bath with 5.1 g. acetic anhydride. After two days, the mixture was hydrolyzed cautiously at 25° with water and ether, and the ether layer was iced and extracted with dilute hydrochloric acid. The extracts were basified (ice) and extracted, giving 3.3 g. of distilled **2**, n$_D^{25}$ 1.4357.

A mixture of 21.5 g. of glycidyl acetate and 27.1 g. of t-butylamine were condensed without solvent in a 20° bath for 11 days. Distillation gave 1-acetoxy-3-t-butylamino-3-propanol, b.p. 86-87°/1 mm; n$_D^{26}$ 1.4471; 31.0 g. (89%); n.m.r. τ (CH$_3$)$_3$C, 8.88, CH$_3$CO, 7.92, NCH$_2$, 7.0-7.5, m, CHOHCH$_2$OAc, 5.6-6.4, m; infrared, 3.0 (b), 3.38, 5.78, 6.8-7.0 (b), 7.35, 8.15 (b), 9.0 (b), 9.6 μ (b).

Anal. Calcd. for C$_9$H$_{19}$NO$_3$:   C, 57.11;   H, 10.12;   N, 7.40. Found: C, 56.98; H, 10.38; N, 6.93.

Acetic anhydride in ether at 0-10° converted the monoacetate to the diacetate **2** in 50% yield. An acetamide was also isolated, and it proved to be identical with the acetamide obtained in 95% yield from the monoacetate or from the diacetate, (**2**) directly, N-t-butyl-N-2,3-diacetoxypropylacetamide, b.p. 135-137°/1mm; n$_D^{?0}$ 1.4508;   n.m.r. τ (CH$_3$)$_3$C, 8.57, 2 CH$_3$COO, 7.94, CH$_3$CON, 7.87, NCH$_2$, 6.2-6.4, 3 lines, CH$_2$OAc, 5.4-6.1, 8 lines, in 2 AB pattern, CHOAc, 4.4-4.9, m; infrared, 3.36, 5.74, 6.09, 7.0 (s), 7.2 (s), 7.3, 8.2 (b), 9.17 (s), 9.6 μ (b). It remained impure after redistillation.

Anal. Calcd. for C$_{13}$H$_{23}$NO$_5$:   C, 57.12;   H, 8.48;   N, 5.13. Found: C, 57.88; H, 8.84; N, 5.20.

The reaction of glycidyl acetate with t-butylamine in methanol at 35° for 2 days gave, by transesterification *in situ*, 1-t-butyl-amino-2,3-propanediol, b.p. 90-92°/1 mm, 67% yield. It solidified after several days, m.p. 67-68°;   n.m.r. τ (CH$_3$)$_3$C, 8.89, NCH$_2$, 7.2-7.5, m, CHOHCH$_2$OH, 6.1-6.6 m.

Anal. Calcd. for $C_7H_{17}NO_2$: C, 57.11; H, 11.64; N, 9.52; amine neutralization equivalent, 147. Found: C, 56.61; H, 11.59; N, 9.23; amine neutralization equivalent, 151.

Runs 2 and 3.

A mixture of 5.7 g. of trifluoroacetic acid in 7.3 g. of *t*-butyl-amine and 10 ml. of methanol (cool, mix cautiously) was treated with 6.5 g. of 1-*t*-butyl-3-azetidinol (6) and heated in the bomb. Concentration in a rotary vacuum evaporator followed by basification and extraction gave 6.4 g. of 1,3-*bis*-(*t*-butylamino)-2-propanol (5), m.p. 58-60°; n.m.r. τ (saturated) (CH_3)$_3$C, 8.92, CH_2, 7.3-7.7, two broad peaks, *OH*-N*H*, 6.6-7.2, broad singlet, C*H*OH, 6.1-6.6 m.

Run 3 was conducted similarly with diethylamine. 1-*t*-Butylamino-3-diethylamino-2-propanol (3b) was also prepared (76% yield) from diethylglycidylamine and a fivefold excess of *t*-butylamine with water catalysis at 120°; n.m.r. τ 2 CH_3CH_2, 9.01, t, (CH_3)$_3$C, 8.92, all CH_2, 7.3-7.8, m, C*H*OH, 6.1-6.6, m.

Run 4.

t-Butylazetidinol (2.60 g.) and 1.2 g. of trifluoroacetic acid in 10 ml. of methanol was heated at 120° for one day and aspirated. The residue was dissolved in aqueous alkali and ether and diluted with sufficient water to just dissolve the sodium **trifluoroacetate** layer yielding 1.15 g. of an oil, b.p. 65-71°/1 mm. Analysis by g.c. indicated the presence of unchanged azetidinol, two very minor unidentified products, and 1-*t*-butylamino-3-methoxy-2-propanol (3c). Comparisons of both the free propanol and its trimethylsilyl derivative on two g.c. columns with authentic samples (below) identified the major product and indicated a 4% conversion from the azetidinol charged.

1,2-Epoxy-3-methoxypropane and *t*-butylamine were condensed at 120° in the presence of 10% water to form 3c in 82% yield, b.p. 60-61°/1 mm. It crystallized upon standing for several weeks. This compound was also prepared from *t*-butylglycidyl-amine (5) with sodium methoxide in methanol at 60° in 67% yield; n.m.r. τ (CH_3)$_3$C, 8.91, NC*H*$_2$, 7.3-7.55, 3 peaks, CH_3OCH_2, 6.5-6.8, 2 major lines, C*H*OH, 6.0-6.5, m.

Runs 5 and 6.

A reaction mixture containing 2.60 g. of azetidinol 1b, 7.3 g. of diethylamine, and 0.28 g. of boron trifluoride ethyl etherate, after being heated, was aspirated, basified, extracted, and distilled. The product was identical with 3b obtained by the above methods.

The cyclohexylazetidinol 1c (6) was condensed similarly with *t*-butylamine, and the product (3e) was also prepared in 85% yield from *t*-butylglycidylamine and cyclohexylamine. Sublimation at 60° or refrigeration in pentane solution gave needles, m.p. 53-54°. Recrystallization from petroleum ether provided a more stable form, m.p. 65-66°. Mixtures from either source melted at the higher temperature. The n.m.r. spectrum showed the expected complex broad resonances and the *t*-butyl singlet at τ 8.9. Sublimation at 60°/1 mm. was necessary to obtain a sample analyzing correctly.

Run 7.

To *t*-butyl mercaptan (9.0 g.) dissolved in 18.7 g. of sodium methoxide - in - methanol (4.82 m.e./g.) and 30 ml. of methanol was added 6.3 g. of *t*-butylazetidinol. The mixture was heated and then taken to dryness at 100°. The residual cake was dissolved in water and extracted with ether. Distillation gave a forerun containing 1.2 g. of the azetidinol which was partially lost in the washes.

1-*t*-Butylamino-3-*t*-butylthio-2-propanol, (3d) was also prepared

from 1-*t*-butylthio-3-chloro-2-propanol, which in turn was obtained from a mixture (0.30 mole each) of *t*-butyl mercaptan and epi-chlorohydrin by adding 0.5 ml. of 40% benzyltrimethylammonium methoxide in methanol. After a slow exotherm to 35°, the mixture was allowed to stand overnight. Water washing and distillation gave 35.5 g. (65%) of 3d, b.p. 66-67°/1 mm.; n_D^{25} 1.4917; n.m.r. τ (CH_3)$_3$C, 8.66, SC*H*$_2$, 7.1-7.3, 3 lines, C*H*O*HCH*$_2$, 6.2-6.8, 5 main lines, C*H*OH, 5.8-6.2, m. It could not be completely purified by redistillation.

Anal. Calcd. for $C_7H_{15}ClOS$: C, 46.01; H, 8.28; Cl, 19.41; S, 17.55. Found: C, 46.60; H, 8.57; Cl, 20.03; S, 18.65.

This compound was condensed with sixfold excess *t*-butyl-amine and aqueous alkali at 60° in 80% yield. The latter sample crystallized after several months, as did the first product when seeded. Both, from pentane, melted at 47-49° and were identical; n.m.r. τ (CH_3)$_3$CN, 8.90, (CH_3)$_3$CS, 8.69, 4 CH_2, 7.0-7.7, m, C*H*OH, 6.0-6.5, m; infrared, 3.0 (b), 3.2 (s), 3.38, 6.87, 7.22, 7.35, 7.5 (s), 8.2 (b), 8.62 (b), 9.3 (b), 9.8, 11.4 μ (b).

Run 8.

t-Butylazetidinol was heated at 150° with fivefold excess diethylamine in methanol. Periodic sampling and g.c. analysis showed that the yield of 3b reached a maximum after about 10 days. Analysis of the isolated crude product indicated a 21% yield of 3b, corrected for sampling, and 14% of 1a remained.

Runs 9, 10 and 11.

N-*t*-Butylazetidine (8), 4.52 g., in fivefold excess diethylamine was treated with 1.4 g. boron trifluoride ethyl etherate and the mixture was heated at 100°. After 3 days only a trace of the azetidine remained. The mixture contained a dark heavy catalyst-complex layer, which was decomposed by aqueous sodium carbonate solution. Diamine 3f was isolated by extraction and distillation; n.m.r. τ 2 CH_3CH_2, 9.00, t, (CH_3)$_3$C, 8.92, $CH_2CH_2CH_2$, 8.1-8.6, m; 6 CH_2N, 7.2-7.7, m.

A similar run with 0.020 mole trifluoroacetic acid was complete in a day but the yield was only 61%. A sizable polymeric residue was present.

A solution without added catalysts at 130° also contained no more than a trace of azetidine after 2 days. Only 16% yield of 3f was indicated by g.c. analysis. A dark polymer was present.

Competitive reactions.

A solution (20 g. in acetonitrile) of 0.010 mole each of 1,1-diethyl-3-hydroxyazetidinium perchlorate (2c, prepared in 5 ml. acetonitrile by titration of 1.66 g. of the chloride with silver perchlorate), 1.29 g. *t*-butylazetidinol, 0.73 g. diethylamine and 1.41 g. boron trifluoride etherate was heated at 110° for 5 days. The isolated product mixture contained no starting materials, nor was any 3b detected. The yield of 1,3-*bis*(diethylamino)-2-propanol (9) was 0.87 g. (43%). A minor unidentified by-product (leading peak) was poorly resolved at 140°. Since both components exhibited tailing, the percentage of the impurity under the product peak was estimated from the proportion of baseline displacement at the product peak front. Calibration of this method was done with known mixtures of 3b, the above diamine, and the methanol adducts (3c and 1-diethylamino-3-methoxy-2-propanol, 10), which gave sharp peak fronts with serious tailing.

A mixture of 0.035 mole of each of the above reactants was heated in 5.0 ml. methanol for a day. The isolated oil was analyzed as described above for the expected adducts. The conversion were: 1-diethylamino-3-methoxy-2-propanol (10), 49%; 1,3-*bis*(diethylamino)-2-propanol, 24%; 1-*t*-butylamino-3-methoxy-2-propanol, 43%, and 3b, not detected.

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