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SUBSTITUTED 1-ALKYL-3-AZETIDINOLS

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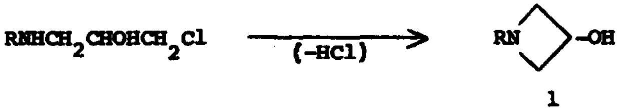
Recent work of Gaertner (1) describes a facile ring closure to 1-alkyl-3-azetidinols (1 a-e)



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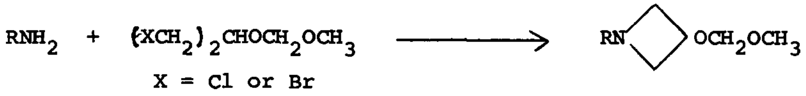
a. cyclohexyl
b. t-butyl
c. 1,1,3,3-tetramethyl butyl
d. 2-propyl
e. neopentyl

when the nitrogen substituent is of high steric bulk. This work accords with an earlier assessment (2) that a bulky nitrogen substituent favors cyclization over competing intermolecular reactions. We describe here a simple preparation of substituted 1-alkyl-3-azetidinols where the nitrogen substituent is of low steric bulk, in order both to extend the utility of this cyclization reaction and to clarify the steric requirements for cyclization.

1,3-Dichloro-2-(methoxymethoxy)propane (3) was reacted with excess aqueous methyl amine at 60-65° for 50 hrs. while passing methylamine gas into the solution. Extraction with chloroform and distillation gave 40-50% yields of 1-methyl-3-(methoxymethoxy) azetidine (2, R=CH_3).



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From 1,3-dibromo-2-(methoxymethoxy)propane, we prepared similarly the additional examples summarized in the table.

1-Alkyl-3-(Methoxymethoxy)Azetidines

R	% Yield	Boiling Point	Refractive Index	% Nitrogen	
				Calcd.	Found
CH_3	40-50	69-73° (40 mm.)	1.4215 at 25°	10.72	10.24**
n-C_4H_9	23*	71-3° (2.5 mm.)	1.4340 at 22°	8.1	7.82
$C_6H_5CH_2$	13-15*	103-5° (0.4 mm.)	1.5117 at 20°	6.77	6.76
$C_6H_5CH_2CH_2$	4*	128-130°(1.0 mm.)	1.5071 at 22.5°	6.34	6.82

* Considerable non-distillable (polymeric?) material formed.
** % C: Calcd 54.9, Found 55.3; % H: Calcd 9.98, Found 10.11.

Under these conditions, excess methylamine reacts with epichlorohydrin or 1,3-dichloro-2-propanol to give principally 1,3-bis(methylamino)-2-propanol in 37% and 53% yields, respectively. No 1-methyl-3-azetidinol could be detected in the reaction mixtures by distillation and gas-liquid chromatographic examination.

These results, when considered with those of Gaertner, are consistent with azetidine 2 formation occurring through intermediate 3, and

$RNHCH_2CHOACH_2X$

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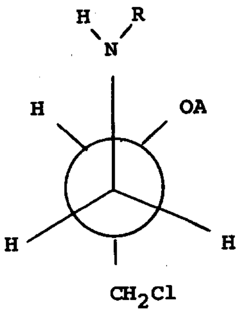
being governed by the total steric bulk of the RNH- and -OA groups. When the sum of the steric bulk of the two groups is low (e.g., CH_3NH- and -OH), the preferred staggered conformation 4 favors intermolecular reactions.



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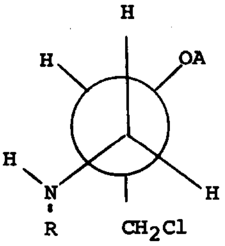

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When the sum of the steric bulk is increased somewhat (e.g., $(CH_3)_2CHNH-$, -OH or CH_3NH-, OCH_2OCH_3), the preferred staggered conformation becomes 5 to minimize the RNH- vs. -OA interaction. This latter conformation approaches the eclipsed transition state required for cyclization, and thus promotes azetidine formation. When the sum of the steric bulk is increased still further, a progressive reduction in the yield of azetidines is observed, indicating that an optimum bulk exists favoring cyclization.

Proper consideration of the steric requirements for cyclization should permit the preparation in satisfactory yield of 3-azetidinols with a wide variety of 1-alkyl substituents.

References

(1) V.R. Gaertner, Tetrahedron Letters, No. 39, 4691 (1966).

(2) W.R. Vaughan, R.S. Klonowski, R.S. McElhinney, and B.B. Millward, J. Org. Chem., 26, 138 (1961).

(3) S. Mamedor, F. Gadzhizade, F. Sharifova, and I. Koval'skaya, Zh. Obshch. Khim., 34, 2868 (1964); Chem. Abstr., 61, 15998 (1964). 1,3-Dibromo-2-(methoxymethoxy) propane was prepared similarly in 81% yield: b.p. 88-92° (2.0 mm.) n_D^{26} 1.4972, % Br Calcd. 61%, Found 61.6%.