The Synthesis of the 1- and 2-Cycloalkyl-1,2,3-benzotriazole System

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The first reported synthesis of 1- and 2-cycloalkyl-1,2,3-benzotriazoles is reported. Physical and spectral data of the system are reported. Molecular orbital calculations on the 1,2,3-benzotriazole anion show that N_1 is a more nucleophilic site than N_2.

1,2,3-Benzotriazole (**1**) and its acyclic alkyl derivatives have found many commercial applications. The cycloalkyl derivatives of **1** have, up to this time, not been reported. We desired to prepare the 1- and 2-cyclopentyl (**6** and **7**), cyclohexyl (**8** and **9**) and cycloheptyl (**10** and **11**) derivatives of **1** so that their properties could be studied and compared with the acyclic derivatives of **1**. The synthetic procedrues utilized for preparing the cycloalkyl derivatives could be used as prototypes for the preparation of heterocyclic derivatives of **1** which should be physiologically active.

The classical procedure (1) for the alkylation of the anion of **1** was used for the preparation of the cyclopentyl and cycloheptyl compounds (Table I). However, cyclohexyl bromide gave only cyclohexene and **1**. Since it is well known that the tosylate is a better leaving group than bromide, we reacted the anion of **1** with cyclohexyl tosylate. The only desired product isolated was **9** (2). Finally, treatment of **1** with tricyclohexyl phosphate (3)
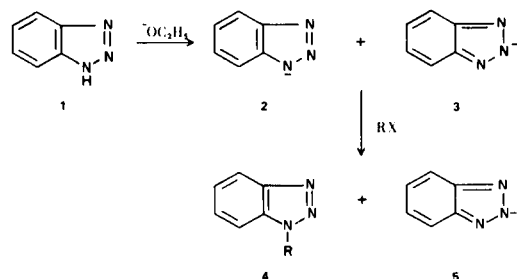
Pi charge densities for the 1,2,3-benzotriazole anion (10)
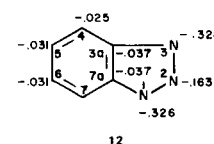
yielded **8** in the complete absence of **9**.

The ultraviolet and nmr spectra (Table I) were very

Table I

Physical and Spectral Properties of the Cycloalkyl-1,2,3-benzotriazoles

Compound	% Yield	M.p. or B.p.	Ultraviolet λ max	Spectrum log ε	Nmr δ ppm (Deuteriochloroform)		Analysis Calcd.		Analysis Found
1-Cyclopentyl (6)	46	144-147° (0.1 mm)	255	4.80	8.0	(1H, m)	C,	70.56	70.42
			263	4.70	7.4	(3H, m)	H,	7.00	6.83
			279	4.72	5.15	(1H, m)	N,	22.44	22.43
					1.8-2.4	(8H, m)			
2-Cyclopentyl (7)	31	130-133° (0.1 mm)	273	5.13	7.9	(2H, m)	C,	70.56	70.38
			279	5.15	7.35	(2H, m)	H,	7.00	7.13
			286	5.08	5.35	(1H, m)	N,	22.44	22.66
					1.7-2.4	(8H, m)			
1-Cyclohexyl (8)	38	103-104°	255	4.24	8.0	(1H, m)	C,	71.61	71.82
			263	4.27	7.4	(3H, m)	H,	7.51	7.69
			279	4.23	4.65	(1H, m)	N,	20.88	21.08
					1.4-2.0	(10H, m)			
2-Cyclohexyl (9)	52	40-42°	273	4.54	7.9	(2H, m)	C,	71.61	71.88
			279	4.53	7.35	(2H, m)	H	7.51	7.73
			286	4.51	4.80	(1H, m)	N,	20.88	20.98
					1.4-2.4	(10H, m)			
1-Cycloheptyl (10)	42	53-55°	255	4.39	8.0	(1H, m)	C,	72.52	72.59
			362	4.58	7.4	(3H, m)	H,	7.96	8.17
			278	4.44	4.9	(1H, m)	N,	19.52	19.80
					1.5-2.4	(12H, m)			
2-Cycloheptyl (11)	28	150-152° (0.1 mm)	273	4.11	7.9	(2H, m)	C,	72.52	72.34
			278	4.15	7.35	(2H, m)	H,	7.96	8.21
			286	4.15	5.0	(1H, m)	N,	19.52	19.30
					1.6-2.5	(12H, m)			

diagnostic in determining the respective 1- and 2-isomers of 1. Of particular note was the λ max at 255 nm for the 4 isomers and the λ max at 273 nm which was characteristic of the 5 isomers. These values are consistent with results calculated for similarly substituted benzotriazoles using CNDO/S molecular orbital theory (4).

We decided to perform an HMO calculation on the anion of 1 represented by structures 2 and 3 in order to ascertain the relative charge densities on N_1 and N_2 so that reaction with the various cyclohexane derivatives could be better understood. The calculations (12) indicate that approximately 85% of the negative π charge is carried on the triazole ring and that N_1 is a much more nucleophilic position than N_2. Since reasonable changes in the parameters do not alter the above results, it is apparent that 2 is the predominant resonance form, which readily explains the product ratio 4:5 = 3:2 reported for the reaction of 1 with acyclic unhindered alkyl halides (5). Since the leaving group being displaced from a cyclohexyl ring normally lies on an equatorial position (6) one can easily visualize that the steric consequences, due to the six-membered ring of 2, which could arise by the attack of 2 via an S_N2 mechanism would cause elimination to be favored over substitution. Attack at position N_2, which is less sterically confined (structure 3), would be expected to yield an S_N2 type reaction. The isolation of only 9 from the reaction of cyclohexyl tosylate and the anion (2,3) demonstrates the severity of the steric situation at N_1 for 2.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. Proton nmr were recorded on a Varian EM-360A. Ultraviolet spectra were recorded on a Cary 14 spectrophotometer. Glpc analysis was performed on a Varian Model 1200 HIFI.

Cyclohexyl Tosylate (7) and tricyclohexyl phosphate (8) were synthesized using reported procedures. Compounds 6, 7, 10 and 11 were prepared using the procedure reported for the synthesis of 1-benzyl-1,2,3-benzotriazole (9). Compound 8 was prepared using the procedure of Yamauchi and Kinoshita (3).

Preparation of 2-cyclohexyl-1,2,3-benzotriazole (9). To a solution containing 1 (0.05 mole) and sodium ethoxide (0.05 mole) in 100 ml. of absolute ethanol was added cyclohexyl tosylate (0.07 mole). The solution was heated at 50° for 2 hours, then refluxed for 2 more hours. Removal of the alcohol under reduced pressure yielded a solid. The solid was placed in water and extracted with ether. The ether solution was dried over sodium sulfate. Vacuum distillation yielded 9. See Table I for relevant physical data.

REFERENCES AND NOTES

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(2) No formation of 8 or 9 was detected by glpc with cyclohexyl bromide. No formation of 8 was detected by glpc with cyclohexyl tosylate.

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(10) HMO calculations were performed using $\alpha_N = 0.5$ and $\beta_{CN} = \beta_{NN} = 1.0$, A. Streitwieser, "Molecular Orbital Theory for Organic Chemists", J. Wiley and Sons, New York, N.Y., 1961.