Shrikant B. Kulkarni and Norman H. Cromwell

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588

Received May 12, 1977

α,γ-Dibromovalerophenone (**3**) reacted with primary amines to give a number of 1-alkyl-2-benzoyl-4-methylazetidines (**4**) in good yield. The results of the base catalyzed reactions performed on these new carboazetidines imply that the *cis* isomer is of greater thermodynamic stability. Furthermore, base catalyzed deuterium exchange studies suggest this to be the case.

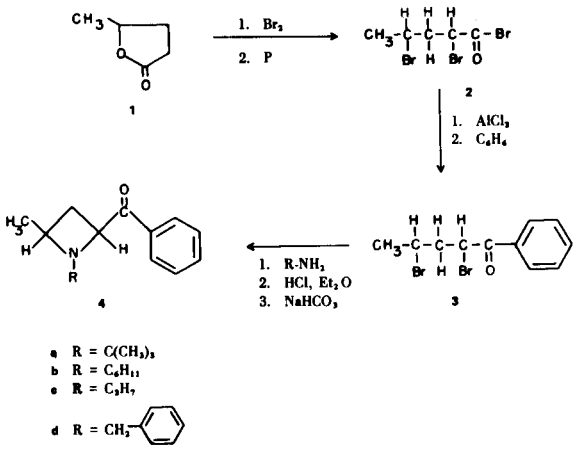
J. Heterocyclic Chem., 14, 981 (1977)

Results and Discussion

Previously it was reported (1) from this laboratory that various primary amines react with α,γ-dibromocarbonyl compounds to give good yields of 2-carboazetidines. Recently (2) this method was extended to include the synthesis of 1-alkyl-2-carbomethoxy-4-methyl(or phenyl)azetidine. We now wish to report the application of the scheme to the synthesis of some 1-alkyl-2-benzoyl-4-methylazetidines desired for our continuing studies of the comparable and contrasting chemistry of the similarly substituted aziridines and azetidines (3).

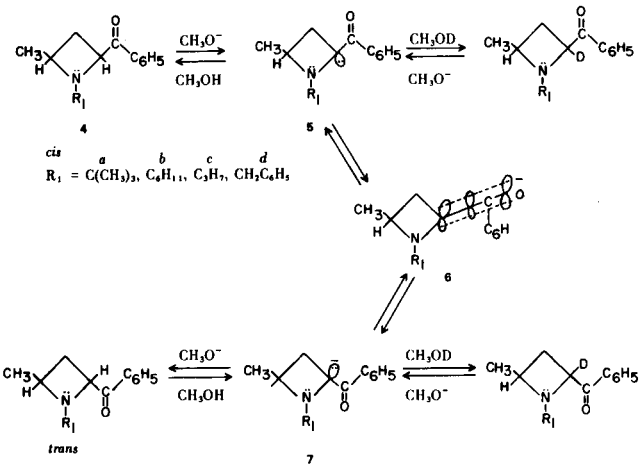
γ-Valerolactone (**1**) was converted to α,γ-dibromovaleryl bromide **2** by treatment of the former with bromine and phosphorus. Tribromo compound **2** was treated with aluminum chloride and benzene to give α,γ-dibromovalerophenone (**3**). 1-Alkyl-2-benzoyl-4-methylazetidines **[4a-d]** were obtained (62-77% yield) by the reaction of **3** with primary amines (see Chart 1).

Chart 1



It has been suggested by Bottini and Roberts (4) that there will be an increase in nitrogen inversion rate when alkyl substituents are attached to carbons on the *N*-substituted aziridine ring. But when these groups are attached in a *cis* orientation to one another, the molecule will have a preferred conformation in which the *N*-substituent will be *anti* to the ring substituents. Nagel and Cromwell (5) have observed that in the case of *cis*-1-alkyl-2-aryl-3-carboaziridines the preferred conformation is the one in which the *N*-alkyl group is *anti* to benzoyl group, and in case of the *trans*-1-alkyl-2-aryl-3-carboaziridines the preferred conformation is the one in which *N*-alkyl and benzoyl groups are *syn* to each other. If the similar situation is assumed in case of *N*-substituted azetidines, the *cis* azetidine should exist in the preferred conformation with *N*-alkyl and benzoyl groups *anti* to each other.

The nmr spectrum of the azetidines **4** showed that each product consisted of only one isomer. When azetidines **4**



were refluxed with sodium methoxide and methanol for 48 hours, the nmr spectrum of the resulting products did not show any epimerization to another isomer. But when azetidines **4** were stirred with potassium *t*-butoxide in deuterated methanol for 72 hours, 65% deuterium incorporation was observed; however, no epimerization was detected.

Molecular models for these *cis* and *trans* pairs of azetidines **4a-d** were examined. The molecular models clearly reveal that 1,2 nonbonded interactions will be

Table 1

Summary of Preparations Data

Dibromoketone **3**		18.12 g. (0.057 mole)				
		Amine g. (mole)	Unreacted Dibromoketone **3** g. (mole)	Amine hydrobromide g. (mole)	Azetidine **4** g. (mole)	% Yield (a)
4a	R = $C(CH_3)_3$	12.55 (0.171)	12.32 (0.038)	3.14 (0.020)	2.60 (0.0112)	62
4b	R = C_6H_{11}	16.92 (0.171)	11.59 (0.036)	4.48 (0.0248)	3.66 (0.0142)	69.4
4c	R = C_3H_7	10.08 (0.171)	11.77 (0.0370)	3.05 (0.0217)	2.71 (0.0124)	62.6
4d	R = CH_2-C_6H_5	18.29 (0.171)	11.05 (0.0347)	5.72 (0.0304)	4.53 (0.0170)	77

(a) Yields of the azetidines are based on the starting material consumed in the reaction.

minimal in case of the *cis* isomer, because in its preferred conformation, the *N*-alkyl group will be *anti* to the groups at C_2 and C_4. (See Chart 2). Also, there will be less lone pair-lone pair interactions in the carbanion of the *cis* isomer **5** than in that of the *trans* carbanion **7**. This is in agreement with Gillespie Nyholm VSEPR theory (4). Therefore, the carbanion of the *cis* isomer will immediately take up the hydrogen or deuterium and retain its configuration. On the other hand, the *trans* carbanion is expected to stereomutate (2) *via* the intermediate enolate **6** to the more stable *cis* carbanion which then again acquires a hydrogen or deuterium to form the *cis* isomer. In the preferred conformation of the *trans* isomer, the group on nitrogen is expected to be oriented mainly *syn* to the carbonyl group (5), which further destabilizes the *trans* isomer and slows the formation of its carbanion.

When these systems tend toward equilibrium, the *cis* isomer seems to be more stable than the *trans* isomer. Hence, the *cis* skeleton is assigned to the 1-alkyl-2-benzoyl-4-methylazetidines (**4a-d**). This result is in agreement with the behavior of the related 1-*t*-butyl-2-carbomethoxy-4-methyl(phenyl)azetidines for which the *cis* isomer was shown to be thermodynamically more stable (2). This result is also comparable to the behavior of the 1-alkyl-2-methyl-3-aroylaziridines in which case the *cis* isomer is also thermodynamically more stable than the *trans* isomer (7,8).

EXPERIMENTAL

Melting points were determined with a Mel-temp, capillary tube melting point apparatus and are uncorrected. Boiling points were determined at pressures recorded on a standard McCleod gauge and are uncorrected. Elemental analyses were performed by MicroTech Laboratories, Skokie, Illinois. The infrared spectra were recorded on a Perkin-Elmer Model 621 Grating infrared spectrophotometer using carbon tetrachloride solutions. The nmr spectra were recorded on a Varian A-60 spectrometer and the chemical shifts are reported in Hertz, with tetramethylsilane as an internal standard. The mass spectra were determined on a AEI MS 5076 spectrometer.

Synthesis of α,γ-Dibromovalerylbromide (**2**).

To a suspension of 6.65 g. of red phosphorus in 49.0 g. (0.49 mole) of γ-valerolactone (**1**) at 20° was added 89.2 g. of bromine in a dropwise manner with cooling and stirring. The reaction mixture was then heated to 60° and an additional 100.1 g. of bromine was added and the reaction mixture stirred overnight at 60°. The unreacted bromine was removed by evaporation under reduced pressure. The dark red mixture was then decanted from the separated phosphoric acid and fractionally distilled in vacuo through a 10-cm- Vigreux column. It afforded 125.44 g. (80% yield) of α,γ-dibromovalerybromide (**2**) which gave an infrared absorption (carbon tetrachloride) at 1790 cm^{-1} (ν C=O). The nmr spectrum (deuteriochloroform) contained, 135-171 Hz, (m, 2H, C_3 protons), 228-268 Hz (m, 1H, C_4-methine proton), 286, 295 Hz, (two t, 1H, C_2 methine proton, two diastereoisomers, J = 4.5 Hz), 106.5, 109.5 Hz, (two d, 3H, C_4 methyl protons, two diastereoisomers, J = 6.5 Hz).

Anal. Calcd. for $C_5H_7Br_3O$: C, 18.57; H, 2.16; Br, 74.30. Found: C, 18.35; H, 2.12; Br, 74.05.

Synthesis of α,γ-Dibromovalerophenone (**3**).

A stirred suspension of 20.3 g. (0.152 mole) of aluminium chloride in 31.2 g. (0.40 mole) of benzene at 0-4° was treated with 51.84 g. (0.162 mole) of **2**, in a dropwise manner over a period of two hours. The reaction complex was immediately hydrolyzed by slowly adding it to a mixture of ice and concentrated hydrochloric acid. After addition of ethyl ether, the organic layer was separated, washed with water and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure followed by vacuum fractional distillation through a 10-cm-Vigreux column afforded 33.48 g. (65% yield), of **3** as a colourless oil, b.p. 110°/(0.1 mm). Compound **3** gave infrared absorption (carbon tetrachloride) at 1685 cm^{-1} (ν > C=O). The nmr spectrum (deuteriochloroform) showed: 435-484 Hz, (m, 5H, aromatic protons), 324, 326.5 Hz (two t, 1H, C_2-methine proton, two diastereoisomers, J = 5.5 Hz), 261, 281 Hz, (m, 1H, C_4 methine proton), 132-172 Hz (m, 2H, C_3 methylene protons), 98.5, 101.5 Hz (two d, 3H, J = 6.5 Hz, C_4-methyl protons, two diastereoisomers).

Anal. Calcd. for $C_{11}H_{12}Br_2O$: C, 41.25; H, 3.75; Br, 50.00. Found: C, 41.05; H, 3.70; Br, 49.90.

General Procedure for the Synthesis of 1-Alkyl-2-benzoyl-4-methylazetidines (**4**).

A 0.057 mole solution of **3** and 0.171 mole of the appropriate primary amine in benzene was stirred in a stoppered flask for 72 hours at room temperature. The solvent was evaporated under reduced pressure and anhydrous ethyl ether was added to the residue. Filtration to remove amine hydrobromide followed by exposure of the filtrate to a stream of hydrogen chloride gas for five minutes gave a syrupy precipitate (*SP*) from which the ether was decanted. The ether was evaporated to give an oily product which was identified as starting material, **3**. After washing with ether, the precipitate (*SP*) was dissolved in 50 ml. of water and 200 ml. of ether was added. An excess of solid sodium bicarbonate was introduced slowly and two liquid layers were separated; the aqueous phase being extracted with an additional 200 ml. of ether. The combined ethereal extracts were dried over magnesium sulfate and the solvent was evaporated under reduced pressure. Evaporation of the ether gave an orange, oily product. This liquid was purified by column chromatography on silica gel using benzene as an eluent. The azetidines **4** were obtained as colourless oils. (See Table 1).

Synthesis of 1-*t*-Butyl-2-benzoyl-4-methylazetidine (**4a**).

The product **4a** gave an infrared absorption (carbon tetrachloride) at, 1695 cm^{-1} (ν_1 >C=O), and 1670 cm^{-1} (ν_2 >C=O). The nmr spectrum (deuteriochloroform) contained, 108-145 Hz, (m, 2H, C_3-methylene protons), 198-222 Hz (m, 1H, C_4-methine proton), 272 Hz, (t, 1H, J = 8.5 Hz, C_2 methine proton), 427-480 Hz, (m, 5H, aromatic protons), 75 Hz (d, 3H, J = 5.9 Hz, C_4 methyl protons), 59 Hz (s, 9H, *t*-butyl); m.p. picrate (ethanol) 182.5-184°.

Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.82; H, 5.33; N, 12.19.

Synthesis of 1-Cyclohexyl-2-benzoyl-4-methylazetidine (**4b**).

The product **4b** gave infrared absorptions (carbon tetrachloride) at 1694 cm^{-1} (ν_1 > C=O), and 1668 cm^{-1} (ν_2 > C=O). The nmr spectrum (deuteriochloroform) contained, 119-154 Hz, (m, 2H, C_3 methylene protons and cyclohexyl, C_1H), 60-112 Hz, (m, remaining cyclohexyl protons), 77 Hz, (d, 3H, J = 6.5 Hz, C_4 methyl protons), 265 Hz (t, 1H, J = 8.5 Hz, C_2 methine proton), 195-218 Hz (m, 1H, C_4 methine proton), 437-485 Hz (m, 5H, aromatic protons).

High resolution mass spectrum M^+: 257.1779.

Molecular wt. calcd. for $C_{17}H_{23}NO$: 257.1774.

Synthesis of 1-Isopropyl-2-benzoyl-4-methylazetidine (**4c**).

The product **4c** gave infrared absorptions (carbon tetrachloride) at 1695 cm^{-1} (ν_1 >C=O) and 1666 cm^{-1} (ν_2 >C=O). The nmr spectrum (deuteriochloroform) contained, 56.5 Hz, (d, 6H, J = 6.7 Hz, isopropyl methylprotons), 112-159 Hz, (m, 2H, C_3 methylene protons), 188-230 Hz (m, 2H, C_4-methine proton and isopropyl methine proton), 269 Hz, (t, 1H, J = 8.5 Hz, C_2 methine proton), 75 Hz (d, 3H, J = 6.0 Hz, C_4 methyl protons), 435-482 Hz, (m, 5H, aromatic protons).

High resolution mass spectrum M^+: 217.1460.

Molecular wt. calcd. for $C_{14}H_{19}NO$: 217.1462.

Synthesis of 1-Benzyl-2-benzoyl-4-methylazetidine (**4d**).

The product **4d** gave infrared absorptions (carbon tetrachloride) at 1695 cm^{-1} (ν_1 >C=O) and 1668 cm^{-1} (ν_2 >C=O). The nmr spectrum (deuteriochloroform) contained, 73.5 Hz (d, 3H, J = 6.1 Hz, C_4 methyl protons), 271 Hz (t, 1H, J = 8.5 Hz, C_2 methine proton), 103-152 Hz (m, 2H, C_3 methylene protons), 188-215 Hz (m, 1H, C_4 methine proton), 228 Hz (s, 2H, CH_2-C_6H_5), 436-481 Hz, (m, 10H, aromatic protons).

High resolution mass spectrum M^+: 265.1466.

Molecular wt. calcd. for $C_{18}H_{19}NO$: 265.1467.

Attempted Epimerization of 1-Alkyl-2-benzoyl-4-methylazetidine (**4a-d**).

A 0.300 g. sample of **4a-d** was refluxed in 5 ml. of absolute methanol with 0.05 g. of sodium methoxide for 48 hours. The methanol was evaporated, ether added and the suspension filtered. Removal of the ether followed by double evaporation with 2 ml. of carbon tetrachloride gave a yellow oil. The nmr spectrum of which indicated no epimerization, to the other isomer.

Reaction of **4a-d** with Deuterated Methanol and Potassium *t*-Butoxide.

A 0.350 g. sample of **4a-d** was stirred in 5 ml. of deuterated methanol with 0.050 g. of potassium *t*-butoxide for 72 hours. The methanol was evaporated, ether added and suspension filtered. Removal of the ether followed by a double evaporation with 3 ml. portion of carbon tetrachloride gave a yellow oil. The nmr spectrum of which indicated 65% deuterium exchange. However no epimerization was detected.

Acknowledgement.

This investigation was supported by Grant No. CA-02931 of the National Cancer Institute, United States Public Health Service.

REFERENCES AND NOTES

(1a) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocyclic Chem.*, **8**, 421 (1971); (b) R. M. Rodebaugh and N. H. Cromwell, *ibid.*, **5**, 309 (1968); (c) R. M. Rodebaugh and N. H. Cromwell, *ibid.*, **6**, 435 (1969); (d) R. M. Rodebaugh and N. H. Cromwell, *ibid.*, **6**, 439 (1969).

(2) S. B. Kulkarni, R. M. Rodebaugh and N. H. Cromwell, *ibid.*, **13**, 329 (1976).

(3) N. H. Cromwell, *ibid.*, **13**, S-1 (1976); ["Lectures in Heterocyclic Chemistry", Vol. III].

(4) A. T. Bottini and J. D. Roberts, *J. Am. Chem. Soc.*, **80**, 5203 (1958).

(5) D. L. Nagel, P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, **36**, 3911 (1971).

(6) For a discussion of lone pair-lone pair interactions see F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3rd Ed., Interscience Publishers, New York, N.Y. 1972, Chapter 4.

(7) E. A. Pohland, R. C. Badger and N. H. Cromwell, *Tetrahedron Letters*, 4369 (1965).

(8) P. Tarburton, A. Chung, R. C. Badger and N. H. Cromwell, *J. Heterocyclic Chem.*, **13**, 295 (1976).