

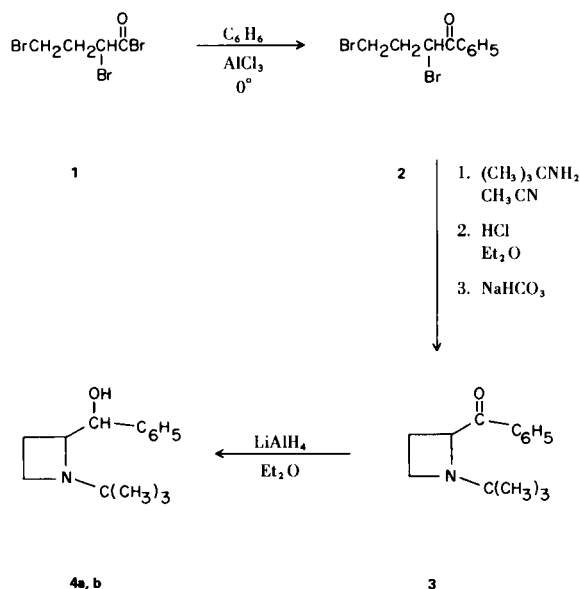
The Synthesis of 1-(*t*-butyl)-2-benzoylazetidines (1a)

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Sir:

In a previous communication (2) we reported that primary amines react with methyl  $\alpha,\gamma$ -dibromobutyrate leading to 1-alkyl-2-carbomethoxyazetidines. The potential value of the ester moiety for providing azetidines with a variety of functional groups in the 2-position has been partially exemplified by the obtainment of DL-azetidine-2-carboxylic acid in good yield from benzyl  $\alpha,\gamma$ -dibromobutyrate (3). To further illustrate the utility of obtaining azetidine derivatives from the reaction of primary amines with  $\alpha,\gamma$ -dibromo carbonyl compounds, we now wish to report our observation that *t*-butylamine reacts with  $\alpha,\gamma$ -dibromobutyrophenone (2) providing the first example of a 2-ketoazetidine (4), 1-(*t*-butyl)-2-benzoylazetidines (3).



Thus, a stirred suspension of 20.3 g. (0.152 mole) of aluminum chloride in 31.2 g. (0.40 mole) of benzene at 0 to  $4^\circ$  was treated in a dropwise manner over a period of two hours with 50.0 g. (0.162 mole of  $\alpha,\gamma$ -dibromo-

butyryl bromide (1) (5). 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 38.1 g. (73% yield) of  $\alpha,\gamma$ -dibromobutyrophenone (2) as a colorless oil, b.p.  $133-135^\circ$  (0.7 mm.). This ketone (2) gave infrared absorption (neat) at  $1688\text{ cm}^{-1}$  ( $\nu\text{ C=O}$ ). The nmr spectrum (carbon tetrachloride) contained a complex multiplet (5H) in the range 435 to 489 Hz (aromatic protons), a triplet (1H) at 326 Hz ( $J = 6.5\text{ Hz}$ ,  $CHBrCO$ ), a triplet (2H) at 216 Hz ( $J = 6.0\text{ Hz}$ ,  $BrCH_2CH_2$ ), and a quartet (2H) at 156 Hz ( $J = 6.2\text{ Hz}$ ,  $BrCH_2CH_2$ ).

Anal. Calcd. for  $C_{10}H_{10}Br_2O$ : C, 39.25; H, 3.29; Br, 52.23. Found: C, 39.53; H, 3.28; Br, 52.46.

A solution of 17.5 g. (0.057 mole) of the dibromo ketone (2) and 12.55 g. (0.171 mole) of *t*-butylamine in 285 ml. of acetonitrile was stirred in a stoppered flask for three days at room temperature. The solvent was evaporated under reduced pressure and anhydrous ethyl ether was added to the residue. Filtration to remove *t*-butylamine hydrobromide followed by exposure of the filtrate to a stream of hydrogen chloride gas for one minute gave a syrupy precipitate from which the ether was decanted. After washing with ether, the precipitate was dissolved in 50 ml. of water and 200 ml. of ether was added. An excess of solid sodium bicarbonate was introduced slowly and the 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. Vacuum distillation of the residual oil using an air-cooled condenser provided 5.1 g. (40.8% yield) of 1-(*t*-butyl)-2-benzoylazetidine (3) as a yellow oil, b.p.  $98.5-99.5^\circ$  (0.1 mm.), which solidified upon standing to a waxy solid, m.p.  $53-55^\circ$  (picrate,

m.p. 188-190°). Compound **3** gave infrared absorption (carbon tetrachloride) at 1695/85 ( $\nu_1$  C=O/% abs.) and 1668  $\text{cm}^{-1}$ /76 ( $\nu_2$  C=O/% abs.) (2). The nmr spectrum (deuteriochloroform) contained a complex multiplet (5H) in the range 434 to 482 Hz (aromatic protons), a triplet (1H) at 285 Hz ( $J = 8.5$  Hz,  $\text{CHCO}$ ), a multiplet (2H) in the range 187 to 205 Hz ( $\text{CH}_2\text{N}$ ), a multiplet (2H) in the range 117 to 147 Hz ( $\text{CH}_2\text{CHCO}$ ), and a singlet (9H) at 60 Hz (*t*-butyl protons).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{19}\text{NO}$ : C, 77.38; H, 8.81; N, 6.45. Found: C, 77.42; H, 8.86; N, 6.47.

The obtainment of a 2-ketoazetidine provides additional possibilities for functionalizing the 2-position of the azetidine ring. For example, reduction of ketone **3** with lithium aluminum hydride provided the corresponding secondary alcohol. Formation of the diastereomer resulting from approach of the hydride to the carbonyl from the most hindered side as well as the one arising *via* attack from the least hindered side was observed under the reaction conditions utilized (6). Thus, a solution of 3.22 g. (0.0148 mole) of 1-(*t*-butyl)-2-benzoylazetidine (**3**) in 25 ml. of dry ethyl ether was added dropwise to a stirred suspension of 1.125 g. (0.0296 mole) of lithium aluminum hydride in 75 ml. of dry ether and the mixture was refluxed for eight hours. Hydrolysis was effected by the careful addition of 7 ml. of water. The mixture was then filtered, dried over magnesium sulfate, and the solvent was evaporated under reduced pressure. Vacuum distillation of the residual oil yielded 2.80 g. (86.2% yield) of 1-(*t*-butyl)-2-azetidinyphenylcarbinol (**4a, b**) as a colorless oil, b.p. 110-115° (0.4 mm.), the nmr spectrum of which indicated it to consist of two diastereomers present in the ratio of *ca.* 30:70. When the distillate was dissolved in Skelly Solve B (b.p. 60-69°), filtered and cooled, 0.47 g. of diastereomer **4a** was obtained as white needles, m.p. 103-105°, which gave infrared absorption (carbon tetrachloride) at 3605 (monomeric OH) and 3310  $\text{cm}^{-1}$  (polymeric OH). The nmr spectrum (carbon tetrachloride), which indicated **4a** to be the minor component of the original diastereomeric mixture, contained a singlet (5H) at 434 Hz (aromatic protons), a doublet (1H) at 264 Hz ( $J_{2,\alpha} = 3.1$  Hz,  $\text{C}_2\text{HC}_\alpha\text{HOH}$ ), a broad singlet (1H) at 249 Hz (OH), a triplet of doublets (1H) at 224 Hz ( $J_{2,\alpha} = 3.1$  Hz,  $J_{2,3} = 8.0$  Hz,  $\text{C}_3\text{H}_2\text{C}_2\text{HC}_\alpha\text{H}$ ), a complex multiplet (2H) in the range 176 to 199 Hz ( $\text{CH}_2\text{N}$ ), a multiplet (2H) in the range 97 to 132 Hz ( $\text{C}_3\text{H}_2\text{C}_2\text{H}$ ), and a singlet (9H) at 46 Hz (*t*-butyl protons).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{21}\text{NO}$ : C, 76.66; H, 9.65; N,

6.39. Found: C, 76.41; H, 9.48; N, 6.49.

Evaporation under reduced pressure of the solvent from the mother liquor obtained in the crystallization of **4a**, followed by vacuum distillation of the residual oil gave 1.64 g. of diastereomer **4b** (contaminated with **4a** to the extent of *ca.* 7%) as a colorless oil, b.p. 110-112° (0.4 mm.). Compound **4b** gave infrared absorption (carbon tetrachloride) at 3360  $\text{cm}^{-1}$  (polymeric OH). The nmr spectrum (carbon tetrachloride), which indicated **4b** to be the major component of the original diastereomeric mixture, contained a singlet (5H) at 432 Hz (aromatic protons), a doublet (1H) at 272 Hz ( $J_{2,\alpha} = 3.6$  Hz,  $\text{C}_2\text{HC}_\alpha\text{HOH}$ ), a broad singlet (1H) at 246 Hz (OH), a triplet of doublets (1H) at 221 Hz ( $J_{2,\alpha} = 3.6$  Hz,  $J_{2,3} = 8.0$  Hz,  $\text{C}_3\text{H}_2\text{C}_2\text{HC}_\alpha\text{H}$ ), a complex multiplet (2H) in the range 171 to 191 Hz ( $\text{CH}_2\text{N}$ ), a multiplet (2H) in the range 96 to 135 Hz ( $\text{C}_3\text{H}_2\text{C}_2\text{H}$ ), and a singlet (9H) at 62 Hz (*t*-butyl protons).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{21}\text{NO}$ : C, 76.66; H, 9.65; N, 6.39. Found: C, 76.78; H, 9.70; N, 6.22.

We are currently conducting further investigations of the chemistry of 2-ketoazetidines and related compounds.

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