Azetidinyl Ketones. Synthesis and Epimerization of 1-*t*-Butyl-2-(*p*-Nitrophenyl)-3-benzoylazetidines.

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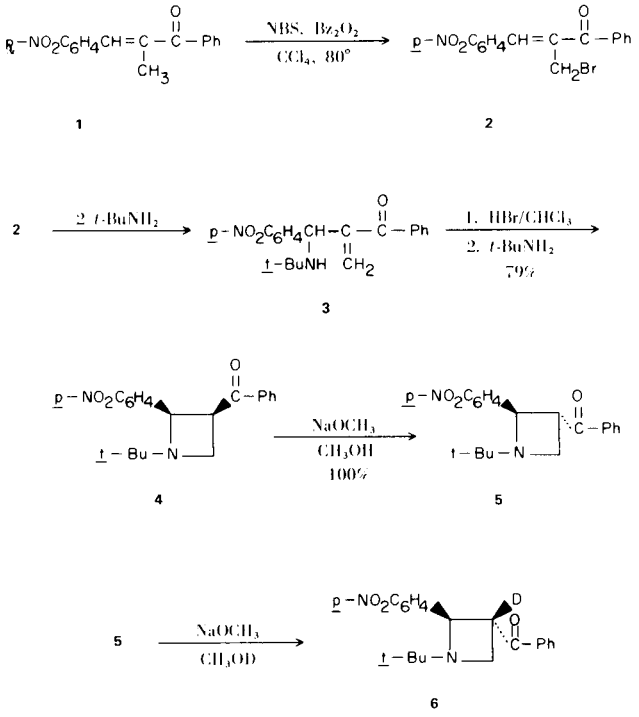
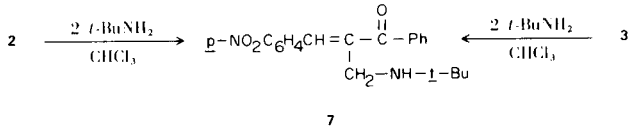
As an extension of our continuing interest in the chemistry of functionally substituted azetidines, in particular aroylazetidines, (2-5) we now wish to report the conversion of 2-[α-(*N*-*t*-butylamino)-*p*-nitrobenzyl] acrylophenone (**3**) to *cis*-1-*t*-butyl-2-(*p*-nitrophenyl)-3-benzoylazetidine (**4**) and its epimerization to the *trans* isomer **5** -- see Scheme I.

SCHEME I



The reaction of **2** with two equivalents of *t*-butylamine (7) in *n*-hexane to afford the kinetically favored, rearrangement-substitution product **3** is analogous to the reaction of amines with other β-keto allyl bromides (8,9). However, when **2** was allowed to react with *t*-butylamine in chloroform only the normal substitution product **7** was observed. That **3** is indeed the kinetically favored product is established by the fact that it undergoes rearrangement to **7** in the presence of *t*-butylamine in chloroform solvent -- see Scheme II.

SCHEME II



The action of an excess of hydrogen bromide gas on **3** followed by neutralization with *t*-butylamine gave **4** in good yield (79%). It may be significant that attempts to cyclize **3** with hydrogen chloride failed to afford detectable quantities of azetidine after neutralization. The high yield of azetidine from the hydrogen bromide reaction, and the failure of the cyclization reaction to proceed when hydrogen chloride was used may be attributed to the greater ease of displacement of bromide (relative to chloride), thus allowing the competing β-elimination reaction to reproduce **3** in the latter case.

Base catalyzed epimerization of **4** gave a quantitative yield of the thermo-dynamically more stable isomer **5**. When the epimerization reaction was conducted in methanol-d_1, deuterium was incorporated in the 3 position, thus the *trans*-3-deuterioazetidine **6** was obtained in good yield. In addition to the above epimerization reactions, the configurations of the isomeric azetidines, **4** and **5**, were readily established by their pmr spectra. Thus, the *cis* configuration was assigned to that isomer which exhibited the larger vicinal coupling constant between the protons at C-2 and at C-3, a situation analogous to that observed for other 2-aryl-3-aroylazetidines (2,3).

EXPERIMENTAL

Melting points are uncorrected. Pmr spectra were determined on either a Varian A-60 or a Varian A-60-D spectrometer in deuteriochloroform solution (unless otherwise indicated), and chemical shifts reported in δ units downfield from tetramethylsilane as an internal standard. Infrared spectra were determined

on a Perkin-Elmer Model 237 spectrophotometer. Ultraviolet spectra were determined on a Cary Model 14 instrument in *ca.* 10^{-4} *M* solutions. Elemental analysis were performed by Micro-Tech Laboratories, Skokie, Illinois.

α-Methyl-4-nitrochalcone (**1**).

A mixture of 13.81 g. (91.4 mmoles) of *p*-nitrobenzaldehyde and 12.25 g. (91.4 mmoles) of propiophenone was cooled to 0° and stirred magnetically while anhydrous hydrogen chloride gas was slowly bubbled in until saturated. The contents were stoppered and allowed to stand while warming to room temperature for one week. Hydrogen chloride and water were removed under vacuum with heating and the residue taken up in 100 ml. of ethanol to which was added 12.8 g. of potassium carbonate and 9.0 g. of potassium acetate. The mixture was refluxed for one hour and cooled to room temperature, filtered, the ethanol evaporated and the residue taken up in ether, filtered, the ether evaporated and the residue taken up in ethanol for crystallization to give a 47% yield, m.p. 82.5-83°; ν C=O 1655 cm^{-1} (carbon tetrachloride), λ max (methanol) 304 mμ (ε, 18,700) and shoulder at 259 mμ (ε, 10,100); pmr peaks (carbon tetrachloride) at δ 7.35-8.25 (m, 9H, aromatic), δ 7.1 (s, 1H, benzal), and δ 2.2 (s, 3H, methyl).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.09; H, 4.98; N, 5.21.

α-(Bromomethyl)-4-nitrochalcone (**2**).

To a mixture of 3.76 g. (21.1 mmoles) of *N*-bromosuccinimide in 50 ml. of carbon tetrachloride was added 5.64 g. (21.1 mmoles) of **1**. A catalytic quantity (*ca.* 0.01 g.) of benzoyl peroxide was added and the mixture heated at reflux for 6 hours under nitrogen. After cooling to room temperature the mixture was filtered and the carbon tetrachloride removed *in vacuo*. The yellow residue was recrystallized from ether affording 4.66 g. (64%) of **2** as yellow crystals, m.p. 113-114°; λ max (methanol) 301 mμ (ε, 16,100); ν C=O 1654 cm^{-1} (potassium bromide), pmr peaks at δ 7.35-8.33 (m, 9H, aromatic), δ 7.18 (s, 1H, vinyl), and δ 4.48 (s, 2H, $-CH_2Br$).

Anal. Calcd. for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05; Br, 23.08. Found: C, 55.36; H, 3.41; N, 3.97; Br, 23.14.

2-[α-(*N*-*t*-Butylamino)-*p*-nitrobenzyl] acrylophenone (**3**).

A 5.0 g. (14.5 mmoles) sample of **2** was partially dissolved in 750 ml. of *n*-hexane containing 2.12 g. (29 mmoles) of *t*-butylamine. The contents were stirred magnetically at room temperature while tightly stoppered for 85 hours. The *t*-butylamine hydrobromide, 1.92 g. (86%), was filtered and the solvent volume reduced to 100 ml. by evaporation and cooled for crystallization of 3.63 g. (74%) of **3**, m.p. 115-116°; ν C=O 1642 cm^{-1} (potassium bromide pellet); λ max (methanol) 261 mμ (ε, 16,800); pmr peaks at δ 7.2-8.2 (m, 9H, aromatic), δ 5.74 and δ 6.13 (s, 1H each, vinylic), δ 5.18 (s, 1H, benzyl), δ 1.45 (N*H*), and δ 1,08 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.23. Found: C, 71.02; H, 6.49; N, 8.36.

cis-1-*t*-Butyl-2-(*p*-nitrophenyl)-3-benzoylazetidines (**4**).

To 50 ml. of chloroform saturated with hydrogen bromide at 0° was added 2.51 g. (74.3 mmoles) of **3**. The solution was tightly stoppered and allowed to stand at room temperature for 5 days. The excess hydrogen bromide was removed *in vacuo*, and *t*-butylamine added. After stirring for one hour, the mixture was then evaporated to dryness *in vacuo*. The resulting yellow solid was placed in a Soxhlet thimble and extracted with ether for 4 hours. The solvent was removed from the extract *in vacuo*. The resulting solid was recrystallized from methanol, affording 1.95 g. (78%) of **4**, m.p. 166-168°; λ max (methanol) 250 mμ (ε, 14,000) and 279 mμ (sh); ν C=O 1680 cm^{-1} (deuteriochloroform); pmr peaks at δ 7.40-7.96 (m, 9H, aromatic protons), δ 5.05 (d (J = 9.8 Hz), 1H, C-2 proton), δ 4.23-4.60 (m, 1H, C-3 proton), δ 3.95 (d-d (J = 3.4, 6.8), 1H, C-4 proton *cis* to benzoyl), δ 3.42 (d-d, (J = 7.8, 6.8), 1H, C-4 proton *trans* to benzoyl), and δ 0.92 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.97; H, 6.56; N, 8.46. Found: C, 71.22; H, 6.59; N, 8.44.

trans-1-*t*-Butyl-2-(*p*-nitrophenyl)-3-benzoylazetidine (**5**).

To 25 ml. of methanol containing *ca.* 0.05 g. of sodium methoxide was added 0.42 g. (1.18 mmoles) of **4**. After *ca.* 1 hour **4** had dissolved, however, the solution was stirred for an additional 2 hours. Water was added until terbid. The solution was warmed to clarify it and then allowed to cool. Nearly colorless crystals (0.42 g., 100%) of m.p. 98-99.5° were obtained; λ max (methanol) 248 mμ (ε, 16,300) and 277 mμ (sh); ν C=O 1678 cm^{-1} (deuteriochloroform); nmr peaks at δ 7.28-8.29 (m, 9H, aromatic), δ 4.96 (d (J = 6.3 Hz), 1H, C-2 proton), δ 3.42-4.00 (m, 3H, C-3 and C-4 protons), and δ 0.91 (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.97; H, 6.55; N, 8.29. Found: C, 70.99; H, 6.56; N, 8.46.

trans-1-*t*-Butyl-2-(*p*-nitrophenyl)-3-deuterio-3-benzoylazetidine (**6**).

To a solution of 5 ml. of methanol-d, and *ca.* 0.05 g. of sodium methoxide was added 0.23 g. of **5**. After 3.5 hours the pmr spectrum indicated only *ca.* 50% deuteration. Consequently, the mixture was stirred for an additional 36 hours followed by addition of deuterium oxide. The pmr spectrum of the product, **6**, showed peaks at δ 4.94 (s, 1H, C-2 proton), δ 3.55 (d-d (J = 6.8 Hz), 2H, C-4 protons), and the same peaks as reported for the aromatic and *t*-butyl protons of **5**.

α-(*t*-Butyl aminomethyl)chalcone (**7**).

A 6.92 g. (20.0 mmoles) sample of **2** dissolved in 50 ml. chloroform was added to 2.92 g. (40.0 mmoles) *t*-butylamine in 25 ml. of the same solvent. The contents were stirred magnetically at room temperature while tightly stoppered for 99 hours. *t*-Butylamine hydrobromide, 2.85 g. (93%), was filtered and the solvent evaporated under reduced pressure to leave a residue which was analyzed by pmr to show only the presence of **7**, m.p. 95-96°; pmr peaks at δ 7.2-8.3 (m, 10H, aromatic and benzal), δ 3.65 (s, 2H, $-CH_2-N$), δ 1.17 (s, 10H, NH and *t*-butyl); ν C=O 1660 cm^{-1} (carbontetrachloride); λ max (methanol) 299 mμ (ε, 14,200) and 258 mμ (ε, 13,200).

Anal. Calcd. for $C_{20}H_{23}BrN_2O_3$ (hydrobromide salt): C, 57.27; H, 5.53; Br, 19.07: N, 6.68. Found: C, 57.11; H, 5.71; Br, 19.28; N, 6.74.

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(1) To whom correspondence concerning this article should be addressed.

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