The Synthesis and Chemistry of 2-Methyl-2-benzoyl-3-phenylaziridine and Some 1-Substituted Derivatives

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In our continuing studies (3) of 2-acylaziridines, we have chosen to investigate compounds which were fully substituted at the 2-position. To our knowledge no 2-alkyl-2-acylaziridines have been previously reported. Our desire to determine the influence of a 2-alkyl group on the chemical properties characteristic of 2-acylaziridines was the purpose for developing a facile synthesis for these compounds.

Previous work has shown that alkylation alpha to the carbonyl of the readily available 1-alkyl-2-acylaziridines was not a practical route to these compounds.

We now wish to report the synthesis of 2-methyl-2-benzoyl-3-phenylaziridine (**2**), 2-methyl-2-benzoyl-3-(*p*-biphenylyl)aziridine (**4**) and several 1-substituted derivatives. Compounds **2** and **4** were synthesized by a modification of the method of Blatt and Cromwell (5) see Fig. 1.

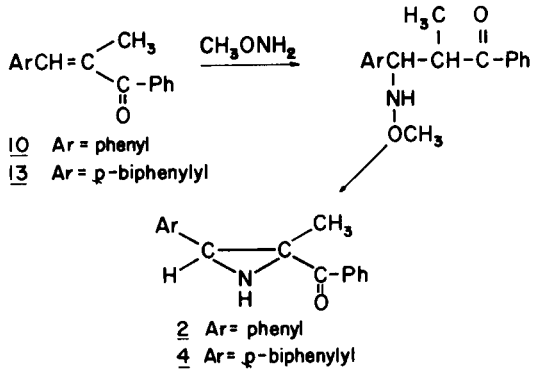

Figure 1. Preparation of 2-Methyl-2-benzoyl-3-arylaziridines.

In contrast to the preparation of *trans*-2-phenyl-3-benzoylaziridine (5), the 1,4 addition of methoxyamine to α-methylchalcone (**10**) required a longer reaction time and a higher temperature than the addition of this reagent to chalcone. This was presumably due to increased steric hindrance to the addition. The resultant ring closure of the intermediate 1,3-diphenyl-2-methyl-3-methoxyaminopropan-1-one (**1**) required more severe conditions than closure of the corresponding chalcone adducts (5). This was presumably due to the presence of the α-methyl group, which destabilized the intermediate carbanion. While the pmr spectrum of **1** clearly indicated a mixture of two diastereomers, only one aziridine isomer was isolated. This was in agreement with the preparation of analogous compounds by this reaction sequence.

Aziridines unsubstituted at the 1-position characteristically react with nitrosyl chloride at low temperatures to form *N*-nitrosoaziridines. Upon warming these compounds decompose stereospecifically to the corresponding olefin with the liberation of nitrous oxide (6). Treatment of **2** with nitrosyl chloride at -70° and warming to room temperature gave E-α-methylchalcone (**10**), indicating the 3-phenyl group and the 2-benzoyl group are *trans* in **2**. Attempts to prepare *N*-alkyl derivatives of **2** by a variety of methods proved unsuccessful. Several *N*-acylated derivatives of **2**, however, were successfully prepared. Treatment of **2** with benzoyl chloride in the presence of triethylamine produced *r*-2-1,2-dibenzoyl-2-methyl-*t*-3-phenylaziridine (**3**) in high yield. Similarly, treatment of *r*-2-benzoyl-2-methyl-*t*-3-(*p*-biphenylyl)aziridine (**4**) with acetyl chloride in the presence of triethylamine gave 1-acetyl-*r*-2-benzoyl-2-methyl-*t*-3-(*p*-biphenylyl)aziridine (**5**).

Also, reaction of **2** with phenyl isocyanate gave 1-(phenylcarbamoyl)-*r*-2-benzoyl-2-methyl-*t*-3-phenylaziridine (**6**). While *N*-acylation and alkylation are relatively facile processes with most aziridines (7), **2** was resistant to alkylation and acylated very slowly. We feel this is due to the 2-carbonyl group, which effectively decreases the electrophilic character of the aziridine nitrogen.

It was recently shown (8) that treatment of *trans*-2-phenyl-3-benzoylaziridine with *t*-butyl hypochlorite gave two *N*-chloroaziridines which were stable and separable by chromatography. In contrast treatment of **4** under identical reaction conditions gave a single *N*-chloro compound whose pmr spectrum was unchanged from 60 to -40°. Examination of Figure II shows that fewer nonbonded interactions are present in **8** than in **7**. Although truly definitive evidence is lacking, we feel the compound obtained from the reaction of **4** with *t*-butyl hypochlorite is **8**.

Earlier studies (9) on the reactions of *cis* and *trans* 1-alkyl-2-aryl-3-aroylaziridines with phenylhydrazine have shown that 1-phenyl-3,5-diarylpyrazoles and 1-phenyl-3,5-

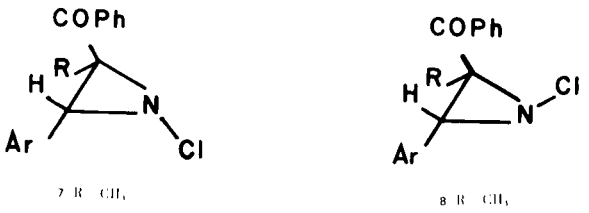

Figure II. Possible Conformation of 1-Chloroaziridines.

diaryl-4-aminopyrazolines respectively were obtained. The reaction products have been shown to depend upon the stereochemistry of the initial aziridine. In contrast to this earlier work, treatment of **2** with phenylhydrazine under conditions similar to those previously reported gave two products. These products were identified as 1,3,5-triphenyl-4-methylpyrazole (**11**) and 1,3,5-triphenyl-4-methyl-4-amino-2-pyrazoline (**12**) on the basis of elemental analyses and spectral data (Figure III). The configuration about C-4, C-5 of **12** is not known but previous work (9) has shown *trans* elimination of ammonia or amines from 4-amino-2-pyrazolines (**15**) to be an extremely facile process whereas *cis* elimination was more difficult. When the reaction time was increased to six hours only **11** was obtained. We feel therefore that the 4-amino group and the C-5 proton in **12** are *cis* and **11** was formed via a slow 1,2-*cis* elimination of ammonia from **12**.

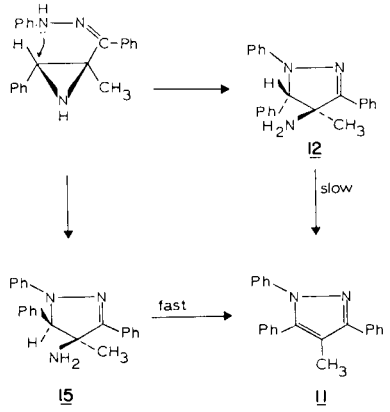

Figure III. Reaction of **2** with Phenylhydrazine.

EXPERIMENTAL

Melting points (m.p.) are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 620 spectrophotometer as potassium bromide discs or as chloroform solutions. Proton magnetic resonance (pmr) spectra were determined on a Varian A-60 or A-60D spectrometer. Chemical shifts are reported in delta (δ) units downfield from tetramethylsilane, an internal standard. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

E-1-Phenyl-2-methyl-3-(*p*-biphenylyl)-2-propen-1-one (**13**).

A 45.5 g. (0.25 mole) sample of *p*-phenylbenzaldehyde (Kent Chemicals Ltd., Vancouver, B. C., Canada) was suspended in 33.3 ml. (0.25 mole) of propiophenone at 0° and saturated with anhydrous hydrogen bromide. The mixture turned red-orange and solidified. After 24 hours, the excess hydrogen bromide was removed *in vacuo*. The brown residue was suspended in 250 ml. of absolute ethanol containing 39.6 g. (0.25 mole) of potassium carbonate and 24.5 g. (0.25 mole) of potassium acetate. After refluxing for 8 hours, the mixture was cooled and filtered to remove the solid. The filtrate was concentrated *in vacuo*. The residue was taken up in chloroform and combined with the chloroform extracts of the original filter cake. The chloroform solution was washed with water, dried (magnesium sulfate), and concentrated. The residue was treated with decolorizing carbon and recrystallized from ethanol to yield 50 g. (65%) of **13**, m.p. 103-105°; pmr (deuteriochloroform): δ 7.86 to 7.11, m (15H, aromatic and vinyl), and 2.38, d, J = 1.6 Hz (3H, methyl); ir (carbon tetrachloride): (ν C=O) 1650 cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.59; H, 6.04. Found: C, 88.72; H, 6.01.

r-2-Benzoyl-2-methyl-3-phenylaziridine (**2**).

A 15 x 150 mm test tube was constricted near the lip and 2.4 (11 mmoles) of α-methylchalcone (10) and 0.9 g. (16 mmoles) of methoxyamine (11) placed in it. The reactants were cooled in a dry ice/acetone bath and the tube sealed. After nine days at 80°, the contents of the tube were washed into a flask with methylene chloride and the volatiles were removed by flash evaporation. The resultant yellow oil was dissolved in dry ether and the solution treated with anhydrous hydrogen chloride. The resultant yellow oil which precipitated was separated from the ether-soluble fraction. The precipitate was dissolved in benzene and treated with aqueous sodium bicarbonate. The benzene layer was dried (magnesium sulfate) and concentrated.

The resultant oil 1,3-diphenyl-2-methyl-3-methoxyaminopropan-1-one (**1**) was dissolved in 15 ml. of dry methanol and added dropwise to a stirred solution of 0.70 g. (13.5 mmoles) of sodium methoxide in 7 ml. of methanol warmed to 60°. The resultant solution became bright yellow. After 18 hours, the mixture was concentrated to a yellow semi-solid. The residue was treated with 50 ml. of water, extracted with methylene chloride, dried (magnesium sulfate), and concentrated. The resultant yellow oil was chromatographed on 100 g. of silica gel. Elution with benzene yielded 1.00 g. (38%) of **2** as a colorless oil which crystallized in *n*-hexane, m.p. 61-62°; pmr (deuteriochloroform): δ 8.00-7.20, m (10H, aromatic) 3.20, s, (1H, C-3H), 3.02 s (1H, N-H), 1.25, s (3H, methyl); ir (chloroform): (ν N-H) 3280 and (ν C=O) 1671 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 81.01; H, 6.33; N, 5.91. Found: C, 81.21; H, 6.21; N, 5.80.

r-2-Benzoyl-2-methyl-*t*-3-(*p*-biphenylyl)aziridine (**4**).

A 1.8 g. (6.5 mmoles) sample of **13**, 0.45 g. (11.0 mmoles) of methoxyamine (11), and 2 ml. of tetrahydrofuran were heated in a sealed tube at 80° for nine days. The reaction mixture was worked up as described in the preparation of **2**. Treatment of the oily residue as was described for **2** produced a yellow oil which was placed on a silica gel column. Elution with petroleum ether:ethyl ether (50:1) yielded a colorless oil. Crystallization from petroleum ether, b.p. 70-80°, produced 22% of **4**, m.p. 117-119°; pmr (deuteriochloroform): δ 8.45-7.10, m (14H, aromatic), 3.20, s (1H,

C-3H), 2.90, s (1H, N-H), 1.30, s (3H, methyl); ir (chloroform): (ν C=O) 1672 cm^{-1}.

Anal. Calcd. for $C_{21}H_{19}NO$: C, 84.34; H, 6.07; N, 4.47. Found: C, 84.53; H, 6.00; N, 4.38.

r-2-1,2-Dibenzoyl-2-methyl-*t*-3-phenylaziridine (**3**).

A 135 mg. (0.57 mmole) sample of **2** and 64 mg. (0.63 mmole) of triethylamine were dissolved in 10 ml. of ether and cooled to 5°. A solution of 89 mg. (0.63 mmole) of benzoyl chloride was added dropwise. After one week's stirring at room temperature, the triethylamine hydrochloride was filtered out. The filtrate was washed with water, dried (magnesium sulfate), and concentrated. The resultant yellow oil was crystallized from ether:hexane to give 85% of **3** as white needles, m.p. 131-132°; pmr (deuteriochloroform): δ 8.25-7.15, m (15H, aromatic), 4.20, s, (1H, C-3H), 1.51, s (3H, methyl); ir (potassium bromide): (ν C=O) 1692 and 1678 cm^{-1}.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.94; H, 5.57; N, 4.11. Found: C, 80.76; H, 5.52; N, 4.06.

1-Acetyl-*r*-2-benzoyl-2-methyl-*t*-3-(*p*-biphenylyl)aziridine (**5**).

A benzene solution of acetyl chloride (47 mg., 0.60 mmole) was added dropwise to a stirred benzene solution of 98 mg. (0.31 mmole) of **4** and 91 mg. (0.91 mmole) of triethylamine. After two days the triethylamine hydrochloride was filtered off. The filtrate was washed with water, dried (magnesium sulfate), and concentrated. The resultant yellow oil was crystallized from ether to yield 105 mg. (96%) of **5**, m.p. 121-122°; pmr (deuteriochloroform): δ 8.00-7.20, m (14H, aromatic), 3.93, s (1H, C-3H), 2.38, s (3H, acetyl), 1.51 s (3H, methyl); ir (chloroform): (ν C=O) 1720 and 1670 cm^{-1}.

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.13; H, 5.91; N, 3.94. Found: C, 81.38; H, 5.87; N, 3.88.

1-(Phenylcarbamoyl)-*r*-2-benzoyl-2-methyl-*t*-3-phenylaziridine (**6**).

A solution of 189 mg. (0.80 mmole) of **2** in 5 ml. of dry ether was added dropwise with stirring to 95 mg. (0.80 mmole) of phenyl isocyanate in 5 ml. of ether. After stirring one week at room temperature the solution was cooled and the resultant white crystals were removed by filtration. Concentration of the solution did not yield additional product. The white crystals were recrystallized from methanol:ether to yield 300 mg. (70%) of **6**: m.p. 139-140°; ir (potassium bromide): (ν C=O) 1685 and 1670 cm^{-1}.

Anal. Calcd. for $C_{23}H_{20}N_2O_2$: C, 77.52; H, 5.62; N, 7.87. Found: C, 77.63; H, 5.62; N, 7.71.

1-Chloro-*r*-2-benzoyl-2-methyl-*t*-3-(*p*-biphenylyl)aziridine (**8**).

A solution of 210 mg. (0.67 mmole) of **4** and 142 mg. (1.3 mmoles) of *t*-butyl hypochlorite (12) in 10 ml. of dry methylene chloride was stirred at room temperature for 2 hours. The volatile components were removed by flash evaporation. The pmr spectra of the crude solid indicated complete and quantitative conversion to a single compound (**8**). Tlc (silica gel) in a variety of solvent systems indicated only a single product was present. The product was recrystallized from hexane:ether, yield 218 mg. (94%) of **8**, m.p. 140°; pmr (deuteriochloroform): δ 8.30-7.10, m (14H, aromatic), 4.15, s (1H, C-3H), 1.33, s (3H, methyl); ir (chloroform): (ν C=O) 1672 cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}ClNO$: C, 75.97; H, 5.18; Cl, 10.22; N, 4.03. Found: C, 76.08; H, 5.16; Cl, 9.98; N, 4.08.

Reaction of **2** with Nitrosyl Chloride.

A solution of 55 mg. (0.82 mmole) of nitrosyl chloride in 5 ml. of ethyl ether was added dropwise to a stirred solution of 203 ml. (0.86 mmole) of **2** and 87 mg. (0.86 mmole) of triethylamine in 50 ml. of ether cooled to -78°. The solution turned deep red upon addition of the nitrosyl chloride and became yellow in 1.5 hours. After the solution turned yellow, stirring was continued for two additional hours at -78°. Upon warming to room temperature the solution turned colorless. The triethylamine hydrochloride was filtered off and the filtrate concentrated *in vacuo*. The pale yellow oil was identified as *E*-α-methylchalcone on the basis of comparison of spectral data with an authentic sample (10).

Reaction of **2** with Phenylhydrazine.

A 104 mg. (0.44 mmole) sample of **2** was dissolved in 0.5 ml. of 95% ethanol and 0.07 ml. (0.66 mmole) of phenylhydrazine. A 0.5 ml. portion of glacial acetic acid was added with stirring. The solution was warmed to 50° for 10 minutes and stirring continued at room temperature for 24 hours. The resultant deep yellow solution was concentrated and poured into an aqueous sodium carbonate solution. The basic aqueous solution was extracted with benzene and the dried (magnesium sulfate) extract was concentrated. The residual oil was chromatographed on silica gel (10 g.). Elution with benzene produced 62 mg. of a yellow oil (**11**) which was crystallized from methanol to yield white needles, m.p. 124-125°; pmr (deuteriochloroform): δ 7.98-7.15, m (15H, aromatic) and 2.23, s (3H, C-4 methyl).

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.16; H, 5.81; N, 9.03. Found: C, 85.32; H, 5.84; N, 9.08.

Further elution with benzene produced 56 mg. of a second yellow oil (**12**) which was crystallized from methanol to yield white needles, m.p. 162-164°; pmr (deuteriochloroform): δ 8.30-7.11, m (15H, aromatic), 4.81, s (1H, C-5H), 1.83, broad s (2H, NH_2) and 1.03, s (3H, C-4 methyl); ir (potassium bromide): (ν N-H) 3400 and 3310, (ν C=N) 1665 cm^{-1}.

Anal. Calcd. for $C_{22}H_{21}N_3$: C, 80.73; H, 6.42; N, 12.84. Found: C, 80.98; H, 6.50; N, 12.62.

Pmr of the crude reaction mixture before chromatography indicated the product ratio (**11**:**12**) was 1:1. If the reaction time at 50° was increased to 6 hours, the pmr spectra of the crude reaction product indicate only **11** was present.

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