Formation of Pyrrole Derivatives Through Aminolysis of 2-Azetidinone Derivatives

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A mixture of 3-(α,β-epoxyisopropyl)-1-phenyl-2-azetidinone and benzylamine was heated in a sealed tube at 120-130° yielding 4-anilinomethyl-1-benzyl-3-hydroxy-3-methyl-2-pyrrolidinone as a mixture of diastereoisomers. By this method, 4-anilinomethyl-3-hydroxy-3-methyl-1-phenyl-2-pyrrolidinone and 4-anilinomethyl-3-hydroxy-3-methyl-1-(3,4-dimethoxyphenethyl)-2-pyrrolidinone were obtained by using aniline and 3,4-dimethoxyphenethylamine, respectively, instead of benzylamine. The reaction of 4-formyl-1-phenyl-2-azetidinone with 3,4-dimethoxyphenethylamine afforded 4-anilino-1-(3,4-dimethoxyphenethyl)-2,3-dihydro-2-oxopyrrole. In a similar fashion, the 1-*n*-butyl and 1-isobutyl analogues were obtained by the use of *n*-butylamine and isobutylamine, respectively, instead of 3,4-dimethoxyphenethylamine.

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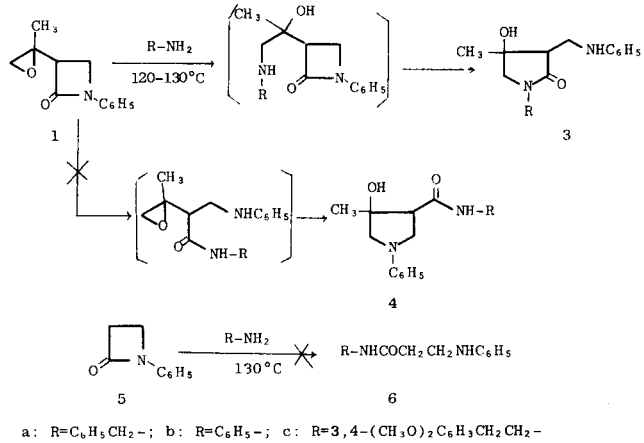
It is well known that the amide bond of 2-azetidinones is easily cleaved by nucleophiles such as amino and hydroxyl groups to form the X – CO – C – C – N (X = N, O) moiety (1,2). This high chemical reactivity of 2-azetidinones has been applied to the synthesis of heterocycles such as quinoline, γ-lactone and indolizine derivatives (3, 4). Thus, 2-azetidinone is considered as a potential synthon of the N – C – C – CO functionality (2). We have investigated an aminolysis of 3-(α,β-epoxyisopropyl)-1-phenyl-2-azetidinone (**1**) and 4-formyl-1-phenyl-2-azetidinone (**2**) in the expectation that pyrrolidine derivatives might be formed as an extension of the previous works (3,4). These results are described in this paper.

First, we examined the aminolysis of 3-(α,β-epoxyisopropyl)-1-phenyl-2-azetidinone (**1**) (5) with benzylamine in a sealed tube at 120-130° to give 3-anilinomethyl-1-benzyl-4-hydroxy-4-methyl-2-pyrrolidinone (**3a**) as a mixture of diastereoisomers (6) in 73% yield. A mixture of **1** and aniline was also heated as above to give 3-anilinomethyl-4-hydroxy-4-methyl-1-phenyl-2-pyrrolidinone (**3b**) and its stereoisomer in 38 and 37% yield, respectively. Although these products were easily separated by column chromatography on silica gel, the stereochemistry of these products was not determined. The same reaction by the use of **1** and 3,4-dimethoxyphenethylamine also afforded the similar result and the products, **3c** and its isomer, were obtained. In these reactions, if the cleavage of the amide bond occurred by the attack of the primary amines at the first stage, the alternative possible structure **4** should also be considered as the product in each case (See Scheme 1). However, the amide (**6**) was not obtained on heating 1-phenyl-2-azetidinone (**5**) (7) with benzylamine, aniline and 3,4-dimethoxyphenethylamine in a sealed tube at 130° for 14 hours and only starting materials were recovered. Therefore, the cleavage of the epoxy ring occurred at the first stage, and then the ethanolamine intermediate was converted to the products through the cleavage of the amide bond at the second stage. Thus, the 3-(α,β-epoxy)-2-azetidinone system was found to be easily convertible to 4-hydroxy-2-pyrrolidinone derivatives by heating with either aromatic or aliphatic amines.

Scheme 1



a: R=$C_6H_5CH_2$–; b: R=C_6H_5–; c: R=3,4-$(CH_3O)_2C_6H_3CH_2CH_2$–

Successively, we examined the aminolysis of 4-formyl-1-phenyl-2-azetidinone (**2**), prepared by the reduction of the acid chloride (7) (8) with bis(triphenylphosphin)copper tetrahydroborate by the method as Sorrel reported (9). Treatment of **2** with 3,4-dimethoxyphenethylamine in ethanol under reflux, followed by further heating in the presence of sodium ethoxide under reflux afforded 4-anilino-2,3-dihydro-1-(3,4-dimethoxyphenethyl)-2-oxopyrrole (**8a**) in 75% yield. In a similar fashion, **2** was treated with *n*-butylamine and isobutylamine to give the corresponding 1-substituted 2,3-dihydro-2-oxopyrrole derivatives (**8b** and **8c**), in 70 and 67% yield, respectively. These 4-anilino-2,3-dihydro-2-oxopyrroles could be considered as the equivalents of pyrrolidin-2,4-dione derivatives. It is of interest that some 2-azetidinones are found to be useful precursors for the preparation of the

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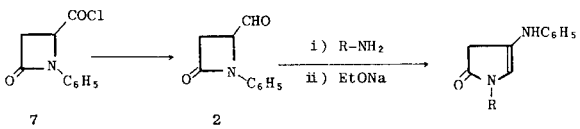
4-hydroxy-2-pyrrolidinone system and the pyrrolidin-2,4-dione analogues.

Scheme 2



7 2 8

a: R=3,4-$(CH_3O)_2C_6H_3CH_2CH_2$-; b: R=n-C_4H_9-; c: R=i-C_4H_9-

EXPERIMENTAL

All melting points are uncorrected. Nmr spectra were recorded with a Varian T-60 spectrometer operating at 60 MHz. Mass spectra were obtained with a Hitachi RMU-7L spectrometer.

3-Anilinomethyl-1-benzyl-4-hydroxy-4-methyl-2-pyrrolidinone (**3a**).

A mixture of 203 mg (1 mmole) of **1** and 107 mg (1 mmole) of benzylamine was heated in a sealed tube at 120-130° for 12 hours. The mixture was carefully chromatographed on silica gel (4 g) by the use of chloroform as an eluent to give 205 mg (66%) of **3a** in an analytically pure state as an oil; nmr (deuteriochloroform): δ 1.28, 1.41 ppm (each 1.5 H, each s, 4-CH_3), 4.38-4.51 (2H, m, $PhCH_2N$); ir (chloroform): 1670 cm^{-1}; ms: m/e 310 (M^+), Calcd. for $C_{19}H_{22}N_2O_2$: 310.1665. Found: 310.1681.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.24; H, 7.40; N, 9.33.

3-Anilinomethyl-4-hydroxy-4-methyl-1-phenyl-2-pyrrolidinone (**3b**) and its Isomer.

A mixture of 203 mg (1 mmole) of **1** and 93 mg (1 mmole) of aniline was heated in a sealed tube as above and the mixture was chromatographed on silica gel (4 g) by the use of chloroform as an eluent. evaporation of the first fraction (20 ml) gave **3b** in 38% yield (110 mg), mp 129-132° (benzene-hexane); nmr (deuteriochloroform): δ 1.34 ppm (3H, s, 4-CH_3), 3.34 (2H, s, 5-H_2); ms: m/e 296 (M^+); ir (nojul): 1710 cm^{-1}.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.00; H, 6.78; N, 9.38.

Evaporation of the second fraction (30 ml) afforded the isomer of **3b** in 37% yield (109 mg), mp 139-140° (benzene-hexane); nmr (deuteriochloroform): δ 1.47 ppm (3H, s, 4-CH_3), 3.20, 3.38 (each 1H, d, J = 12.5 Hz, 5-H_2); ms: m/e 296 (M^+); ir (nujol): 1710 cm^{-1}.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.99; H, 6.99; N, 9.41.

3-Anilinomethyl-4-hydroxy-1-(3,4-dimethoxyphenethyl)-4-methyl-2-pyrrolidinone (**3c**) and its Isomer.

A mixture of 203 mg (1 mmole) of **1** and 181 mg (1 mmole) of 3,4-dimethoxyphenethylamine was heated at 120-130° as above and the mixture was chromatographed on silica gel (4 g) by using chloroform as an eluent. Evaporation of the first fraction (30 ml) gave 131 mg of **3c** (34%) as an oil, which was further chromatographed on silica gel by using chloroform. Evaporation of the solvent (30 ml) gave 120 mg of **3c** in an analytically pure state; nmr (deuteriochloroform): δ 1.39 ppm (3H, s, 4-CH_3), 3.19 (2H, s, 5-H_2), 3.80, 3.83 (6H, each s, 2 x OCH_3); ir (chloroform): 1665 cm^{-1}; ms: m/e 384 (M^+), Calcd. for $C_{22}H_{28}N_2O_4$: 384.2035. Found: 384.2049.

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.45; H, 7.36; N, 7.51.

The second fraction (30 ml) gave 146 mg (38%) of the isomer of **3c** as an oil, which was further purified by column chromatography on silica gel (4 g) by using chloroform. Evaporation of the solvent (30 ml) gave 125 mg of analytically pure product; nmr (deuteriochloroform): δ 1.25 ppm (3H, s, 4-CH_3); 3.10-3.22 (2H, m, 5-H_2), 3.80, 3.83 (6H, each s, 2 x OCH_3);ir (chloroform): 1668 cm^{-1}; ms: m/e 384 (M^+).

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.99; H, 7.06; N, 7.55.

4-Formyl-1-phenyl-2-azetidinone (**2**).

To a suspension of bis(triphenylphosphin)copper tetrahydroborate (2 g, 3.3 mmoles) in 10 ml of acetone was added a solution of 629 mg (3 mmoles) of **7** in 3.5 ml of acetone at room temperature under stirring. After stirring for 80 minutes, the insoluble substance was filtered off and the filtrate was evaporated. The residual oil was chromatographed on silica gel (5 g). Elution with benzene-chloroform (1:1) gave 220 mg (42%) of **2**, which was further purified by column chromatography on silica gel (5 g) by using benzene-chloroform (1:1) to give 200 mg of **2**; nmr (deuteriochloroform): δ 3.01 ppm (1H, dd, J = 2.5, 4 Hz, 3-H), 3.19 (1H, dd, J = 3.5, 4 Hz, 3-H), 4.29-4.50 (1H, m, 4-H), 9.68 (1H, d, J = 4 Hz, CHO); ms: m/e 175 (M^+), Calcd. for $C_{10}H_9NO_2$: 175.0654. Found: 175.0633.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.27; H, 5.44; N, 8.21.

General Procedure for the Preparation of 1-Alkyl-4-anilino-2,3-dihydro-2-oxopyrrole (**8**).

A mixture of 350 mg (2 mmoles) of **2** and amine (2 mmoles) in 20 ml of ethanol was heated under reflux for 2 hours and 136 mg of sodium ethoxide was then added to the mixture. The mixture was further heated under reflux for 1.5 hours. After removal of the solvent, the residue was diluted with water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate and evaporated. The residue was chromatographed on silica gel (2 g). Elution with 2% methanol-chloroform yielded **8** in a pure state.

4-Anilino-2,3-dihydro-1-(3,4-dimethoxyphenethyl)-2-oxopyrrole (**8a**).

This compound was obtained in 75% yield (507 mg), mp 179-179.5° (methanol-hexane); nmr (deuteriochloroform): δ 3.80 ppm (6H, s, 2 x OCH_3), 3.85 (2H, s, 3-H_2), 5.13 (1H, s, 5-H); ms: m/e 338 (M^+); ir (nujol): 1590 cm^{-1}.

Anal. Calcd. for $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.53; N, 8.23. Found: C, 71.03; H, 6.42; N, 8.39.

4-Anilino-1-*n*-butyl-2,3-dihydro-2-oxopyrrole (**8b**).

This compound was obtained in 70% yield (322 mg), mp 183-184° (methanol-benzene); nmr (deuteriochloroform): δ 4.05 ppm (2H, s, 3-H_2), 5.14 (1H, s, 5-H); ms: m/e 230 (M^+); ir (nujol): 1592 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.00; H, 7.68; N, 12.45.

4-Anilino-1-isobutyl-2,3-dihydro-2-oxopyrrole (**8c**).

This compound was obtained in 67% yield (308 mg), mp 184-185° (methanol-benzene); nmr (deuteriochloroform): δ 4.05 ppm (2H, s, 3-H_2), 5.19 (1H, s, 5-H); ms: m/e 230 (M^+); ir (nujol): 1595 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found, C, 72.94; H, 7.82; N, 12.15.

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(6) Since **1** used in this reaction was a mixture of diastereoisomers, the product should be a mixture of diastereoisomers.

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