Cyclization of 2-ethylene ketal-cyclohexyl-1-propionamide in PPA-AcOH†

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All efforts made for the preparation of 2-oxocyclohexyl-1-propionamide 3, have led to the preparation of quinolone 4. 2-Ethylene ketal-cyclohexyl-1-propionamide 8 on reaction with PPA/AcOH affords a new quinolone 9, which on reduction with NaBH₄ furnishes another reduced quinolone 10. All compounds have been characterised by their spectral data analysis.

4-(2-Oxocyclopentyl)butyric acid¹, 4-(2-oxocyclohexyl)butyric acid² and cyclohexene propionamide³ undergo cyclization in the presence of PPA. To study the effect of PPA on the 2-oxo-cyclohexyl-1-propionamide 3, we needed it. The preparation of amide 3 was attempted by the michael addition of cyclohexene enamine 1 with acrylamide 2. The product formed was not the amide 3 as the intermediate undergoes subsequent cyclization to yield the quinolone 4⁴ (Scheme I).

We therefore tried the preparation of 3 through the intermediary of 6, 7 and 8. All approaches led to the facile formation of quinolone 4. Use of different experimental conditions such as PPA in acetic acid led to the preparation of 8-acetyl 3,4,5,6,7,8-hexahydro[1H]quinolin-2-one 9, which was subsequently reduced with NaBH₄ to yield a new product 8-(1-hydroxy ethyl) 3,4,5,6,7,8-hexahydro-[1H]-quinolin-2-one 10. The detailed results are summarized in the Scheme I. The reaction of 1-morpholino-1-cyclohexene ¹ with ethyl acrylate 5 in refluxing dry dioxane yielded the ethyl β-(2-oxocyclohexane) propionate 6⁵ (b.p. 100/1.5 mm), which on reaction with methanolic ammonia in steel bomb at 130°C gave quinolone 4⁴ in quantitative yield. As the cyclization process involves the interaction between amino and carbonyl group the carbonyl group in 6 was masked via ketal formation [ethylene glycol/pyridinium p-toluene sulfonate (PPTS)⁶]

to give ethyl β-(2-ethylene ketal-cyclohexyl) propionate 7 in 95% yield. 7 on reaction with methanolic ammonia in steel bomb at 125°C produced the ketal amide 8 in quantitative yield, but all attempts to deketalization of 8 employing acetic acid, PPA, HCl rendered quinolone 4⁴ exclusively (Scheme I).

The cyclization of 2-oxo-cyclohexyl-1-propionamide ethanediyl acetal 8 has been successfully effected in PPA-acetic acid medium. We have, therefore, studied the cyclization in this medium.

Accordingly the ketal amide 8 was heated with PPA(CH₃)₂COOH for 3 hr, followed by usual work-up when quinolone 9 in which the acyl group is substituted at eight position was obtained. It was characterised by its spectral data analysis. The NH peak of quinolone 9 in PMR appears at low field at δ 12.2 due to its hydrogen bonding with carbonyl group of COCH₃. Methyl proton of COCH₃ appears at δ 2.1. Quinolone 9 also gives the unsaturation test. Presence of double bond, carbonyl and amide group was confirmed by ¹³C NMR and IR spectroscopy.

Ketone group in 9 was reduced with sodium borohydride to give the corresponding alcohol 10. PMR and IR spectra are in agreement with the structure 10. The NH peak in 10 shifted to δ 8.1, which is further in agreement of acetyl group at 8 position in 9. Further limitation and applications of the reactions are under study.

Experimental Section

¹H NMR and ¹³C NMR were recorded on a Perkin Elmer R-32 (90 MHZ) and Bruker 400 FT or Bruker 300 FT NMR instruments using TMS as an internal reference, IR spectra on Perkin-Elmer 881 and Beckman Acculab-10 IR spectrometer and mass spectra on a Jeol D-300 (E-I/Cl) mass spectrometer. Elemental analyses were preformed on Carlo Erba 1108, Heraeus and Coleman N analyser.

Preparation of 7. A mixture of 6 (49.5 g, 0.25 mole), ethylene glycol (77.5 g, 1.25 mole) and catalytic amount of pyridinium p-toluene sulfonate (PPTS) in dry benzene was refluxed in an oil bath for 5 hr using a Dean stark apparatus. Benzene layer separated from the aqueous portion was collected and aqueous portion washed with ether (2× 100 mL). Combined ether and benzene layer were washed with
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NH₃/M₅OH

Scheme 1

saturated sodium bicarbonate solution (2 x 20 mL) and brine (20 mL). Removal of the solvent under reduced pressure after drying over Na₂SO₄ afforded light brown coloured compound, which on distillation gave neat liquid of 7 in 95% yield; b.p. 120/2.5 mm; IR (Neat): 3030 (m), 2950 (m), 1730 (VS, CO), 1450 (m), 1225 (w) cm⁻¹; ¹H NMR (CDCl₃/TMS): δ 1.2 (3H, t, CH₃), 1.35-1.80 (10 H, m), 2.15-2.40 (3H, m), 3.8-4.2 (6H, m); MS: m/z 242 (M⁺, 14), 200(3), 197(12), 155(21) 99(100).

Preparation of 8. 7 (24 g, 0.0988 mole) was heated with saturated solution of methanolic ammonia (24 mL) in steel bomb at 125°C. Reaction was completed in 24 hr as monitored by TLC [C₆H₆-MeOH (80:20, v/v)]. Removal of the methanol under reduced pressure gave 8 as white colour solid in quantitative yield; m.p. 132°C; IR (KBr): 3340, 3160 (S,NH₂), 2940 (S), 2880 (m), 1670 (m), 1630 (S)(amide I and II band), 1450 (m), 1415 (m), 1330 (w) cm⁻¹; ¹H NMR (CDCl₃/TMS): δ 1.1-1.9 (10H, m), 2.08-2.40 (3H,m), 3.9 (4H,m), 5.7 (2H,d); MS: m/z 213 (M⁺9), 185 (2), 184(1), 171(2), 170(24), 99(100); ¹³C NMR (CDCl₃): δ 23.5, 24.2, 24.3, 29.1, 34, 34.3, 43.8(-CH), 64.2 and 64.4 (CH₂-CH₃), 110.5 (C attach to ketal group), 176.2 (-CO-NH₂).

Preparation of 9. Compound 8 (5 g), polyphosphoric acid (15 g) and acetic acid (30 mL) were heated at 95°C in an oil bath for 4 hr under mechanical stirring. Reaction mixture was poured on to ice cold water and extracted with chloroform. The organic layer was washed with saturated aqueous sodium carbonate and water. Evaporation of chloroform after drying over Na₂SO₄ afforded yellow colour liquid which was leached repeatedly with hot hexane. The combined hexane layer was cooled in refrigerator to yield light yellow powder of 9 (54% yield); m.p. 105°C; IR (KBr): 3120 (m), 2930 (m), 2870 (w), 1680 (S,C=O), 1640 (VS, C=O), 1590 (m, C=C), 1380 (w) cm⁻¹ etc.; ¹³C NMR (CDCl₃): δ 21.6, 25.9, 26.7, 28.2, 28.8, 32, 34.9 (-CH-C), 107.3 (-C=NH), 149.9 (HN-C=C), 170.9 (NH-CO), 201.8 (CO-CH₃); ¹H NMR (CDCl₃/TMS): δ 1.18-1.62 (4H,m,2CH₂), 1.84-2.05 (4H,m,2CH₂), 2.2 (3H, s, CH₃), 2.3-2.6 (3H, m, CH, CH₂), 12.2 (1H,
bs, NH); MS: m/z 193 (M+ 100), 192 (6.8), 178 (67), 165(37), 150(45); Anal. Caled for C₁₁H₁₃NO₂: C, 68.39; H, 7.77; N, 7.25. Found: C, 68.62; H, 7.8; N, 7.28%.

Preparation of 4

**Procedure a:** 6 (2.0 g, 10.1 mmole) was heated at 130°C with saturated methanolic ammonia (25 mL) in steel bomb for 18 hr. Reaction mixture was then treated with charcoal under reflux and filtered over celite. The filtrate on evaporation afforded 4 as white solid in 91.8% yield; m.p. 138°C (lit 140°C).

**Procedure b:** 8 (5 g, 0.023 mole) was kept in glacial acetic acid (30 mL) at room temperature and the reaction monitored by TLC [C₆H₆-MeOH (80:20, v/v)]. After 45 hr the acetic acid was distilled off from the reaction mixture and ether (50 mL) was added into it. Ether layer was washed with saturated aqueous sodium bicarbonate (10 mL), water (20 mL) and dried over Na₂SO₄. Evaporation of solvent under reduced pressure gave 4 in 57.58% yield; m.p. 138°C (lit 140°C).

**Procedure c:** 8 (2 g) was heated with PPA (6 g) at 95°C under mechanical stirring for 2 hr. This mixture was then poured on to ice-chilled water. The reaction mixture was stirred for 5 min and extracted with dichloromethane. The organic extract was washed with saturated aqueous sodium bicarbonate (10 mL), water (20 mL) and dried over Na₂SO₄. The solid residue obtained after evaporation of solvent was recrystallized from hexane:ether (1:1) to give 4 in 50% yield; m.p. 140°C (lit 140°C).

**Preparation of 10.** Sodium borohydride (304 mg, 0.008 mole) was dissolved in dry methanol (10 mL) in three neck 50 mL round bottom flask equipped with refluxing condenser. The solution was heated and then cooled for 10 min. Thereafter to it was added the solution of quinolone 9 (386 mg 0.002 mole) in methanol (10 mL), during 20 min. Reaction was slowly completed in 2 hr as monitored by TLC [benzene-methanol (80:20 v/v)]. Water (2 mL) was slowly added to the reaction mixture. Methanol was evaporated. Reaction mixture was washed with brine (2 x 5 mL) and dried over Na₂SO₄. Evaporation of solvent afforded dirty white solid of 10 in 90% yield; m.p. 125°C; IR (KBr): 3336, 3232 (m,NH,OH), 2927 (w), 2862(w), 1679(m), 1639(C=O and C=C), 1450 (w), 1386 (w) cm⁻¹; ¹H NMR (CDCl₃/TMS): δ 1.60-1.80 (7H,m,CH₃,2CH₂), 2.12-2.22 (2H,m,CH₂), 2.25-2.40 (4H,m,CH₃OH,CH), 2.44-2.54 (2H, m, CH₂), 5.3-5.4 (m, 1H , CH), 7.02 (bS , NH); MS: m/z 195 (M+ 29), 194(3), 180(100), 177(20), 150(16), 149(20).

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References