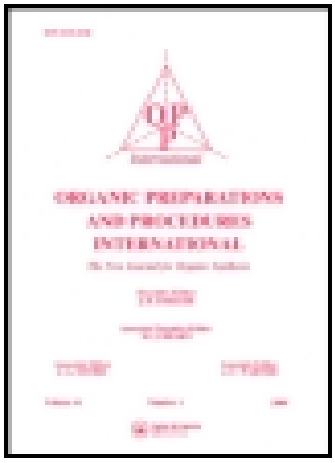

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

SYNTHESIS OF 6-HYDROXY-3,4,5,6-TETRAHYDRO-2-PYRIDONES AND 3,4-DIHYDRO-2-PYRIDONES BY H_2O_2/DMSO HYDRATION OF Δ-KETONITRILES

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Published online: 09 Feb 2009.

To cite this article: Attilio Citterio , Elena Carnevali , Alessandra Farina , Valdo Meille , Stefano Alini & Livius Cotarca (1997) SYNTHESIS OF 6-HYDROXY-3,4,5,6-TETRAHYDRO-2-PYRIDONES AND 3,4-DIHYDRO-2-PYRIDONES BY H_2O_2/DMSO HYDRATION OF Δ-KETONITRILES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 29:4, 465-470, DOI: 10.1080/00304949709355219

To link to this article: http://dx.doi.org/10.1080/00304949709355219

ORGANIC PREPARATIONS AND PROCEDURES INT., 29 (4), 465-470 (1997)

SYNTHESIS OF 6-HYDROXY-3,4,5,6-TETRAHYDRO-2-PYRIDONES AND 3,4-DIHYDRO-2-PYRIDONES BY H_2O_2/DMSO HYDRATION OF δ-KETONITRILES

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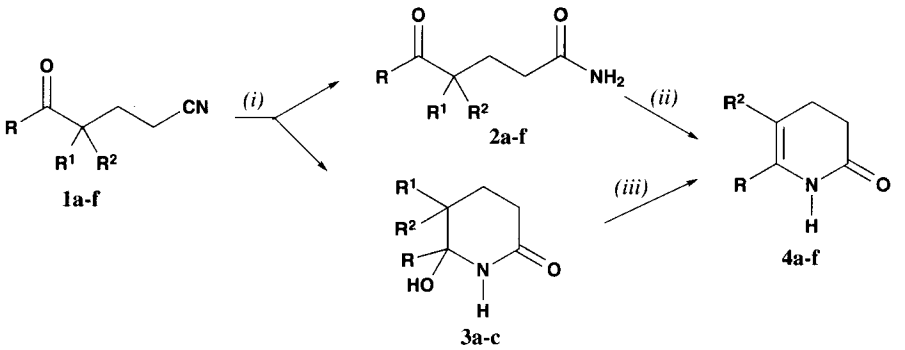
3,4-Dihydro-2-pyridones (*ene*-lactams) are highly versatile intermediates for the synthesis of piperidine[1] and hydroquinoline[2] ring systems. They can be obtained by the $RuH_2(PPh_3)_4$ catalyzed hydration-cyclization of the corresponding δ-ketonitriles under neutral conditions[3] or by the Michael addition of N,N-dialkylenamines to acrylamide and cyclization.[4] We now report that the procedure developed by Katritzky[5] for the oxidative hydration of nitriles to amides by basic hydrogen peroxide in dimethyl sulfoxide may be efficiently applied to the synthesis of 3,4-dihydro-2-pyridones (**4a-f**) from cyanoethylated ketones (**1a-f**).[6]

Depending on the nature of the substituents, δ-ketoamides (**2a-f**) or 6-hydroxy-3,4,5,6-tetrahydro-2-pyridones (**3a-c**) are in fact obtained in good yield (Table 1) by treatment of the nitrile (**1**) in DMSO at 0° (***CAUTION***: strong exotherm)[7] with a slight excess of 35% hydrogen peroxide in the presence of potassium carbonate.



a) R = R' = -$(CH_2)_4$-, R^2 = H b) R = R' = -$(CH_2)_4$-, R^2 = CH_3 c) R = -$(CH_2)_3$-, R' = R^2 = H
d) R = R' = -$(CH_2)_3$-, R^2 = H e) R = R' = -$(CH_2)_5$-, R^2 = H f) R = Ph, R' = R^2 = H

i) H_2O_2, DMSO, K_2CO_3 *ii*) PhOPh, 220° *iii*) 1-5 mmHg, Δ

Either compounds **2** and **3** can be efficiently converted to 3,4-dihydro-2-pyridones (**4a-f**) by thermal dehydration [**2d-f**, 220°, diphenyl ether (path *ii*)] or under reduced pressure (**3a-c**, path *iii*) (Table 2). Attempts to obtain higher conversion of nitriles by increasing the H_2O_2/substrate molar ratio resulted in complex mixtures containing 6-hydroperoxy-3,4,5,6-tetrahydro-2(1H)-pyridone derivatives **5**. For example, compound **1a** gave a 70% yield of stereoisomers **5a/5a'** (58:42).[8]

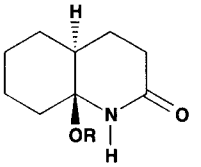
Stereoelectronic stabilization in six-membered cyclic aminals **3** may help rationalize the preferential formation of **3** over **2** with **1a-c**.[9] In fact, *trans* stereoisomer **3a**[8] predominates over *cis* isomer **3a'** (ratio of *trans-cis* 9:1). In the dehydration step, **3a'** gives **4a'**.

Table 1. Preparation of Amides **2** or **3** from Cyanoethylated Ketones **1a-f**

Compd.	Product	Time (h)	Yield (%)	mp. (°C)	lit. mp. (°C)
1a	**3a**	3	86	148	—
1b	**3b**	4	66	109	—
1c	**3c(2c)**	3	68 (20)	85 (114-115)	(113-114)[10]
1d	**2d**	3	82	77	77-78[11]
1e	**2e**	4	70	65	—
1f	**2f**	3	62	144	144[12]

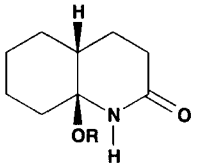
Table 2. Preparation of *ene*-Amides **4** from Ketoamides **2** or Hydroxyamides **3**

Compd.	**4**	Method	Yield (%)	mp. (°C)	lit. mp. (°C)
3a	**4a**	A	91	142-143	142[3]
3b	**4b'**	A	92	151-152	156-157[3]
3c(+2c)	**4c**	A	85	120-121	119-120[13]
2d	**4d**	B	82	106-107	(103-105) 117-118[14]
2e	**4e**	B	91	112-113	112-113[3]
2f	**4f**	B	86	151-152	150-153[15]



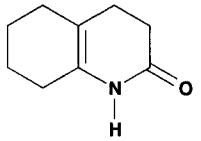
3a) R = H

5a) R = OH

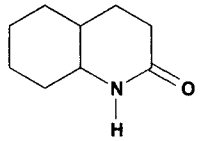


3a') R = H

5a') R = OH



4a



4a'

The present method has the advantage over previous procedures in that neither sealed tube nor expensive catalyst are necessary and that the carbonyl group is tolerated. This selectivity may be attributed to a preferential addition of the powerful α-nucleophile HOO^- to the nitrile group, followed by the reduction of the iminoperoxyacid intermediate by DMSO to the amide and dimethyl sulfone.[16]

The method also provides an efficient access to 6-hydroxy-3,4,5,6-tetrahydro-2-pyridones, which are useful intermediates in acyliminium chemistry.[17]

EXPERIMENTAL SECTION

Melting points were determined on a hot stage Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer in $CDCl_3$ solution and reported in ppm (δ units) against TMS. IR analyses (KBr) were performed on a Perkin Elmer 467 instrument. Mass spectra (MS) were recorded at 70 eV using a Finnigan TSQ 70 GCMS spectrometer equipped with a CB-SE-54 fused-silica capillary column *(25* m x 0.2 min i.d.) with He as a carrier gas. Quantitative GC analyses were performed by the internal standard method (2-hydroxy-6-methylpyridine) [*for the determination of conversions and isomer distributions*] on: 1) Dani 8610 instrument equipped with a CB-OV1 fused-silica capillary column (25 m x 0.2 min i.d.) and a PTV injection device, and 2) Dani 3800 instrument with a FID detector and equipped with a pyrex packed column SP 1000 (1=2 m, d_1 = 3 min); [*for the determination of the yield*] on: 1) OV1 SE 54 fused-silica capillary column, with the temperature program 70° x 1'-15°' to 150° x 5' and 15°' to 280° x 15' and 2) SP 1000 pyrex packed column, 1 = 2 m, d-= 3 min, with the temperature program: 150° x 2'-3°' to 215°. Preparative separations were carried out by flash chromatography on Kieselgel 60 (Merck 230-400 mesh) with hexane/AcOEt (8:2-1:1) as eluent. All nitriles **1a-f** are known compounds prepared by cyanoethylation of the corresponding ketone enamines.[6]

Hydrolysis of Nitriles 1a-f with Hydrogen Peroxide. General Procedure.- A 35% aqueous solution of H_2O_2 (3.19 mL, 0.035 mol) was added dropwise over 20 min to a vigorously stirred and chilled (0°) solution of the nitrile (0.03 mol) in DMSO (10 mL). Potassium carbonate (0.7 g) was added and then, after 15 min, the ice-bath was removed. After 5-15 min at 25°, a rapid and sudden rise in temperature occurred,[7] the flask was cooled to 35-40° in ice-bath and the mixture was stirred for additional 3 h at 25°. If a solid forms, water (4-8 mL) was added to reaction mixture and the solid was collected, washed with water and dried (30°/3 h) to give **2** or **3** (*Procedure A*). If no solid was present, the reaction mixture was concentrated under vacuum (1-5 mmHg) to a volume of 2-3 mL and a mixture of AcOEt/H_2O 1:2 (50 mL) was added to the residue. The phases were separated and the aqueous layer was extracted with AcOEt (2 x 10 mL). The combined extracts were washed (brine), dried (Na_2SO_4), concentrated and the residue chromatographed on Kieselgel using *n*-C_6H_{14}/AcOEt 7:3-1:1 as eluent (*Procedure B*). Dimethyl sulfone was isolated in 85-93% yield from the residue of crystallization of **2** or **3** (*Procedure A*) by SiO_2 column chromatography (*n*-C_6H_{14}/AcOEt 1:1).

***trans*-3,4,4a,5,6,7,8,8a-Octahydro-8a-hydroxy-2-quinolinone (3a)**, mp. 148-149° (from AcOEt). ^1H NMR: δ 7.80 (s, 1H), 2.3-2.0 (m, 3H), 1.9-1.2 (m, 10H). ^{13}C NMR: δ 170.94, 79.50, 41.45, 37.53, 31.52, 27.43, 25.20, 21.20, 21.09. MS: m/z (%) = 151 (M+-H_2O, 100), 149 (31), 147 (12), 123 (81), 122 (66), 117 (12), 109 (11), 96 (34), 95 (39), 94 (54), 79 (13). IR: 3325, 3200, 1715, cm^{-1}.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.86; H, 8.94; N, 8.28. Found: C, 63.93; H, 8.79; N, 8.33

***cis*-3,4,4a,5,6,7,8,8a-Octahydro-8a-hydroxy-2(1H)-quinolinone (3a')**, mp. 136° (from Et_2O-*n*-hexane) isolated in 6% yield by chromatography from the residue of crystallization of **3a**. ^1H NMR: δ 7.80 (s, 1H), 2.28-2.02 (m, 3H), 1.88-1.20 (m, 10H). ^{13}C NMR: δ 171.14, 81.25, 41.99, 37.72, 31.52,

26.82, 25.20, 22.88, 21.09. MS: m/z (%) 151 (M+-$H_2$0, 100), 149 (26), 136 (13), 123 (93), 122 (29), 108 (18), 96 (20), 95 (54), 94 (77), 81 (12), 80 (14), 79 (17). IR: 3340, 3220, 3200, 1725 cm-[1].

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.86; H, 8.94; N, 8.28. Found: C, 63.81; H, 8.77; N, 8.18

***trans*-3,4,4a,5,6,7,8,8a-Octahydro-8a-hydroxy-4a-methyl-2(1H)quinolinone (3b)**, mp. 109° (from Et_2O/hexane). ^{1}H NMR: δ 6.85 (bs, 1H, NH), 4.2 (bs, 1H, OH), 2.39 (m, 2H), 2.1 (m, 1H), 1.8 (m, 1H), 1.7-1.18 (m, 8H), 1.1 (s, 3H). ^{13}C NMR: δ 173.82, 84.69, 35.93, 35.68, 32.79, 29.71, 28.08, 23.14, 21.74, 20.74. MS: m/z (%) 183, 166, 151, 138, 125, 112, 97, 83, 72, 69, 59. IR: 420, 3160, 1670, 1610 cm^{-1}.

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.68; H, 9.28; N, 7.54

6-Hydroxy-6-methyl-3,4,5,6-tetrahydro-2(1H)pyridone (3c), a mixture of three products (compound **2c** (mp. 114-115°, lit. mp. 113-114°,[8b] 20%) and an inseparable mixture of two isomers of **3c** (55:45) (mp. 85°, 68%) was isolated by chromatography (AcOEt/*n*-C_6H_{14} 8:2) from the reaction with acetone as substrate following the work up procedure B. The mixture of **3c** presents the following analytical data: ^{1}H NMR: δ 6.35 (bs, 1H), 2.5-1.7 (m, 6H), 1.5 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (major isomer) 175.06, 81.22, 42.44, 35.49, 31.15, 19.38; δ (minor isomer) 172.47, 81.22, 42.44, 34.52, 30.04, 16.95. MS for both isomers m/z (%): 129, 112, 110, 96, 82, 68, 66, 54. The dehydration data of Table 2 for **4c** refer to the reaction carried out on the crude mixture of **2c** and **3c** without purification.

2-Oxo-1-cyclopentanepropionamide (2d), mp. 77° (from Et_2O/*n*-C_6H_{14}) isolated by chromatography following procedure B. ^{1}H NMR: δ 5.88 (sb, 2H), 2.41-2.28 (m, 2H), 2.27-1.88 (m, 5H), 1.88-1.67 (m, 2H), 1.67-1.49 (m, 2H). ^{13}C NMR: δ 221.38, 175.62, 49.06, 38.15, 33.47, 29.70, 25.59, 20.63. MS: m/z (%) 155 (M^+, 2), 138 (100), 110 (22), 82 (19), 72 (20), 59 (90), 55 (45). IR: 3400, 3200, 1730 cm-[1].

Anal. Calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.03; H, 8.31; N, 9.14

2-Oxo-1-cycloheptanepropionamide (2e), mp. 65° (from Et_2O). ^{1}H NMR: δ 5.88 (sb, 2H), 2.4-2.6 (m, 3H), 2.1-2.3 (m, 2H), 1.5-2.0 (m, 7H), 1.2-1:5 (m, 3H). ^{13}C NMR: δ 216.22 (s), 175.47 (s), 51.1, 42.6, 33.3, 31.5, 29.3, 28.3, 27.9, 24.3. MS: m/z (%) 183 (M^+, 2), 166 (63), 138 (38), 98 (18), 72 (22), 59 (100), 54 (40). IR: 3500, 3200, 1790, 1700 cm[1].

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.41; H, 9.50; N, 7.74

***cis*-3,4,4a,5,6,7,8,8a-Octahydro-3a-hydroperoxy-2(1H)quinolinone (5a)**, following the general procedure with a four-fold excess of H_2O_2, the final solution was concentrated at 30° under vacuum, the residue taken up with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL) and the extracts concentrated. Isomeric hydroperoxides **5a/5a'** (42:58 by ^{13}C NMR, 4.5 g, 70 %) were obtained by crystallization from Et_2O. Recrystallization from MeOH affords a pure sample of **5a'** (mp. 132-133°, 35%).[8] ^{1}H NMR: δ 10.30 (s broad, 1H), 8.00 (s broad, 1H), 2.40 (m, 2H), 2.3-2.1 (m, 2 H), 2.0-1.85 (m, 1H), 1.8-1.2 (m, 8H). ^{13}C NMR: δ 171.0, 87.35, 40.77, 32.31, 31.16, 27.39, 25.0, 22.31, 20.81. IR: 3213, 1635 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.28; H, 8.30; N, 7.44

Cyclization of δ-Ketoamide (2d-f) to 3,4-Dihydro-2-pyridone (4d-f). General Procedure.- δ-Ketoamide **2d-f** (1.5 g) and ammonium acetate (0.5 g) were added to diphenyl ether (10 mL). The mixture, flushed with N_2 for 5 min, was heated in 15 min under N_2 to 220° and kept at 220° for 2.5 h. The products were separated by chromatography from the reaction mixture, without solvent removal, using hexane/AcOEt 6:4 as eluent or by distillation.

Dehydration of 6-Hydroxy-3, 4, 5, 6-tetrahydro-2-pyridones (3a-c) to 3,4-Dihydro-2-pyridones (4a-c). General Procedure.

Method A. Compound **3a-c** (1.5 g), purified or as mixture of isomers, was heated at 180°/1 mmHg for 3 h in a sublimation apparatus (cold finger at - 30° to ensure good recovery). The residue and sublimated product were dissolved in warm AcOEt and crystallized at 0-5°.

Method B. The substrate **2d-f** (1.5 g) was dissolved in diphenyl ether (10 mL) and ammonium acetate (0.5 g) was added. The mixture was stirred at 220° under nitrogen for 2-3 h, then cooled and flash column chromatographed, using hexane/AcOEt 6:4 as eluent.

3,4,4a,5,6,7-Hexahydro-2(1H)-quinolinone (4a'), mp. 132° (from cyclohexane) isolated in 6% yield by chromatography of the crystallization residue of **4a** (mp. 142°). **4a'** ^{1}H NMR: δ 8.11 (sb, 1H), 4.93 (dd, 1H, *J* = 3.5 and 5.5 Hz), 2.53 (ddd, 1H, *J* = 2.4, 5.9 and 17.6Hz), 2.42 (ddd, 1 H, *J* = *5.6,* 12.5 and 17.6 Hz), 2.34-2.18 (m, 1H); 2.1-2.0 (m, 2 H); 2.0-1.8 (m, 4H), 1.6-1.4 (m, 3H), 1.27 (dddd, 1H, *J* = 2.7, 11.0, 12.7 and 12.7Hz). ^{13}C NMR: δ 171.0, 136.2, 103.9, 33.5, 32.0, 29.5, 27.3, 23.5, 22.1. IR: 3200, 3085, 1678, 1624 cm^{-1}.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.61; H, 8.82; N, 9.14

Isomers of **4d** and **4e** were also detected by GC-MS in 5% and 12% yield, respectively.

4d'. MS: m/z (%) 137 (M^+, 100), 136 (80), 109 (75), 108 (70), 96 (40), 81(40), 67 (30).

4e'. MS: m/z (%) 165 (M^+, 50), 150 (20), 136 (35), 122 (20), 111 (100), 108 (35), 94 (42), 82 (24), 55 (20).

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7. This high exothermic reaction requires efficient cooling!

8. Structures of **3a** *(trans* junction) and **5a'** *(cis* junction) were determined by single crystal X-ray diffraction. The hydroperoxide mixture **5a/5a'** (50:50) has been previously reported as a colorless oil (ref. 3, p. 8823). X-ray structures will be reported elsewhere.

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16. Stoichiometric amounts of dimethyl sulfone were formed.

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(Received July 15, 1996; in revised form April 14, 1997)