

HETEROCYCLES, Vol. 78, No. 12, 2009, pp. 3011 - 3021. © The Japan Institute of Heterocyclic Chemistry
 Received, 5th August, 2009, Accepted, 24th September, 2009, Published online, 25th September, 2009
 DOI: 10.3987/COM-09-11813

BENZYLIC OXIDATION OF *N*-ACYL-1,2,3,4-TETRAHYDRO-QUINOLINES

Roxanne C. Higgins, Norman O. Townsend, and Yvette A. Jackson*

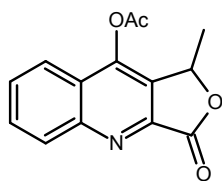
Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica W.I.

yvette.jackson@uwimona.edu.jm

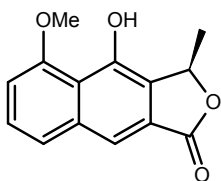
Abstract – Chromium hexacarbonyl/*tert*-butyl hydroperoxide has been identified as a general reagent for the benzylic oxidation of *N*-acyl-1,2,3,4-tetrahydroquinolines.

INTRODUCTION

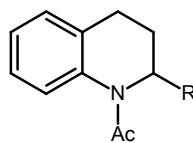
During the synthesis of compound **1**, a nitrogen analogue of eleutherol (**2**),¹ the benzylic oxidation of tetrahydroquinoline **3** was required. A review of the literature showed that except for the work of Bonvin *et al.*² and Bolm and Nakanishi,³ who investigated the bismuth catalyzed oxidation of *N*-acyl tetrahydroquinoline (**4**) and the iron-catalyzed benzylic oxidation of *N*-tosyl tetrahydroquinoline respectively, no oxidation studies have been reported for tetrahydroquinolines.



1



2



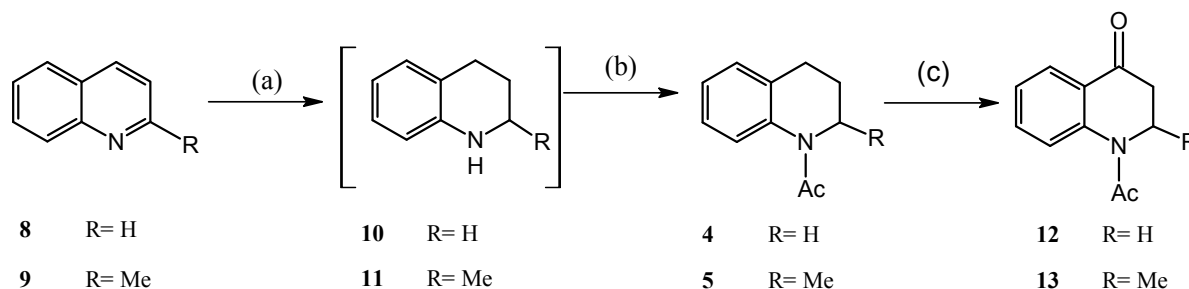
3 R = CO₂Me **5** R = Me **7** R = CO₂H
4 R = H **6** R = CN

This led to the exploration of benzylic oxidation of compounds of this type using well known oxidants such as selenium dioxide, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), chromium trioxide, ceric ammonium nitrate (CAN)⁴ and chromium hexacarbonyl (Cr(CO)₆).⁵

RESULTS AND DISCUSSION

Benzylic oxidation of compounds **4** and **5**, which were easily obtained from readily available quinoline

(8) and quinaldine (9) by NaCNBH₃/HOAc reduction and subsequent *N*-acylation with acetic anhydride (Scheme 1), was first investigated.



Scheme 1. *Reagents and conditions:* (a) NaCNBH₃, AcOH; (b) Ac₂O, 90°C (82% over 2 steps); (c) Various oxidants

As shown in Table 1, the overall yields of the oxidation reactions were usually quite low. Use of CAN and SeO₂ resulted in little or no conversion of starting material. Better results were obtained from the chromium oxide-derived oxidants. In fact, a slight increase in the yield and a decrease in reaction time were observed when *tert*-butyl hydroperoxide (*t*-BuO₂H) was used as a co-oxidant.⁶

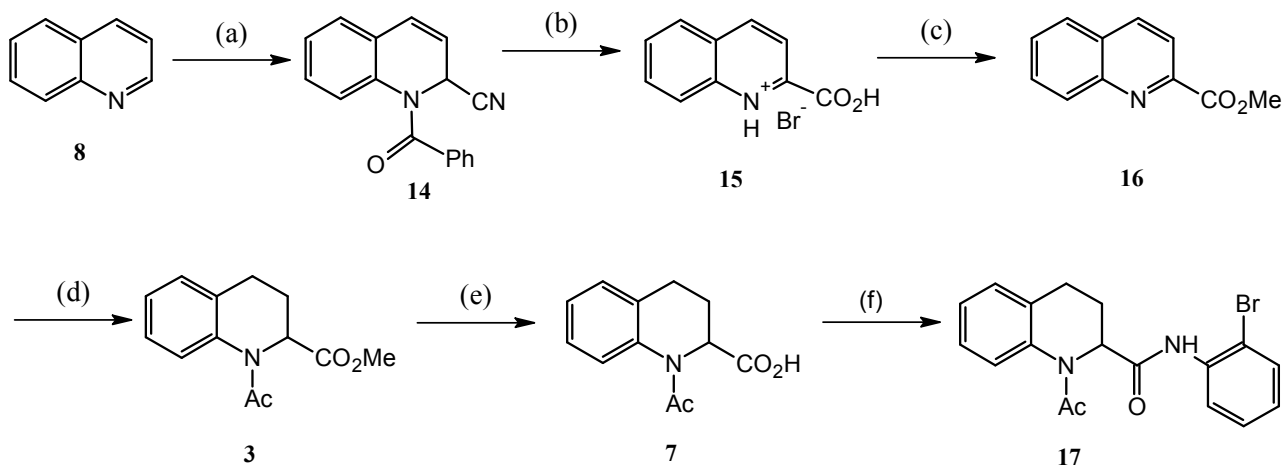
Table 1. Benzylic oxidations of tetrahydroquinolines (THQs) – product yield

Substrate	Oxidant				
	CAN, 4 mol. equivs. CAN/ aq. HOAc/ rt, 24 h.	SeO ₂ / CH ₂ Cl ₂ / rt, 24 h.	PCC/ benzene/reflux, 12 h.	PDC/CH ₂ Cl ₂ / reflux, 8 -16 h.	CrO ₃ / aq. HOAc/ -10 °C to rt, 8 h.
4	0	7 ^a	40 ^a , 30 ^b	37 ^a	30 ^b
5	0	6 ^a	38 ^a , 30 ^b	36 ^a	25 ^b

(a) *t*-BuO₂H as co-oxidant

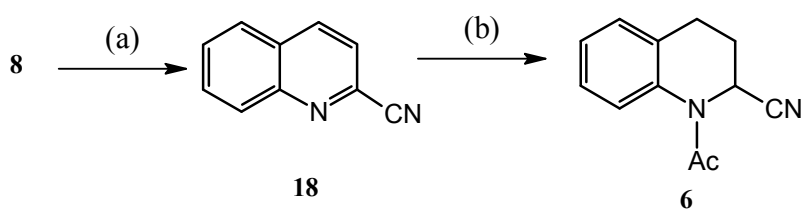
(b) without co-oxidant.

Pearson *et al.*⁵ investigated the oxidation of cyclic alkenes to enones and reported reasonable yields when Cr(CO)₆ and *t*-BuO₂H in refluxing acetonitrile was used. We attempted this reaction on substrates **4** and **5** with good results, obtaining yields of 65% and 90% respectively (Table 2). Percentage conversions were over 70%, whereas conversion was usually below 60% with use of other oxidants. We therefore synthesized compounds **3**, **6**, **7** and **17**, and explored the use of Cr(CO)₆ and *t*-BuO₂H for their oxidation. Reissert reaction⁷⁻⁹ on quinoline (**8**) using the heterogenous phase modification¹⁰ produced compound **14**. This was hydrolyzed using hydrobromic acid to give quinaldic acid hydrobromide (**15**)¹¹ which on treatment with MeI and K₂CO₃ yielded methyl quinaldate (**16**), (Scheme 2).



Scheme 2. *Reagents and conditions:* (a) CH_2Cl_2 , PhCOCl , KCN , H_2O (74%); (b) AcOH , HBr , reflux (100%); (c) MeI , K_2CO_3 , MeOH , reflux (59%); (d) i) NaCNBH_3 , AcOH ; ii) Ac_2O , 90°C (55% over two steps); (e) K_2CO_3 , MeOH (quant.) (f) CH_2Cl_2 , DCC , DMAP , 2-bromoaniline (66%)

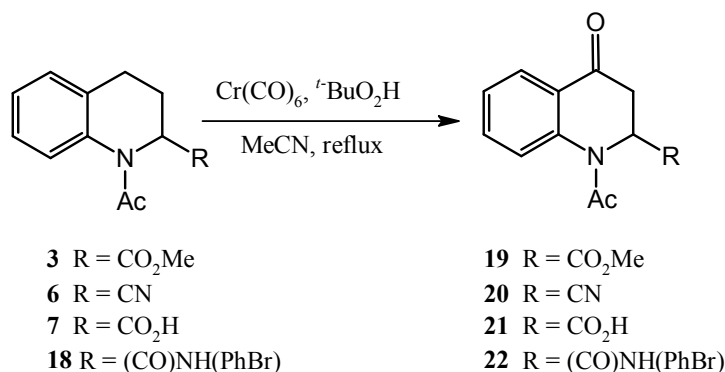
Subsequent reduction with sodium cyanoborohydride (NaCNBH_3) in acetic acid, followed by *N*-acetylation, with acetic anhydride gave compound **3** (55% over two steps). [Reduction of **16** with hydrogen and 10% Pd/C resulted in lower yields and even after 52 h the reaction had not gone to completion.] Hydrolysis of **3** using K_2CO_3 in MeOH provided acid **7**. Amide **17** was obtained by coupling 2-bromoaniline with acid **7** using dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dichloromethane.



Scheme 3. *Reagents and conditions:* (a) CH_2Cl_2 , KCN , *p*- TsCl (65%); (b) i) NaCNBH_3 , AcOH ; ii) Ac_2O , 90°C (55% over two steps).

For the synthesis of compound **6**, the Boger protocol¹² was used to install the nitrile group at position 2 (Scheme 3). The heterocyclic ring of **18** was then reduced and acetylated utilizing the same methods as before, to produce **6**.

The results obtained from oxidation of compounds **3**, **6**, **7** and **17** (Scheme 4) are shown in Table 2. The reaction of **7** was monitored by NMR-analysis as acids **7** and **21** are inseparable by column chromatography.



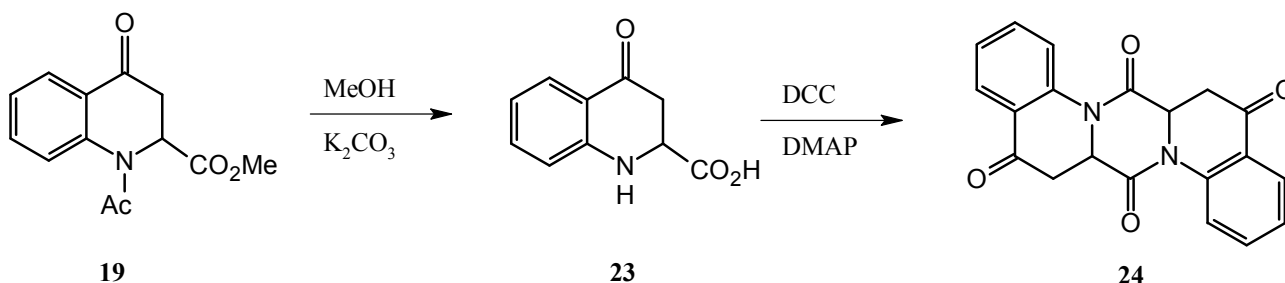
Scheme 4

Table 2. Yields of benzylic oxidation of different *N*-acyl THQs using Cr(CO)₆/ *t*-BuO₂H

<i>N</i> -acyl THQ	4-oxo <i>N</i> -acyl THQ (Yield*/ %)	Recovered SM/ %
3	19 (60)	30
4	12 (65)	30
5	13 (90)	25
6	20 (50)	50
7	21 (55)	25
17	22 (50)	25

*Yields based on converted starting material (SM)

Requiring the 2-carboxamide of compound **19**, we proceeded with hydrolysis of the ester using K₂CO₃ in refluxing MeOH, and obtained the corresponding deacylated carboxylic acid **23** in 80% yield (Scheme 5). Deacylation under these mild reaction conditions was quite unexpected. The keto group at position 4 may be facilitating a weakening of the *N*-acyl bond. This will be explored further.



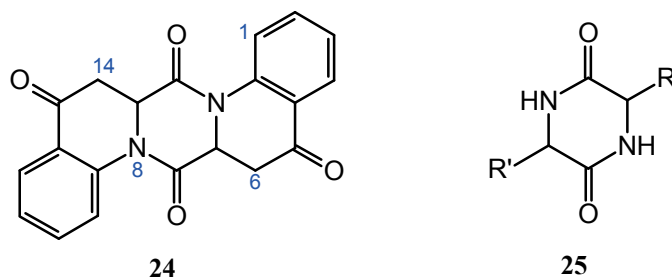
Scheme 5

Coupling of **23** with 2-bromoaniline using DCC and DMAP in dichloromethane resulted not in the desired amide but impure **24**. The reaction was repeated in the absence of 2-bromoaniline and produced

the novel diketopiperazine (DKP) **24** in about 40% yield. All attempts at purification of **24** were, however, unsuccessful.

When the reaction was done using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) with triethylamine in acetonitrile or 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI) with DMAP in dichloromethane at room temperature for 4 h, DKP **24** was obtained in 33% and 45% yields respectively. The NMR spectra of starting material and product were quite similar. The product, however, was much less polar than the starting material (R_f 0.45 and 0.07 respectively in hexane: EtOAc - 1:1), had a much higher melting point (299-302 °C vs. 183-185 °C (SM)), and analyzed well for $C_{20}H_{14}N_2O_4$.

DKPs of general structure **25** occur widely in nature¹³ and exhibit a wide spectrum of biological properties, including antiviral,¹⁴ antifungal, antibacterial and cytotoxic activities with antithrombotic effects.¹⁴⁻¹⁷ DKPs have also shown affinities for calcium channels, serotonergic 5-HT_{1A}, GABAergic, oxytocin and DNA topoisomerase I receptors^{14-16,18,19} and have even been used as a drug delivery system for oral administration.²⁰ These biological properties and their interesting chemical properties have made DKP substrates useful in medicinal chemistry and promising agents for drug development and potential lead compounds.^{14,18}



We have thus identified a new general method for the benzylic oxidation of *N*-acyl-1,2,3,4-tetrahydroquinolines using chromium hexacarbonyl and *tert*-butyl hydroperoxide. This has led to the synthesis of novel DKP **24**.

EXPERIMENTAL

Unless otherwise stated the following generalizations apply. All melting points are uncorrected. ¹H-NMR and ¹³C-NMR spectra were determined in deuteriochloroform (CDCl₃) solution on a 200 MHz or 500 MHz Bruker ACE 200 instruments. Resonances are in δ units (ppm) downfield from TMS. *J* values are given in Hz. Elemental analysis was carried out by MEDAC Ltd. All chromatography was carried out using silica as support.

General method for preparation of *N*-Acyl-1,2,3,4-tetrahydroquinolines

A solution of the quinoline (2.5 mmol) in glacial AcOH was cooled to below 30 °C and sodium cyanoborohydride (NaCNBH₃) (3.0 mmol) added in small portions. The mixture was then allowed to stir at room temperature for 3 h, neutralized with saturated aqueous NaHCO₃ then extracted with Et₂O (3 × 15 mL). The combined extract was dried over Na₂SO₄ then concentrated under reduced pressure. The crude product was treated with Ac₂O (10 mL) and the resulting solution heated at 90 – 100 °C for 4 h. After allowing the mixture to cool to room temperature it was diluted with water (50 mL) and solid NaHCO₃ was added until no further evolution of CO₂ was observed. The mixture was then extracted with Et₂O, and the organic extract dried over Na₂SO₄ then evaporated under vacuum. The crude product was purified by flash column chromatography (hexane: EtOAc – 3:1) to give the product.

From quinoline: **1-Acetyl-1,2,3,4-tetrahydroquinoline (4)**,²¹ yellow oil, 82%.

From quinaldine: **1-Acetyl-2-methyl-1,2,3,4-tetrahydroquinoline (5)**,²¹ yellow oil, 82%.

From **16**: **Methyl 1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (3)**,¹ yellow oil, 55%.

Quinaldic Acid Hydrobromide (15)

Reissert compound¹⁰ (**14**) (3.00 g, 11.6 mmol) was suspended in glacial AcOH (7.5 mL) and 49% aqueous HBr (3.5 mL, 63.2 mmol) was added. The mixture was heated at reflux for 30 min. On cooling, the monohydrate of quinaldic acid hydrobromide crystallized. The solid was collected by filtration and washed with glacial AcOH followed by Et₂O, to give **15** as orange crystals (3.00 g, 100%): mp 225 – 230 °C [lit.,¹¹ 220 – 224 °C]; ¹H-NMR (DMSO-*d*₆) δ 7.20 (1H, s), 7.50 (1H, s, NH), 7.81 (1H, t, *J* 8.4, 5-H), 7.94 (1H, t, *J* 8.4, 6-H), 8.05-8.25 (3H, m, 3,8,7-H), 8.56 (1H, d, *J* 8.5, 4-H); ¹³C-NMR δ 120.6, 126.6, 128.1, 129.0, 129.4, 132.3, 141.0, 143.6, 146.8, 164.8.

Methyl Quinaldate (16)

Quinaldic acid hydrobromide **15**, (2.00 g, 7.85 mmol) was dissolved in acetone/water (80 mL: 8 mL) and K₂CO₃ (6.09 g, 44.1 mmol) and MeI (3 mL) added. The mixture was heated at reflux for 2 h, filtered hot and concentrated under reduced pressure. The product was extracted with EtOAc (3 × 20 mL), dried over Na₂SO₄ and concentrated to give the crude methyl quinaldate (1.25 g, 6.68 mmol) which was recrystallized from aqueous MeOH to give compound **16** as white crystals (0.86 g, 59%); mp 79-80 °C [lit.,²² 79 °C].

1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (7)

Methyl 1-acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylate¹ (**3**) (600 mg, 2.5 mmol) was dissolved in MeOH (15 mL) and K₂CO₃ added. The mixture was heated at reflux for 2 h, concentrated under reduced pressure and the residue diluted with water (20 mL). The resulting solution was acidified with dilute HCl

(5% v/v) until effervescence ceased, and extracted with EtOAc (3×15 mL). The combined organic layer was concentrated under reduced pressure to yield **7**²³ (546 mg, 100%).

1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carbonitrile (**6**)

Quinoline-2-carbonitrile **18**¹² (900 mg, 6.42 mmol) was dissolved in glacial HOAc (10 mL) and the solution cooled in an ice-water bath until it began to solidify. NaCNBH₃ (610 mg, 9.7 mmol) was added to the mixture over 2 min. and the whole stirred at room temperature for 2 h. The mixture was neutralized with saturated aqueous NaHCO₃ (20 mL) then extracted with EtOAc (3×10 mL). The combined extract was washed with water (2×5 mL) dried over Na₂SO₄ then evaporated *in vacuo*. The residue was purified by column chromatography (hexane: EtOAc – 4:1) to give 1,2,3,4-tetrahydroquinoline-2-carbonitrile **18**¹² (620 mg, 60%). The product (620 mg, 3.92 mmol) was then dissolved in Ac₂O (10 mL) and the solution heated at 90 °C for 3 h. The mixture was allowed to cool to room temperature, neutralized with saturated aqueous NaHCO₃ solution then extracted with EtOAc (3×10 mL). The combined organic extract was washed with water (3×10 mL) then dried over anhydrous Na₂SO₄. After removing the solvent the crude product was purified by column chromatography (hexane: EtOAc – 2:1) to give **6**²⁴ as a brown oil (720 mg, 92%; 55% overall yield).

1-Acetyl-N-(2-bromophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxamide (**17**)

1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**7**) (250 mg, 1.14 mmol) was dissolved in CH₂Cl₂ (20 mL), and DCC (0.21 g, 1.20 mmol), DMAP (0.01 g, 0.1 mmol) and 2-bromoaniline (210 mg, 1.20 mmol) added. The mixture was stirred at room temperature overnight. The mixture was concentrated and the crude product was purified by column chromatography (hexane: EtOAc - 3:1) to give **17** as a viscous orange oil (0.29 g, 66%); ¹H-NMR 2.18 (4H, m, -CH₃, 3-H_a), 2.43 (2H, m, 3-H_b, 4-H_a), 2.77 (1H, m, 4-H_b), 5.40 (1H, t, *J* 9.7 2-H), 6.92 (1H, t, 6-H) 7.20 (5H, m, 5,7-H and 3,4,5-H), 7.49 (1H, d, 6-H), 8.28 (1H, d, H-8), 8.89 (1H, s, NH); ¹³C-NMR δ 22.8, 26.0, 27.0, 56.9, 113.7, 122.1, 125.2, 125.6, 126.9, 127.8, 128.2, 132.3, 135.7, 137.0, 169.2, 171.9.

General Procedure for Oxidation using Pyridinium Dichromate (PDC)

N-Acetyl-1,2,3,4-tetrahydroquinoline (3.14 mmol) was dissolved in CH₂Cl₂ (15 mL). PDC (130 mg, 0.345 mmol) and 70% *t*-BuO₂H (6 mL, 46.4 mmol) were added to the solution and the resulting mixture heated at reflux for 16 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (hexane: EtOAc - 3:1) to give the product.

From **4**: 1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline²⁵ (**12**), viscous oil that solidified on standing, 37 %;

From **5**: 1-Acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (**13**), cream solid, mp 120-122 °C, 36%;

$^1\text{H-NMR}$ δ 1.25 (3H, d, J 8.4, $-\text{CH}_3$), 2.34 (3H, s, $-\text{COCH}_3$), 2.60 (1H, d, J 15.7, 3- H_a), 3.02 (1H, dd, J 15.7 & 8.4, 3- H_b), 5.38 (1H, m, 2-H), 7.29 (1H, t, J 9.7, 6-H), 7.38 (1H, m, 5-H), 7.57 (1H, t, J 9.7, 7-H), 8.02 (1H, d, J 9.7, 8-H); $^{13}\text{C-NMR}$ δ 17.9, 23.5, 45.1, 48.5, 125.2, 125.4, 125.6, 127.3, 134.3, 141.3, 169.4, 193.5. Anal. Calcd For $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.92; H, 6.45; N, 6.89 %. Found C, 70.79; H, 6.63; N, 7.00%.

General Procedure for Oxidation using Selenium Dioxide

Selenium dioxide (150 mg, 1.35 mmol) and 90% t -Bu t -BuO₂H (1 mL) were added to a round bottom flask containing CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 30 min. A solution of N -acetyl-1,2,3,4-tetrahydroquinoline (2.28 mmol) in CH_2Cl_2 (9 mL) was added dropwise to the reaction mixture and the whole stirred at room temperature for 24 h. The filtrate was evaporated under reduced pressure and the crude product purified by column chromatography (hexane: EtOAc - 3:1).

From 4: 1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline²⁵ (**12**), 7%;

From 5: 1-Acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (**13**), 6%.

General Procedure for Oxidation using Pyridinium Chlorochromate (PCC)

Celite (2.2 g) was heated at 140 °C for 2 h then cooled. Dry benzene (25 mL) was added followed by PCC (2.0 g, 9.27 mmol) and the mixture stirred for 15 min. A solution of N -acetyl-1,2,3,4-tetrahydroquinoline (2.28 mmol) in dry benzene (25 mL) was added and the mixture heated at reflux for 12 h. Upon cooling the reaction mixture was filtered through a pad of celite and the bed washed with benzene. The combined organic extracts were washed with water (15 mL) and brine (15 mL) then dried over Na_2SO_4 . The solvent was removed *in vacuo* and the crude product purified by column chromatography (hexane: EtOAc - 3:1).

From 4: 1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline²⁵ (**12**), 30%.

From 5: 1-Acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (**13**), 30%.

Using PCC/ t -BuO₂H

Repeating the reaction but adding 70% t -BuO₂H (3 mL) after the tetrahydroquinoline.

From 4: 1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline²⁵ (**12**), 40%.

From 5: 1-Acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (**13**), 38%.

General Procedure for Oxidation using Chromium Trioxide

A solution of chromium trioxide (1.15 g, 11.5 mmol) in AcOH (2.5 mL) and water (0.5 mL) was added dropwise to a cooled (~10 °C) solution of N -acetyl-1,2,3,4-tetrahydroquinoline (2.85 mmol) in AcOH (2.0 mL). The reaction mixture was warmed to room temperature, stirred for 8 h, and cautiously quenched with saturated aqueous NaHCO_3 solution, and extracted with Et_2O . The combined organic layers were

dried and concentrated to leave a residue, which was purified by column chromatography on silica gel (EtOAc: hexane - 1:1).

From **4**: **1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline**²⁵ (**12**), 30%.

From **5**: **1-Acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline** (**13**), 25%.

General Procedure for Oxidation using Chromium Hexacarbonyl / *t*-Butyl Hydroperoxide

N-Acetyl-1,2,3,4-tetrahydroquinoline (4.50 mmol), Cr(CO)₆ (0.54 g, 2.34 mmol) and *t*-BuO₂H (70 wt% in water, 6.0 mL) were added to a round bottom flask containing MeCN (30.0 mL). The mixture was heated at reflux for 48 h, then cooled to room temperature, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (hexane: EtOAc - 3:1) to give the product. (Yields below are based on recovered starting material. See Table 2.)

From **4**: **1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline**²⁵ (**12**), 65%.

From **5**: **1-Acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline** (**13**), 90%.

From **3**: **Methyl 1-acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxylate** (**19**), a white crystalline solid (0.66 g, 60%), mp 119-120 °C, [lit.,¹ 120-122 °C];

From **6**: **1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-2-carbonitrile** (**20**), a white solid (50%), mp 123-124 °C, ¹H-NMR 2.36 (3H, s, -CH₃), 3.08 (2H, m, 3-H_a and b), 6.44 (1H, m, 2-H), 7.39 (2H, m, 5,6-H), 7.68 (1H, m, 7-H), 8.08 (1H, d, H-8); ¹³C-NMR δ 22.6, 42.2, 43.3, 116.9, 124.7, 125.4, 127.3, 128.3, 135.3, 140.5, 168.8, 189.5. Anal. Calcd For C₁₂H₁₀N₂O₂: C, 67.28; H, 4.70; N, 13.07 %. Found C, 67.64; H, 4.80; N, 13.14 %.

From **18**: **1-Acetyl-*N*-(2-bromophenyl)-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxamide** (**22**), a white solid (50%), mp 181-182 °C, ¹H-NMR 2.51 (3H, s, -CH₃), 2.99 (1H, dd, *J* 16.9 and 8.4, 3-H_a), 3.47 (1H, d, *J* 16.9, 3-H_b), 6.03 (1H, d, *J* 8.4 2-H), 6.92 (1H, t, 6-H) 7.28 (3H, m, 7-H and 4,5-H), 7.55 (2H, m, 7-H and 3-H), 8.04 (2H, m, H-8 and 6-H), 8.44 (1H, s, NH); ¹³C-NMR δ 23.1, 39.0, 56.0, 121.7, 124.0, 125.5, 126.5, 128.2, 128.4, 132.3, 134.5, 135.0, 140.3, 167.1, 171.4, 191.3. Anal. Calcd For C₁₈H₁₅N₂O₃Br: C, 55.83; H, 3.90; N, 7.23%. Found C, 55.88; H, 3.66; N, 7.20 %.

4-Oxo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**23**)

Methyl 1-acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxylate (**19**) (0.51 g, 2.05 mmol) was added to a round bottom flask containing MeOH (15 mL). K₂CO₃ (0.57 g, 1.34 mmol) was then added and the mixture heated at reflux for 4 h. MeOH was removed *in vacuo*, then water (5.0 mL) was added to the residue. Dilute HCl was added dropwise until effervescence ceased. The mixture was extracted with EtOAc (3 × 15 mL), dried over anhydrous Na₂SO₄ and the solvent concentrated under reduced pressure to give a yellow solid. The residue was triturated with CH₂Cl₂ to give **23**, a yellow powdery solid (80%); mp

183-185 °C, [lit.,²⁶ 183-184 °C].

Coupling Reactions

5,6,6a,7,13,14,14a,15-Octahydrodiquino[1,2-*a*:1',2'-*d*]pyrazine-5,7,13,15-tetraone (**24**)

i) Using Dicyclohexylcarbodiimide (DCC)/4-Dimethylaminopyridine (DMAP)

4-Oxo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**23**) (100 mg, 0.52 mmol) was dissolved in CH₂Cl₂ (10 mL), and DCC (70 mg, 0.39 mmol) and DMAP (4 mg, 0.04 mmol) added. The mixture was stirred at room temperature overnight. The product was isolated by filtering and concentrating the filtrate under reduced pressure. The crude product was purified using column chromatography (hexane: EtOAc - 1:1). An impure sample of compound **24** was obtained as a cream solid (41 mg).

ii) Using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)

4-Oxo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**23**) (100 mg, 0.53 mmol) was dissolved in MeCN (1.5 mL). Triethylamine (110 mg, 0.11 mmol) and HBTU (200 mg, 0.53 mmol) were then added and the mixture stirred at room temperature for 4 h. Compound **24**, (30 mg, 33%) precipitated as a white solid, mp 299-302 °C. ¹H-NMR (DMSO, *d*₆) δ 3.12 (2H, dd, *J* 17.5 and 3.0, H-14_a, 6_a), 3.59 (2H, dd, *J* 17.5 and 3.8, H-14_b, 6_b), 5.04 (2H, dd, *J* 13.5 and 3.1, H-6a,14a), 7.40 (2H, t, *J* 7.5, H-3,10), 7.70 (2H, t, *J* 7.3, H-2,10), 7.98 (4H, m, H-1,4,9,12). ¹³C-NMR δ 57.3, 124.8, 125.7, 126.6, 134.0, 141.1, 162.3, 191.7. Anal. Calcd For C₂₀H₁₄N₂O₄·½ H₂O: C, 67.60; H, 4.22; N, 7.89%. Found C, 67.46; H, 3.92; N, 7.73%.

iii) Using 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI)

4-Oxo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**23**) (100 mg, 0.52 mmol) was dissolved in CH₂Cl₂ (5.0 mL), and EDCI (330 mg, 0.17 mmol) and DMAP (10 mg, 0.08 mmol) added. The mixture was stirred at room temperature for 4 h. The solution was diluted with EtOAc (10.0 mL), washed with brine, and the organic layer concentrated under reduced pressure. The crude product was purified using column chromatography (hexane: EtOAc - 1:1). Compound **24** was obtained as a cream solid (40 mg, 45%).

REFERENCES

1. N. O. Townsend and Y. A. Jackson, *Heterocycles*, 2007, **71**, 669.
2. Y. Bonvin, E. Callens, I. Larrosa, D. A. Henderson, J. Oldham, A. J. Burton, and A. G. M. Barrett, *Org. Lett.*, 2005, **7**, 4549.
3. M. Nakanishi and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 861.
4. F. Carey and R. Sundberg, *Advanced Organic Chemistry* 4th Ed. Part B: Reactions and Synthesis, Springer, New York, U.S.A., 2001.
5. A. J. Pearson, Y.-S. Chen, G. Rin Han, and T. Ray, *J. Chem. Soc., Perkin Trans. I*, 1985, 267.

6. J. Muzart, *Tetrahedron Lett.*, 1986, **27**, 3139
7. A. Reissert, *Ber.*, 1905, **38**, 1603.
8. H. Rupe, R. Paltzer, and K. Engel, *Helv. Chim. Acta*, 1937, **20**, 209.
9. W. E. McEwen and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511.
10. F. D. Popp, *Adv. Heterocycl. Chem.*, 1968, **9**, 1.
11. J. W. Davies Jr., *J. Org. Chem.*, 1959, **24**, 1691.
12. D. L. Boger, C. E. Botherton, and J. S. Panek, *J. Org. Chem.*, 1998, **63**, 1767.
13. S. Bull, S. Davies, R. Parkin, and F. Sanchez-Sancho, *J. Chem. Soc., Perkin Trans. I*, 1998, 2313.
14. M. Martins and I. Carvalho, *Tetrahedron*, 2007, **63**, 9923.
15. Y. Funabashi, T. Horiguchi, S. Iinuma, S. Tanida, and S. Harada, *J. Antibiot.*, 1994, **47**, 1202.
16. L. Lin, S. Okada, D. A. York, and G. A. Bray, *Peptides*, 1994, **15**, 849.
17. D. Wang, M.-T. Liang, G.-J. Tian, H. Lin, and H.-Q. Liu, *Tetrahedron Lett.*, 2002, **43**, 865.
18. F. R. Lucietto, P. J. Milne, G. Kilian, C. L. Frost, and M. Van de Venter, *Peptides*, 2006, **27**, 2706.
19. R. J. Martin, A. P. Robertson, and H. Bjorn, *Parasitology*, 1997, **114**, 111.
20. R. Feldstein, J. Glass, and S. Steiner, United States Patent, 1994, 5352461.
21. K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683.
22. H. Meyer, *Monatsh.*, 1914, **25**, 1196.
23. G. P. Zecchini and M. P. Paradisi, *J. Heterocycl. Chem.*, 1979, **16**, 1589.
24. W. K. Anderson, J. DeRuiter, and A. R. Heider, *J. Org. Chem.*, 1985, **50**, 722.
25. T. A. Crabb and S. L. Soilleux, *J. Chem. Soc., Perkin Trans. I*, 1985, 1381.
26. T. Tokuyama, S. Senoh, T. Sakan, K. Brown, Jr., and B. Witkop, *J. Am. Chem. Soc.*, 1967, **89**, 1017.