The Synthesis of the Kynurenamines K_1 and K_2, Metabolites of Melatonin

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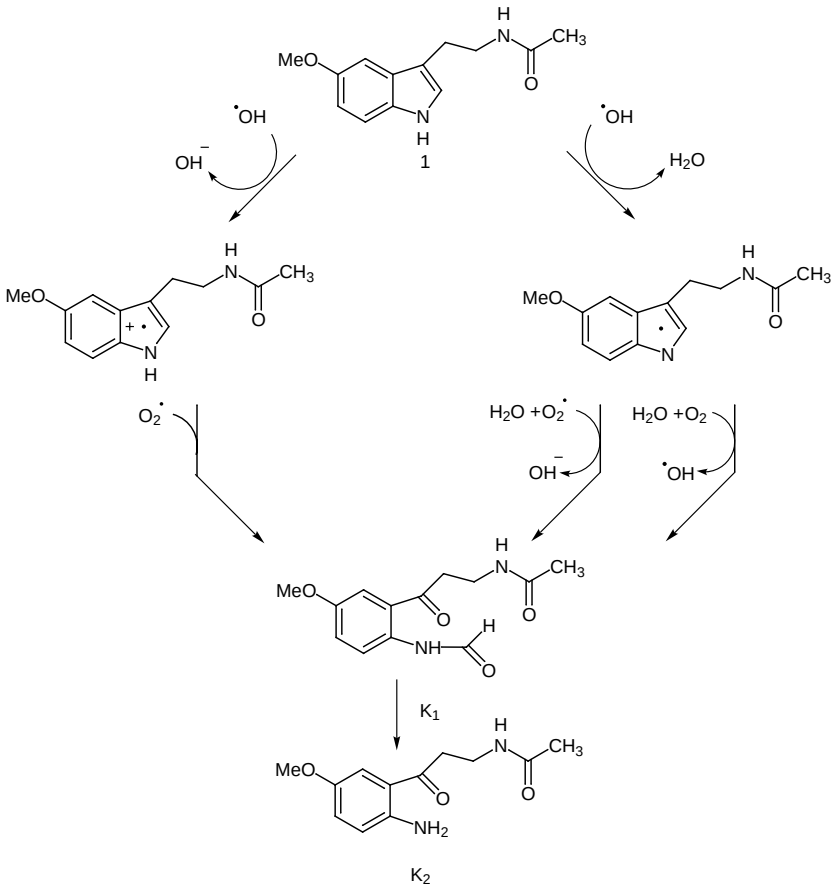
Abstract: An efficient synthesis of the kynurenamines K_1 and K_2, the major brain and antioxidant metabolites of melatonin **1** is described. Regioselective lithiation of *tert*-butyl(4-methoxyphenyl) carbamate and iodination provided the (2-iodoaryl)carbamate which when coupled with *N*-acetyl-propargylamine underwent a Sonogashira reaction. Simultaneous alkyne hydration and N-formylation produced K_2, whereas alkyne hydration only, produced K_2.

Key words: kynurenamine synthesis, ortho lithiation, Sonogashira coupling, arylpropargylamine, alkyne hydration

Biological rhythms are essential to life. The biosynthesis of the neurohormone melatonin (*N*-acetyl-5-methoxytryptamine, **1**) varies at different times during the day and this is known as a circadian rhythm. Melatonin has been implicated in pathologies associated with circadian rhythm disorders. The administration of **1** to humans has illustrated it can induce sleep,[1] alleviate jet lag,[2] and to advance the sleep rhythm of subjects with delayed sleep phase syndrome.[3] It has been proposed to protect against damage caused by free radicals in vivo.[4] In vitro experiments have demonstrated that **1** is able to scavenge ·OH radicals. The proposed mechanism[5] which involves the abstraction of an electron to form an indolyl cation radical has been computed to be an enderogonic reaction and calculations have shown that an alternative thermodynamically more feasible process whereby hydrogen abstraction leading to a neutral indole radical as shown in Scheme 1, is bioenergetically more likely to occur.[6]



Scheme 1

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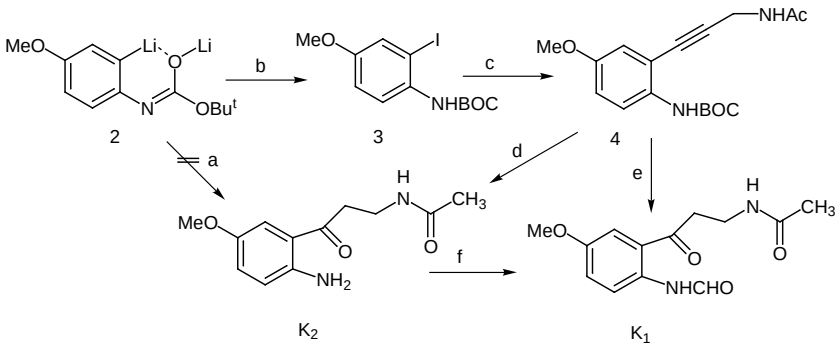

Scheme 2 (a) *N*-acetyl-2-azetidione; (b) 1.5 equiv 1,2-diiodoethane, 63%; (c) *N*-acetylpropargylamine, 5 mol% $PdCl_2(PPh_3)_2$, CuI 10 mol%, Et_3N, 76%; (d) $HgSO_4$, 10% H_2SO_4, 41 °C, 59%; (e) $HgSO_4$, H_2O, HCOOH, CH_2Cl_2, r.t., 54%; (f) HCOOH, reflux, 54%.

There are no known morphophysiological barriers to melatonin and it is generally believed that it readily enters every cell in the organism. To further investigate the claims that **1,** as an antioxidant, protects against damage caused by free radicals, we required quantities of its metabolites,[7] K_1 and K_2 for biological testing and analysis to determine if they can serve as an index for melatonin's antioxidant activity.

Whilst N_b-acetyl-5-methoxykynurenamine has been previously prepared by the ozonolysis[8] of **1** and the photosensitized oxygenation of N_b-methoxycarbonyltryptamines[9] also produced kynurenamines, our repeated efforts using these approaches met with limited success.

The synthesis (Scheme 2) commenced with the directed ortho lithiation of 4-methoxy-*N*-(*tert*-butoxycarbonyl)aniline[10] to give the dilithio intermediate **2**. Quenching with the lactam *N*-acetyl-2-azetidione, to give K_2 was unsuccessful.[11] Lithium-iodine exchange produced **3**,[14] followed by a Sonogashira reaction[12] (the Pd^0/Cu^1-catalyzed coupling of aryl halides with terminal acetylenes under basic conditions) with *N*-acetylpropargylamine that resulted in formation of the arylalkynamide **4**.[15] This compound was directly converted into K_1 by hydration of the triple bond with catalytic mercuric sulfate in formic acid solution, which also replaced the NHBOC group with NHCHO substituent. Alternatively, when the triple bond in **4** was hydrated with $HgSO_4$ in 10% H_2SO_4, the β-aminoketone derivative,[13] K_2[16,17]was prepared, which when refluxed with formic acid was converted into K_1.[16]

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(14) To a solution of *tert*-butyl (4-methoxyphenyl) carbamate (10.0 g, 44.82 mmol) in dry THF (112 mL) under N_2 at –78 °C, was added a solution of *tert*-butyllithium in pentane (68.56 mL, 116.53 mmol). After 15 min the solution was warmed to –20 °C and kept at that temperature for 2.5 h whereupon a solution of 1,2-iodoethane (18.95 g, 67.23 mmol) in dry THF (40 mL) was added. The reaction mixture was stirred at ambient temperature overnight. After quenching with sat. aq $Na_2S_2O_3$ solution (170 mL), the reaction mixture was extracted with Et_2O (3 × 270 mL). The organic phase was washed with brine (160 mL), dried over

Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/Et_2O, 10:1) afforded **3** (9.97 g. 63.74%) as colorless prisms, mp 49–51 °C. IR (KBr): 3346 (s), 2978 (m), 1700 (s), 1515 (s), 1163 (s)cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 9.1 Hz, 1 H), 7.23 (d, *J* = 2.9 Hz), 6.85 (dd, *J* = 2.9, 9.0 Hz), 6.55 (br, 1 H), 3.76 (s, 3 H), 1.53 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 155.9, 153.0, 132.3, 123.6, 114.8, 80.7, 55.6, 28.3; MS: *m/z* = 349 [M^+].

(15) To a solution of **3** (1.75 g, 5 mmol), $PdCl_2[PPh_3]_2$ (140.3 mg, 0.2 mmol), CuI (85 mg, 0.45 mmol), in dry Et_3N (9.12 mL) at r.t. under N_2 atmosphere, was slowly added *N*-acetyl propargylamine (0.65 g, 6.65 mmol) (30 min). The reaction mixture was stirred at r.t. for 1 h and then partitioned between Et_2O (25 mL) and brine (7 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to give 176 mg. Flash chromatography (ethyl acetate/hexane, 2:1) afforded **4**, *tert*-butyl(2-[3′-*N*-acetylaminopropargyl]-4-methoxy phenyl) carbamate, (122 mg, 76.7%) as white crystals, mp 114–118 °C. IR (KBr): 3328 (s), 1698 (s), 1652 (s), 1525 (s), 1292 (s), 1163 (s)cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.89 Hz, 1 H), 6.96 (br, 1 H), 6.96–6.83 (mt, 2 H), 6.05 (br, 1 H), 4.33 (d, *J* = 5.11 Hz, 2 H), 3.75 (s, 3 H), 2.05 (s, 3 H), 1.53 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 199.91, 154.32, 152.69, 133.13, 119.68, 116.28, 115.83, 111.91, 91.42, 80.55, 78.50, 55.36, 29.91, 28.20, 22.79; HRMS (ES, Na): *m/z* = 341.1473 ([M + Na]$^+$; calcd for $C_{17}H_{22}N_2O_4Na$: 341.3564).

(16) Mercuric sulfate (0.36 g, 1.13 mmol), distd H_2O (2.75 mL), formic acid (19.25 mL) and DCM (11 mL) were magnetically stirred in a 100 mL round bottom flask until the mixture had dissolved. To this solution, **4** (0.36 g, 1.12 mmol) was added over 0.5 h and stirring at 42 °C was continued for 4 h. Solid $NaHCO_3$ was added to adjust solution to pH 7–8 and the reaction mixture was freeze dried followed by extraction with EtOAc (3 × 50 mL). The organic phase was washed with H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc–MeOH, 30:1) afforded $\mathbf{K_1}$ (0.165 g, 62%) as fine white needles, mp 142–144 °C and $\mathbf{K_2}$ (0.0421 g, 14.1%), mp $\mathbf{K_1}$ IR (KBr): 3331 (m), 1687 (s), 1671 (s), 1649 (s), 1540 (s), 1195 (s)cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 11.15 (br, 1 H), 8.53 (d, *J* = 9.16 Hz, 1 H), 8.31 (d, *J* = 1.65 Hz, 1 H), 7.26 (d, *J* = 2.75 Hz, 1 H), 7.03 (dd, *J* = 2.75, 9.16 Hz), 6.99 (dd, *J* = 2.75, 9.16 Hz), 6.2 (br, 1 H), 3.72 (s, 3 H), 3.6–3.4 (m, 2 H), 3.2–3.1 (m, 2 H), 1.86 (s, 3 H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 203.20, 170.242, 159.35, 154.83, 133.10, 123.07, 120.66, 118.07, 115.46, 55.64, 39.64, 34.42, 23.19; HRMS (ES, Na): *m/z* = 287.1004 ([M + Na]$^+$; calcd for $C_{13}H_{16}N_2O_4Na$: 287.2662).

(17) Mercuric sulfate (0.36 g, 1.13 mmol), 10% H_2SO_4 (25 mL) and CH_3OH (10 mL) were magnetically stirred in a 100 mL round bottom flask until the mixture had dissolved. To this solution, **4** (0.36 g, 1.12 mmol) was added over 0.5 h and stirring at 42 °C was continued for 5 h. Solid $NaHCO_3$ was added to adjust solution to pH 7–8 and the reaction mixture was freeze dried followed by extraction with EtOAc (3 × 50 mL). The organic phase was washed with H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (EtOAc–MeOH, 30:1) afforded $\mathbf{K_2}$ (0.154 g, 58%) as yellow powder, mp 86–88 °C. IR (KBr): 3446 (s), 3339 (s), 2937 (s), 1731 (s), 1651 (s), 1557 (s), 1237 (s)cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 2.93 Hz, 1 H), 6.99 (dd, *J* = 2.93, 8.9 Hz, 1 H), 6.95 (dd, *J* = 2.93, 8.9 Hz, 1 H), 6.3 (br, 1 H), 5.8–5.0 (br, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 200.87, 170.10, 150.14, 145.04, 123.94, 118.83, 117.32, 112.95, 55.91, 38.72, 34.49, 23.30; HRMS (ES, Na): *m/z* = 259.1054 ([M + Na]$^+$; calcd for $C_{12}H_{16}N_2O_3Na$: 259.2623).