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An efficient synthesis of 6-hydroxymelatonin, a human metabolite of melatonin

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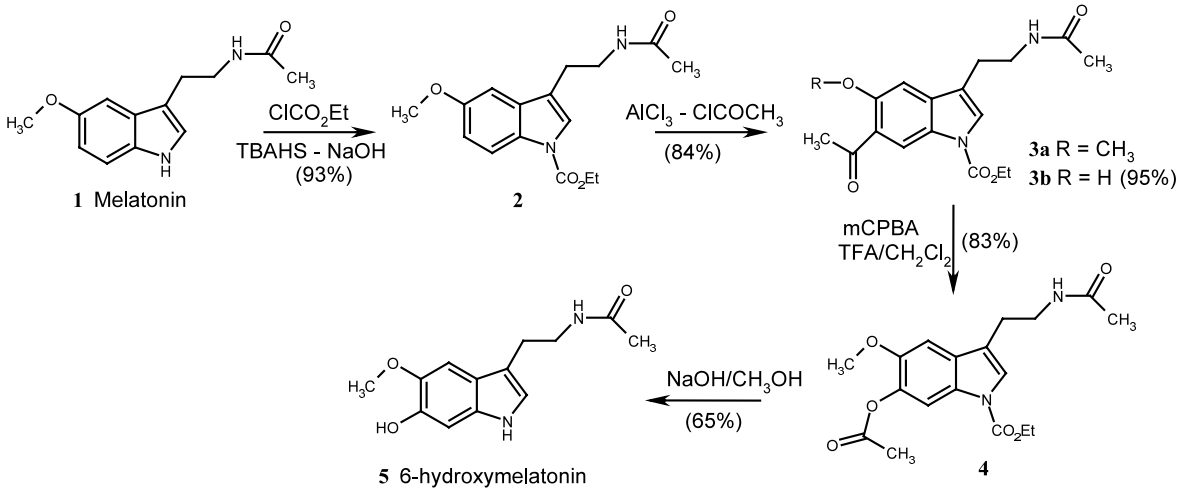
Abstract—A four-step synthesis of 6-hydroxymelatonin **5**, major human metabolite of melatonin **1**, is reported starting from melatonin. The synthesis involves in the keys steps a regioselective Friedel–Crafts acylation followed by a Baeyer–Villiger oxidation. The overall yield is 48%.

1. Introduction

5-Methoxy *N*-acetyltryptamine (**1**), the compound known as melatonin, is a hormone produced and secreted in the pineal gland.[1] The exact role of this hormone has not yet been determined, the most important action of melatonin being in reproductive activity of animals.[2] The possible involvement of melatonin **1** in seasonal affective disorder, circadian rhythm disorder, depression or aging has also been reported.[3]

Hydroxylation is an important route by which mammals detoxify aromatic compounds. The major metabolic process for removal of melatonin **1** is by hydroxylation of benzene rings in liver microcosms.[4] The resulting 6-hydroxymelatonin **5** is conjugated as a sulfate ester (55–80%) and a glucuronide (5–30%), and excreted in urine.[5] The use of 6-hydroxymelatonin **5** in combination with a progesterone and/or an estrogen has been reported as a method for contraception by an ovulation-inhibiting effect.[6]



Scheme 1.

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The synthesis of the 6-hydroxymelatonin **5** has been reported starting from non-commercial 6-benzyloxy-5-methoxyindole,[7] utilizing the Mannich base methodology (six steps, 23%),[8] or by the Knoevenagel condensation route (five steps, 19%).[9]

In this paper, we describe a more efficient four-step synthesis of this metabolite from melatonin.

2. Results and discussion

Whereas the elaboration of the tryptamine side-chain is readily effected by conventional means, versatile methods for the introduction of functionality into the benzene ring are lacking and usually involve classical electrophile substitution or prior incorporation of the substitution in the de novo indole ring construction.[10] Direct oxidation of melatonin with ozone or *m*-chloroperbenzoic acid (*m*-CPBA),[11] singlet oxygen,[12] or a mixture of HCl and DMSO,[13] always affects the pyrrole ring of melatonin **1**. Herein, we report a more efficient synthesis of 6-hydroxymelatonin **5** prepared as outlined in Scheme 1.

The improvement of the synthesis is based on the choice of the *N*-protecting groups of melatonin **1**. Therefore, compound **2** was prepared to favour acylation on the benzene ring, the *N*-acylation protecting the pyrrole ring.[14]

The reaction of melatonin **1** with ethyl chloroformate, tetrabutylammonium hydrogenosulfate (TBAHS) and sodium hydroxide in dichloromethane gave the carbamate **2** in good yield (93%).

A regioselective Friedel–Crafts acylation at the 6-position of **2**,[15] using acetyl chloride and aluminium chloride for 60 min at 20°C, afforded the desired compound **3a**[16] (84% yield). Structure of compound **3a** was determined using COSY ^{1}H–^{1}H and HMQC spectra. It should be pointed out that phenol **3b** was formed (95%) when the reaction was carried out overnight under the same conditions.

Baeyer–Villiger oxidation of compound **3a**, with *m*-CPBA in dichloromethane in the presence of trifluoroacetic acid at 20°C for 60 min, afforded compound **4**[17] in good yield (83%). Removal of the acyl and carbamate groups was accomplished under basic conditions (NaOH/MeOH) furnishing 6-hydroxymelatonin **5**[18] in 65% yield.

3. Conclusion

This work constitutes an efficient direct functionalization of the benzene moiety of melatonin **1**. Selective 6-substitution can be achieved via carbamate protection and Friedel–Crafts acetylation. The utility of this methodology for the modification of indole derivatives in total synthesis is noteworthy. This strategy provided access to the major melatonin metabolite **5** in four steps with a satisfactory overall yield (48%) from melatonin.

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15. *Preparation of* ***2***: To a stirred suspension of melatonin **1** (1.01 g, 4.3 mmol) and sodium hydroxide (5.2 g, 0.13 mol) was added ethylchloroformate (1.75 mL, 18.3 mmol) and tetrabutylammonium hydrogensulfate (1.46 g, 4.3 mmol) in dichloromethane (92 mL). The mixture was then stirred for 1 h at rt. The reaction mixture was filtered, and the organic phase was washed three times with water, dried over $MgSO_4$, and evaporated to dryness. Upon the addition of ether a white solid was obtained. Recrystallization from ether gave white crystalline **2** (1.24 g, 93%): mp 100–101°C; IR ($CHCl_3$): ν_{max} 3289, 1731, 1652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (1H, d, $J=8.2$ Hz, H-7), 7.41 (1H, s, H-2), 7 (1H, s, $J=2.3$, H-4), 6.94 (1H, dd, $J=9$, 2.6 Hz, H-6), 5.82 (1H, sl, NH), 4.44 (2H, q, $J=7.1$ Hz, H-12), 3.86 (3H, s, CH_3O), 3.57 (2H, q, 6.9 Hz, H-9), 2.87 (2H, t, $J=6.75$ Hz, H-8), 1.98 (3H, s, $NCOCH_3$), 1.48 (3H, t, $J=6.3$ Hz, H-13); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 118.25 (C-2), 116.07 (C-7), 113.30 (C-6), 101.77 (C-4), 63.07 (C-12), 55.75 (CH_3O), 39.04 (C-9), 25.14 (C-8), 23.34 ($NCOCH_3$), 14.45 (C-13); EIMS: m/z 304 $[M]^+$ (60), 245 (100), 232

(30), 160 (95). Anal. calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.40; H, 6.83; N, 9.26%.

16. *Preparation of* ***3a***: To a suspension of $AlCl_3$ (7.17 g, 53 mmol) in 1,2-dichloroethane (210 mL) was added acetylchloride (5 mL, 70 mmol) dropwise at 0°C. The mixture was stirred at rt for 5 min. To this solution was added **2** (3 g, 9.8 mmol) in 1,2-dicholorethane (150 mL). The resulting mixture was stirred for an additional 30 min at rt, then poured into water (50 mL) and extracted with dichloroethane. The combined extracts were then dried over $MgSO_4$ and evaporated under reduced pressure to give **3a** as white solid. Recrystallization from ethylacetate gave white crystalline **3a** (2.87 g, 84%): mp 184–185°C; IR ($CHCl_3$): ν_{max} 3403, 1721, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.35 (1H, s, H-7), 7.48 (1H, s, H-2), 7.03 (1H, s, H-4), 6.51 (1H, t, $J=5.5$ Hz, NH), 4.42 (2H, q, $J=7.1$ Hz, H-13), 3.94 (3H, s, CH_3O), 3.57 (2H, q, $J=6.8$ Hz, H-9), 2.87 (2H, t, $J=6.9$ Hz, H-8), 2.62 (3H, s, CH_3CO), 2.00 (3H, s, $NCOCH_3$), 1.44 (3H, t, $J=7.2$ Hz, H-14); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 125.5 (C-2), 118.24 (C-7), 100.68 (C-4), 63.36 (C-13), 55.79 (CH_3O), 39.05 (C-9), 31.82 ($\underline{C}H_3CO$), 25.09 (C-8), 23.25 (C-11), 14.37 (C-14); EIMS: m/z 346 $[M]^+$ (60), 287 (100), 272 (85), 202 (86). Anal. calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.48; H, 6.50; N, 8.13%.
17. *Preparation of* ***4***: To a solution of **3a** (1.22 g, 3.5 mmol) and trifluoroacetic acid (0.3 mL, 4 mmol) was added 80% *m*-CPBA (800 mg, 4.6 mmol) at 0°C and the mixture was stirred at rt for 2 h. Na_2HPO_4 (3.5 mmol) and Na_2SO_3 (3.5 mmol) were added successively to the mixture, and the suspension was vigorously stirred for 30 min. Insoluble materials were filtered off and the filtrate was quickly washed with chilled $NaHCO_3$ solution, dried, and concentrated. The residue was purified by column chromatography eluted with $CHCl_3$:MeOH (95:5) to give **4** (1.05 g, 83%): ^1H NMR ($CDCl_3$, 300 MHz): δ 7.85 (1H, sl, H-7), 7.37 (1H, s, H-2), 7.06 (1H, s, H-4), 5.05 (1H, sl, NH), 4.42 (2H, q, $J=7.1$ Hz, H-13), 3.87 (3H, s, CH_3O), 3.48 (2H, q, $J=6.8$ Hz, H-9), 2.82 (2H, t, $J=6.75$ Hz, H-8), 2.34 (3H, s, CH_3CO), 1.91 (3H, s, $NCOCH_3$), 1.43 (3H, t, $J=7.1$ Hz, H-14); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 123.499 (C-2), 110.496 (C-7), 101.896 (C-4), 63.598 (C-13), 56.639 (CH_3O), 39.376 (C-9), 25.445 (C-8), 23.542 ($NCOCH_3$), 21.038 (CH_3COO), 14.772 (C-14); EIMS: m/z 362 $[M]^+$ (35), 320 (80), 261 (100), 176 (67). Anal. calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.43; H, 6.25; N, 7.62%.
18. *Spectral data for* ***5***: ^1H NMR ($CDCl_3$, 300 MHz): δ 7.86 (1H, s, NH), 7.00 (1H, s, H-8), 6.93 (1H, s, H-7), 6.85 (1H, s, H-2), 5.73 (1H, s, OH), 5.44 (1H, sl, NHCO), 3.95 (3H, s, CH_3O), 3.60 (2H, q, $J=6.5$ Hz, H-8), 2.94 (2H, t, $J=6.8$ Hz, H-9), 1.94 (3H, s, H-10); ^{13}C NMR ($CDCl_3$, 75 MHz): δ CH aromatics, 57 (CH_3O), 40 (C-8), 26 (C-9), 24 (C-10).