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Wilhelmina Marais [a] & Cedric W. Holzapfel [a]
[a] Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa
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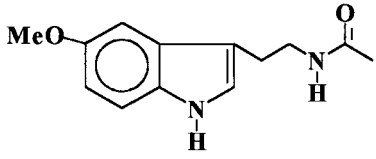
ON A FACILE SYNTHESIS OF MELATONIN AND OTHER RELATED INDOLES

Wilhelmina Marais and Cedric W. Holzapfel*

Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa.

Abstract: An efficient laboratory synthesis for melatonin and other related indoles utilising enamides and enecarbamates is described.

Melatonin (**1**), a substituted indole derivative, is of significant importance as a neurohormone of the vertebrate pineal gland and plays a unique role in the in the regulation of sleep and temperature rhythms.[1]



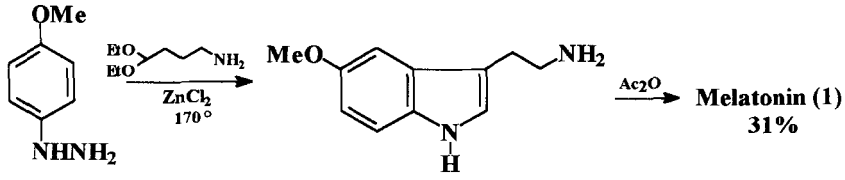
1

Melatonin (**1**) has been prepared by a linear approach comprising the synthesis of 5-methoxyindole followed by side chain attachment onto the indole using various methods.[1] However, most of the syntheses for melatonin (**1**) are based on modifications of the Fischer indole synthesis.[1] Since the aldehydes required for

* Author to whom correspondence should be addressed.

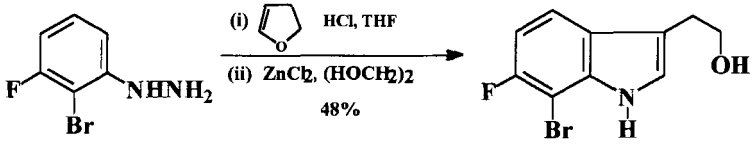
the reaction are prone to oxidation and aldol reactions, they are generally protected as acetals which are hydrolysed during hydrazone formation.[2] However, the construction of the indole and the introduction of the aminoalkyl group in one pot is low yielding.[1] In addition, the required amino aldehyde is not readily available.

Scheme 1



In this communication we report an efficient laboratory method for the preparation of melatonin (**1**) and other related indoles utilising readily accessible enamides and enecarbamates.

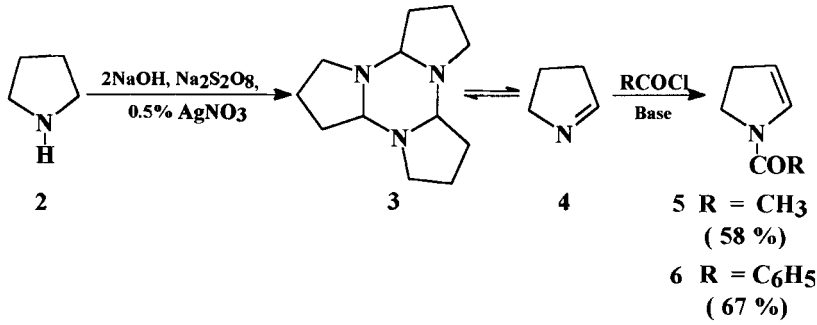
Scheme 2



Soll and his colleagues[3,4] used the Fischer reaction of dihydrofuran to synthesize etodolac derivatives (see Scheme 2). By analogy, we reasoned that cyclic enamides could act as synthetic equivalents of the amino aldehydes required for the melatonin (**1**) synthesis. It is of interest to note that cyclic enamides have found considerable application as versatile synthetic intermediates.[5,6,7] However, the methods available for the synthesis of cyclic enamides are rather limited, allowing neither the use of a wide variety of reactants nor reaction conditions. Stille and co-workers[8] reported a novel, but expensive transition metal mediated

isomerization of N-acyl-3-pyrrolines into the corresponding enamides. Anodic oxidation of N-acyl cyclic amines in methanol by Shono *et al.*[9,10] provided the corresponding α-methoxylated amides and carbamates which could either be used as masked aldehydes to prepare β-substituted indoles or transformed into the corresponding cyclic enamides and enecarbamates through acid-catalysed elimination of methanol. However, electrosynthesis has limited use and is inaccessible to many laboratories.

Scheme 3



2 **3** **4**

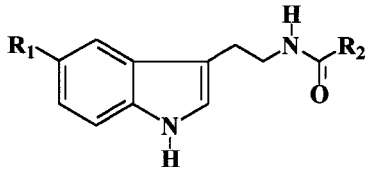
5 R = CH_3 (58 %)

6 R = C_6H_5 (67 %)

The enamides (**5,** and **6**) were prepared (Scheme3) by oxidation of pyrrolidine (**2**) in aqueous alkaline peroxodisulfate and 0.5% silver nitrate to furnish the trimer (**3**) which dissociates into **4** on heating to 80 °C.[11,12] Kraus *et al*[13] distilled a THF solution of trimer (**3**) into a precooled (- 78 °C) flask followed by the addition of triethylamine and an acid chloride to furnish the corresponding enamides in a low overall yield. We have found that the direct conversion of **3** into **5** or **6** by heating with the required acid chloride in the presence of Hünig's base resulted in significantly improved yield.

Reaction of *p*-methoxyphenylhydrazine hydrochloride with N-benzoyl-2-pyrroline (**5**) in an acetic acid/water/ethyl acetate-mixture under reflux for 20 minutes afforded melatonin (**1**) in isolated yield of 85 %. A series of other indoles were

Table 1



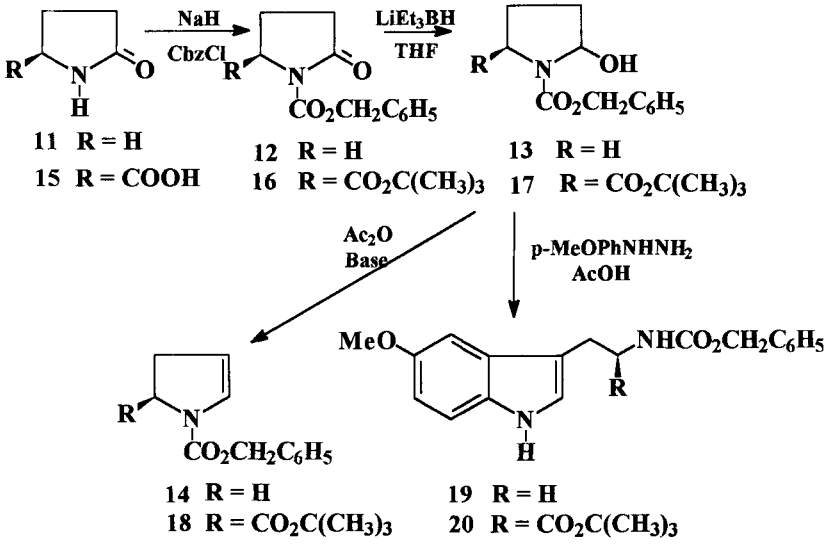
Compound	R_1	R_2	Isolated yield	Method*
1	OMe	CH_3	75%	(a) AcOH/EtOH/H_2O (25:35:40)
7	OMe	C_6H_5	85%	(a) AcOH/EtOH/H_2O (25:35:40)
8	H	CH_3	62%	(b) 1.2 mol eq $ZnCl_2$/Xylene
9	H	C_6H_5	65%	(b) 1.2 mol eq $ZnCl_2$/Xylene
10	Br	C_6H_5	30%	(c) AcOH/Ac_2O

*Method (a) and (c) give better results with the phenylhydrazine hydrochloride and method (b) with the phenylhydrazine.

prepared (see Table 1) in a similar fashion. Reaction times were short (< 30 min) and TLC analysis indicated nearly quantitative conversion into the corresponding indoles except in the case of *p*-bromophenylhydrazine hydrochloride. This is in line with observations that Fischer indole syntheses using hydrazines with electron-withdrawing substituents are often sluggish and low yielding.[2] In addition, purification of the products by column chromatography resulted in some composition and consequently lower indole yields. Nevertheless, significantly higher yields of indoles were obtained with this reaction than with the corresponding free aldehydes or their acetals. We suggest that the reaction proceeds *via* a reactive acyliminium ion intermediate.

An attractive alternative to the above cyclic carbamates in the Fischer indole synthesis involves the use of the corresponding N-acyl-carbinolamines (Scheme4).

Scheme 4



The compounds are easily prepared from readily available pyrrolidone (**11**). Protection of the nitrogen atom *e.g.* selective reduction of the N-benzyloxycarbonylderivative of **11** with $LiEt_3BH$ in THF at -78 °C provided the 2-hydroxyl derivative (**13**)[14,15] in a quantitative yield. It was anticipated that this compound would react in the same way as Shono's α-methoxylated cyclic amides to furnish indoles.[9,10] Reaction of **13** with *p*-methoxyphenylhydrazine under acidic conditions did, indeed, furnish the indole **19** in high yield (>95%). Attempts to dehydrate the alcohol **13** in the presence of acid gave only oligomeric products. Even triflation or mesylation of the hydroxyl group failed to provide the required enecarbamate **14** in useful yields. This is in agreement with the problems experienced by Leonard[16] in the preparation of enecarbamates. However, the enecarbamate (**14**) could be synthesised from the 2-hydroxyl derivative (**13**) by heating with acetic anhydride in the presence of Hünig's base.

Application of this methodology to the corresponding *tert*-butyl ester (**16**) of L-pyroglutamic acid (**15**) (prepared by the method of Taschner *et al*[17,18]) lead to the

quantitative formation of **17** which upon treatment with *p*-methoxyphenylhydrazine afforded **20**, an L-tryptophan precursor. Dehydration of **17** could also be effected by heating with acetic anhydride and base. However, the resultant product **18** was difficult to purify and could not be fully characterised.

We were also able to expand[19] this methodology successfully for the preparation of 6- and 7-membered cyclic enecarbamates from δ-valerolactam and ε-caprolactam.

In conclusion, an alternative and effective method for the preparation of cyclic enamides has been developed. In addition, the application of these and related compounds in the Fischer indole synthesis is demonstrated.

EXPERIMENTAL

General: All reactions were conducted under an inert atmosphere. ^{1}H (300.060 MHz) and ^{13}C (75.459 MHz) NMR data were recorded on a Varian Gemini 2000 (300 MHz) spectrometer in $CDCl_3$. Mass spectra were recorded on a Finnigan MAT 8200 spectrometer (70 eV). Optical rotations were obtained on a Jasco DIP 370 digital polarimeter. Melting points were taken on a Reichert Kofler hot-stage apparatus and are uncorrected. Analytical TLC was performed on Merck silica gel (60 F_{254}) plates precoated (0.25 mm) with fluorescent indicator and the indoles visualized by spraying with van Urk's reagent (4-dimethylaminobenzaldehyde-HCl). Flash chromatography was performed with silica gel 60 (0.040 - 0.063mm mesh) using v/v mixtures of the indicated eluents.

General procedure for the preparation of N-acyl-2-pyrrolines by oxidation: The trimer (**3**) was prepared in yields of *ca.* 60% by oxidation of pyrrolidine (**2**) with sodium peroxodisulfate in the presence of 0.5% silver nitrate using published methods.[11,12] The trimer (**3**) (7.2 mmol) dissolved in benzene (30 ml) was added dropwise to a refluxing solution of acid chloride (21.7 mmol) and Hünigs base (N-

ethyldiisopropylamine) (2.8g, 21.7 mmol) in benzene (10 ml). After 20 minutes the reaction mixture was allowed to cool to rt, diluted with dichloromethane and washed with water. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The product was purified by flash chromatography on silica gel (deactivated with triethylamine) using ethyl acetate and hexane (1:1). The following compounds were prepared:

N-Acetyl-2-pyrroline (**5**): Colourless oil (0.46 g, 58 %) The ^1H and ^{13}C NMR spectra are in correspondence with the data given in the literature.[8] High Resolution MS (M^+, 36%) , found 111.0682, calculated 111.0684 for C_6H_9NO.

N-benzoyl-2-pyrroline (**6**): Colourless oil (2.51 g; 67%). ^1H NMR ($CDCl_3$) (main isomer of the rotameric pair) δ 2.84 (2 H, m), 3.99 (2H, t J = 8.7 Hz), 5.12 (1H, td J = 2.7 and 4.2 Hz), 6.42 (1H, td J = 1.2 and 4.2 Hz), 7.39 - 7.46 (5H, m). ^{13}C NMR ($CDCl_3$) δ 28.27, 45.54, 111.75, 127.68, 128.41, 130.31, 130.66, 135.82, 166.99. HRMS (M^+, 62%), found 173.0845, calculated 173.0840 for $C_{11}H_{11}NO$.

General procedure for the preparation of indoles using enamides: A solution of enamide (0.21 mmol) and the required phenylhydrazine (0.24 mmol) in the appropriate solvent (1.5 - 5 ml) with catalyst (see Table 1) was refluxed for 20 minutes, allowed to cool to rt, diluted with dichloromethane and washed with water. The organic layer was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated *in vacuo*. The products were isolated by flash chromatography on silica gel (deactivated with triethylamine) using ethyl acetate-hexane (1:1). The following compounds were prepared:

Melatonin (**1**) (75 %) mp 112°C (lit[20] 116- 118 °C)

N-[2-(5-methoxy-1H-indol-3-yl)ethyl]benzamide (**7**) (85%)

N-[2-(5-methoxy-1H-indol-3-yl)ethyl]acetamide (**8**) (62%)

N-[2-(1H-indol-3-yl)ethyl]benzamide (**9**) (65%)

*N-[2-(5-bromo-1*H*-indol-3-yl)ethyl]benzamide* (**10**) (30%)

The ^{1}H and ^{13}C NMR of **7**, **8**, **9** and **10** were in agreement with that of authentic samples.[11,12]

General procedure for the preparation of 2-hydroxyl carbamates: To a solution of the required pyrrolidone (**11** or **15**) (11.8 mmol) and sodium hydride (0.52g, 12.9 mmol) in tetrahydrofuran (3 ml) at -50°C was added benzyloxychloroformate (2.2g, 12.9 mmol) and stirred for 6 hours. After extractive work up with water and dichloromethane, the organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to provide a crude reaction mixture (**12** or **16**). A portion of the crude reaction mixture (**12** or **16**)(0.84 mmol) was dissolved in dry THF (2 ml), cooled to -78°C and followed by the addition of 1.0 M solution of lithium triethylborohydride in THF (1ml, 1mmol). After 1 hour the reaction mixture was quenched with a saturated aqueous $NaHCO_3$-solution (2 ml), allowed to warm to room temperature and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to furnish the essentially pure products, **13** and **17**, respectively.

N-(benzyloxycarbonyl)-2-hydroxy-pyrrolidine (**13**).Colourless oil (0.16 g; 84%). ^{1}H NMR ($CDCl_3$) (main isomer of rotameric pair) δ 1.85 (2 H,m), 3.33 (2H, m), 3.56 (2H,), 5.12 (2H, s), 5.48 (1H, s), 7.33 (5H, m). ^{13}C NMR ($CDCl_3$) δ 22.59, 32.74, 45.67, 67.02, 81,89, 127.85, 128.19, 136.37, 155.54. HRMS (M^+, 1.2%), found 221.10515, calculated 221.10519 for $C_{12}H_{15}NO_3$.

(S)-tert-*Butyl-[N-(benzyloxycarbonyl)-2-hydroxy-pyrrolidinyl]5-carboxylic acid* (**17**) Colourless oil (0.25 g; 91%). $[\alpha]_D^{22}$ -48.9 (*c*, 1.0, $CHCl_3$) ^{1}H NMR (acetone-d_6,) (main isomer of rotameric pair) δ 1.93 (2H, m), 2.47 (2 H, m), 2.88 (1H,br s), 3.62 (1H, m), 5.06 (2H, s), 5.59 (1H, m), 7.34 (5H, m). ^{13}C NMR (acetone- d_6,) δ 27.94, 28.78, 32.33, 60.34, 67.12, 81.12, 82.89, 128.61, 129.19, 137.85, 154.92, 172.26. HRMS (M^+, 2.2%), found 321.16120, calculated 321.15762 for $C_{17}H_{23}NO_5$.

General procedure for the preparation of indoles using 2-hydroxyl pyrrolidine derivatives: A solution of *p*-methoxyphenylhydrazine hydrochloride (0.58 mmol) and **13** or **17** (0.94 mmol) in an acetic acid/water/ethanol mixture (25:40:35) (3ml) was refluxed for 35 minutes. After extractive work up with water and dichloromethane, the organic layer was washed with a saturated $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography on silica gel (deactivated with triethylamine) using ethyl acetate-hexane (1:1) furnished the pure indoles. The following products were prepared:

*N-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]benzyloxycarboxamide* (**19**): Orange oil (> 95%). ^{1}H NMR ($CDCl_3$) δ 2.94 (2H, t J = 6.6 Hz), 3.52 (2H, dt J = 6,6 Hz), 3.84 (3H, s), 4.96 (1H, br s), 5.11 (1H, s), 6.86 (1H, dd J = 8.7 and 1.8 Hz), 6.93 (1H, s), 7.04 (1H, s), 7.23 (1H, d J = 8.7 Hz), 7.35 (5H, m), 8.21 (1H,br s). ^{13}C NMR ($CDCl_3$) δ 25.56, 41.12, 55.77, 66.52, 100.37, 111.98, 112.25, 122.93, 127.59, 128.06, 128.48, 131.52, 136.54, 153.94, 156.47. Accurate m/z (M^+, 79.9%), found 324.1466, calculated 324.1474 for $C_{19}H_{20}N_2O_3$.

(S)-tert-*Butyl-[1-(5-methoxy-1*H*-indol-3-yl)-2-N-(benzyloxycarbamoyl)propanoate* (**20**): Orange oil (> 95 %). $[\alpha]_D^{22}$ -11.7 (*c*, 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ 1.35 (9H, s), 3.21 (2H, dd J = 5.6 and 3.3 Hz), 3.78 (3H, s), 4.59 (1H, dd J = 7.9 and 5.6 Hz), 5.07 (2H, ^{i}s),), 5.31 (1H, d J = 7.9 Hz), 6.82 (1H, dd J = 8.7 and 2.4 Hz), 6.95 (1H, d J = 2.4 Hz), 7.02 (1H, d J = 2.1 Hz), 7.23 (1H, d J = 8.7 Hz), 7.30 (5H, m), 7.96 (1H, br s). ^{13}C NMR ($CDCl_3$) δ 27.74, 27.86, 54.97, 55.78, 66.80, 82.00, 100.63, 110.16, 111.84, 112.56, 123.45, 127.80, 128.14, 128.51. 131.20, 136.38, 154.21, 155.85, 171.12. HRMS (M^+, 13.4%), found 424.1989, calculated 424.1998 for $C_{24}H_{28}N_2O_5$.

Dehydration of 13 to form cyclic enecarbamate 14: A mixture of **13** (0.21g, 0.93 mmol), acetyl chloride (0.36g, 4.64 mmol) and Hünig's base (0.6g, 4.64 mmol) in benzene (5ml) was refluxed for 15 minutes, evaporated *in vacuo* and flash chromatographed on silica (deactivated with triethylamine) using ethyl acetate hexane (1:1).

N-(benzyloxycarbonyl)-2-pyrroline (**14**): Colourless oil (0.20g, 98 %). ^{1}H NMR ($CDCl_3$) δ 2.63 (2 H, m), 3.76 (2H, m), 5.07 (1H, m), 5.15 (2H, s), 6.52 (1H, td J = 1.8 and 3.9 Hz), 7.34 (5H, m). ^{13}C NMR ($CDCl_3$) δ 28.54, 45.15, 66.97, 108.81, 128.08, 128.50, 129.01, 136.56, 163.82. Accurate m/z (M^+, 65%) , found 203.0899, calculated 203.0946 for $C_{12}H_{13}NO_2$.

Reaction of (**14**) with *p*-methoxyphenylhydrazine hydrochloride using standard procedures furnished the required indole (**19**) (81%).

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