Tetrahedron 68 (2012) 6269–6275

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A convenient iodination of indoles and derivatives

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ARTICLE INFO

Article history:
Received 9 March 2012
Received in revised form 13 May 2012
Accepted 15 May 2012
Available online 24 May 2012

Keywords:
Iodoindoles
Iodoazaindoles
Electrophilic substitution
Iodine reagents and iodination

ABSTRACT

We report a direct iodination of indole and derivative compounds with iodine monochloride (ICl) in the presence of Celite®. This procedure has now been extended to the iodination of substituted indoles, azaindoles and pyrroles. The scope of this procedure is exemplified by the iodination of melatonin in 98% yield.

1. Introduction

Halogenation of indoles and azaindoles is of prime importance because of the versatility of halogenated compounds as starting material for the synthesis of various bioactive molecules of pharmaceutical interest.[1a] also the use of iododerivatives as radioactively labelled diagnostic markers provides an incentive for the study of new iodination methods.[1b]

Indoles and azaindoles bearing iodide at the 2- or 3-position are of interest to synthetic chemists due to their reactivity and ease of derivatization.[1a,2]

The preparation of iodoindoles is laborious and, in general, the yields are low.[3] Direct halogenation of the indole takes place preferentially at the 3-position.[4] It is more nucleophilic and could give mixture of secondary compounds, such as polyhalogenated, oxidized and indole-coupled compounds.[4c–f] The direct synthesis of iodinated benzene and derivatives is well known but the iodination of substituted indoles has received less attention.[5] Activation by metallation at the 2-position of *N*-protected indoles has been developed and constitutes an efficient strategy for the substitution with several electrophilic halogens.[6,7]

The Katritzky method is efficient for halogenation at the C-2 of indole, but requires *N*-protection, previously or in situ, using CO_2 gas, and metallation followed by addition of a halogenating agent.[4a,8] Two *N*-protected-3-iodoindoles were preparared by Benhida and col. using bis-(trifluroacetoxy)iodobenzene/iodine/pyridine reagent system in a moderate yield.[9] Consequently we focused on the development of a more suitable method for the iodination of indoles and azaindoles.

2. Results and discussion

We found that the low electrophilicity of iodine hindered the procedure for the iodination of indoles and derivatives. We required several iodoindoles for the synthesis of arylated compounds and we were interested in developing a procedure for the preparation of monoiodated compounds, considered intermediates in the synthetic routes to various biologically active compounds.

In the reaction conditions described below substituted and unsubstituted indoles gave moderate to high yields of the corresponding iodinated indoles as shown in Tables 1–4. When indole was treated with I_2 and Al_2O_3 in dichloromethane at room temperature for 2 h, 2,3-diiodoindole was formed in 61% yield (Table 1, entry 1). At first, essays using only molecular iodine (I_2) in different solvents were performed but the desired monoiodated product was not observed under the conditions tested.

The choice of iodination reagent was important; I_2 and catalyst in different conditions gave reduced reactivity (Table 1, entry 3) or complex mono- and diiodoindole reaction mixtures (Table 2, entry 1). Moreover, the options of classical stirring or ultrasound were also tested; ultrasound simplifies the reaction, reduces the time of reaction and facilitates the work-up procedure increasing the yield in some cases (Table 1, entry 6 and Table 2, entries 2, 3, 7 and 11).

ICl, as a source of electrophilic iodine, is a suitable iodination reagent.[10a,b] Several authors generated ICl in situ by adding NaI or another salt to MCl_n.[11] Our method is based on the mixture of ICl–Celite (both commercially available as separate ingredients) in

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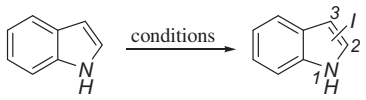
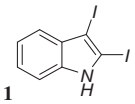
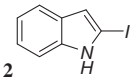
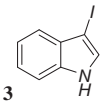
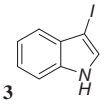
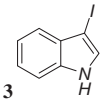
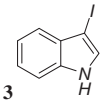
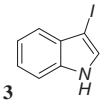
doi:10.1016/j.tet.2012.05.053

Table 1
Iodination of 2,3-unsubstituted indoles



Entry	Conditions	Product[a]	Yield (%)[b]
1	Al_2O_3/CH_2Cl_2 I_2/2 h	 **1**	61
2	I_2/KI/CuI Cyclodextrine CH_2Cl_2/2 h	 **2**	36
3	I_2/KI/$CuCl_2$ Celite®/CH_2Cl_2/2 h	 **3**	43
4	ICl (1.2 equiv)/CH_2Cl_2 Celite®/rt/2 h	 **3**	58
5	ICl (1 equiv)/CH_2Cl_2 Celite®/rt/2 h	 **3**	78
6	ICl (1 equiv)/CH_2Cl_2 Celite®/2 h	 **3**	82
7	ICl (1 equiv)/CH_2Cl_2/2 h	 **3**	37

[a] Structures were confirmed from their spectral data (NMR and IR).
[b] Isolated yields.

dichloromethane at room temperature. Celite is a porous inorganic material (we used Celite-521®, a neutral form of SiO_2 purchased from Sigma–Aldrich) with enormous surface area and several hydroxyl groups. These properties and the absence of chemical reactivity turn Celite to an interesting inorganic carrier for supporting different reagents.[10c] The reaction was tested in other solvents, such as chloroform or acetonitrile but the yields were lower than in dichloromethane. This method constitutes a mild, efficient and relatively safe process for the iodination of indoles and derivatives. Purification can be accomplished by filtration of the reaction mixture through silica gel and provides the desired iodinated compound in good yield (Table 2, entries 3 and 7). The results of this study show that ICl–Celite is the reagent of choice for the iodination of indoles. Thus, using dichloromethane as the solvent at room temperature, the desired monoiodinated compounds were obtained in 89% or 93% yields (Table 2, entries 6 and 7). The iodoindole (**5**)[12] was obtained in gram quantities in 85% yield under the conditions of entry 6 (Table 2). The direct iodination of *N*-phenylsulfonylindole in absence of Celite could also be achieved but the yield was lower and the times of reaction are longer (Table 2, entry 8).

The stoichiometry of the reaction was studied and when more than 1 equiv of ICl was used, the monoiodinated compound was obtained, but in slightly lower isolated yield than when only 1 equiv was used (Table 2 compares entries 5 and 6). This procedure led to the formation of 3-iodoindole from unsubstituted indole, while the 5-bromoindole selectively gave the iodination at the position 3 (Table 2, entries 10 and 11).

Indoles with alkyl substituents at C-3 gave lower yields, except for the iodination of melatonin (Table 3, entries 8 and 9). The iodination of indoleacetal (Table 3, entry 1) gave two products; a compound that was monoiodinated at the methyl group and the triiodoindole, in low yields. The 3-indoleacetonitrile was iodinated regioselectively at the 2-position of indole (Table 3, entries 2 and 4) but when ICl was present in excess the diiodo-compound was obtained (Table 3, entry 3). The acetamidoethylindole was also converted to the corresponding monoiodoindole (Table 3, entry 6). In contrast, when the starting indole had a bromoalkyl substituent (Table 3, entry 5) the 2-iodination was moderate.

The order of addition of the reagents affected the yield. Thus, adding the indole to a suspension of ICl and Celite in dichloromethane gave higher yield than the addition of ICl to the suspension of indole and Celite in dichloromethane.

The iodination protocol was also applied to other substrates substituted with different groups in the aromatic ring, and the desired products were isolated in good yields (50%–98%) as show in Table 3.

It should be mentioned that when the iodination was performed using ICl–Celite at room temperature for 1 h the reaction was found to be incomplete (Table 3, entries 1 and 8). An 1:1 (w/w) ICl–Celite ratio gave maximum yield of the desired product. The Celite was recycled from reaction mixture and the effectiveness of this recycling was studied and found effective up to three times. The Celite was recovered by filtration, washed in methanol and activated at 150 °C for 24 h.

Interestingly, 1 equiv of ICl gave better selectivity and the best yield (Table 3, entry 4). Similar results were obtained with acetamidoethylindole (Table 3, entry 6).

We used the iodination conditions for the synthesis of iodoazaindole and iodopyrrole (Table 4). Similarly, we also found that an excess of ICl gave a mixture of mono- and diiodoindoles (Table 4, entries 2 and 4).

Evaluation of various iodination reactions showed that the ICl/Celite strategy is effective for a range of indole or derivative compounds (Table 4, entries 1, 5 and 6). Interestingly, when we used 2.2 equiv of ICl the 2,3-diiodoazaindole was obtained in 89% yield, but the reaction was slower (24 h) (Table 4, entry 4).

ICl is an environmentally benign reagent for the oxidation process. The scope, limitation, and further application of ICl/Celite in iodination of heterocycles remain to be examined. Further studies into the optimization of this method are currently underway.

3. Conclusion

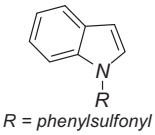
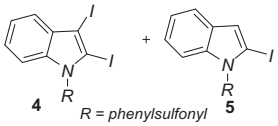
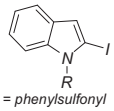
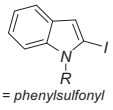
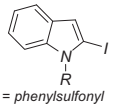
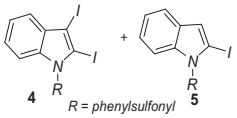
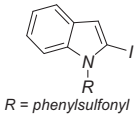
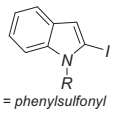
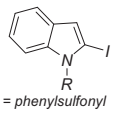
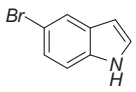
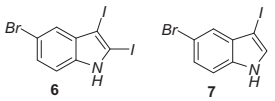
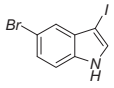
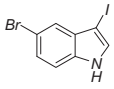
In summary, we have developed a method for the iodination of a wide range of indoles and derivatives using ICl. This type of direct conversion has proved to be attractive to chemists in general for synthesizing new chemical compounds. We expect that these substrates will become useful building blocks for the preparation of more complex structures.

4. Experimental section

4.1. Materials

Commercial reagents and solvents were purchased from Sigma–Aldrich and SDS–Carlo Erba.

Table 2
Iodination of substituted indoles

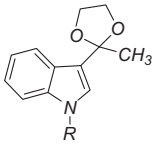
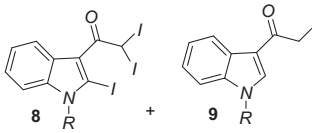
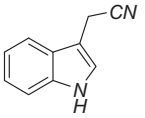
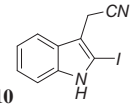
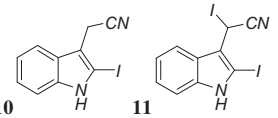
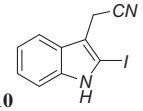
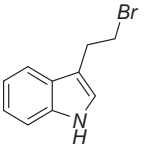
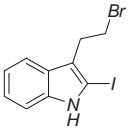
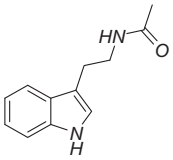
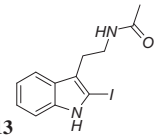
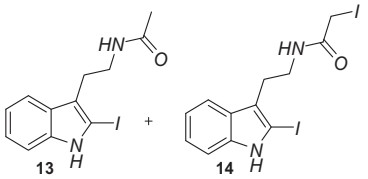
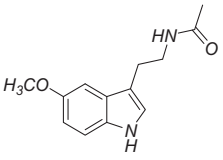
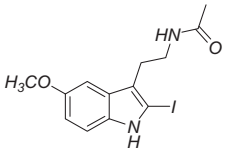
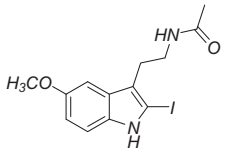
Entry	Starting compound	Conditions	Product[a]	Yield (%)[b]
1	 R = phenylsulfonyl	I_2/KI/$CuCl_2$ cyclodextrine CH_2Cl_2/2 h	 **4** R = phenylsulfonyl **5**	37+18
2		I_2/KI/$CuCl_2$ Celite®/CH_2Cl_2/2 h	 R = phenylsulfonyl **5**	67
3		ICl (1 equiv)/KI/$CuCl_2$ Celite®/CH_2Cl_2/1 h	 R = phenylsulfonyl **5**	92
4		ICl (1 equiv)/KI/$CuCl_2$ Celite®/CH_2Cl_2 8 h	 R = phenylsulfonyl **5**	87
5		ICl (1.4 equiv)/CH_2Cl_2 Celite®/rt/8 h	 **4** R = phenylsulfonyl **5**	16+60
6		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/4 h	 R = phenylsulfonyl **5**	89 (85 in multigram scale,from 6 g of *N*-phenylsulfonylindole)
7		ICl (1 equiv)/CH_2Cl_2 Celite®/1 h	 R = phenylsulfonyl **5**	93
8		ICl (1 equiv)/CH_2Cl_2/4 h	 R = phenylsulfonyl **5**	38
9		ICl (1.2 equiv)/CH_2Cl_2 Celite®/rt/4 h	 **6** **7**	25+34
10		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/4 h	 **7**	68
11		ICl (1 equiv)/CH_2Cl_2 Celite®/1 h	 **7**	76

[a] Structures were confirmed from their spectral data (NMR and IR).
[b] Isolated yields.

4.2. General

Melting points were obtained on an MFB-595010M Gallenkamp apparatus with digital thermometer in open capillary tubes and are uncorrected. IR spectra were obtained using a FTIR Perkin–Elmer 1600 Infrared Spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 and 50.3 MHz, respectively) or Varian Gemini-300

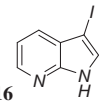
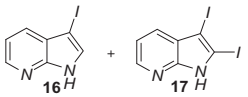
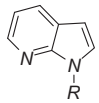
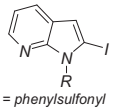
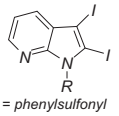
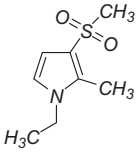
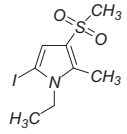
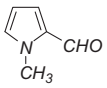
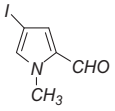
Table 3
Iodination of 3-substituted indoles

Entry	Starting compound	Conditions	Product[a]	Yield (%)[b]
1	 R = 4-methoxyphenylsulfonyl	ICl (excess)/CH_2Cl_2 Celite®/rt/1 h	 **8** + **9** R = 4-methoxyphenylsulfonyl	16+33
2		I_2/KI/$CuCl_2$ Celite® CH_2Cl_2/4 h	 **10**	58
3		ICl (1.4 equiv)/CH_2Cl_2 Celite®/rt/4 h	 **10** **11**	24+38
4		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/4 h	 **10**	60
5		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/7 h	 **12**	50
6		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/5 h	 **13**	57
7		ICl (1.2 equiv)/CH_2Cl_2 Celite®/rt/8 h	 **13** **14**	8+33
8		ICl (1.2 equiv)/KI/$CuCl_2$/Celite®/CH_2Cl_2/1 h	 **15**	78
9		ICl (1.2 equiv)/CH_2Cl_2 Celite®/rt/8 h	 **15**	98

[a] Structures were confirmed from their spectral data (NMR and IR).
[b] Isolated yields.

(300 and 75.5 MHz) Instrument using $CDCl_3$ as solvent with tetramethylsilane as internal standard, $(CD_3)_2CO$ or $(CD_3)_2SO$. Other ^1H, ^{13}C NMR spectra and heterocorrelation ^1H–^{13}C (HSQC and HMBC) experiments were recorded on a Varian Gemini-400 (400 MHz and 100.6 MHz). Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent (δ=7.26 ppm for $CDCl_3$ in ^1H NMR and δ=77.16 ppm for $CDCl_3$ in ^{13}C NMR). Mass spectra were taken on a Hewlett–Packard 5988-A and high resolution mass spectra (HRMS) were recorded on. LC/MSD-TOF mass spectrometer (Agilent Technologies). Column chromatography was

Table 4
Iodination of 7-azaindole and pyrrole

Entry	Starting compound	Conditions	Product[a]	Yield (%)[b]
1		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/4 h	 **16**	65
2		ICl (1.4 equiv)/CH_2Cl_2 Celite®/rt/24 h	 **16** + **17**	60+traces
3	 R = phenylsulfonyl	ICl (1 equiv)/CH_2Cl_2 Celite®/rt/4 h	 **18** R = phenylsulfonyl	59
4		ICl (2.2 equiv)/CH_2Cl_2 Celite®/rt/24 h	 **19** R = phenylsulfonyl	89
5		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/2 h	 **20**	78
6		ICl (1 equiv)/CH_2Cl_2 Celite®/rt/2 h	 **21**	63

[a] Structures were confirmed from their spectral data (NMR and IR).
[b] Isolated yields.

performed with silica gel (E. Merck, 70–230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel F-254 (E. Merck). Elemental analysis for C, H and N were determined on a Carlo Erba–1106 Analyser. All reagents were of commercially quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures. Reactions were carried out under argon.

4.3. Representative procedure for iodination of indoles and derivatives 1–20

A solution of indole, azaindole or pyrrole (0.1 mmol) in dichloromethane (5 mL) was added to a suspension of 1:1 (w/w) ICl (concentration indicated in the Table; 0.1 mmol=162 mg) and Celite® (162 mg) ratio in dichloromethane (10 mL). The mixture was stirred at room temperature for the time indicated in Tables 1–4 The reaction mixture was then poured into saturated thiosulfate solution (20 mL) extracted with dichloromethane (2×15 mL). The organic layer was washed in brine and, dried over sodium sulfate and the solvent was removed at reduced pressure. The desired compound was purified by chromatography column using hexane and ethyl acetate mixtures as eluting solvent. Yields of iodinated compounds are summarized in Tables 1–4. All the compounds were characterized by IR, NMR and were compared with authentic samples.

*4.3.1. 5-Bromo-2,3-diiodo-1H-indole (**6**).* Following the general procedure, compound **6** was obtained as oil in 25% yield. ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 7.14 (d, J=8.60 Hz, 1H, H-7); 7.31 (d, J=8.60 Hz, 1H, H-6); 7.67 (s, 1H, H-4); 8.20 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm), 58.1 (C-3); 112.1 (CH, C-7); 114.7 (C, C-2); 123.4 (CH, C-4); 126.5 (CH, C-6); 129.4 (C-5); 132.0 (C-3a); 133.7 (C-7a). HMRS ($C_8H_4BrI_2N$) Calcd 446.7616, Found 446.7598.

*4.3.2. 5-Bromo-3-iodo-1H-indole (**7**).* Following the general procedure, compound **7** was obtained as a yellow solid in 76% yield. ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 7.14 (d, J=8.5 Hz, 1H, H-7); 7.29 (s, 1H, H-3); 7.33 (d, J=8.5 Hz, 1H, H-6); 7.77 (s, 1H, H-4); 8.18 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm), 56.6 (C, C-3); 112.7 (CH, C-7); 114.1 (C-5); 120.9 (C-3a); 122.0 (C-7a); 123.7 (CH, C-2); 126.1 (CH, C-4); 129.5 (CH, C-6). HMRS (C_8H_5BrIN) Calcd 320.8650, Found 320.8639.

*4.3.3. 2,2-Diiodo-1-(2-iodo-1-(4-methoxyphenylsulfonyl)-1H-indol-3-yl)ethanone (**8**).* Following the general procedure but using excess of ICl (4 equiv), compound **8** was obtained as a yellow solid in 16% yield. Mp: 122–124 °C (CH_2Cl_2). ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 3.88 (s, 3H, OCH_3); 6,89 (d, J=8.9 Hz, 2H, H-3′, H-5′); 7.27 (s, 1H, CHI_2); 7.34 (d, J=8.3 Hz, 1H, H-7); 7.41 (t, J=8.34 Hz, 1H, H-6); 7.45 (t, J=8.3 Hz, 1H, H-5); 7.82 (d, J=8.9 Hz, 2H, H-2′, H-6′); 8.06 (d, J=8.3 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75,5 MHz) δ (ppm), −22.0 (CHI_2); 55.8 (CH_3–O); 112.8 (C-2); 114.3 (CH, C-7); 114.6 (CH, C-3′, C-5′); 125.2 (CH, C-4); 126.2 (CH, C-6); 128.3 (C-3); 123.4 (CH, C-5); 127.1 (C-3a); 130.6 (CH, C-2′, C-6′); 132.6 (CH, C-5); 134.0 (C, C-1′); 136.5 (C-3a); 140.6 (C-7a); 164.9 (C-4′); 166.4 (CO). HMRS ($C_{17}H_{12}I_3NO_4S$) Calcd 706.7621, Found 706.7601.

*4.3.4. 2-Iodo-1-(1-(4-methoxyphenylsulfonyl)-1H-indol-3-yl) ethanone (**9**).* Following the general procedure but using excess of ICl (4 equiv), compound **9** was obtained as a solid in 33% yield. Mp: 147–149 °C (CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm), 3.82 (s, 3H, OCH_3); 4.30 (s, 2H, CH_2); 6.93 (d, J=9.2 Hz, 2H, H-3′, H-5′); 7.37

(m, 2H, H-5, H-6); 7.90 (d, J=9.2 Hz, 2H, H-2′, H-6′); 7.93 (m, 1H, H-7); 8.28 (m, 1H, H-4); 8.33 (s, 1H, H-2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm), 2.63 (CH_2); 55.8 (CH_3—O); 113.1 (CH, C-7); 114.1 (C-3); 114.9 (CH, C-3′, C-5′); 117.4 (CH, C-4); 123.2 (CH, C-6); 124.7 (CH, C-5); 126.0 (CH, 127.6 (C-3a)); 128.7 (C-1′); 129.6 (CH (×2), C-2′, C-6′); 132.8 (C, C-2); 134.8 (C-7a); 164.8 (C-4′); 188.5 (CO). HMRS ($C_{17}H_{14}INO_4S$) Calcd 454.9688, Found 454.9702.

*4.3.5. 2-(2-Iodo-1H-indol-3-yl) acetonitrile (**10**).*[13] Following the general procedure, compound **10** was obtained as a yellow solid in 60% yield. Mp: 118—120 °C (ethyl acetate), (Lit. 116—118 °C)[13] ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 3.88 (s, 2H, CH_2CN); 7.59—7.17 (m, 4H, H-Ar (×4)); 8.25 (s, 1H, NH). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 14.7 (CH_2); 77.3 (C-2); 104.9 (C-3); 111.9 (CH, C-7); 118.4 (CH, C-4); 120.5 (CH, C-6); 123.2 (CN); 123.2 (CH, C-5); 126.5 (C-3a); 136.6 (C-7a).

*4.3.6. 2-Iodo-2-(2-iodo-1H-indol-3-yl)acetonitrile (**11**).* Following the general procedure from the 2-indolylacetonitril but using excess of ICl (1.4 equiv), compound **11** was obtained as a solid in 39% yield. ^{1}H RMN ($(CD_6)_2CO$, 300 MHz) δ (ppm), 4.15 (s, 1H, CHCN); 7.22 (d, J=8.2 Hz, 1H, H-7); 7.40—7.31 (m, 1H, H-5); 7.60—7.54 (m, 1H, H-6); 7.85 (t, J=8.2 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75,5 MHz) δ (ppm), 25.4 (CH-I); 78.1 (C-2); 109.5 (CH, C-7); 114.0 (C-3); 117.1 (CN); 118.7 (CH, C-4); 122.5 (CH, C-6); 124.2 (CH, C-5); 128.4 (C-3a); 138.2 (C, C-7a). HMRS ($C_{10}H_6I_2N_2$) Calcd 407.8620, Found 407.8647.

*4.3.7. 3-(2-Bromoethyl)-2-iodo-1H-indole (**12**).* Following the general procedure from the 3-(2-bromoethyl)indole with ICl (1 equiv), compound **12** was obtained as yellow oil in 50% yield. ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 3.32 (t, J=7.7 Hz, 2H, CH_2-Ar); 3.63 (t, J=7.7 Hz, 2H, CH_2Br); 7.24 (m, 2H, H-5, H-6); 7.36 (d, J=7.9 Hz, 1H, H-7); 7.50 (d, J=7.9 Hz, 1H, H-4); 8.03 (s, 1H, NH). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 28.7 (CH_2); 32.5 (CH_2—Br); 69.8 (C-2); 109.4 (CH, C-7); 115.4 (C-3); 119.0 (CH, C-4); 121.2 (CH, C-6); 124.4 (CH, C-5); 126.2 (C-3a); 139.7 (C-7a). Anal. Calcd(%) for$C_{10}H_9BrIN$: C, 34.32; H, 2.59; N, 4.00. Found: 34.60; H, 2.21; N, 4.36.

*4.3.8. N-(2-(2-Iodo-1H-indol-3-yl)ethyl)acetamide (**13**).* Following the general procedure from the *N*-(2-(1*H*-indol-3-yl)ethyl)acetamide compound **13** was obtained as a solid in 57% yield. Mp: 54—56 °C (ethyl acetate). ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 1.92 (s, 3H, CH_3); 2.96 (t, J=6.0 Hz, 2H, CH_2—Ar); 3.55 (t, J=6.0 Hz, 2H, CH_2NH); 5.50 (s, 1H, NH); 7.20—7.11 (m, 2H, H-5, H-6); 7.29 (d, J=6.0 Hz, 1H, H-7); 7.51 (d, J=6.0 Hz, 1H, H-4); 8.28 (s, 1H, NH). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 24.2 (CH_3); 30.0 (CH_2—Ar); 39.7 (CH_2—N); 81.8 (C-2); 109.6 (C-3); 110.9 (CH, C-7); 118.4 (CH, C-4); 120.7 (CH, C-6); 122.9 (CH, C-5); 134.8 (C-3a); 141.9 (C-7a); 170.5 (C═O). Anal. for $C_{12}H_{13}IN_2O$. Calcd: C, 43.92; H, 3.99; N, 8.54. Found: 44.12; H, 4.32; N, 8.22.

*4.3.9. N-(2-(2-Iodo-5-methoxy-1H-indol-3-yl) ethyl) acetamide (**15**).*[14] Following the general procedure from the *melatonin* the iodo—*melatonin* **15** was obtained as a solid in 98% yield. Mp: 53—55 °C (hexane/ethyl acetate). ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 1.93 (s, 3H, CH_3); 2.92 (t, J=6.5 Hz, 2H, CH_2—Ar); 3.53 (t, J=6.5 Hz, 2H, CH_2N); 3.84 (s, 3H, OCH_3); 5.55 (s, 1H, NH); 6.84 (d, J=8.8 Hz, 1H, H-6); 6.96 (s, 1H, H-4); 7.18 (d, J=8.8 Hz, 1H, H-7); 8.21 (s, 1H, NH). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 22.6 (CH_3); 24.5 (CH_2); 40.3 (CH_2); 55.5 (CH_3—O); 59.8 (C-2); 100.6 (CH, C-4); 109.3 (C-3); 111.9 (CH, C-7); 112.2 (CH, C-6); 122.2 (C, C-3a); 132.8 (CH, C-7a); 154.2 (C-5); 169.6 (C, CO). MS (EI) m/z 359 (M+H); 232 (MH^+—I).

*4.3.10. 3-Iodo-1H-pyrrolo[2,3-b]pyridine (**16**).*[15] Following the general procedure from 7-azaindole the 3-iodo-azaindole **16** was obtained as a white solid in 65% yield. Mp=204—205 °C (hexane/ethyl acetate 6:4) (201—204 °C (methanol))[16] ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 7.20 (dd, J_1=4.8, J_2=7.9 Hz, 1H, H-5); 7.49 (s, 1H, H-2); 7.80 (d, J=7.9 Hz, 1H, H-4); 8.34 (d, J=4.8 Hz, 1H, H-6). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 55.3 (C-3); 116.9 (CH, C-5); 124.5 (C-3a); 130.6 (CH, C-2); 131.1 (CH, C-4); 143.2 (CH, C-6); 146.7 (C-7a). *2-Iodo-1H-pyrrolo[2,3-b]pyridine* (**17**).[16] The compound **17** was obtained as a solid in <2% yield. Mp=112—114 °C (hexane/ethyl acetate 1:1) (115—116 °C).[16] ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 6.54 (s, 1H, H-3); 7.28 (t, J=8.0 Hz, 1H, H-5); 7.50 (m, 2H, H-3′ and H-5′); 7.72—7.81 (m, 2H, H-4, H-4′); 7.89 (d, J=7.5 Hz, 2H, H-2′ and H-6′); 8.43 (d, J=8.0 Hz, 1H, H-6). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 76.2 (C); 119.3 (CH, C-3), 120.6 (CH, C-5); 123.9 (C, C-3a), 127.8 (CH, C-4); 128.1 (CH, C-2′, C-6′); 129.4 (CH, C-3′, C-5′); 134.8 (CH, C-4′); 138.9 (C-1′); 149.5 (C, C-7a). Anal.Calcd(%) for $C_7H_4I_2N_2$: C, 22.73; H, 1.09; N, 7.57. Found: C, 23.02; H, 1.34; N, 7.34.

*4.3.11. 2,3-Diiodo-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b] pyridine (**19**).* Following the general procedure from 7-azaindole but using excess of ICl (2.2 equiv), compound **19** was obtained as a solid in 89% yield. ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 6.95 (dd, J_1=4.86 Hz, J_2=7.89 Hz, 1H, H-5); 7.50 (m, 3H, H-3′, H-5′, H-4′); 7.84 (d, J=7.89 Hz, 1H, H-4); 8.18 (m, 2H, H-2′, H-6′); 8.43 (d, J=4.86 Hz, 1H, H-6). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 73.4 (C); 109 (C), 120.9 (CH, C-5); 123.3 (C, C-3a), 126.1 (CH, C-4); 128.9 (CH, C-2′, C-6′); 129.1 (CH, C-3′, C-5′); 134.8 (CH, C-4′); 138.3 (C-1′); 141.1 (CH, C-6); 149.2 (C, C-7a). Anal.Calcd(%) for $C_{13}H_8I_2N_2O_2S$: C, 30.61; H, 1.58; N, 5.49. Found: C, 31.10; H, 1.88; N, 5.87.

*4.3.12. 1-Ethyl-5-iodo-2-methyl-3-(methylsulfonyl)-1H-pyrrole (**20**).* Following the general procedure from the substituted pyrrole, the compound **20** was obtained as yellow oil in 78% yield. ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 1.28 (t, J=7.3 Hz, 3H, CH_3); 2.48 (s, 3H, CH_3—Ar); 3.01 (s, 3H, CH_3S); 3.95 (q, J=7.3 Hz, 2H, CH_2N); 6.39 (s, 1H, H-3). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 10.7 (CH_3); 15.9 (CH_3); 42.6 (CH_2—N); 44.9 (CH_3—S); 117.6 (CH, C-4); 121.3 (C-3); 122.8 (C-5); 134.1 (C-2). Anal.Calcd(%) for $C_8H_{12}INO_2S$: C, 30.68; H, 3.86; N, 4.47. Found: C, 30.45; H, 3.97; N, 4.89.

*4.3.13. 4-Iodo-1-methyl-1H-pyrrole-2-carbaldehyde (**21**).*[17] Following the general procedure from *N*-methylpyrrole-3-carbaldehyde, the compound **21** was obtained as solid in 63% yield. Mp=72—75 °C. ^{1}H RMN ($CDCl_3$, 300 MHz) δ (ppm), 3.94 (s, 3H, CH_3); 6.91 (s, 1H, H-3); 6.98 (s, 1H, H-5); 9.50 (s, 1H, CHO). ^{13}C RMN ($CDCl_3$, 75.5 MHz) δ (ppm), 36.9 (CH_3); 77,0 (C, C-4); 130.3 (CH, C-3); 133.9 (C, C-2); 136.3 (CH, C-5); 179.1 (CHO). Anal.Calcd(%) for C_6H_6INO: C, 30.66; H, 2.57; N, 5.96. Found: C, 30.96; H, 2.23; N, 5.55.

Acknowledgements

We thank to the Ministerio de Economia y Competitividad (Spain) (CTQ2011-29285-C02-01) for financial support.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.053.

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