Carbonylation of various organolithium reagents. A novel approach to heterocycles *via* intramolecular trapping of aromatic acyllithiums

Keith Smith,* Gamal A. El-Hiti,† Gareth J. Pritchard and Anna Hamilton

Department of Chemistry, University of Wales Swansea,‡ Swansea, UK SA2 8PP

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Doubly lithiated *N*-pivaloylanilines react smoothly with carbon monoxide at 0 °C to give 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-ones in good yields. Similarly, carbonylation of doubly lithiated 4-pivaloylamino- and 2-pivaloylaminopyridines at 0 °C affords the corresponding 5-aza- and 7-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-ones, respectively, in good yields. However, carbonylation of doubly lithiated *N*-pivaloyl-*o*-toluidines takes a different course due to direct intramolecular cyclisation of the dilithio reagents to afford 2-*tert*-butylindoles without uptake of carbon monoxide.

Introduction

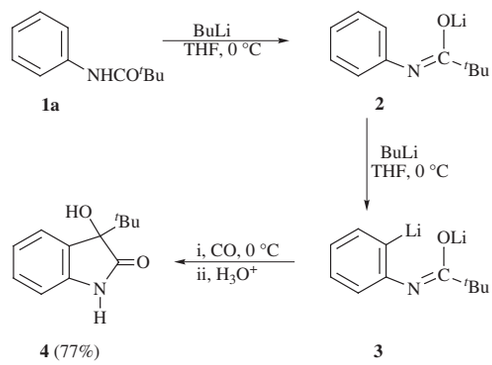
The carbonylation of organometallic reagents has been reviewed.[1] The nature of the reactions that occur depends on the nature of the organometallic reagent. Trapping of acyllithiums, generated from alkyllithiums and carbon monoxide, generally requires the electrophile to be present *in situ* and use of low temperature reaction conditions for efficient reactions.[2] However, intramolecular reactions can be more favourable.[3,4]

As part of our continuing interest in lithiation reactions,[5] we have also made use of intramolecular trapping of acyllithiums formed *via* carbonylation reactions. For example, we have shown that carbonylation of doubly lithiated *N′*-aryl-*N*,*N*-dimethylthioureas affords indigotins in good yields.[6] We have also reported on the formation of isatins in good yields from the appropriate *N′*-(2-bromoaryl)-*N*,*N*-dimethylureas *via* bromine–lithium exchange followed by treatment with carbon monoxide.[7] Moreover, recently we have obtained unexpected products from the carbonylation of 3-pivaloylaminoquinazolin-4(3*H*)-one and 3-amino-2-alkylquinazolin-4(3*H*)-ones.[8]

In our first foray into this area we studied the carbonylation of doubly lithiated *N*-pivaloylanilines. In a preliminary communication we reported that the reaction was useful for the production of 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-ones.[9] We now report the full details of this work, as well as the investigation of the scope of the reaction by including carbonylation of *N*-pivaloylaminopyridines and *N*-pivaloyl-*o*-toluidines.

Results and discussion

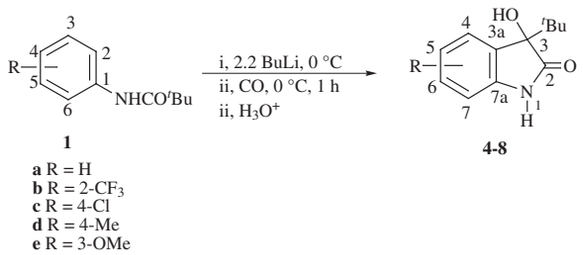
N-Pivaloylanilines (**1**) were prepared by reaction of substituted anilines with pivaloyl chloride according to literature procedures.[10] *N*-Pivaloylaniline (**1a**) was doubly lithiated by addition of butyllithium (2.2 equiv.) to a stirred solution of **1a** in THF to give initially the monolithio reagent **2** and then the dilithio reagent **3** (Scheme 1), according to the method of Führer and Gschwend.[10] The dilithio reagent **3** was then exposed at room temperature to carbon monoxide, held in a balloon, and almost instantly the mixture turned black in colour. The mixture was stirred, under carbon monoxide, for 1 h, during which time the black colour faded to a dark brown. On being worked up, the mixture gave a substantial amount of a crystalline product, identified as 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (**4**). The yield was even better (77% after purification) when the carbonylation was carried out at 0 °C.



1a **2** **4** (77%) **3**

Scheme 1

In order to test the generality of the method for the synthesis of substituted 3-*tert*-butyl-3-hydroxy-2,3-dihydroindolones, a range of ring substituted *N*-pivaloylanilines **1b–e** were subjected to identical reaction conditions, without optimisation of the individual cases. Indeed, these reactions afforded the corresponding substituted 3-*tert*-butyl-3-hydroxy-2,3-dihydroindolones **5–8** (Scheme 2) in good yields (Table 1).



1

a R = H
b R = 2-CF_3
c R = 4-Cl
d R = 4-Me
e R = 3-OMe

4-8

Scheme 2

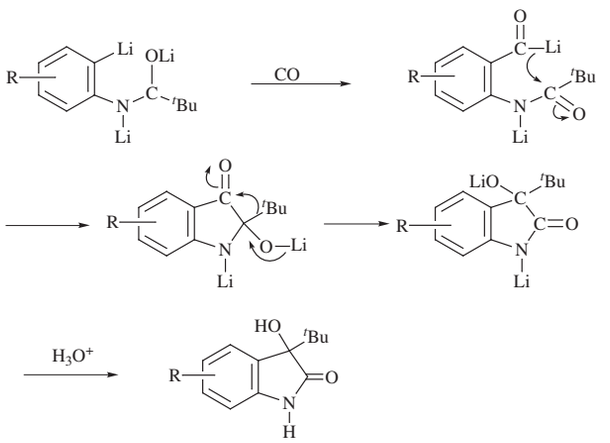
The unusual nature of the products **4–8** can be rationalised by the pathway shown in Scheme 3.[9] There is literature precedent for the rearrangement of 2-*tert*-butyl-2-hydroxy-2,3-dihydroindol-3-one to 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (**4**) under basic conditions.[11–13] In order to provide some

† Permanent address: Department of Chemistry, Faculty of Science, Tanta University, Tanta, Egypt.
‡ Formerly known as the University College of Swansea.

Table 1 Yields of 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-ones **4**–**8** from *N*-pivaloylanilines **1**

Product	R	Yield (%)[a]	Mp/°C
4	H	77	224–225 (decomp.) (lit.,[11,12] 220 or 222)
5	7-CF_3	80	149
6	5-Cl	82	280–285 (decomp.)
7	5-Me	61	263 (lit.,[12] 260–261)
8	4-OMe	78	194–195

[a] Yields of isolated, purified product.



4-8

Scheme 3

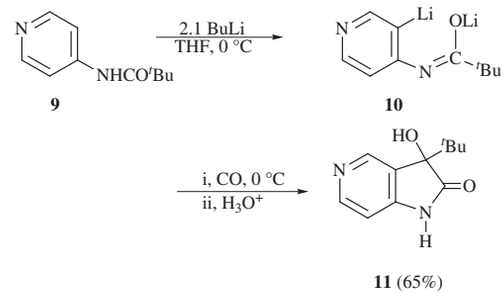
support for this mechanism, the reaction of **1c** was carried out with ^{13}CO, and the product **6** was shown to have the label at position 3, as evidenced by ^{13}C NMR. Moreover, the structure of 4-methoxy-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (**8**) was confirmed by X-ray crystal structure determination.

The ease of incorporation of carbon monoxide into the indole nucleus holds out the prospect that such reactions might be applicable to reactions of ^{11}C carbon monoxide ($t_{1/2} = 22$ min), which could present opportunities for use in positron emission tomography (PET).[14]

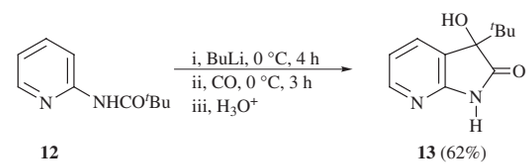
In order to investigate further the scope of the new reaction, our attention was turned to carbonylation of doubly lithiated *N*-pivaloylaminopyridines, which if successful would provide an interesting new approach to the synthesis of azahydroxy-2,3-dihydroindolones. Lithiation of 4-pivaloylaminopyridine (**9**) was achieved using 2.1 equivalents of BuLi in THF to give the dilithio reagent **10** according to the published procedure.[15] Upon exposure to carbon monoxide at 0 °C, the suspension of the dilithio reagent **10** turned to a dark colour over a short time, about 2 min. The mixture was nevertheless stirred for 3 h at 0 °C under a carbon monoxide atmosphere before being quenched by the addition of aqueous ammonium chloride solution. After work up, followed by crystallisation of the crude product from ethyl acetate, 5-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (**11**) was obtained in 65% purified yield (Scheme 4).

Similarly 2-pivaloylaminopyridine (**12**) was doubly lithiated using BuLi.[15] The dilithio reagent thus obtained reacted with carbon monoxide at 0 °C to afford 7-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (**13**) in 62% yield (Scheme 5).

Our attention was next turned to carbonylation of *N*-pivaloyl-*o*-toluidine (**14**), which, if successful, would afford a six membered heterocycle since the second lithiation takes place in the methyl group rather than on the aromatic ring.[10] Double lithiation of *N*-pivaloyl-*o*-toluidine (**14**) was achieved using butyllithium (2.2 equiv.) at 0 °C in THF.[10] A balloon of carbon monoxide was introduced into the reaction mixture containing

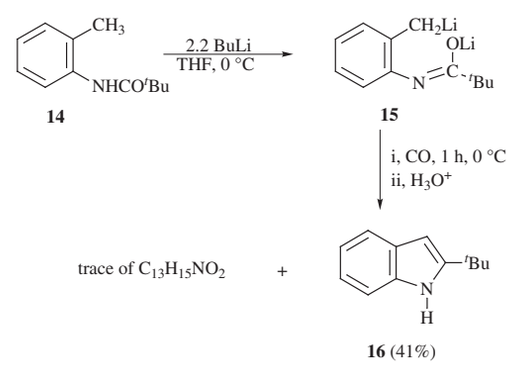


Scheme 4



Scheme 5

the dilithio reagent **15** *via* a needle and septum. After 1 h the reaction mixture was quenched and worked up. Purification of the crude product by column chromatography afforded unreacted **14** (40%) and 2-*tert*-butylindole (**16**), isolated in 41% yield (Scheme 6), along with a small amount of unidentified product

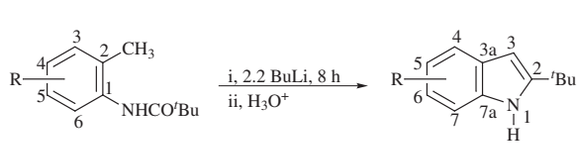


Scheme 6

with a molecular formula $C_{13}H_{15}NO_2$. It appeared likely that **16** was produced directly *via* cyclisation of the dilithio reagent **15** without involvement of carbon monoxide. Indeed, when the dilithio reagent **15** was stirred at room temperature for 16 h, compound **16** was obtained in 90% isolated yield in line with earlier findings.[10]

The unidentified product appeared to involve the uptake of carbon monoxide, but the yield was very low, and it appeared unlikely that it could be substantially improved because of the propensity of dilithio compound **15** to cyclise. Therefore, no further attempts were made to carbonylate **15**.

However, since the cyclisation of **14** to give **16** was capable of giving a high yield, the reaction was applied to a range of substituted examples, **17**. Double lithiation followed by cyclisation led to substituted 2-*tert*-butylindoles **18**–**20** (Scheme 7) in good



a R = 6-Me
b R = 4-Cl
c R = 4-OMe

Scheme 7

Table 2 Yields of 2-*tert*-butylindoles **16** and **18**–**20** from *N*-pivaloyl-*o*-toluidines (**14** or **17**) according to Scheme 8

Product	R	Yield (%)[a]	Mp/°C
16	H	90	73 (lit.,[10] 77)
18	7-CH_3	68	97–98 (lit.,[16] 98–99)
19	5-Cl	80	66–68 (lit.,[16] 62–66)
20	5-OMe	59	63–65

[a] Yields of isolated, purified product.

yields (Table 2). Thus, the reaction evidently has considerable generality.

Conclusion

Doubly lithiated pivaloylamino aromatic compounds, where the pivaloylamino group and the *ortho*-position to it on the aromatic ring have been lithiated, undergo a fairly general reaction with carbon monoxide at 0 °C to give hydroxydihydroindolone derivatives. The reaction probably involves intramolecular trapping of intermediate acyllithiums, even though the trapping centre is a weakly electrophilic amide anion. The reaction is applicable both to hydroxydihydroindolones prepared from substituted pivaloylaminobenzenes and azahydroxydihydroindolones prepared from 2- and 4-pivaloylaminopyridines.

Experimental

Melting points were determined on an electrothermal digital melting point apparatus and are reported uncorrected. IR spectra were recorded on a Perkin-Elmer 1725X spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C measurements or Bruker WM 250 operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C measurements. Chemical shifts are reported in parts per million relative to tetramethylsilane. *J* values are given in Hz. Assignments of signals are based on coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra were recorded on a VG 12-253 spectrometer, electron impact (EI) at 70 eV and chemical ionisation (CI) by use of ammonia as ionising gas. Accurate mass data were obtained on a VG ZAB-E instrument. Elemental analyses were obtained from the laboratories of the University of Wales Cardiff. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Butyllithiums were obtained from Aldrich Chemical Company and their concentration estimated prior to use by the method of Watson and Eastham.[17] THF was distilled from sodium benzophenone ketyl. Other chemicals were obtained from Aldrich Chemical Company and used without further purification. Solvents were purified by standard procedures.[18,19] IR spectra of products were in agreement with the assigned structures.

Synthesis of 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-ones 4–8

To a cooled solution (0 °C) of the appropriate *N*-pivaloylaniline (**1**) (4.7 mmol) in dry THF (20 ml) under a nitrogen atmosphere was added a solution of butyllithium (6.5 ml, 1.6 M, 10.4 mmol) in hexane. The mixture was stirred at 0 °C for 2 h then exposed to carbon monoxide, which was introduced to the reaction vessel from a balloon fitted with a needle, *via* a septum. The dilithio reagent was stirred under carbon monoxide for 1 h, after which the mixture was diluted with ethyl acetate (20 ml) and then quenched with aqueous saturated ammonium chloride solution (10 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product obtained was recrystallised from ethyl acetate to give the corresponding 3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one **4**–**8** as a white solid. The yields and physical properties are recorded in Table 1.

3-*tert*-Butyl-3-hydroxy-2,3-dihydroindol-2-one 4. δ_H([$^2H_6$]-DMSO) 10.10 (br s, exch., 1 H, NH), 7.24 (t, *J* 8.0, 1 H, 6-H), 7.16 (dd, *J* 2.0, 8.0, 1 H, 7-H), 6.94 (t, *J* 8.0, 1 H, 5-H), 6.79 (d, *J* 8.0, 1 H, 4-H), 5.65 (s, exch., 1 H, OH) and 0.96 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.41 (s, C-2), 142.27 (s, C-7a), 131.42 (s, C-3a), 128.42 (d, C-6), 125.56 (d, C-4), 120.60 (d, C-5), 108.92 (d, C-7), 79.81 (s, C-3), 36.67 [s, *C*$(CH_3)_3$] and 23.88 [q, C(*C*$H_3)_3$]; *m*/*z* (CI) 223 ($M^+ + NH_4$, 100%), 206 (MH^+, 22) and 188 (13) (Found: MH^+, 206.1181. Calc. for $C_{12}H_{16}NO_2$: 206.1181).

7-Trifluoromethyl-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 5. δ_H([$^2H_6$]DMSO) 10.61 (br s, exch., 1 H, NH), 7.52 (d, *J* 7.0, 1 H, 6-H), 7.49 (d, *J* 7.0, 1 H, 4-H), 7.13 (t, *J* 7.0, 1 H, 5-H), 5.90 (s, exch., 1 H, OH) and 0.96 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.79 (s, C-2), 139.73 (s, C-7a), 133.45 (s, C-3a), 128.38 (d, C-4), 124.90 (d, C-5), 123.67 (d, C-6), 120.87 (s, C-7), 110.09 (s, CF_3), 78.63 (s, C-3), 36.82 [s, *C*$(CH_3)_3$] and 23.76 [q, C(*C*$H_3)_3$]; *m*/*z* (CI) 291 ($M^+ + NH_4$, 100%), 274 (MH^+, 13) and 202 (44) (Found: $M^+ + NH_4$, 291.1320. Calc. for $C_{13}H_{18}F_3N_2O_2$: 291.1320) (Found: C, 57.1; H, 5.2; N, 5.0. Calc. for $C_{13}H_{14}F_3NO_2$: C, 57.15; H, 5.16; N, 5.13%).

5-Chloro-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 6. δ_H([$^2H_6$]DMSO) 10.26 (br s, exch., 1 H, NH), 7.22 (dd, *J* 2.0, 8.0, 1 H, 6-H), 7.19 (d, *J* 2.0, 1 H, 4-H), 6.76 (d, *J* 8.0, 1 H, 7-H), 5.82 (s, exch., 1 H, OH) and 0.94 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.05 (s, C-2), 141.18 (s, C-7a), 133.50 (s, C-3a), 128.30 (d, C-4), 125.51 (d, C-6), 124.83 (s, C-5), 110.39 (d, C-7), 80.02 (s, C-3), 36.70 [s, *C*$(CH_3)_3$] and 23.81 [q, C(*C*$H_3)_3$]; *m*/*z* (EI) 185 (34), 184 (12), 183 (100), 182 (32), 93 (16), 57 (87) and 41 (32); *m*/*z* (CI) 259 ($M^{+37}Cl + NH_4$, 34%), 257 ($M^{+35}Cl + NH_4$, 100), 242 ($MH^{+37}Cl$, 24), 240 ($MH^{+35}Cl$, 83), 224 (46), 222 (52) and 178 (23) (Found: MH^+, 240.0791. Calc. for $C_{12}H_{15}{}^{35}ClNO_2$: 240.0791) (Found: C, 60.1; H, 5.9; N, 5.8. Calc. for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.88; N, 5.84%).

5-Methyl-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 7. δ_H([$^2H_6$]DMSO) 10.06 (br s, exch., 1 H, NH), 7.11 (s, 1 H, 4-H), 7.02 (d, *J* 8.0, 1 H, 6-H), 6.67 (d, *J* 8.0, 1 H, 7-H), 5.67 (s, exch., 1 H, OH), 2.29 (s, 3 H, CH_3) and 0.99 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.44 (s, C-2), 139.83 (s, C-7a), 131.53 (s, C-3a), 129.27 (s, C-5), 128.62 (d, C-4), 126.34 (d, C-6), 108.65 (d, C-7), 79.90 (s, C-3), 36.65 [s, *C*$(CH_3)_3$], 23.93 (q, CH_3) and 20.73 [q, C(*C*$H_3)_3$]; *m*/*z* (EI) 219 (M^+, 8%), 163 (100), 133 (12), 106 (30), 77 (25), 57 (44) and 41 (38); *m*/*z* (CI) 237 ($M^+ + NH_4$, 39%), 220 (MH^+, 65) and 202 (100) (Found: MH^+, 220.1388. Calc. for $C_{13}H_{18}NO_2$: 220.1388).

4-Methoxy-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 8. δ_H([$^2H_6$]DMSO) 10.01 (br s, exch., 1 H, NH), 7.14 (dd, *J* 7.0, 9.0, 1 H, 6-H), 6.60 (d, *J* 9.0, 1 H, 7-H), 6.41 (d, *J* 7.0, 1 H, 5-H), 5.34 (s, exch., 1 H, OH), 3.72 (s, 3 H, OCH_3) and 0.96 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.73 (s, C-2), 156.64 (s, C-4), 143.69 (s, C-7a), 129.83 (d, C-6), 116.83 (s, C-3a), 105.67 (d, C-5), 102.42 (d, C-7), 82.19 (s, C-3), 54.87 (q, OCH_3), 38.29 [s, *C*$(CH_3)_3$] and 25.23 [q, C(*C*$H_3)_3$]; *m*/*z* (EI) 179 (100%), 164 (48), 135 (10), 105 (10), 57 (24) and 41 (24); *m*/*z* (CI) 253 ($M^+ + NH_4$, 24%), 236 (MH^+, 29), 218 (100) and 204 (10) (Found: MH^+, 236.1287. Calc. for $C_{13}H_{18}NO_3$: 236.1287)

(Found: C, 66.4; H, 7.4; N, 5.8. Calc. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%).

Synthesis of [3-^{13}C]-5-chloro-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 6

The procedure was identical to that used above except that the scale was reduced to accommodate 4-chloro-*N*-pivaloylaniline (0.25 g, 1.18 mmol) and that carbon-^{13}C monoxide was used. The carbon-^{13}C monoxide was generated from [^{13}C] formic acid and concentrated sulfuric acid at 100 °C. [3-^{13}C]-5-Chloro-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (0.226 g, 0.94 mmol; 80%) was obtained. δ_C([$^2H_6$]DMSO) 80.01 was massively enriched; *m*/*z* (CI) 260 ($M^{+37}Cl + NH_4$, 33%), 258 ($M^{+35}Cl + NH_4$, 100), 241 (17) and 223 (17) (Found: $M^{+35}Cl + NH_4$, 258.1090. Calc. for $C_{11}{}^{13}CH_{18}{}^{35}ClN_2O_2$: 258.1090).

Synthesis of 5-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 11

To a cooled solution (−78 °C) of 4-pivaloylaminopyridine (0.534 g, 3.0 mmol) in dry THF (20 ml) under a nitrogen atmosphere was added a solution of butyllithium (3.94 ml, 1.6 M, 6.3 mmol) in hexane. The reaction mixture was stirred at −78 °C for 15 min, then was allowed to warm rapidly to 0 °C. The reaction mixture was stirred at 0 °C for 2.5 h, by which time a thick white precipitate had formed. The dilithio reagent thus obtained was stirred under carbon monoxide for 3 h, after which the mixture was diluted with ethyl acetate (10 ml) and then quenched with aqueous saturated ammonium chloride solution (10 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product obtained was purified by crystallisation from ethyl acetate to give 5-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (0.40 g, 1.95 mmol; 65%) as colourless needles. Mp 276–277 °C (decomp.); δ_H([$^2H_6$]DMSO) 10.57 (br s, exch., 1 H, NH), 8.27 (d, *J* 5.0, 1 H, 6-H), 8.25 (s, 1 H, 4-H), 6.81 (d, *J* 5.0, 1 H, 7-H), 5.92 (s, exch., 1 H, OH) and 0.96 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.24 (s, C-2), 149.91 (d, C-4), 149.67 (s, C-7a), 145.09 (d, C-6), 127.36 (s, C-3a), 105.11 (d, C-7), 79.20 (s, C-3), 36.73 [s, $C(CH_3)_3$] and 23.87 [q, $C(CH_3)_3$]; *m*/*z* (EI) 150 (100%), 94 (10) and 57 (85); *m*/*z* (CI) 207 (MH^+, 100%) and 179 (10) (Found: MH^+, 207.1134. Calc. for $C_{11}H_{15}N_2O_2$: 207.1133) (Found: C, 64.1; H, 6.8; N, 13.5. Calc. for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.84; N, 13.59%).

Synthesis of 7-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one 13

To a cooled solution (−78 °C) of 2-pivaloylaminopyridine (0.534 g, 3.0 mmol) in dry THF (20 ml) under a nitrogen atmosphere was added a solution of butyllithium (3.94 ml, 1.6 M, 6.3 mmol) in hexane. The reaction mixture was stirred at −78 °C for 15 min, then was allowed to warm rapidly to 0 °C. The reaction mixture was stirred at 0 °C for 2 h, by which time a thick white precipitate had formed. The dilithio reagent thus obtained was stirred under a carbon monoxide atmosphere for 2 h, after which the mixture was diluted with ethyl acetate (10 ml) and then quenched with aqueous saturated ammonium chloride solution (10 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product obtained was purified by column chromatography using diethyl ether to give 7-aza-3-*tert*-butyl-3-hydroxy-2,3-dihydroindol-2-one (0.38 g, 1.86 mmol; 62%) as a white solid. Mp 182 °C; δ_H([$^2H_6$]DMSO) 10.77 (br s, exch., 1 H, NH), 8.02 (d, *J* 5.2, 1 H, 6-H), 7.56 (d, *J* 5.2, 1 H, 4-H), 6.93 (2 d, *J* 5.2, 1 H, 5-H), 5.90 (s, exch., 1 H, OH) and 0.93 [s, 9 H, $C(CH_3)_3$]; δ_C([$^2H_6$]DMSO) 179.13 (s, C-2), 157.04 (s, C-7a), 147.24 (d, C-6), 133.07 (d, C-4), 125.76 (s, C-3a), 117.20 (d, C-5), 79.92 (s, C-3), 36.87 [s, $C(CH_3)_3$] and 23.92 [q, $C(CH_3)_3$]; *m*/*z* (EI) 157 (10%), 141 (10), 93 (10), 79 (100), 63 (100) and 45 (80); *m*/*z* (CI) 207 (MH^+, 3%), 157 (100), 96 (95) and 79 (93) (Found: MH^+, 207.1134. Calc. for $C_{11}H_{15}N_2O_2$: 207.1133) (Found: C, 64.0; H, 6.8; N, 13.6. Calc. for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.84; N, 13.59%).

Synthesis of 2-*tert*-butylindoles 16 and 18–20

To a cooled solution (0 °C) of the appropriate *N*-pivaloyl-*o*-toluidine (**14** or **17**) (1.30 mmol) in dry THF (10 ml) under a nitrogen atmosphere was added a solution of butyllithium (1.30 ml, 2.0 M, 2.60 mmol) in hexane. The mixture was stirred at 0 °C for 1 h then for 8 h at room temperature, after which the mixture was diluted with ethyl acetate (10 ml) and then quenched with saturated aqueous ammonium chloride solution (10 ml). The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product obtained was purified by column chromatography using ethyl acetate–hexane to give the appropriate substituted 2-*tert*-butylindoles **16** or **18**–**20**. The yields and physical properties are recorded in Table 2.

2-*tert*-Butylindole 16. $\delta_H(CDCl_3)$ 7.92 (s, exch., 1 H, NH), 7.53 (dd, *J* 1.0, 7.5, 1 H, 7-H), 7.29 (dd, *J* 1.0, 7.5, 1 H, 4-H), 7.11 (dt, *J* 1.0, 7.5, 1 H, 6-H), 7.06 (dt, *J* 1.0, 7.5, 1 H, 5-H), 6.25 (d, *J* 1.0, 1 H, 3-H) and 1.38 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 148.77 (s, C-2), 135.72 (s, C-7a), 128.47 (s, C-3a), 121.04 (d, C-5), 119.94 (d, C-4), 119.57 (d, C-6), 110.34 (d, C-7), 96.89 (d, C-3), 31.80 [s, $C(CH_3)_3$] and 30.29 [q, $C(CH_3)_3$]; *m*/*z* (EI) 173 (M^+, 9%), 159 (10), 158 (100), 143 (7), 130 (17), 89 (9), 63 (8), 42 (12), 41 (31) and 39 (32) (Found: M^+, 173.1204. Calc. for $C_{12}H_{15}N$: 173.1204).

7-Methyl-2-*tert*-butylindole 18. $\delta_H(CDCl_3)$ 7.81 (br s, exch., 1 H, NH), 7.38 (d, *J* 7.2, 1 H, 4-H), 6.98 (2 d, *J* 7.2, 1 H, 5-H), 6.91 (dd, *J* 2.0, 7.2, 1 H, 6-H), 6.25 (d, *J* 2.0, 1 H, 3-H), 2.47 (s, 3 H, CH_3) and 1.39 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 148.47 (s, C-2), 135.32 (s, C-7a), 128.06 (s, C-3a), 121.80 (d, C-5), 119.84 (d, C-6), 119.53 (s, C-7), 117.71 (d, C-4), 95.57 (d, C-3), 31.90 [s, $C(CH_3)_3$], 30.41 [q, $C(CH_3)_3$] and 16.78 (q, CH_3); *m*/*z* (EI) 187 (M^+, 10%), 158 (23), 130 (5), 89 (2), 77 (12) and 57 (100) (Found: M^+, 187.1361. Calc. for $C_{13}H_{17}N$: 187.1361).

5-Chloro-2-*tert*-butylindole 19. $\delta_H(CDCl_3)$ 7.94 (s, exch., 1 H, NH), 7.48 (d, *J* 2.1, 1 H, 4-H), 7.19 (d, *J* 8.5, 1 H, 7-H), 7.05 (dd, *J* 2.1, 8.5, 1 H, 6-H), 6.18 (d, *J* 2.1, 1 H, 3-H) and 1.37 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 150.35 (s, C-2), 134.11 (s, C-7a), 128.68 (s, C-3a), 125.12 (s, C-5), 121.22 (d, C-4), 119.35 (d, C-6), 111.32 (d, C-7), 96.82 (d, C-3), 31.89 [s, $C(CH_3)_3$] and 30.21 [q, $C(CH_3)_3$]; *m*/*z* (EI) 209 ($M^{+37}Cl$, 22%), 207 ($M^{+35}Cl$, 65), 194 (30), 192 (100), 177 (9), 164 (10), 157 (23), 151 (6), 141 (5), 115 (4) and 57 (5); *m*/*z* (CI) 210 ($MH^{+37}Cl$, 35%), 208 ($MH^{+35}Cl$, 100) and 192 (11) (Found: M^+, 207.0815. Calc. for $C_{12}H_{14}{}^{35}ClN$: 207.0815).

5-Methoxy-2-*tert*-butylindole 20. $\delta_H(CDCl_3)$ 7.86 (s, exch., 1 H, NH), 7.18 (d, *J* 8.8, 1 H, 7-H), 7.02 (d, *J* 2.0, 1 H, 4-H), 6.78 (dd, *J* 2.0, 8.8, 1 H, 6-H), 6.19 (d, *J* 2.0, 1 H, 3-H), 3.83 (s, 3 H, OCH_3) and 1.33 [s, 9 H, $C(CH_3)_3$]; $\delta_C(CDCl_3)$ 154.10 (s, C-5), 149.69 (s, C-2), 130.87 (s, C-7a), 128.94 (s, C-3a), 111.01 (d, C-7), 110.50 (d, C-4), 102.19 (d, C-6), 96.85 (d, C-3), 55.98 (q, OCH_3), 31.88 [s, $C(CH_3)_3$] and 30.31 [q, $C(CH_3)_3$]; *m*/*z* (EI) 203 (M^+, 60%), 189 (18), 188 (100), 137 (12), 140 (10) and 130 (5); *m*/*z* (CI) 204 (MH^+, 100%), 188 (18) and 124 (4) (Found: M^+, 203.1310. Calc. for $C_{13}H_{17}NO$: 203.1310).

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