Efficient selective synthesis of 2-substituted indoles from complex-base-promoted arynic cyclisations

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2-Substituted indoles have been efficiently obtained by selective arynic cyclisation of halogenated aryl imines of methyl ketones in the presence of the complex-base $NaNH_2$–Bu^tONa and by $PhCH_2SH$–$AlCl_3$ opening of tetrahydrothiopyranoindoles also obtained from arynic cyclisation of imines.

As part of a programme dealing with medicinal chemistry we were interested in a selective, inexpensive and large-scale synthesis of 2-substituted indoles. From the literature[1] it appeared that the numerous available synthetic methods presented a number of drawbacks such as the use of hazardous starting materials or expensive reagents. About twenty years ago[2] we explored for the first time the synthesis of indoles by arynic cyclisation of imines in the presence of the complex-base[3] $NaNH_2$–Bu^tONa. Based upon easily available starting materials we have, more recently, exemplified the usefulness of this new access to indole derivatives.[4] Moreover the complex-base, which is essential to the generation of benzyne intermediates, may be handled on an industrial scale[5] and avoids the use of liquid ammonia as a solvent.

These data, joined to our experience of the special properties of the complex-base aggregates,[3,6] led us to conclude that our arynic cyclisation of imines could find some applications in the synthesis of 2-substituted indoles. We report herein that, as expected, such compounds may be selectively prepared either directly through the arynic pathway or after a simple transformation of the products resulting from such a cyclisation.

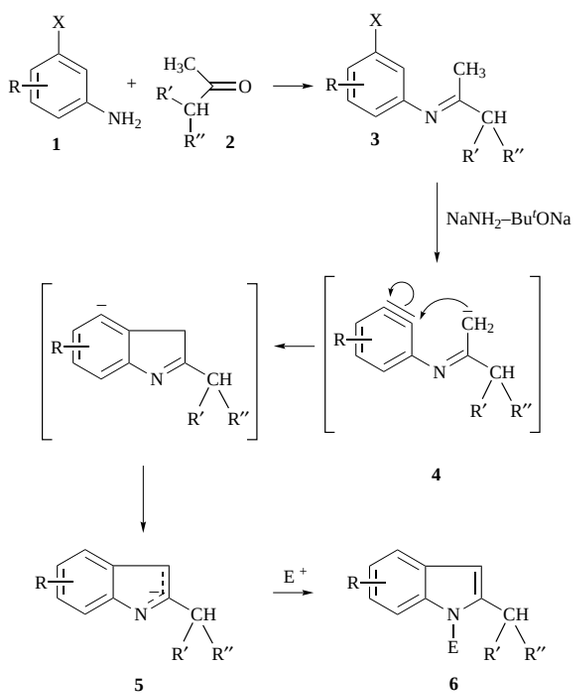
Results and discussion

The first approach considered is reported in Scheme 1. We reasoned that the kinetic basicity of the complex-base could be fitted to the selective abstraction of the methyl hydrogens. Moreover the formation of appropriate three-component mixed aggregates between $NaNH_2$–Bu^tONa and the imine enolates should favour the arynic cyclisation while avoiding the equilibration of imine enolates. The experiments whose results are reported in Table 1 completely verified our expectations.

The reported data deserve some comment. Worthy of note is the selective kinetic enolisation of imines **3** leading, through the arynic enolate intermediate **4**, to only or the preponderant formation of 2-alkylindoles **6**. Curiously, variations in the yields of isomers **7**, coming from the α′-enolisation of imine intermediates **3**, accompanied structural changes remote from the reaction centre of the imines (runs 6–9). Taking into account the properties of aggregates[3,7] this behaviour can be ascribed to modifications in the interaction between intermediates **3** and the complex-base and/or to the structure of the three-component aggregate intermediates.[4]

From a practical point of view it must be mentioned that imines **3** were used as crude products, thereby avoiding tedious purifications, and that taking account of the two-step reactions yields vary from fair to good.

As mentioned above, indole derivatives bearing an easily

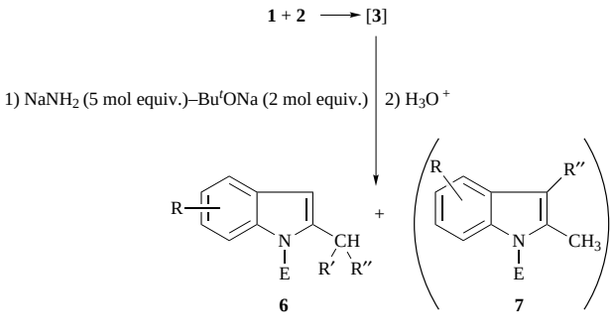


Scheme 1

transformed function on the C-2 position could also be of interest as starting materials for the synthesis of 2-substituted indoles. Within this framework our investigations were continued by a study of the synthesis of compounds **6** starting from anilines **1** and pyruvic derivatives **2**. Systematic unreported experiments rather surprisingly showed that pyruvaldehyde dimethyl acetal (**2**; R′ = R″ = OMe) was the most prone to lead to the corresponding imine **3** accompanied by only a few side-products. A crude representative of such imines compound **3** (R′ = R″ = MeO) submitted to our arynic cyclisation conditions led to the expected indoles in good to very good yields (Table 1, runs 14–18). The corresponding indolecarbaldehyde may be quantitatively obtained by simple hydrolysis as checked with the acetal of run 14. This efficient and easily performed synthesis of indole-2-carbaldehydes opens up a simple access to a large variety of 2-substituted indole derivatives.

Finally, during our studies dealing with the demethylation of methoxyindoles in the presence of AlX_3–RSH[8] we accidentally found another, indirect access to a few 2-substituted indoles. Thus in the presence of $AlCl_3$–$PhCH_2SH$, the (methoxy)-tetrahydrothiopyranoindole **8a**, also obtained from arynic

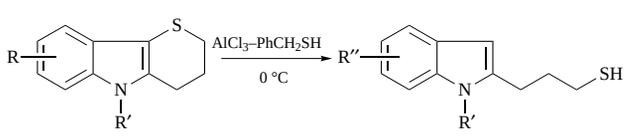
Table 1



Run	Starting materials R	X	R′	R″	Temp.	Time (*t*/h)	Compound obtained	E	Yield (%)[a]
1	4-OMe	3-Cl	H	$(CH_2)_2Me$	RT[e]	17	**6a**	H	40
2	4-OMe	3-Cl	H	$CHMe_2$	RT	40	**6b** (**7b**)	H	30 (1)[b]
3	4-OMe	3-Cl	H	$CH_2CH{=}CH_2$	RT	24	**6c**	Me	36[c]
4	4-OMe	3-Cl	H	$CH_2CH{=}CMe_2$	RT	22	**6d**	H	30
5	4-OMe	3-Cl	2,6,6-Me_3-cyclohex-2-enyl-CH=		RT	24	**6e**	Me	30[c]
6	4-OMe	3-Cl	H	$(CH_2)_2NEt_2$	RT	19	**6f** (**7f**)	H	35 (7)[b]
7	4-OMe	3-Cl	H	$(CH_2)_2NBn_2$	RT	46	**6g** (**7g**)	H	38 (18)
8	4-OMe	3-Cl	H	$(CH_2)_3NMe_2$	RT	21	**6h** (**7h**)	H	40 (4)[b]
9	4-OMe	3-Cl	H	$(CH_2)_3NBn_2$	RT	48	**6i** (**7i**)	H	27 (14)
10	4-OMe	3-Cl	H	$(CH_2)_2OEt$	RT	48	**6j** (**7j**)	H	32 (5)[b]
11	4-Me	3-Cl	H	$(CH_2)_2Me$	RT	18	**6k** (**7k**)	H	31 (2)[b]
12	4-F	3-Cl	H	$(CH_2)_2Me$	RT	18	**6l** (**7l**)	H	30 (<1)[b]
13	6-Me	3-Cl	H	$(CH_2)_2Me$	50 °C	48	**6m** (**7m**)	H	27 (7)[b]
14	4-OMe	3-Cl	MeO	MeO	RT	48	**6n**	H	54[d]
15	4-Me	3-Cl	MeO	MeO	RT	48	**6o**	H	55
16	4-F	3-Cl	MeO	MeO	RT	16	**6p**	H	50
17	4-Cl	3-Cl	MeO	MeO	RT	29	**6q**	H	35
18	H	3-Br	MeO	MeO	RT	44	**6r**	H	35

[a] Isolated yield calculated for the two steps relative to the starting amine **1**. [b] Identified only by spectroscopic data. [c] Yield in N-methylated derivative obtained by trapping intermediates **5** with Me_2SO_4 (see text). [d] Quantitatively transformed into aldehyde with HCl–acetone. [e] Room temperature.

Table 2



Starting material R	R′	Time (*t*/h)	Compound obtained	R″	Yield (%)[a]
8-MeO	H	1	**9a**	5-OH	55
8-MeO	Me	3	**9b**	5-OH	63
8-MeO	CH_2Ph	3	**9c**	5-OH	80
8-MeO	CH_2CO_2Et	2.5	**9d**	5-OH	70
6-MeO	H	2	**9e**	7-OH	65

[a] Isolated yield.

cyclisation,[4] led to compound **9a** according to the reaction of Table 2.

From a systematic study not reported here we determined the best experimental procedure (see Experimental section), which was then applied to some representative substrates. The results obtained are reported in Table 2.

The yields obtained varied from good to excellent and the excess of thiol reagent was easily recovered. This opening of the thiopyran ring must be related to previously described reductions of aryl alkyl ethers and sulfides by $AlCl_3$–RSH reagents.[8,9] However, as far as the demethylation of aryl methyl ethers is concerned, the present results confirm the selectivity of $AlCl_3$–$PhCH_2SH$[8] compared with other analogous reagents, since no reduction of the methoxy group was observed. This access to 2-substituted indoles, although more restricted, nicely completes the syntheses described above.

Conclusions

In the present work we have shown that arynic cyclisation of imines in the presence of a complex-base is very efficient in the direct or indirect synthesis of 2-substituted indoles. Since we showed that imines obtained from aldehydes were also easily cyclised into 3-substituted indoles[4] it appears that these arynic reactions ought to find further applications in heterocyclic synthesis.

Experimental

General methods

Mps were determined on a Tottoli melting point apparatus and are uncorrected. ^{13}C NMR spectra were recorded in $CDCl_3$, with a Bruker AM 400 or a Bruker 250 MHz spectrometer (Attached Proton Test method, APT). ^1H NMR spectra were recorded in $CDCl_3$ with the same apparatus. Me_4Si was the internal standard. IR spectra of thin films between NaCl plates were recorded with a Perkin-Elmer 841 instrument. Elemental analyses were performed by CNRS laboratory (Vernaison) and by ENSCM Microanalysis Department, Montpellier. Mass spectra were recorded on a Hewlett Packard 5971 A instrument. TLC was performed with plates coated with Kieselgel G (Merck). The plates were developed with hexane–EtOAc. The silica gels used for column chromatography and flash chromatography were Kieselgels of 0.063–0.2 mm and 0.04–0.063 mm particle size, respectively.

Materials

Sodium amide powder was obtained commercially (Merck). Reagent-grade tetrahydrofuran (THF) (BASF) was first distilled from potassium hydroxide and then from sodium benzophenone ketyl and stored over sodium until used. 6-(Dimethylamino)hexan-2-one,[10] 5-ethoxypentan-2-one,[11] 5-(dibenzylamino)pentan-2-one,[12] and 6-(dibenzylamino)hexan-2-one[12] were prepared according to the literature methods.[13] Other ketones **2** were commercially available.

General procedure for the preparation of imines 3

Imines were prepared from an equimolar mixture of ketone and amine in refluxing benzene or toluene. The water formed was collected in a Dean–Stark apparatus. When necessary, the reaction was catalysed by *p*-TsOH. When the reaction was complete the mixture was left to cool to room temperature, dried over $MgSO_4$, and solvents were removed under vacuum. Crude imines were used without further purification.

General procedure for arynic cyclisation of imines 3 into N-unsubstituted indoles

The reactions were performed with the complex-base $NaNH_2$–Bu^tONa.

(a) Preparation of the complex-base. To a magnetically stirred suspension of 7 mol equiv. of $NaNH_2$ in THF (7 ml for 70 mmol of $NaNH_2$) was added dropwise at room temperature 2 mol equiv. of Bu^tOH under a nitrogen flush. After completion of the addition, the mixture was warmed at 45 °C for 2 h.

(b) Condensation. To the amount of the complex-base calculated according to the amount of starting ketone (see Table 1) was added at 0 °C the corresponding crude imine. The mixture was stirred at room temperature during the time indicated in Table 1. The reaction was monitored by gas chromatography (GC) (capillary HP1, 6 m). After completion the reaction mixture was hydrolysed at 0 °C, extracted with CH_2Cl_2, and the extract was washed twice with water. After drying of the extract over $MgSO_4$ and removal of the solvent under vacuum, product **6** (and **7**) was isolated by flash chromatography (Kieselgel 60–43 μ) with EtOAc–hexane as eluent of progressive polarity (from 50 : 50 to 100% EtOAc for compounds f, g, h and i; from 10 : 90 to 30 : 70 for the others).

General procedure for arynic cyclisation of imine 3 into N-substituted indoles

The arynic condensation was performed as described above. Upon completion, the reaction mixture was decanted under a stream of nitrogen. The supernatant liquid was then added to 3 mol equiv. of electrophile at 0 °C and stirred at room temperature. After completion of the reaction and usual work-up, the solvent was evaporated off under reduced pressure, and the indoles were purified by flash chromatography (Kieselgel 40–63 μ) with EtOAc–hexane as eluent of progressive polarity (from 5 : 95 to 30 : 70).

General procedure for the preparation of indoles 9

1 Mol equiv. of a compound **8** in CH_2Cl_2 (5 ml for 3 mmol) was added dropwise at 0 °C to a mixture of 1.5 mol equiv. of $AlCl_3$ and 20 mol equiv. of $PhCH_2SH$. After the reaction mixture had been stirred for 30 min at 0 °C, 1.5 mol equiv. of $AlCl_3$ and 20 mol equiv. of $PhCH_2SH$ were added. The reaction was monitored by GC (capillary HP1, 6 m) and stopped when the maximum amount of the desired product was reached. The reaction mixture was hydrolysed with 1 M HCl at 0 °C and extracted with CH_2Cl_2. The organic layer was washed successively with water and brine, dried over Na_2SO_4, and the solvent was removed under vacuum. The product was isolated by flash chromatography (Kieselgel 40–63 μ) with EtOAc–hexane as eluent of progressive polarity (from 20 : 80 to 50 : 50).

2-Butyl-5-methoxy-1*H*-indole 6a. Mp 52 °C; ν_{max}/cm^{-1} 3404 (NH); δ_H 7.74 (s, 1 H, NH), 7.18–6.74 (m, 3 H, ArH), 6.16 (s, 1 H, ArH), 3.83 (s, 3 H, CH_3O), 2.72 (t, 2 H, CH_2), 1.69 (m, 2 H, CH_2), 1.40 (m, 2 H, CH_2) and 0.94 (t, 3 H, CH_3); δ_C 153.95 (arom CO), 140.90, 130.89 and 129.22 (arom C), 110.90, 110.57, 101.93 and 99.18 (arom CH), 55.84 (CH_3O), 31.25, 27.93 and 22.32 (CH_2) and 13.80 (CH_3) (Found: C, 76.94; H, 8.18; N, 6.87. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N, 6.89%); *m/z* (CI, CH_4) 204 (M + 1).

2-Isobutyl-5-methoxy-1*H*-indole 6b. Mp 40 °C; ν_{max}/cm^{-1} 3404 (NH); δ_H 7.73 (s, 1 H, NH), 7.18–6.75 (m, 3 H, ArH), 6.16 (s, 1 H, ArH), 3.84 (s, 3 H, CH_3O), 2.59 (d, 2 H, CH_2), 1.96 (m, 1 H, CH) and 0.97 (d, 6 H, 2 CH_3); δ_C 153.88 (arom CO), 139.81, 130.88 and 129.20 (arom C), 110.93, 110.55, 101.84 and 100.14 (arom CH), 55.81 (CH_3O), 37.66 (CH_2), 28.84 (CH) and 22.41 (2 × CH_3) (Found: C, 76.57; H, 8.32; N, 7.06%); *m/z* (CI, CH_4) 204 (M + 1).

3-Isopropyl-5-methoxy-2-methyl-1*H*-indole 7b. ν_{max}/cm^{-1} 3403 (NH); δ_H 7.49 (s, 1 H, NH), 7.12–6.73 (m, 3 H, ArH), 3.85 (s, 3 H, CH_3O), 3.12 (m, 1 H, CH), 2.33 (s, 3 H, CH_3) and 1.39 (d, 6 H, 2 × CH_3); δ_C 153.04 (arom CO), 130.53, 130.42, 127.64 and 117.24 (arom C), 110.88, 109.61 and 102.10 (arom CH), 55.81 (CH_3O), 25.66 (2 × CH_3), 22.71 (CH) and 11.95 (CH_3); *m/z* (CI, CH_4) 204 (M + 1).

2-(But-3-enyl)-5-methoxy-1-methyl-1*H*-indole 6c. Mp 65 °C; ν_{max}/cm^{-1} 3097–3074 and 1641 (HC=CH_2); δ_H 7.09–6.76 (m, 3 H, ArH), 6.15 (s, 1 H, ArH), 5.94–5.83 (m, 1 H, CH=C), 5.13–4.99 (m, 2 H, C=CH_2), 3.78 (s, 3 H, CH_3O), 3.51 (s, 3 H, CH_3N), 2.74 (t, 2 H, CH_2) and 2.44 (m, 2 H, CH_2); δ_C 153.85 (arom CO), 140.93 (arom C), 137.47 (−C=), 132.54 and 128.00 (arom C), 115.19 (=CH_2), 110.29, 109.22, 101.86 and 98.33 (arom CH), 55.73 (CH_3O), 32.51 (CH_2), 29.28 (CH_3N) and 26.24 (CH_2) (Found: C, 78.39; H, 7.93; N, 6.66. $C_{14}H_{17}NO$ requires C, 78.10; H, 7.96; N, 6.50%).

5-Methoxy-2-(4-methylpent-3-enyl)-1*H*-indole 6d. Mp 48 °C; ν_{max}/cm^{-1} 3390 (NH); δ_H 7.75 (s, 1 H, NH), 7.10–6.75 (m, 3 H, ArH), 6.15 (s, 1 H, ArH), 5.20 (m, 1 H, CH=C), 3.80 (s, 3 H, CH_3O), 2.70 (t, 2 H, CH_2), 2.35 (m, 2 H, CH_2), 1.70 (s, 3 H, CH_3) and 1.60 (s, 3 H, CH_3); δ_C 153.77 (arom CO), 140.61, 132.48 (arom C), 130.93 (=C), 129.07 (arom C), 123.34 (−CH=), 110.96, 110.49, 101.87 and 99.10 (arom CH), 55.66 (CH_3O), 28.22 and 27.58 (CH_2) and 25.54 and 17.56 (CH_3) (Found: C, 78.84; H, 8.13; N, 6.06. $C_{15}H_{19}NO$ requires C, 78.56; H, 8.35; N, 6.11%); *m/z* (CI, CH_4) 230 (M + 1).

5-Methoxy-1-methyl-2-[(*E*)-2-(2,6,6-trimethylcyclohex-2-enyl)ethenyl]-1*H*-indole 6e. Mp 113 °C; ν_{max}/cm^{-1} 1615 (C=C); δ_H 7.11–6.78 (m, 3 H, ArH), 6.48 (s, 1 H, ArH), 6.40–6.03 (m, 2 H, CH=CH), 5.47 (m, 1 H, CH=C), 3.79 (s, 3 H, CH_3O), 3.63 (s, 3 H, NMe), 2.29 (d, 1 H, CH), 2.04 (m, 2 H, CH_2), 1.64 (s, 3 H, CH_3), 1.55–1.17 (m, 2 H, CH_2), 0.94 (s, 3 H, CH_3) and 0.89 (s, 3 H, CH_3); δ_C 154.12 (arom CO), 139.08 (arom C), 134.81, 121.40 and 120.04 (=CH), 111.27, 109.61, 101.64 and 97.55 (arom CH), 55.68 (CH_3O), 55.06 (CH), 32.49 (aliph C), 31.62 (CH_2), 29.77 (CH_3N), 27.54 and 26.96 (CH_3), 23.04 (CH_2) and 22.94 (CH_3) (Found: C, 81.63; H, 8.68; N, 4.65. $C_{21}H_{27}NO$ requires C, 81.50; H, 8.79; N, 4.52%).

***N*,*N*-Diethyl-3-(5-methoxy-1*H*-indol-2-yl)propanamine 6f.** ν_{max}/cm^{-1} 3402 (NH); δ_H 10.11 (s, 1 H, NH), 7.23–6.73 (m, 3 H, ArH), 6.12 (s, 1 H, ArH), 3.82 (s, 3 H, CH_3O), 2.83 (m, 2 H, CH_2), 2.63–2.47 (m, 6 H, 3 × CH_2), 1.85 (m, 2 H, CH_2) and 1.08 (t, 6 H, 2 × CH_3); δ_C 153.68 (arom CO), 140.74, 131.15 and 129.24 (arom C), 110.96, 110.25, 101.76 and 98.60 (arom CH), 55.79 (CH_3O), 53.34 (CH_2N), 46.53 (2 × CH_2N), 27.16 and 25.93 (CH_2) and 11.17 (2 × CH_3) (Found: C, 74.15; H, 9.23; N, 10.91. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29; N, 10.76%); *m/z* (CI, CH_4) 261 (M + 1).

***N*,*N*-Diethyl-2-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethanamine 7f.** ν_{max}/cm^{-1} 3402 (NH); δ_H 8.24 (s, 1 H, NH), 7.25–6.70 (m, 3 H, ArH), 3.81 (s, 3 H, CH_3O), 2.82–2.44 (m, 8 H, 4 × CH_2), 2.25 (s, 3 H, CH_3) and 1.00 (m, 6 H, 2 × CH_3); δ_C 153.33 (arom CO), 132.11, 130.30 and 128.71 (arom C), 110.80 and 109.76 (arom CH), 108.65 (arom C), 100.02 (arom CH), 55.61

(CH_3O), 52.68 (CH_2N), 46.35 (2 × CH_2N), 21.20 (CH_2), 11.20 (2 × CH_3) and 11.06 (CH_3); *m/z* (CI, CH_4) 261 (M + 1).

***N*,*N*-Dibenzyl-3-(5-methoxy-1*H*-indol-2-yl)propanamine 6g.** Mp 86 °C; ν_{max}/cm^{-1} 3410 (NH); δ_H 7.58 (s, 1 H, NH), 7.39–7.27 (m, 10 H, ArH), 7.02–6.71 (m, 3 H, ArH), 6.02 (s, 1 H, ArH), 3.81 (s, 3 H, CH_3O), 3.57 (s, 4 H, 2 × CH_2), 2.71 (t, 2 H, CH_2), 2.51 (t, 2 H, CH_2) and 1.84 (m, 2 H, CH_2); δ_C 153.79 (arom CO), 140.71 (arom C), 139.57 (2 × arom C), 130.75 and 129.02 (arom C), 129.01 (4 × arom CH), 128.25 (4 × arom CH), 126.95 (2 × arom CH), 110.99, 110.37, 101.72 and 99.00 (arom CH), 58.54 (2 × CH_2N), 55.75 (CH_3O), 52.68 (CH_2N) and 27.20 and 25.51 (CH_2) (Found: C, 81.35; H, 7.41; N, 7.13. $C_{26}H_{28}N_2O$ requires C, 81.21; H, 7.34; N, 7.29%).

***N*,*N*-Dibenzyl-2-(5-methoxy-2-methyl-1*H*-indol-3-yl)ethanamine 7g.** ν_{max}/cm^{-1} 3410 (NH); δ_H 7.53 (s, 1 H, NH), 7.41–7.19 (m, 10 H, ArH), 7.08 (d, 1 H, ArH), 6.71–6.64 (m, 2 H, ArH), 3.71 (s, 3 H, CH_3O), 3.69 (s, 4 H, 2 × CH_2), 2.83 (m, 2 H, CH_2), 2.65 (m, 2 H, CH_2) and 2.19 (s, 3 H, CH_3); δ_C 153.54 (arom CO), 139.86 (2 × arom C), 131.77, 130.10 and 128.93 (arom C), 128.60 (4 × arom CH), 128.06 (4 × arom CH), 126.68 (2 × arom CH), 110.70 and 110.46 (arom CH), 109.97 (arom C), 99.97 (arom CH), 58.41 (2 × CH_2N), 55.76 (CH_3O), 53.47 (CH_2N), 22.06 (CH_2) and 11.36 (CH_3) (Found: C, 81.37; H, 7.58; N, 6.99. $C_{26}H_{28}N_2O$ requires C, 81.21; H, 7.34; N, 7.29%).

***N*,*N*-Dimethyl-4-(5-methoxy-1*H*-indol-2-yl)butanamine 6h.** Mp 72 °C; ν_{max}/cm^{-1} 3402 (NH); δ_H 8.51 (s, 1 H, NH), 7.15–6.73 (m, 3 H, ArH), 6.15 (s, 1 H, ArH), 3.83 (s, 3 H, CH_3O), 2.74 (t, 2 H, CH_2), 2.31 (t, 2 H, CH_2), 2.23 (s, 6 H, 2 × CH_3) and 1.76–1.53 (m, 4 H, 2 × CH_2); δ_C 153.69 (arom CO), 140.65, 130.97 and 129.08 (arom C), 110.94, 110.36, 101.68 and 98.90 (arom CH), 59.06 (CH_2), 55.72 (CH_3O), 45.20 (2 × CH_3N) and 27.87, 26.96 and 26.84 (CH_2) (Found: C, 73.09; H, 9.02; N, 11.44. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00; N, 11.37%); *m/z* (CI, CH_4) 247 (M + 1).

***N*,*N*-Dimethyl-3-(5-methoxy-2-methylindol-3-yl)propanamine 7h.** ν_{max}/cm^{-1} 3400 (NH); δ_H 7.87 (s, 1 H, NH), 7.25–7.12 (m, 3 H, ArH), 3.84 (s, 3 H, CH_3O), 2.66 (m, 2 H, CH_2), 2.33 (m, 2 H, CH_2), 2.27 (s, 6 H, 2 × CH_3N), 2.20 (s, 3 H, CH_3) and 1.82 (m, 2 H, CH_2); δ_C 153.37 (arom CO), 140.54, 131.93, 130.31 and 110.79 (arom C), 110.74, 109.87 and 100.33 (arom CH), 59.13 (CH_2N), 55.78 (CH_3O), 44.99 (2 × CH_3N), 28.06, 21.62 (CH_2) and 11.43 (CH_3).

***N*,*N*-Dibenzyl-4-(5-methoxy-1*H*-indol-2-yl)butanamine 6i.** ν_{max}/cm^{-1} 3413 (NH); δ_H 7.62 (s, 1 H, NH), 7.37–6.74 (m, 13 H, ArH), 6.08 (s, 1 H, ArH), 3.82 (s, 3 H, CH_3O), 3.53 (s, 4 H, 2 × CH_2N), 2.57–2.42 (m, 4 H, 2 × CH_2) and 1.69–1.54 (m, 4 H, 2 × CH_2); δ_C 153.85 (arom CO), 140.54 (arom C), 139.82 (2 × arom C), 130.79 and 129.14 (arom C), 128.74 (4 × arom CH), 128.09 (4 × arom CH), 126.72 (2 × arom CH), 110.85, 110.50, 101.82 and 99.12 (arom CH), 58.29 (2 × CH_2N), 55.75 (CH_3O), 52.59 (CH_2N) and 27.66, 26.49 and 26.32 (CH_2) (Found: C, 81.43; H, 7.58; N, 6.80. $C_{27}H_{30}N_2O$ requires C, 81.37; H, 7.59; N, 7.03%).

***N*,*N*-Dibenzyl-3-(5-methoxy-2-methyl-1*H*-indol-3-yl)propanamine 7i.** ν_{max}/cm^{-1} 3413 (NH); δ_H 7.53 (s, 1 H, NH), 7.35–6.75 (m, 13 H, ArH), 3.77 (s, 3 H, CH_3O), 3.57 (s, 4 H, 2 × CH_2N), 2.63–2.39 (m, 4 H, 2 × CH_2), 2.25 (s, 3 H, CH_3) and 1.83–1.73 (m, 4 H, 2 × CH_2); δ_C 153.45 (arom CO), 140.03 (arom C), 139.63 (2 × arom C), 131.39 and 130.21 (arom C), 128.20 (4 × arom CH), 126.56 (4 × arom CH), 126.38 (2 × arom CH), 111.54 (arom C), 110.67, 110.08 and 100.17 (arom CH), 57.99 (2 × CH_2N), 55.48 (CH_3O), 52.53 (CH_2N), 26.52 and 21.72 (CH_2) and 11.35 (CH_3) (Found: C, 81.74; H, 7.77; N, 7.00. $C_{27}H_{30}N_2O$ requires C, 81.37; H, 7.59; N, 7.03%).

2-(3-Ethoxypropyl)-5-methoxy-1*H*-indole 6j. ν_{max}/cm^{-1} 3405 (NH); δ_H 8.25 (s, 1 H, NH), 7.09–6.72 (m, 3 H, ArH), 6.13 (s, 1 H, ArH), 3.81 (s, 3 H, CH_3O), 3.50–3.42 (m, 4 H, 2 × CH_2), 2.74 (t, 2 H, CH_2), 1.90 (m, 2 H, CH_2) and 1.22 (t, 3 H, CH_3); δ_C 153.54 (arom CO), 140.04, 130.88 and 128.92 (arom C), 110.85, 110.25, 101.63 and 98.87 (arom CH), 69.45 (CH_2), 65.84 (CH_2O), 55.40 (CH_3O), 28.83 and 24.72 (CH_2) and 14.88 (CH_3) (Found: C, 71.68; H, 8.22; N, 6.29. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.0%); *m/z* (CI, CH_4) 234 (M + 1).

3-(2-Ethoxyethyl)-5-methoxy-2-methyl-1*H*-indole 7j. ν_{max}/cm^{-1} 3405 (NH); δ_H 7.75 (s, 1 H, NH), 7.10–6.49 (m, 3 H, arom H), 3.84 (s, 3 H, CH_3O), 3.51–3.40 (m, 4 H, 2 × CH_2), 2.94 (t, 2 H, CH_2), 2.32 (s, 3 H, CH_3) and 1.23 (m, 3 H, CH_3); δ_C 153.35 (arom CO), 132.60, 130.14 and 128.82 (arom C), 110.73 and 109.94 (arom CH), 107.32 (arom C), 100.04 (arom CH), 55.50 (CH_3O) and 14.94 and 11.04 (CH_3); *m/z* (CI, CH_4) 234 (M + 1).

2-Butyl-5-methyl-1*H*-indole 6k. Mp 78 °C; ν_{max}/cm^{-1} 3393 (NH); δ_H 7.72 (s, 1 H, NH), 7.30–6.90 (m, 3 H, ArH), 6.14 (s, 1 H, ArH), 2.71 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.68 (m, 2 H, CH_2), 1.40 (m, 2 H, CH_2) and 0.94 (m, 3 H, CH_3); δ_C 140.12, 133.99, 128.99 and 128.50 (arom C), 122.21, 119.37, 109.96 and 98.69 (arom CH), 31.16, 27.79 and 22.32 (CH_2) and 21.37 and 13.80 (CH_3) (Found: C, 83.33; H, 9.20; N, 7.59. $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48%); *m/z* (CI, CH_4) 188 (M + 1).

2,5-Dimethyl-3-propyl-1*H*-indole 7k. ν_{max}/cm^{-1} 3404 (NH); δ_H 7.57 (s, 1 H, NH), 7.27–6.90 (m, 3 H, ArH), 2.63 (t, 2 H, CH_2), 2.44 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 1.63 (m, 2 H, CH_2) and 0.93 (m, 3 H, CH_3); δ_C 133.46, 130.86, 129.01 and 127.90 (arom C), 122.07 and 117.88 (arom CH), 111.61 (arom C), 109.73 (arom CH), 26.12 and 23.81 (CH_2) and 21.50, 14.05 and 11.57 (CH_3); *m/z* (CI, CH_4) 188 (M + 1).

2-Butyl-5-fluoro-1*H*-indole 6l. Mp 50 °C; ν_{max}/cm^{-1} 3418 (NH); δ_H 7.84 (s, 1 H, NH), 7.12–6.82 (m, 3 H, ArH), 6.19 (s, 1 H, ArH), 2.72 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 1.39 (m, 2 H, CH_2) and 0.94 (m, 3 H, CH_3); δ_C 158.98–156.67 (arom CF), 141.97, 132.20 and 129.07 (arom C), 110.61–110.70, 108.84–108.80, 104.65–104.41 and 99.59–99.54 (arom CH), 31.13, 27.93 and 22.33 (CH_2) and 13.80 (CH_3) (Found: C, 75.76; H, 7.57; N, 7.58. $C_{12}H_{14}FN$ requires C, 75.36; H, 7.38; N, 7.32%); *m/z* (CI, CH_4) 192 (M + 1).

5-Fluoro-2-methyl-3-propyl-1*H*-indole **7l** was obtained in traces, *m/z* (CI, CH_4) 192 (M + 1).

2-Butyl-7-methyl-1*H*-indole 6m. Mp 61 °C; ν_{max}/cm^{-1} 3409 (NH); δ_H 7.76 (s, 1 H, NH), 7.38–6.90 (m, 3 H, ArH), 6.24 (s, 1 H, ArH), 2.76 (m, 2 H, CH_2), 2.46 (s, 3 H, CH_3), 2.70 (m, 2 H, CH_2), 2.42 (m, 2 H, CH_2) and 0.95 (t, 3 H, CH_3); δ_C 139.60, 135.25 and 128.29 (arom C), 121.47 and 119.64 (arom CH), 119.34 (arom C), 117.39 and 99.82 (arom CH), 31.32, 27.94 and 22.36 (CH_2) and 16.62 and 13.82 (CH_3) (Found: C, 83.46; H, 8.96; N, 7.27. $C_{13}H_{17}N$ requires C, 83.37; H, 9.15; N, 7.48%); *m/z* (CI, CH_4) 188 (M + 1).

2,7-Dimethyl-3-propyl-1*H*-indole **7m** was obtained in very low yield. ν_{max}/cm^{-1} 3415 (NH); δ_H 7.61 (s, 1 H, NH), 7.36–6.89 (m, 3 H, ArH), 2.65 (t, 2 H, CH_2), 2.45 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 1.63 (m, 2 H, CH_2) and 0.94 (m, 3 H, CH_3); δ_C 134.60, 130.37 and 128.29 (arom C), 121.33 (arom CH), 119.15 (arom C), 119.03 and 115.87 (arom CH), 112.57 (arom C), 26.21 and 23.82 (CH_2) and 16.46, 14.02 and 11.54 (CH_3); *m/z* (CI, CH_4) 188 (M + 1).

2-Dimethoxymethyl-5-methoxy-1*H*-indole 6n. Mp 87 °C; ν_{max}/cm^{-1} 3338 (NH); δ_H 8.67 (s, 1 H, NH), 7.18–6.81 (m, 3 H, ArH), 6.47 (s, 1 H, ArH), 5.59 (s, 1 H, CH), 3.79 (s, 3 H, CH_3O) and 3.34 (s, 6 H, 2 × CH_3O); δ_C 153.97 (arom CO), 135.49, 130.82 and 128.27 (arom C), 112.40, 111.72 and 102.23 (arom CH), 100.85 (CH), 98.64 (arom CH) and 55.58 and 52.47 (CH_3O) (Found: C, 65.32; H, 6.81; N, 6.14. $C_{12}H_{15}NO_3$ requires C, 65.13; H, 6.83; N, 6.33%).

Hydrolysis of compound 6n. Compound **6n** (100 mmol) was stirred at room temperature in a mixture of 150 ml of acetone and 50 ml of 2.5% HCl for 1 h. The mixture was then extracted with diethyl ether, the extract was washed twice with water and dried over $MgSO_4$, and the solvents were removed under reduced pressure. From the residue, washed with hexane, was obtained 5-methoxy-1*H*-indole-2-carbaldehyde[14] in quantitative yield.

2-Dimethoxymethyl-5-methyl-1*H*-indole 6o. Mp 86 °C; ν_{max}/cm^{-1} 3399 (NH); δ_H 8.58 (s, 1 H, NH), 7.37–6.96 (m, 3 H, ArH), 6.45 (s, 1 H, ArH), 5.58 (s, 1 H, CH), 3.33 (s, 6 H, 2 × CH_3O) and 2.41 (s, 3 H, CH_3); δ_C 134.83, 134.01, 128.77 and 128.19 (arom C), 123.69, 120.33, 110.67 and 100.73 (arom CH), 98.75 (CH), 52.48 (2 × CH_3O) and 21.25 (CH_3) (Found: C, 70.38; H, 7.26; N, 6.90. $C_{12}H_{15}NO_2$ requires C, 70.21; H, 7.36; N, 6.82%); *m/z* (CI, CH_4) 188 (M + 1).

2-Dimethoxymethyl-5-fluoro-1*H*-indole 6p. Mp 82 °C; ν_{max}/cm^{-1} 3415–3319 (NH); δ_H 8.71 (s, 1 H, NH), 7.25–6.86 (m, 3 H, ArH), 6.49 (s, 1 H, ArH), 5.60 (s, 1 H, CH) and 3.36 (s, 6 H, 2 × CH_3O); δ_C 159.64–155.91 (arom CF), 136.68, 132.19 and 128.31–128.16 (arom C), 111.70–111.55, 110.67–110.25, 105.55–105.18 and 101.24 (arom CH), 98.58 (CH) and 52.69 (2 × CH_3O) (Found: C, 63.34; H, 5.81; N, 6.52; F, 9.02. $C_{11}H_{12}FNO_2$ requires C, 63.14; H, 5.78; N, 6.69; F, 9.08%).

5-Chloro-2-dimethoxymethyl-1*H*-indole 6q. Mp 84 °C; ν_{max}/cm^{-1} 3431–3311 (NH); δ_H 9.05 (s, 1 H, NH), 7.52 (s, 1 H, ArH), 7.13–7.04 (m, 2 H, ArH), 6.44 (s, 1 H, ArH), 5.53 (s, 1 H, CH) and 3.32 (s, 6 H, 2 × CH_3O); δ_C 136.23, 133.98, 128.74 and 124.87 (arom C), 122.04, 119.79, 111.95 and 100.65 (arom CH), 98.42 (CH) and 52.48 (2 × CH_3O) (Found: C, 58.49; H, 5.31; N, 6.44; Cl, 15.61. $C_{11}H_{12}ClNO_2$ requires C, 58.54; H, 5.36; N, 6.20; Cl, 15.71%).

2-Dimethoxymethyl-1*H*-indole 6r. Mp 100 °C; ν_{max}/cm^{-1} 3270 (NH); δ_H 8.74 (s, 1 H, NH), 7.60–7.04 (m, 4 H, ArH), 6.53 (s, 1 H, ArH), 5.57 (s, 1 H, CH) and 3.32 (s, 6 H, 2 × CH_3O); δ_C 135.70, 134.73 and 127.86 (arom C), 122.02, 120.68, 119.61, 111.02 and 101.19 (arom CH), 98.73 (CH) and 52.54 (2 × CH_3O) (Found: C, 68.75; H, 6.77; N, 7.14. $C_{11}H_{13}NO_2$ requires C, 69.08; H, 6.85; N, 7.32%).

8-Methoxy-2,3,4,5-tetrahydrothiopyrano[3,2-*b*]indole 8a. Obtained according to the literature method.[4]

8-Methoxy-5-methyl-2,3,4,5-tetrahydrothiopyrano[3,2-*b*]-indole 8b. Mp 136 °C; δ_H 7.25–6.81 (m, 3 H, ArH), 3.84 (s, 3 H, CH_3O), 3.59 (s, 3 H, CH_3N), 3.01 (m, 2 H, CH_2), 2.84 (m, 2 H, CH_2) and 2.35 (m, 2 H, CH_2); δ_C 153.60 (arom CO), 131.52, 130.97 and 125.78 (arom C), 111.23, 109.27 and 99.64 (arom CH), 99.28 (arom CS), 55.77 (CH_3O), 29.02 (CH_3N), 26.64 (CH_2S) and 24.49 and 21.71 (CH_2) (Found: C, 67.01; H, 6.51, N, 5.90; S, 13.74. $C_{13}H_{15}NOS$ requires C, 66.92; H, 6.48; N, 6.00; S, 13.74%).

5-Benzyl-8-methoxy-2,3,4,5-tetrahydrothiopyrano[3,2-*b*]-indole 8c. Mp 147 °C; δ_H 7.28–6.77 (m, 8 H, ArH), 5.22 (s, 2 H, CH_2), 3.85 (s, 3 H, CH_3O), 3.02 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2) and 2.30 (m, 2 H, CH_2); δ_C 153.90 (arom CO), 137.75, 131.88 and 130.82 (arom C), 128.68 (2 × arom CH), 127.22 (arom CH), 126.17 (arom C), 125.91 (2 × arom CH), 111.71 and 109.83 (arom CH), 100.36 (arom CS), 99.84 (arom CH), 55.81 (CH_3O), 46.25 (CH_2N), 26.73 (CH_2S) and 24.46 and 21.80 (CH_2) (Found: C, 74.02; H, 6.28; N, 4.27; S, 10.34. $C_{19}H_{19}NOS$ requires C, 73.75; H, 6.19; N, 4.53; S, 10.36%).

Ethyl 2-(8-methoxy-2,3,4,5-tetrahydrothiopyrano[3,2-*b*]indol-5-yl)acetate 8d. Obtained according to the literature method.[8]

6-Methoxy-2,3,4,5-tetrahydrothiopyrano[3,2-*b*]indole 8e. Mp 144 °C; ν_{max}/cm^{-1} 3350 (NH); δ_H 8.04 (s, 1 H, NH), 7.04–6.64 (m, 3 H, ArH), 3.96 (s, 3 H, CH_3O), 3.06–2.90 (m, 4 H, 2 × CH_2) and 2.33 (m, 2 H, CH_2); δ_C 145.46 (arom C), 128.39, 127.57 and 125.38 (arom C), 119.75, 110.81 and 102.10 (arom CH), 101.60 (arom CS), 55.28 (CH_3O), 26.86 (CH_2S) and 24.16 and 22.76 (CH_2) (Found: C, 65.79; H, 6.02; N, 6.23; S, 14.21. $C_{12}H_{13}NOS$ requires C, 65.72; H, 5.98; N, 6.39; S, 14.62%).

2-(3-Sulfanylpropyl)-1*H*-indol-5-ol 9a. ν_{max}/cm^{-1} 3396 (OH, NH) and 2556 (SH); δ_H 7.77 (s, 1 H, NH), 7.03–6.63 (m, 3 H, ArH), 6.06 (s, 1 H, ArH), 5.30 (m, 1 H, OH), 2.71 (t, 2 H, CH_2), 2.47 (m, 2 H, CH_2), 1.89 (m, 2 H, CH_2) and 1.35 (t, 1 H, SH); δ_C 149.16 (arom CO), 139.63, 131.07 and 129.34 (arom C), 110.98, 110.52, 104.46 and 99.24 (arom CH), 32.89 and 26.53 (CH_2) and 23.85 (CH_2S) (Found: C, 64.12; H, 6.49; N, 6.49; S, 15.39. $C_{11}H_{13}NOS$ requires C, 63.73; H, 6.31; N, 6.75; S, 15.46%).

1-Methyl-2-(3-sulfanylpropyl)-1*H*-indol-5-ol 9b. Mp 73 °C; ν_{max}/cm^{-1} 3370 (OH) and 2553 (SH); δ_H 7.04–6.67 (m, 3 H, ArH), 6.06 (s, 1 H, ArH), 5.51 (m, 1 H, OH), 3.51 (s, 3 H, CH_3N), 2.74 (t, 2 H, CH_2), 2.54 (m, 2 H, CH_2), 1.92 (m, 2 H, CH_2) and 1.37 (t, 1 H, SH); δ_C 149.13 (arom CO), 140.59, 132.71 and 128.17 (arom C), 110.14, 109.21, 104.44 and 98.21 (arom CH), 32.33 (CH_2), 29.35 (CH_3N), 25.11 (CH_2) and 23.91 (CH_2S) (Found: C, 65.04; H, 6.90; N, 6.03; S, 14.30. $C_{12}H_{15}NOS$ requires C, 65.12; H, 6.83; N, 6.32; S, 14.48%).

1-Benzyl-2-(3-sulfanylpropyl)-1*H*-indol-5-ol 9c. Mp 90–95 °C; ν_{max}/cm^{-1} 3389 (OH) and 2559 (SH); δ_H 7.21–6.01 (m, 8 H, ArH), 6.19 (s, 1 H, ArH), 5.22 (s, 2 H, CH_2), 5.13 (s, 1 H, OH), 2.73 (s, 2 H, CH_2), 2.52 (m, 2 H, CH_2), 1.89 (m, 2 H, CH_2) and 1.25 (m, 1 H, SH); δ_C 149.45 (arom CO), 140.59, 137.78, 132.50 and 128.52 (arom C), 128.66 (2 × arom CH), 127.17 (arom CH), 125.72 (2 × arom CH), 110.46, 109.84, 104.53 and 99.04 (arom CH), 46.37 (CH_2N), 32.34 and 25.08 (CH_2) and 23.93 (CH_2S) (Found: C, 72.63; H, 6.39; N, 4.63; S, 11.15. $C_{18}H_{19}NOS$ requires C, 72.69; H, 6.44; N, 4.71; S, 10.78%).

Ethyl 2-[5-hydroxy-2-(3-sulfanylpropyl)-1*H*-indol-1-yl]acetate 9d. ν_{max}/cm^{-1} 3412 (OH) and 1738 (CO_2Et); δ_H 6.97–6.66 (m, 3 H, ArH), 6.14 (s, 1 H, ArH), 5.78 (m, 1 H, OH), 4.71 (s, 2 H, CH_2N), 4.12 (m, 2 H, CH_2O), 2.74 (t, 2 H, CH_2), 2.58 (m, 2 H, CH_2), 1.97 (m, 2 H, CH_2) and 1.22 (m, 4 H, CH_3, SH); δ_C 169.52 (C=O), 150.45 (arom CO), 140.78, 132.04 and 129.20 (arom C), 111.18, 109.43, 105.33 and 100.13 (arom CH), 62.20 (OCH_2), 45.32 (NCH_2), 32.61 and 25.31 (CH_2), 24.40 (CH_2S) and 14.57 (CH_3) (Found: C, 61.52; H, 6.47; N, 4.72; S, 11.28. $C_{15}H_{19}NO_3S$ requires C, 61.41; H, 6.52; N, 4.77; S, 10.93%).

2-(3-Sulfanylpropyl)-1*H*-indol-7-ol 9e. ν_{max}/cm^{-1} 3396 (NH, OH) and 2553 (SH); δ_H 8.33 (s, 1 H, NH), 7.14–6.46 (m, 3 H, ArH), 6.17 (s, 1 H, ArH), 2.64 (t, 2 H, CH_2), 2.39 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2) and 1.30 (t, 1 H, SH); δ_C 140.58 (arom CO), 138.62, 130.93 and 125.46 (arom C), 119.95, 112.92, 106.11 and 100.16 (arom CH), 32.89 and 26.35 (CH_2) and 23.77 (CH_2S) (Found: C, 64.08; H, 6.38; N, 6.50; S, 15.15. $C_{11}H_{13}NOS$ requires C, 63.73; H, 6.31; N, 6.75; S, 15.46%).

Acknowledgements

LCO1 thanks ADIR for financial support. We thank the referees for their interesting suggestions and the editor for useful corrections.

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Paper 7/02548C
Received 14*th April* 1997
Accepted 6*th June* 1997