Novel indole-ring formation by thermolysis of 2-(*N*-acylamino)-benzylphosphonium salts. Effective synthesis of 2-trifluoromethyl-indoles[1]

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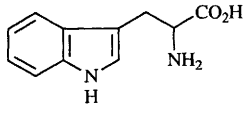
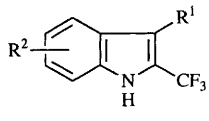
Thermolysis of 2-(*N*-acylamino)benzyl methyl ethers, in the presence of an acid catalyst and triphenylphosphine, or 2-(*N*-acylamino)benzylphosphonium salts is found to serve as a novel method for indole formation, in particular for the synthesis of 2-trifluoromethylindoles. The reaction of the benzyl methyl ethers is suggested to involve a phosphonium intermediate, which thermally decomposes to the indoles.

Indole derivatives, widely distributed in nature as the amino acid tryptophan (**1**) and its metabolites, indole-alkaloids, are very useful as lead compounds for the discovery or development of novel, biologically active compounds, as they are known to have various significant biological activities.[2] Consequently, synthetic methods for the construction of the indole ring have been studied for some time.[3] On the other hand, in the field of medicinal chemistry, introduction of fluorine or a perfluoroalkyl group into the lead molecule has been employed as one of the most efficient methods for modification of the lead compound and many successful examples have been reported.[4] However, examples of fluorinated or perfluoroalkylated indoles are rare, and deal with indoles modified with fluorine only on the benzene ring.[5] From such a viewpoint, we are interested in the biological activities of the 2-trifluoromethyl derivatives **2**.



tryptophan **1**



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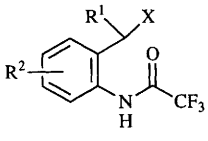
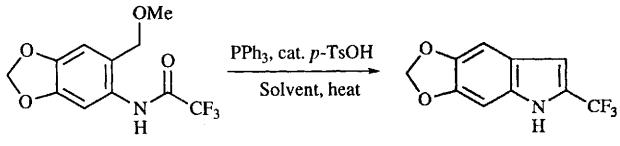


3

4: X = OMe
5: X = P^+Ph_3

Although the synthesis of 2-trifluoromethylindole (**2**, R^1 = R^2 = H) has been achieved *via* direct trifluoromethylation of indole[6] and by the use of 3-trifluoromethylquinoline as the starting material,[7] there still remain problems in the regioselectivity of trifluoromethylation and the number of reaction steps. As another possible method of preparing various 2-trifluoromethylindoles **2**, pyrrole ring formation from 2-(*N*-trifluoroacetylamino)toluene derivatives **3** would be suitable. Although available methods for the synthesis of indoles by pyrrole ring formation of **3** are represented by the Madelung reaction[8] and its modified reactions,[9] all involve nucleophilic attack of the benzylic carbanion, generated by the action of a strong base, at the amide carbonyl carbon. However, because of the base-labile nature of the trifluoromethyl group,[7] this approach cannot be applied in our case. In this paper we describe two methods for indole-ring formation, starting from 2-(*N*-acylamino)benzyl methyl ether **4** and 2-(*N*-acylamino)benzylphosphonium salt **5**, both of which are especially effective for the synthesis of 2-trifluoromethylindoles **2**.

Table 1 Solvent effects for the indole formation reaction



4a **12a**

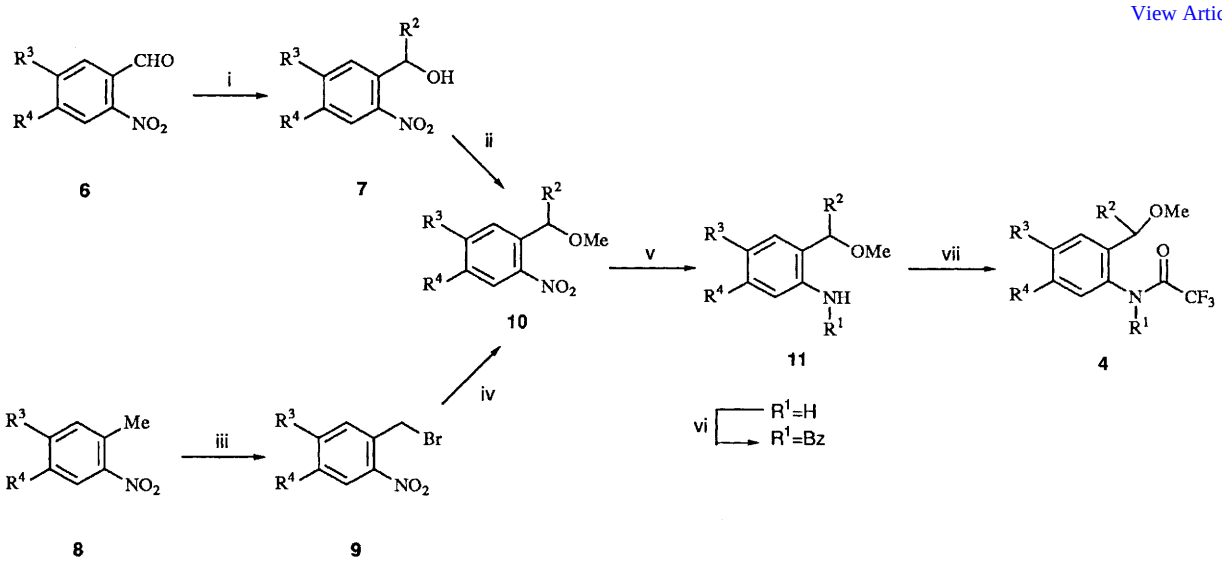
Run	Solvent (bp/°C)	*T*/°C	*t*/h	Yield (%)[a]
1	toluene (111)	reflux	12	—
2	toluene (111)	180[b]	12	44 (69)
3	chlorobenzene (132)	reflux	6	—
4	DMF (153)	reflux	19	36 (84)
5	*p*-cymene (177)	reflux	8	48
6	*o*-DCB (180.5)	reflux	6	60
7	DMSO (189)	reflux	1	—

[a] Yield in parentheses is based on the consumed starting material. [b] Reaction was carried out in a sealed tube.

Results and discussion

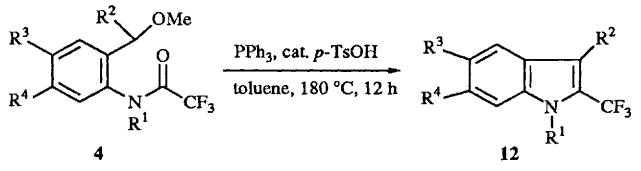
2-(*N*-Trifluoroacetylamino)benzyl methyl ethers **4** were prepared from the nitrobenzaldehydes **6**, nitrobenzyl alcohol **7**, or nitrotoluenes **8** as shown in Scheme 1 (see Experimental section). By choosing the appropriate starting material, it is possible to synthesize benzyl methyl ethers **4** bearing various types of oxygen substituent on the benzene ring.

After several attempts it was found that, when a toluene solution of the 4,5-methylenedioxy derivative **4a** and triphenylphosphine (PPh_3) in a sealed tube was heated at 180 °C in the presence of a catalytic amount of toluene-*p*-sulfonic acid (*p*-TsOH), the 2-trifluoromethylindole **12a** was obtained in 44% yield. The structure of the reaction product **12a** was confirmed by spectroscopic methods. The effect of solvent is summarized in Table 1, which shows that solvent polarity does not affect the reaction to any great extent. The reaction is, however, dependent on the boiling point of the solvent used, which means that the reaction temperature is an important factor for this reaction and that, by employing *N*,*N*-



Scheme 1 *Reagents and conditions:* i, ref. 12; ii, NaH, MeI, DMF, room temp.; iii, ref. 15; iv, MeONa, MeOH, room temp.; v, Raney-Ni, EtOH, room temp.; vi, PhCHO, C_6H_6, room temp., then $NaBH_3CN$, MeOH, room temp.; vii, $(CF_3CO)_2O$, pyridine, 0 °C then room temp. (For the substituents R^1–R^4, see Table 2.)

Table 2 Indole formation reaction of 2-(*N*-trifluoroacetylamino)benzyl methyl ethers **4**



Run	Comp.	R^1	R^2	R^3	R^4	Yield (%)[a]
1	**a**	H	H	$-OCH_2-$		44 (69)
2	**b**	H	H	H	H	—
3	**c**	H	H	MeO	MeO	60 (67)
4	**d**	H	H	H	MeO	48 (52)
5	**e**	H	H	MeO	H	—
6	**f**	H	Ph	H	H	—
7	**g**	H	*p*-MeOPh	H	H	49
8	**h**	H	Ph	MeO	H	34
9	**i**	H	Ph	MeO	MeO	57
10	**j**	Bz	Ph	MeO	MeO	82
11	**k**	Bz	Ph	MeO	H	—
12	**l**	Bz	Ph	H	MeO	54

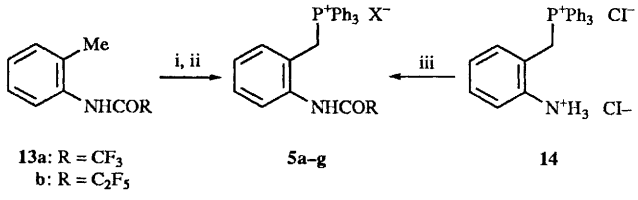
[a] Yield in parentheses is based on the consumed starting material. Bz = benzyl.

dimethylformamide (DMF), *p*-cymene or *o*-dichlorobenzene (*o*-DCB) as the solvent, it is not necessary to introduce the dangers of using a sealed tube. Despite dimethyl sulfoxide (DMSO) having the highest boiling point of all the solvents examined, when it was used the indole **12a** was not formed. This is probably because the PPh_3 was consumed by the reduction of DMSO to dimethyl sulfide and, furthermore, the benzylic cation intermediate might have been quenched by the dimethyl sulfide generated.

We applied this procedure to compounds **4b–l** and examined the effects of the substituents on the benzene ring on the reaction (Table 2). Obviously, these substituents play an important role in this reaction and the oxygen function at the *para*-position was found to be essential for this reaction (runs 1–5). Although, when R^2 is a phenyl group, the benzylic cation is expected to be stabilized by the two phenyl rings, this does not seem to be sufficient for the reaction because the reaction of **4f** did not afford the indole (run 6).[10] It is interesting that the compound **4g** bearing a *p*-methoxy group on the phenyl group of R^2 afforded the indole **12g** in moderate yield (run 7). These results indicate that the formation and stabilization of the benzylic cation are crucial steps for this reaction. Similar tendencies for the reactions of the *N*-benzyl derivatives to those of the *N*-unsubstituted derivatives were also observed. Comparison of the reactions of **4e**, **h** and **k** (runs 5, 8 and 11), all of which have a methoxy group at the *meta*-position (R^3 = OMe), suggests the effects of the substituents R^1 and R^2. In these compounds, the methoxy group may not be helpful for stabilization of the benzylic cation but may increase the electron density of the benzene ring. Therefore, another phenyl group at a suitable position (**4h**, R^2 = Ph), able to stabilize the benzylic cation, may be required for the reaction. However, the results of the reactions of **4h** and **4k** (runs 8 and 11) suggested that the substituent R^1 could also affect the reaction and that the electron-donating property of the nitrogen to the carbonyl centre also has an effect on the reactivity.

As described in the above reactions, the crucial step is the formation of the benzylic cation, which limits the applicability of this reaction. These results prompted us to examine the reaction of the phosphonium salt, for the following reasons. (i) This reaction seems to proceed *via* the phosphonium intermediate formed by the nucleophilic attack of PPh_3 on the benzylic cation. (ii) If formation of the phosphonium salt is the rate-determining step and requires an oxygen-substituent at the correct position to stabilize the benzylic cation precursor, then it may be possible to expand the application of this reaction by starting from the phosphonium salt.

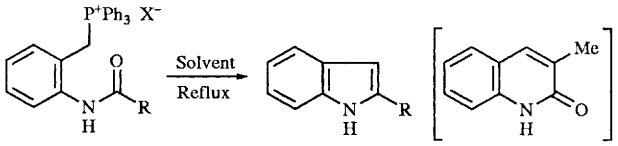
The phosphonium salts **5**, containing various types of *N*-acyl substituents and lacking an oxygen-function on the benzene ring, were prepared by two methods as shown in Scheme 2 (see Experimental section).



Scheme 2 *Reagents and conditions:* i, NBS, CCl_4, reflux (ref. 14); ii, PPh_3, toluene, 60 °C; iii, RCOCl, pyridine-DMF, 0 °C then room temp.

The indole **15a** was obtained without acid catalyst or PPh_3, simply by heating in the solvent shown in Table 3. Other phosphonium salts **5b–g** were also examined under similar conditions. The indoles **15c–g** not bearing a fluorinated group

Table 3 Indole formation reaction of the phosphonium salts **5**



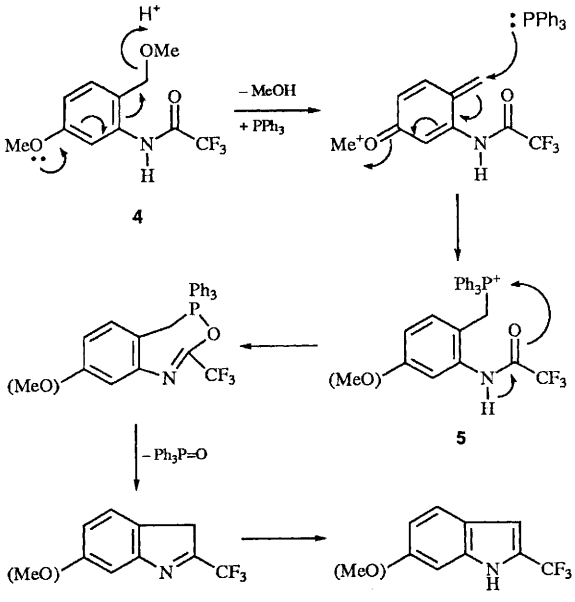
5 **15** **16**

Run	Comp.	R	X	Solvent	*t*/h	Yield (%)
1	**a**	CF_3	Br	toluene[a]	12	28
2	**a**	CF_3	Br	*o*-DCB	7	82
3	**a**	CF_3	Br	DMSO	7	—
4	**a**	CF_3	Br	DMF	15	82
5	**b**	C_2F_5	Br	DMF	12	92
6	**c**	$PhCH_2$	Cl	*o*-DCB	7	42
7	**d**	Ph	Cl	*o*-DCB	7.5	29
8	**e**	*p*-$NO_2C_6H_4$	Cl	*o*-DCB	8	48
9	**f**	CH_3CO	Cl	*o*-DCB	1	19
10	**g**	EtO_2C	Cl	*o*-DCB	7.5	53

[a] Reaction was carried out in a sealed tube at 180 °C.

at C-2 were also obtained, although their yields were lower than those of **15a** and **b**. Interestingly, in the case of **5f**, the quinolone **16** was obtained as the major product, in addition to the indole **15f**.

Concerning the reaction mechanism, the formation of the benzylic cation is apparently important for the reaction starting from the methyl ether **4** but not for the reaction starting from the phosphonium salt **5**. This strongly suggests that formation of the phosphonium intermediate does occur by the nucleophilic attack of PPh_3 as the next step from the benzylic cation as shown in Scheme 3. The Wittig-type reaction of the 2-



Scheme 3

(*N*-acylamino)benzylphosphonium salt to give the indole by employing a strong base has been reported[9b–d] and a mechanistic study revealed that the phosphorus ylide is involved as an intermediate.[9c] However, our reaction from the phosphonium salt seems to proceed in a different manner from the Wittig-type reaction, as strong base is not used in our reaction and polar solvents such as DMF do not accelerate the reaction rate (Table 1). This suggests that our reaction does not involve the formation of a polar intermediate such as a phosphorus ylide. Although the latter part of the reaction from the phosphonium intermediate to the indole is unclear, a possible reaction mechanism is shown in Scheme 3. That a phosphonium salt rather than an ammonium or sulfonium salt is effective for this reaction† suggests that, as a consequence of the greater affinity of phosphorus for oxygen, the nucleophilic attack of the carbonyl oxygen to phosphorus occurs to form the P–O bond initially. The fact that the reaction temperature rather than the polarity of the solvent is important suggests that this reaction may involve a concerted process. Therefore, subsequent thermal elimination of triphenylphosphine oxide might take place to afford the indole.‡ In the case of the pyruvamide derivative **5f** (Table 2, run 9), it is possible that reaction between the terminal carbonyl oxygen and the phosphonium functionality took place preferentially to afford the quinolone **16**.

In conclusion, these two methods, starting from the benzyl methyl ether **4** and the benzylphosphonium salt **5**, are complementary to each other and are particularly useful for the synthesis of 2-trifluoromethylindoles. It should be emphasized that the source of the trifluoromethyl group in this reaction is trifluoroacetic acid, which is safe, easy to handle and cheap.[11]

Experimental

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were measured on a JASCO FT/IR-200 Fourier-transfer infrared spectrometer. ^{1}H NMR spectra were measured on a JEOL GX-500 (500 MHz), Hitachi R-250HT (250 MHz), or Varian VXR-200 (200 MHz) spectrometer with tetramethylsilane as an internal standard; *J* values are given in Hz. ^{19}F NMR spectra were taken on a Varian VXR-200 (180 MHz) with hexafluorobenzene (0 ppm) as an internal standard. ^{13}C NMR spectra were taken on a JEOL EX-270 (67.5 MHz) with $CDCl_3$ (77.0 ppm) as an internal standard. Low and high resolution mass spectra were obtained with a JEOL D-300 mass spectrometer. For silica gel and alumina column chromatography, E. Merck Kieselgel 60 (0.063–0.200 mm) and Merck Aluminiumoxid 90 (0.063–0.200 mm) were used, respectively. 4,5-Methylenedioxy-2-nitrobenzyl alcohol **7a**, 4,5-dimethoxy-2-nitrobenzyl alcohol **7c**, 4-methoxy-2-nitrotoluene **8d**, and 5-methoxy-2-nitrotoluene **8e** were purchased from the Aldrich chemical company.

Synthesis of α-phenylbenzyl alcohols 7f–i

Grignard reaction of nitrobenzaldehydes **6** according to the literature procedure[12] afforded the α-phenylbenzyl alcohols, which were immediately used for methylation as described below.

4,5-Dimethoxy-2-nitrobenzyl methyl ether 10c

A solution of the alcohol **7c** (1.02 g, 4.8 mmol) in DMF (10 cm^3) was added dropwise to a stirred suspension of NaH (60%, 0.21 g, 5.3 mmol) in THF (10 cm^3) at room temperature and stirring was continued for 1 h at the same temperature. Methyl iodide (0.33 cm^3, 5.3 mmol) was added dropwise to the reaction mixture and the whole was stirred for 6 h at the same temperature. After addition of saturated aq. $NaHCO_3$, the

† Reaction of the corresponding triethylammonium derivative instead of the phosphonium salt under the same conditions afforded the bromomethyl derivative, which is a product of the attack by the counter anion (Br^-) at the benzylic position, while, by employing the dimethylsulfonium derivative, the 4*H*-3,1-benzoxazine derivative, which is a product of the attack by the carbonyl oxygen at the benzylic position, was detected in the reaction mixture. These results suggest that nucleophilic attack at the carbon centre is the preferred mode of reaction in both cases.

‡ It is well known that the Wittig reaction involves an elimination of triphenylphosphine oxide from an oxaphosphetane intermediate to afford the double bond.[17] Thermal extrusion of triphenylphosphine oxide from the stable oxaphosphetane intermediate possessing two trifluoromethyl groups has been reported.[18] Similar reaction from an α-oxophosphorus ylide to afford the alkyne has also been reported previously.[19]

reaction mixture was extracted with chloroform and the chloroform layer was washed with saturated $NaHCO_3$, water, and saturated aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography (hexane–ethyl acetate, 2:1) and recrystallisation with ethanol to afford the title compound **10c** (0.41 g, 38%) as colourless crystals, mp 99–101 °C (lit.,[13] 101.5–101.8 °C).

Other methyl ethers **10a**, **f–i** and **l** were prepared from the corresponding alcohols **7** by methylation according to the method described for **10c**, while **10b** was prepared according to a literature method.[14]

4,5-(Methylenedioxy)-2-nitrobenzyl methyl ether 10a. Yield 39%, colourless crystals, mp 112–114 °C (ethanol) (Found: M^+, 211.0479. $C_9H_9NO_5$ requires *M*, 211.0479); ν_{max}(KBr)/cm^{-1} 2823, 1618, 1514, 1484, 1324, 1262, 1110 and 1032; δ_H($CDCl_3$) 3.48 (3 H, s, OMe), 4.78 (2 H, s, benzylic H), 6.12 (2 H, s, OCH_2O), 7.23 (1 H, s, 6-H) and 7.72 (1 H, s, 3-H); *m/z* 211 (M^+, 45%) and 179 (10).

2-Nitro-α-phenylbenzyl methyl ether 10f. Yield 49%, a yellow oil (Found: $M^+ - H$, 242.0817. $C_{14}H_{13}NO_3$ requires *M*, 242.0817); ν_{max}(KBr)/cm^{-1} 2988, 1608, 1527, 1355, 1094 and 701; δ_H($CDCl_3$) 3.36 (3 H, s, OMe), 5.96 (1 H, s, benzylic H) and 7.2–7.9 (9 H, m, aromatic H); *m/z* 242 ($M^+ - H$, 0.3%) and 211 (29).

α-(4-Methoxyphenyl)-2-nitrobenzyl methyl ether 10g. Yield 87%, yellow crystals, mp 33–34 °C (ethanol) (Found: C, 66.0; H, 5.6; N, 5.1. $C_{15}H_{15}NO_4$ requires C, 65.92; H, 5.53; N, 5.16%); ν_{max}(KBr)/cm^{-1} 2934, 2823, 1525, 1462, 1354, 1248, 1173, 1092, 1033 and 853; δ_H($CDCl_3$) 3.33 (3 H, s, OMe), 3.79 (3 H, s, PhOMe), 5.90 (1 H, s, benzylic H), 6.86 and 7.24 (each 2 H, d, *J* 8.5, aromatic H) and 7.3–7.9 (4 H, m, aromatic H); *m/z* 273 (M^+, 2%) and 241 (17).

5-Methoxy-2-nitro-α-phenylbenzyl methyl ether 10h. Yield 85%, colourless crystals, mp 87–89 °C (ethanol) (Found: C, 65.8; H, 5.6; N, 5.1. $C_{15}H_{15}NO_4$ requires C, 65.92; H, 5.53; N, 5.13%); ν_{max}(KBr)/cm^{-1} 2939, 2824, 1516, 1483, 1350, 1237, 1092, 1032 and 848; δ_H($CDCl_3$) 3.39 (3 H, s, OMe), 3.90 (3 H, s, PhOMe), 6.11 (1 H, s, benzylic H), 6.87 (1 H, dd, *J* 2.5, 9.0, 4-H), 7.2–7.4 (6 H, m, aromatic H) and 8.05 (1 H, d, *J* 9.0, 3-H); *m/z* 272 ($M^+ - H$, 0.3%) and 242 (9).

4,5-Dimethoxy-2-nitro-α-phenylbenzyl methyl ether 10i. Yield 88%, yellow crystals, mp 103–105 °C (ethanol) (Found: C, 63.3; H, 5.6; N, 4.6. $C_{16}H_{17}NO_5$ requires C, 63.36; H, 5.69; N, 4.62%); ν_{max}(KBr)/cm^{-1} 2937, 2924, 1580, 1520, 1332, 1273, 1091 and 1060; δ_H($CDCl_3$) 3.38 (3 H, s, OMe), 3.94 and 3.98 (each 3 H, s, PhOMe), 6.11 (1 H, s, benzylic H), 7.2–7.4 (6 H, m, aromatic H) and 7.60 (1 H, s, 3-H); *m/z* 303 (M^+, 6%) and 271 (24).

4-Methoxy-2-nitro-α-phenylbenzyl methyl ether 10l. Yield 87%, a yellow oil (Found: $M^+ - H$ 272.0910. $C_{15}H_{14}NO_4$ requires *M*, 272.0920); ν_{max}(KBr)/cm^{-1} 2933, 2824, 1621, 1532, 1358, 1244, 1091, 1035 and 700; δ_H($CDCl_3$) 3.42 (3 H, s, OMe), 3.85 (3 H, s, PhOMe), 5.88 (1 H, s, benzylic H), 7.13 (1 H, dd, *J* 2.5 and 8.5, 5-H), 7.2–7.35 (5 H, m, aromatic H), 7.40 (1 H, d, *J* 2.5, 3-H) and 7.53 (1 H, d, *J* 8.5, 6-H); *m/z* 272 ($M^+ - H$, 0.7%) and 241 (100).

4-Methoxy-2-nitrobenzyl methyl ether 10d

Under a nitrogen atmosphere, a solution of sodium methoxide (0.52 g, 9.6 mmol) in methanol (5 cm^3) was added dropwise to a stirred solution of the bromide **9d** (1.2 g, 4.8 mmol), prepared from the toluene derivative **8d** according to the literature procedure,[15] in methanol (5 cm^3) at room temperature and the whole was stirred for 2.5 h at room temperature. After addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with chloroform and the chloroform layer was washed with saturated aq. $NaHCO_3$, water, and saturated aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was purified by recrystallisation from ethanol to give the title compound **10d** (0.72 g, 76%) as light yellow crystals, mp 64–64.5 °C (Found: C, 54.6; H, 5.6; N, 7.0. $C_9H_{11}NO_4$ requires C, 54.82; H, 5.62; N, 7.10%); ν_{max}(KBr)/cm^{-1} 2934, 2833, 1570, 1523, 1458, 1345, 1239, 1106, 1035 and 846; δ_H($CDCl_3$) 3.46 (3 H, s, OMe), 3.87 (3 H, s, PhOMe), 4.76 (2 H, s, benzylic H), 7.18 (1 H, dd, *J* 2.5 and 8.8, 5-H), 7.57 (1 H, d, *J* 2.5, 3-H) and 7.64 (1 H, d, *J* 8.8, 6-H); *m/z* 197 (M^+, 6%) and 165 (72).

5-Methoxy-2-nitrobenzyl methyl ether 10e. Compound **10e** was prepared from **8e** *via* the bromide **9e** by the same method described for **10d** as colourless crystals (80%), mp 42–44 °C (ethanol) (Found: C, 54.7; H, 5.6; N, 7.1. $C_9H_{11}NO_4$ requires C, 54.82; H, 5.62; N, 7.10%); ν_{max}(KBr)/cm^{-1} 2941, 2830, 1590, 1342, 1245, 1109, 1073 and 847; δ_H($CDCl_3$) 3.53 (3 H, s, OMe), 3.92 (3 H, s, PhOMe), 4.88 (2 H, s, benzylic H), 6.87 (1 H, dd, *J* 2.5 and 9.3, 4-H), 7.30 (1 H, d, *J* 2.5, 6-H) and 8.17 (1 H, d, *J* 9.3, 3-H); *m/z* 197 (M^+, 9%) and 165 (5).

4,5-Dimethoxy-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4c

An ethanolic suspension of Raney-Ni (2 cm^3) was added to a stirred solution of the nitro compound **10c** (320 mg, 1.4 mmol) in ethyl acetate (5 cm^3)–ethanol (5 cm^3) and the reaction mixture was stirred at room temperature. After disappearance of the starting material by TLC, the catalyst was filtered off and washed with ethyl acetate–ethanol and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with saturated aq. $NaHCO_3$, water, and saturated aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude amine **11c** (R^1 = H) as a brown oil, which was used for the next reaction without further purification; δ_H($CDCl_3$) 3.35 (3 H, s, OMe), 3.80 and 3.83 (each 3 H, s, PhOMe), 4.40 (2 H, s, benzylic H), 6.30 (1 H, s, 3-H) and 6.65 (1 H, s, 6-H).

Trifluoroacetic anhydride (0.20 cm^3, 1.4 mmol) was added dropwise to a stirred solution of amine **11c** in pyridine (4 cm^3) at 0 °C and stirring was continued overnight at room temperature. After the addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with ethyl acetate and the ethyl acetate layer washed with 5% HCl, water, saturated aq. $NaHCO_3$, and saturated aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane–dichloromethane, 1:2) to afford the title compound **4c** (185 mg, 45%) as colourless crystals, mp 96–98 °C (hexane–benzene) (Found: C, 49.2; H, 4.8; N, 4.9. $C_{12}H_{14}NO_4F_3$ requires C, 49.15; H, 4.81; N, 4.78%); ν_{max}(KBr)/cm^{-1} 3277, 2940, 2841, 1720, 1623, 1551, 1221, 1151, 1103 and 871; δ_H($CDCl_3$) 3.45 (3 H, s, OMe), 3.87 and 3.91 (each 3 H, s, PhOMe), 4.54 (2 H, s, benzylic H), 6.68 (1 H, s, 6-H), 7.86 (1 H, s, 3-H) and 9.86 (1 H, br s, NH); δ_F($CDCl_3$) 85.4; *m/z* 293 (M^+, 71%), 262 (31) and 261 (37).

Other amide derivatives **4a**,**b**,**d–i** were synthesized from the corresponding nitro compounds *via* amines according to the procedure described for **4c**.

2-Amino-4,5-(methylenedioxy)benzyl methyl ether 11a (R^1 = H). A brown oil; δ_H($CDCl_3$) 3.31 (3 H, s, OMe), 3.83 (2 H, s, NH_2), 4.36 (2 H, s, benzylic H), 5.84 (2 H, s, OCH_2O), 6.27 (1 H, s, 3-H) and 6.58 (1 H, s, 6-H).

4,5-(Methylenedioxy)-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4a. Yield 81% from **10a**, colourless needles, mp 134–136 °C (ethanol) (Found: C, 47.7; H, 3.8; N, 5.15. $C_{11}H_{10}NO_4F_3$ requires C, 47.66; H, 3.64; N, 5.05%); ν_{max}(KBr)/cm^{-1} 3254, 2921, 1722, 1568, 1206, 1153, 1088, 1039 and 882; δ_H($CDCl_3$) 3.43 (3 H, s, OMe), 4.47 (2 H, s, benzylic H), 5.99 (2 H, s, OCH_2O), 6.66 (1 H, s, 6-H), 7.72 (1 H, s, 3-H) and 9.78 (1 H, br s, NH); δ_F($CDCl_3$) 85.5; *m/z* 277 (M^+, 13%) and 245 (51).

2-Aminobenzyl methyl ether 11b (R^1 = H). A colourless oil; δ_H($CDCl_3$) 3.31 (3 H, s, OMe), 4.07 (2 H, br s, NH_2), 4.45 (2 H, s, benzylic H) and 6.6–7.2 (4 H, m, aromatic H).

2-(*N*-Trifluoroacetylamino)benzyl methyl ether 4b. Yield 97% from **10b**, a light yellow oil (Found: M^+, 233.0658. $C_{10}H_{10}NO_2F_3$ requires *M*, 233.0661); ν_{max}(KBr)/cm^{-1} 3291, 2938, 1735, 1595, 1541, 1458, 1158 and 1088; δ_H($CDCl_3$) 3.46 (3 H, s, OMe), 4.60 (2 H, s, benzylic H), 7.1–7.4 (3 H, m, aromatic H), 8.21 (1 H, d, *J* 8.1, 3-H) and 9.80 (1 H, br s, NH); δ_F($CDCl_3$) 85.5; *m*/*z* 233 (M^+, 72%) and 202 (15).

2-Amino-4-methoxybenzyl methyl ether 11d (R^1 = H). A brown oil; δ_H($CDCl_3$) 3.38 (3 H, s, OMe), 3.73 (3 H, s, PhOMe), 3.83 (2 H, br s, NH_2), 4.40 (2 H, s, benzylic H), 6.25 (2 H, m, 3, 4-H) and 6.95 (1 H, d, *J* 8.2, 6-H).

4-Methoxy-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4d. Yield 49% from **10d**, colourless crystals, mp 55–58 °C (hexane–dichloromethane) (Found: C, 48.45; H, 4.4; N, 5.2. $C_{11}H_{12}NO_3F_3$·1/2H_2O requires C, 48.53; H, 4.81; N, 5.15%); ν_{max}(KBr)/cm^{-1} 3273, 2943, 2840, 1728, 1597, 1210, 1174, 1079, 1038 and 869; δ_H($CDCl_3$) 3.43 (3 H, s, OMe), 3.83 (3 H, s, PhOMe), 4.54 (2 H, s, benzylic H), 6.68 (1 H, dd, *J* 2.5, 8.5, 5-H), 7.09 (1 H, d, *J* 8.5, 6-H), 7.86 (1 H, d, *J* 2.5, 3-H) and 9.95 (1 H, br s, NH); δ_F($CDCl_3$) 85.4; *m*/*z* 263 (M^+, 91%) and 232 (92).

2-Amino-5-methoxybenzyl methyl ether 11e (R^1 = H). A brown oil; δ_H($CDCl_3$) 3.35 (3 H, s, OMe), 3.59 (2 H, br s, NH_2), 3.74 (3 H, s, PhOMe), 4.43 (2 H, s, benzylic H) and 6.5–6.8 (3 H, m, aromatic H).

5-Methoxy-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4e. Yield 50% from **10e**, colourless crystals, mp 49–50 °C (hexane–dichloromethane) (Found: C, 50.2; H, 4.6; N, 5.4. $C_{11}H_{12}NO_3F_3$ requires C, 50.19; H, 4.50; N, 5.32%); ν_{max}(KBr)/cm^{-1} 3297, 2939, 2837, 1728, 1615, 1281, 1159, 1087 and 1045; δ_H($CDCl_3$) 3.44 (3 H, s, OMe), 3.81 (3 H, s, PhOMe), 4.54 (2 H, s, benzylic H), 6.74 (1 H, d, *J* 2.8, 6-H), 6.89 (1 H, dd, *J* 2.8 and 8.3, 4-H), 8.09 (1 H, d, *J* 8.3, 3-H) and 9.70 (1 H, br s, NH); δ_F($CDCl_3$) 85.5; *m*/*z* 263 (M^+, 73%) and 231 (58).

2-Amino-α-phenylbenzyl methyl ether 11f (R^1 = H). A brown oil; δ_H($CDCl_3$) 3.40 (3 H, s, OMe), 3.90 (2 H, br s, NH_2), 5.29 (1 H, s, benzylic H), 6.61 (1 H, d, *J* 7.7, 3-H), 6.71 (1 H, t-like, *J* 7.7, 5-H), 7.01 (1 H, d, *J* 7.7, 6-H), 7.10 (1 H, t-like, *J* 7.7, 4-H) and 7.2–7.4 (5 H, m, aromatic H).

α-Phenyl-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4f. Yield 79% from **10f**, colourless crystals, mp 54–56 °C (hexane–dichloromethane) (Found: M^+, 309.0976. $C_{16}H_{14}NO_2F_3$ requires *M*, 309.0976); ν_{max}(KBr)/cm^{-1} 3294, 2940, 1734, 1593, 1542, 1456, 1155, 1074 and 759; δ_H($CDCl_3$) 3.48 (3 H, s, OMe), 5.42 (1 H, s, benzylic H), 7.1–7.5 (8 H, m, aromatic H), 8.23 (1 H, d, *J* 8.5, 3-H) and 10.00 (1 H, br s, NH); δ_F($CDCl_3$) 85.4; *m*/*z* 309 (M^+, 70%) and 277 (53).

2-Amino-α-(4-methoxyphenyl)benzyl methyl ether 11g (R^1 = H). A yellow oil; δ_H($CDCl_3$) 3.40 (3 H, s, OMe), 3.80 (3 H, s, PhOMe), 4.04 (2 H, br s, NH_2), 5.26 (1 H, s, benzylic H) and 6.6–7.4 (8 H, m, aromatic H).

α-(4-Methoxyphenyl)-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4g. Yield 63% from **10g**, colourless crystals, mp 78–80 °C (hexane–dichloromethane) (Found: C, 60.0; H, 4.8; N, 4.1. $C_{17}H_{16}NO_3F_3$ requires C, 60.18; H, 4.75; N, 4.13%); ν_{max}(KBr)/cm^{-1} 3281, 2938, 2836, 1733, 1613, 1592, 1250, 1157, 1082 and 760; δ_H($CDCl_3$) 3.45 (3 H, s, OMe), 3.79 (3 H, s, PhOMe), 5.37 (1 H, s, benzylic H), 6.87 (2 H, d, *J* 8.5, 3′-H), 7.0–7.5 (5 H, m, aromatic H), 8.24 (1 H, d, *J* 8.5, 3-H) and 10.11 (1 H, br s, NH); δ_F($CDCl_3$) 85.4; *m*/*z* 339 (M^+, 63%) and 307 (86).

2-Amino-5-methoxy-α-phenylbenzyl methyl ether 11h (R^1 = H). A brown oil; δ_H($CDCl_3$) 3.42 (3 H, s, OMe), 3.72 (3 H, s, PhOMe), 5.27 (1 H, s, benzylic H), 6.4–6.8 (3 H, m, aromatic H) and 7.0–7.4 (5 H, m, aromatic H).

5-Methoxy-α-phenyl-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4h. Yield 65% from **10h**, colourless crystals, mp 78–80 °C (Found: C, 60.2; H, 4.8; N, 4.2. $C_{17}H_{16}NO_3F_3$ requires C, 60.18; H, 4.75; N, 4.13%); ν_{max}(KBr)/cm^{-1} 3300, 2943, 2830, 1722, 1610, 1539, 1225, 1159, 1087, 1037 and 699; δ_H($CDCl_3$) 3.47 (3 H, s, OMe), 3.79 (3 H, s, PhOMe), 5.34 (1 H, s, benzylic H), 6.70 (1 H, d, *J* 2.5, 6-H), 6.89 (1 H, dd, *J* 2.5 and 8.8, 4-H), 7.2–7.4 (5 H, m, aromatic H), 8.11 (1 H, d, *J* 8.8, 3-H) and 9.73 (1 H, br s, NH); δ_F($CDCl_3$) 85.5; *m*/*z* 339 (M^+, 57%) and 307 (69).

2-Amino-4,5-dimethoxy-α-phenylbenzyl methyl ether 11i (R^1 = H). A brown oil; δ_H($CDCl_3$) 3.42 (3 H, s, OMe), 3.76 and 3.83 (each 3 H, s, PhOMe), 5.26 (1 H, s, benzylic H), 6.27 (1 H, s, 3-H), 6.62 (1 H, s, 6-H) and 7.2–7.4 (5 H, m, aromatic H).

4,5-Dimethoxy-α-phenyl-2-(*N*-trifluoroacetylamino)benzyl methyl ether 4i. Yield 74% from **10i**, a light yellow oil (Found: M^+, 369.1185. $C_{18}H_{18}NO_4F_3$ requires *M*, 369.1185); ν_{max}(KBr)/cm^{-1} 3290, 2939, 2834, 1728, 1617, 1540, 1326, 1220, 1160 and 1103; δ_H($CDCl_3$) 3.48 (3 H, s, OMe), 3.82 and 3.91 (each 3 H, s, PhOMe), 5.34 (1 H, s, benzylic H), 6.60 (1 H, s, 6-H), 7.2–7.4 (5 H, m, aromatic H), 7.89 (1 H, s, 3-H) and 9.94 (1 H, br s, NH); δ_F($CDCl_3$) 85.4; *m*/*z* 369 (M^+, 100%) and 337 (85).

2-(*N*-Benzylamino)-4,5-dimethoxy-α-phenylbenzyl methyl ether 11j (R^1 = Bz). A mixture of a solution of the nitro compound **10i** (3.20 g, 10.6 mmol) in ethyl acetate (30 cm^3)–ethanol (30 cm^3) and an ethanolic suspension of Raney-Ni (10 cm^3) was treated and worked up according to the procedure described for **10c**. To a stirred solution of the resultant crude amine in benzene (40 cm^3), benzaldehyde (1.04 cm^3, 1.2 mmol) was added and the reaction mixture was stirred overnight and then concentrated under reduced pressure to give the imine, which was immediately suspended in methanol (40 cm^3). $NaBH_3CN$ (1.60 g, 25.5 mmol) was added in portions to the solution at 0 °C and the reaction mixture was stirred at room temperature overnight. After the addition of saturated aq. $NaHCO_3$, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aq. $NaHCO_3$, water and saturated aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant crude product was purified by alumina column chromatography (hexane–ethyl acetate, 25:1) to afford the title compound **11j** (2.50 g, 65%) as a white powder (Found: M^+, 363.1836. $C_{23}H_{25}NO_3$ requires *M*, 363.1835); ν_{max}(KBr)/cm^{-1} 3418, 2933, 2829, 1592, 1451, 1221, 1088, 1029, 729 and 698; δ_H($CDCl_3$) 3.40 (3 H, s, OMe), 3.75 and 3.76 (each 3 H, s, PhOMe), 4.23 (2 H, d, *J* 5.0, NCH_2Ph), 4.85 (1 H, br s, NH), 5.27 (1 H, s, benzylic H), 6.24 (1 H, s, 3-H), 6.65 (1 H, s, 6-H) and 7.1–7.4 (10 H, m, aromatic H); *m*/*z* 363 (M^+, 76%) and 331 (54).

Other benzylamine derivatives **11k** and **l** were synthesized starting from nitro compounds according to the above procedure.

2-(*N*-Benzylamino)-5-methoxy-α-phenylbenzyl methyl ether 11k (R^1 = Bz). Yield 83% from **10h**, a yellow oil (Found: M^+, 333.1728. $C_{22}H_{23}NO_2$ requires *M*, 333.1728); ν_{max}(KBr)/cm^{-1} 3418, 2933, 2829, 1514, 1221, 1090, 1044, 728 and 698; δ_H($CDCl_3$) 3.40 (3 H, s, OMe), 3.72 (3 H, s, PhOMe), 4.21 (2 H, s, NCH_2Ph), 4.73 (1 H, br s, NH), 5.29 (1 H, s, benzylic H), 6.4–6.8 (3 H, m, aromatic H) and 7.0–7.5 (10 H, m, aromatic H); *m*/*z* 333 (M^+, 100%) and 301 (44).

2-(*N*-Benzylamino)-4-methoxy-α-phenylbenzyl methyl ether 11l (R^1 = Bz). Yield 68% from **10l**, a yellow oil (Found: M^+, 333.1734. $C_{22}H_{23}NO_2$ requires *M* 333.1728); ν_{max}(KBr)/cm^{-1} 3420, 2933, 2838, 1615, 1585, 1524, 1214, 1087, 1045, 728 and 697; δ_H($CDCl_3$) 3.39 (3 H, s, OMe), 3.72 (3 H, s, PhOMe), 4.23 (2 H, d, *J* 5.0, NCH_2Ph), 5.24 (1 H, br s, NH), 5.29 (1 H, s, benzylic H), 6.14 (1 H, d, *J* 2.5, 3-H), 6.20 (1 H, dd, *J* 2.5, 8.5, 5-H), 6.91 (1 H, d, *J* 8.5, 6-H) and 7.0–7.4 (10 H, m, aromatic H); *m*/*z* 333 (M^+, 73%) and 301 (59).

Trifluoroacetylation of 2-(*N*-benzylamino)benzyl methyl ethers§

Trifluoroacetylation of the *N*-benzylamino derivatives was

§ 2-(*N*-Benzyl-*N*-trifluoroacetylamino)-α-phenylbenzyl methyl ethers **4j–l** were obtained as a mixture of two diastereoisomers due to atropisomerism, which was used for the indole formation reaction without separation.

achieved by treatment with trifluoroacetic anhydride in pyridine and subsequent purification by silica gel column chromatography (hexane–dichloromethane, 3:4) according to the procedure for the trifluoroacetylation of *N*-unsubstituted aminobenzyl alcohols.

2-(*N*-Benzyl-*N*-trifluoroacetylamino)-4,5-dimethoxy-α-phenylbenzyl methyl ether 4j. Yield 79% (obtained as a *ca.* 2:3 mixture of stereoisomers), colourless crystals, mp 83–85 °C (hexane–dichloromethane) (Found: C, 64.1; H, 5.7; N, 2.9. $C_{25}H_{24}NO_4F_3 \cdot 1/2H_2O$ requires C, 64.10; H, 5.38; N, 2.99%); ν_{max}(KBr)/cm^{-1} 2938, 1695, 1516, 1455, 1267, 1213, 1178, 1150, 1084 and 1029; δ_H($CDCl_3$) 3.36, 3.41, 3.43 and 3.45 (total 6 H, each s, OMe and PhOMe), 3.72 and 3.96 (total 3 H, each s, PhOMe), 2.84, 4.23, 5.34 and 5.84 (total 2 H, each d, *J* 14, NCH_2Ph), 5.29 and 5.36 (total 1 H, each s, benzylic H), 5.83 and 5.92 (total 1 H, each s, 3-H) and 6.7–7.6 (total 11 H, m, aromatic H); δ_F($CDCl_3$) 93.6 and 93.9; *m*/*z* 459 (M^+, 29%), 428 (29) and 368 (32).

2-(*N*-Benzyl-*N*-trifluoroacetylamino)-5-methoxy-α-phenylbenzyl methyl ether 4k. Yield 69% (obtained as a *ca.* 1:1 mixture of stereoisomers), light yellow crystals, mp 114–116 °C (hexane–dichloromethane) (Found: C, 67.1; H, 5.4; N, 3.2. $C_{24}H_{22}NO_3F_3$ requires C, 67.13; H, 5.16; N, 3.26%); ν_{max}(KBr)/cm^{-1} 2939, 2825, 1695, 1496, 1207, 1155, 1084 and 1046; δ_H($CDCl_3$) 3.35 and 3.40 (total 3 H, each s, OMe), 3.70 and 3.85 (total 3 H, each s, PhOMe), 2.84, 4.25, 5.24 and 5.77 (total 2 H, each d, *J* 14, NCH_2Ph), 5.28 and 5.34 (total 1 H, each s, benzylic H) and 6.3–7.4 (total 13 H, m, aromatic H); δ_F($CDCl_3$) 93.7 and 93.9; *m*/*z* 429 (M^+, 18%), 397 (11) and 338 (27).

2-(*N*-Benzyl-*N*-trifluoroacetylamino)-4-methoxy-α-phenylbenzyl methyl ether 4l. Yield 66% (obtained as a *ca.* 1:1 mixture of stereoisomers), colourless crystals, mp 83–85 °C (hexane–dichloromethane) (Found: C, 67.0; H, 5.3; N, 3.3. $C_{24}H_{22}NO_3F_3$ requires C, 67.13, H, 5.16; N, 3.26%); ν_{max}(KBr)/cm^{-1} 2939, 1695, 1610, 1502, 1455, 1248, 1205, 1170, 1150 and 1082; δ_H($CDCl_3$) 3.32 and 3.40 (total 3 H, s, OMe), 3.52 and 3.54 (total 3 H, s, PhOMe), 3.12, 4.29, 5.32 and 5.81 (total 2 H, each d, *J* 14, NCH_2Ph), 5.22 and 5.35 (total 1 H, each s, benzylic H), 6.04 and 6.08 (total 1 H, each d, *J* 2.0, 3-H), 6.75–7.7 (total 12 H, m, aromatic H); δ_F($CDCl_3$) 93.7 and 94.0; *m*/*z* 429 (M^+, 11%), 398 (23) and 338 (47).

General procedure for indole formation from benzyl methyl ethers

A mixture of the methyl ether **4** (0.050 mmol), toluene-*p*-sulfonic acid (1.0 mg, 0.005 mmol) and PPh_3 (17.0 mg, 0.065 mmol) in toluene (0.2 cm^3) was sealed in a glass tube under an Ar atmosphere and heated at 180 °C for 12 h. After being cooled to room temperature, the reaction mixture was diluted with chloroform, washed with saturated aq. $NaHCO_3$, water and saturated aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography to afford the indole **12**.

6-Trifluoromethyl-5*H*-[1,3]dioxolo[4,5-*f*]indole 12a. Colourless needles, mp 134–136 °C (hexane–dichloromethane) (Found: C, 52.6; H, 2.9; N, 6.1. $C_{10}H_6NO_2F_3$ requires C, 52.41; H, 2.64; N, 6.11%); ν_{max}(KBr)/cm^{-1} 3408, 2890, 1611, 1557, 1478, 1260, 1175, 1119 and 1042; δ_H($CDCl_3$) 5.97 (2 H, s, OCH_2O), 6.79 and 6.84 (each 1 H, s, 4, 8-H), 7.00 (1 H, s, 7-H) and 8.27 (1 H, br s, NH); δ_F($CDCl_3$) 101.6; δ_C($CDCl_3$) 92.0, 99.8, 101.0, 104.5, 120.6, 121.2 (q, *J* 267), 124.1 (q, *J* 39), 131.5, 144.1 and 147.1; *m*/*z* 229 (M^+, 100%), 210 (7) and 209 (11).

5,6-Dimethoxy-2-trifluoromethylindole 12c. Colourless crystals, mp 86–88 °C (hexane–dichloromethane) (Found: C, 53.8; H, 4.2; N, 5.8. $C_{11}H_{10}NO_2F_3$ requires C, 53.88; H, 4.11; N, 5.71%); ν_{max}(KBr)/cm^{-1} 3325, 2947, 2830, 1633, 1598, 1556, 1485, 1250, 1170, 1110 and 1005; δ_H($CDCl_3$) 3.92 (6 H, s, OMe), 6.81 and 6.88 (each 1 H, s, 4, 7-H), 7.00 (1 H, s, 3-H) and 8.27 (1 H, br s, NH); δ_F($CDCl_3$) 101.7; δ_C($CDCl_3$) 56.0, 56.2, 94.1, 102.5, 104.2, 119.4, 121.3 (q, *J* 266), 124.0 (q, *J* 39), 130.8, 146.1 and 149.1; *m*/*z* 245 (M^+, 100%), 230 (54) and 202 (35).

6-Methoxy-2-trifluoromethylindole 12d. Colourless crystals, mp 89–91 °C (hexane–dichloromethane) (Found: C, 55.8; H, 3.9; N, 6.45. $C_{10}H_8NOF_3$ requires C, 55.82; H, 3.75; N, 6.51%); ν_{max}(KBr)/cm^{-1} 3304, 2969, 2840, 1628, 1595, 1560, 1265, 1177, 1116 and 1018; δ_H($CDCl_3$) 3.86 (3 H, s, OMe), 6.86 (1 H, d, *J* 8.3, 5-H), 6.87 (1 H, s, 7-H), 7.07 (1 H, s, 3-H), 7.54 (1 H, d, *J* 8.3, 4-H), 8.27 (1 H, br s, NH); δ_F($CDCl_3$) 101.4; δ_C($CDCl_3$) 55.6, 94.2, 104.4, 111.9, 120.8, 121.3 (q, *J* 267), 122.8, 124.4 (q, *J* 39), 137.1 and 158.3; *m*/*z* 215 (M^+, 100%), 200 (91) and 172 (33).

3-(4-Methoxyphenyl)-2-trifluoromethylindole 12g. Colourless crystals, mp 160–162 °C (hexane–dichloromethane) (Found: C, 65.9; H, 4.3; N, 4.8. $C_{16}H_{12}NOF_3$ requires C, 65.98; H, 4.15; N, 4.81%); ν_{max}(KBr)/cm^{-1} 3314, 2964, 2842, 1611, 1587, 1511, 1240, 1175, 1110 and 1024; δ_H($CDCl_3$) 3.88 (3 H, s, OMe), 7.01 (2 H, d, *J* 9.2, 3′-H), 7.19 and 7.35 (each 1 H, t, *J* 7.3, 5, 6-H), 7.45 (3 H, br d, *J ca.* 8, 2′, 7-H), 7.64 (1 H, d, *J* 7.3, 4-H) and 8.45 (1 H, br s, NH); δ_F($CDCl_3$) 104.8; δ_C($CDCl_3$) 55.3, 111.6, 113.9, 119.5 (q, *J* 2), 121.0 (q, *J* 34), 121.1, 121.2, 121.7 (q, *J* 269), 124.3, 125.1, 127.5, 131.0, 134.9 and 159.1; *m*/*z* 291 (M^+, 100%), 276 (44), 272 (2) and 248 (9).

5-Methoxy-3-phenyl-2-trifluoromethylindole 12h. A colourless oil (Found: M^+, 291.0865. $C_{16}H_{12}NOF_3$ requires *M*, 291.0868); ν_{max}(KBr)/cm^{-1} 3407, 2960, 2838, 1626, 1608, 1567, 1497, 1249, 1167, 1118 and 1029; δ_H($CDCl_3$) 3.79 (3 H, s, OMe), 7.0–7.1 (2 H, m, 4, 6-H), 7.3–7.6 (6 H, m, 7-H and aromatic H) and 8.40 (1 H, br s, NH); δ_F($CDCl_3$) 104.9; δ_C($CDCl_3$) 55.8, 101.5, 112.6, 116.3, 119.4 (q, *J* 4), 121.6 (q, *J* 270), 121.8 (q, *J* 38), 127.5, 127.7, 128.4, 129.8, 130.0, 132.3 and 155.2; *m*/*z* 291 (M^+, 100%), 276 (30) and 248 (10).

5,6-Dimethoxy-3-phenyl-2-trifluoromethylindole 12i. Colourless crystals, mp 160–162 °C (hexane–dichloromethane) (Found: C, 63.4; H, 4.6; N, 4.4. $C_{17}H_{14}NO_2F_3$ requires C, 63.55; H, 4.39; N, 4.36%); ν_{max}(KBr)/cm^{-1} 3324, 2960, 2836, 1635, 1609, 1564, 1497, 1271, 1166, 1112 and 1011; δ_H($CDCl_3$) 3.86 and 3.95 (each 3 H, s, OMe), 6.91 and 6.99 (each 1 H, s, 4, 7-H), 7.3–7.6 (5 H, m, aromatic H) and 8.32 (1 H, br s, NH); δ_F($CDCl_3$) 105.4; δ_C($CDCl_3$) 56.1, 56.2, 93.9, 101.3, 119.5 (q, *J* 37), 119.7 (q, *J* 4), 120.0, 121.7 (q, *J* 269), 127.4, 128.4, 129.5, 129.7, 132.5, 146.3 and 149.4; *m*/*z* 321 (M^+, 100%), 306 (39) and 278 (13).

1-Benzyl-5,6-dimethoxy-3-phenyl-2-trifluoromethylindole 12j. Colourless crystals, mp 96–97 °C (hexane–dichloromethane) (Found: C, 70.0; H, 5.0; N, 3.5. $C_{24}H_{20}NO_2F_3$ requires C, 70.07; H, 4.90; N, 3.40%); ν_{max}(KBr)/cm^{-1} 2960, 2838, 1628, 1607, 1558, 1496, 1244, 1167, 1100 and 1030; δ_H($CDCl_3$) 3.81 and 3.82 (each 3 H, s, OMe), 5.48 (2 H, s, benzylic H), 6.64 and 6.89 (each 1 H, s, 4, 7-H) and 7.0–7.6 (10 H, m, aromatic H); δ_F($CDCl_3$) 107.9; δ_C($CDCl_3$) 48.6, 56.1, 56.2, 93.0, 101.6, 119.6, 120.8 (q, *J* 35), 120.8 (q, *J* 4), 122.0 (q, *J* 270), 125.9, 127.3, 127.5, 128.1, 128.6, 130.3, 132.2, 133.2, 137.1, 146.4 and 149.7; *m*/*z* 411 (M^+, 73%), 396 (3) and 320 (65).

1-Benzyl-6-methoxy-3-phenyl-2-trifluoromethylindole 12l. A colourless oil (Found: M^+, 381.1329. $C_{23}H_{18}NOF_3$ requires *M*, 381.1337); ν_{max}(KBr)/cm^{-1} 2960, 2839, 1623, 1606, 1566, 1497, 1260, 1174, 1113 and 1032; δ_H($CDCl_3$) 3.76 (3 H, s, OMe), 5.48 (2 H, s, benzylic H), 6.65 (1 H, s, 7-H), 6.81 (1 H, d, *J* 7.3, 5-H), 7.10 (2 H, d, *J* 7.3, 4-H and aromatic H) and 7.2–7.6 (9 H, m, aromatic H); δ_F($CDCl_3$) 107.7; δ_C($CDCl_3$) 48.4, 55.5, 93.2, 111.7, 121.2 (q, *J* 35), 121.1 (q, *J* 4), 121.3, 122.0 (q, *J* 270), 122.2, 126.0, 127.4, 127.5, 128.0, 128.7, 130.4, 132.9, 137.0, 138.4 and 158.7; *m*/*z* 381 (M^+, 59%) and 290 (69).

[2-(*N*-Trifluoroacetylamino)benzyl]triphenylphosphonium bromide 5a

Bromination of **13a** was carried out according to the literature procedure.[14] A solution of the bromide (1.0 g, 3.55 mmol) and PPh_3 (1.1 g, 4.25 mmol) in toluene (10 cm^3) was warmed to

60 °C and stirred overnight. After cooling, the precipitate was collected by filtration, washed with dry diethyl ether, and dried under reduced pressure to afford the phosphonium salt **5a** as a white powder (1.8 g, 93%), ν_{max}(KBr)/cm^{-1} 1723, 1588, 1545, 1437, 1161, 1029 and 755; δ_H($CDCl_3$) 5.77 (2 H, d, *J* 13.9, benzylic H), 6.98 (2 H, m, aromatic H), 7.4–7.9 (17 H, m, aromatic H) and 11.16 (1 H, s, NH); δ_F($CDCl_3$) 88.6.

[2-(*N*-Pentafluoropropanoylamino)benzyl]triphenylphosphonium bromide 5b. Compound **5b** was prepared from **13b** by the same method described for **5a**, as a white powder (68%); ν_{max}(KBr)/cm^{-1} 1714, 1588, 1534, 1438, 1216, 1027 and 751; δ_H($CDCl_3$) 5.76 (2 H, d, *J* 13.9, benzylic H), 6.94 (2 H, m, aromatic H) and 7.4–8.0 (17 H, m, aromatic H); δ_F($CDCl_3$) 41.9 (3 F, s) and 79.4 (2 F, s).

General procedure for the preparation of [2-(*N*-acylamino)benzyl]triphenylphosphonium chlorides 5c–g

Phosphonium salts **5c–g** were prepared from the (2-aminobenzyl)triphenylphosphonium salt **14**[16] according to the literature[9c] with some modification as follows. Acid chloride (0.55 mmol) was added dropwise to a stirred solution of **14** (200 mg, 0.45 mmol) in a mixture of DMF (0.5 cm^3) and pyridine (0.15 cm^3) at 0 °C. After being stirred overnight at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform. The chloroform solution was washed with 5% HCl and saturated aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The resultant residue was washed with diethyl ether several times and dried under reduced pressure to afford the desired phosphonium salt.

[2-(*N*-Phenylacetylamino)benzyl]triphenylphosphonium chloride 5c. Yield 84%, a white powder; ν_{max}(KBr)/cm^{-1} 1685, 1586, 1526, 1438, 1030 and 750; δ_H($CDCl_3$) 3.67 (2 H, s, NCOCH_2Ph), 5.65 (2 H, d, *J* 14.5, benzylic H), 6.6–7.0 (2 H, m, aromatic H), 7.0–7.8 (22 H, m, aromatic H) and 10.96 (1 H, s, NH).

[2-(*N*-Benzoylamino)benzyl]triphenylphosphonium chloride 5d. Yield 45%, a white powder; ν_{max}(KBr)/cm^{-1} 1660, 1585, 1516, 1437, 1298, 1027 and 750; δ_H($CDCl_3$) 5.83 (2 H, d, *J* 13.5, benzylic H), 6.82 (2 H, m, aromatic H), 7.0–7.8 (17 H, m, aromatic H), 8.24 (2 H, d, *J* 4.8) and 10.90 (1 H, s, NH).

{2-[*N*-(4-Nitrobenzoyl)amino]benzyl}triphenylphosphonium chloride 5e. Yield 76%, a yellow solid; ν_{max}(KBr)/cm^{-1} 1668, 1586, 1521, 1438, 1346, 1268, 1014, 850 and 750; δ_H($CDCl_3$) 5.79 (2 H, d, *J* 14.0, benzylic H), 6.8–7.0 (2 H, m, aromatic H), 7.0–7.8 (17 H, m, aromatic H), 8.0–8.6 (4 H, m, aromatic H) and 11.29 (1 H, s, NH).

{2-[*N*-(2-Oxopropanoyl)amino]benzyl}triphenylphosphonium chloride 5f. Yield 48%, a white powder; ν_{max}(KBr)/cm^{-1} 3370, 1722, 1685, 1587, 1522, 1437, 1248, 1137 and 749; δ_H($CDCl_3$) 2.28 (3 H, s, COMe), 5.83 (2 H, d, *J* 13.7, benzylic H), 6.8–7.0 (2 H, m, aromatic H), 7.4–7.8 (17 H, m, aromatic H) and 10.71 (1 H, s, NH).

{2-[*N*-(Ethoxycarbonylformyl)amino]benzyl}triphenylphosphonium chloride 5g. Yield 61%, a white powder; ν_{max}(KBr)/cm^{-1} 1745, 1694, 1588, 1538, 1436, 1246, 1181, 1016 and 755; δ_H($CDCl_3$) 1.40 (3 H, t, *J* 7.3, OCH_2CH_3), 4.34 (2 H, q, *J* 7.3, OCH_2CH_3), 5.89 (2 H, d, *J* 14.6, benzylic H), 6.91 (2 H, m, aromatic H), 7.4–8.0 (17 H, m, aromatic H) and 11.25 (1 H, s, NH).

General procedure for indole formation from phosphonium salts 5

A solution of the phosphonium salt **5** (0.18 mmol) in *o*-DCB or DMF (3 cm^3) was refluxed under an Ar atmosphere for the period as indicated in Table 3. After concentration under reduced pressure, the residue was dissolved in chloroform and the chloroform solution was washed with saturated aq. $NaHCO_3$, water and saturated aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography to afford the indole derivative **15**. The structures of indoles **15a**, **c–g** and the quinolone **16** were identified by comparison of their spectral data and melting points with those reported in the literature; **15a**, colourless crystals, mp 107–108 °C (hexane) [lit.,[6a] 107–108 °C (hexane)]; **15c**, colourless crystals, mp 80–81 °C (ethanol) [lit.,[16] 84–85 °C (hexane)]; **15d**, colourless crystals, mp 190–191 °C (ethanol) [lit.,[9c] 189–190 °C (ethanol)]; **15e**, yellow crystals, mp 253–255 °C (ethanol) [lit.,[9c] 249–251 °C (ethanol)]; **15f**, colourless crystals, mp 154–156 °C [lit.,[9d] 150 °C (benzene–hexane)]; **15g**, colourless crystals, mp 121–123 °C (ethanol) [lit.,[9d] 123 °C (ethanol)]; **16**, colourless crystals, mp 232–234 °C (ethanol) [lit.,[9d] 234 °C (ethanol)].

2-Pentafluoroethylindole 15b. Colourless crystals, mp 93–94 °C (hexane) (Found: C, 50.8; H, 2.8; N, 6.1. $C_{10}H_6NF_5$ requires C, 51.08; H, 2.57; N, 5.96%); ν_{max}(KBr)/cm^{-1} 3398, 1551, 1429, 1211, 1180, 1148 and 1027; δ_H($CDCl_3$) 6.97 (1 H, s, 3-H), 7.1–7.4 (2 H, m, 5, 6-H), 7.45 and 7.70 (each 1 H, d, *J* 8.0 4, 7-H) and 8.40 (1 H, br s, NH); δ_F($CDCl_3$) 49.9 (2 F, s) and 77.2 (3 F, s); *m/z* 235 (M^+, 74%), 216 (4), 166 (100) and 119 (10).

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