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**THERMAL CONDENSATION OF INDOLES WITH TRIFLUOROACETALDEHYDE**

**YASUO MAKI, HIROSHI KIMOTO\* , SHOZO FUJII**

**Government Industrial Research Institute, Nagoya;  
Hirate-cho, Kita-ku, Nagoya 462 (Japan)**

**MUNEHIRO SENGA**

**Department of Applied Chemistry, Aichi Institute of Technology;  
1247 Yachigusa, Yagusa-cho, Toyota 470-03 (Japan)**

and **LOUIS A. COHEN**

**Laboratory of Chemistry, National Institute of Arthritis, Diabetes,  
Digestive and Kidney Diseases, National Institutes of Health;  
Bethesda, Maryland 20892 (U.S.A.)**

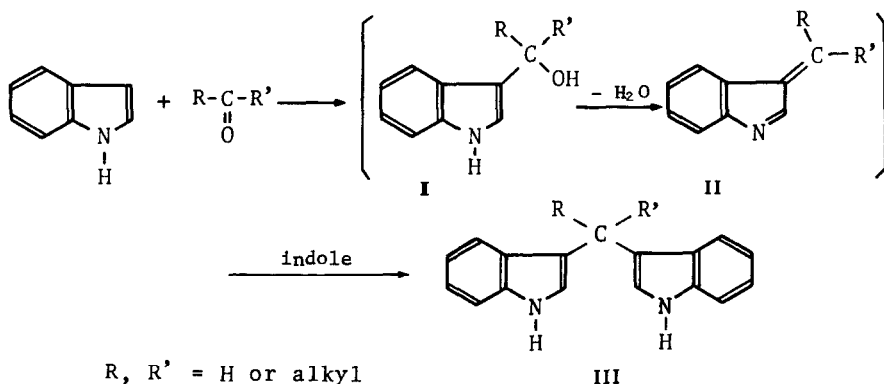
**SUMMARY**

The title condensations provide the corresponding (1'-hydroxy-2',2',2'-trifluoroethyl)indoles. Indole itself, 1-methylindole and 2-methylindole gave 3-adducts in yields of 77%, 49% and 84%, respectively. 3-Substituted indoles (3-methylindole, ethyl indole-3-acetate and indole-3-ethyl acetate) afforded 2-adducts in yields of 69%, 21% and 23%, respectively. The indole adduct eliminates water at 137°C to form a transient 3-(trifluoromethylmethylene)indolenine, which reacts rapidly with nucleophiles including indole.

**INTRODUCTION**

We have recently described [1] the facile thermal condensation of imidazoles with trifluoroacetaldehyde, using its ethyl hemiacetal (TFAE) as a convenient reagent. In continuation of the study, the condensation has been extended to indoles.

Reactions of indoles with carbonyl compounds under acidic conditions have been reviewed [2]. The electrophilic carbonyl carbon attacks the indole at C-3 and the final products are usually bis(3-indole)alkanes (III). Under acidic conditions, I readily eliminates water to form II; further



condensation may involve the electrophilic attack of a carbocation (derived from I or II) on indole, or the nucleophilic addition of indole to II. On the other hand, hexafluoroacetone gives a stable 1:1 adduct corresponding to I as the final product [3]. The electronegative trifluoromethyl groups strongly retard the formation of a carbocation from I ( $R = R' = CF_3$ ) [4]; even the formation of the highly polarized azadiene (II), which might occur via an E2 pathway, is not evident. Although we might expect the adduct with trifluoroacetaldehyde (I,  $R = H$ ,  $R' = CF_3$ ) to be intermediate in reactivity, literature data [4] indicate that carbocation destabilization by one trifluoromethyl group is almost as severe as with two.

## RESULTS AND DISCUSSION

Indole and some of its derivatives were found to undergo thermal condensation with TFAE and afforded 1:1 adducts (I) in yields dependent on reaction conditions and substituents as shown in Table. The products were readily isolated by silica gel chromatography and/or recrystallization, and were characterized by elemental analysis, IR, mass and NMR spectra.

### Thermal condensation of indole

Indole itself condensed with TFAE at C-3 exclusively; no other regioisomers were detected. The structural assignment for the adduct (Ia) is based on its  $^1H$  NMR spectrum. Peaks at 7.03, 7.15, 7.37 and 7.79 ppm

TABLE

## Thermal Condensation of Indoles with TFAE

Run	Indoles			Reaction conditions <sup>a</sup>			Conversion of indoles (%)	Yields of I (%)
	R <sup>1</sup> (N-1)	R <sup>2</sup> (C-2)	R <sup>3</sup> (C-3)	EtOH (ml)	Temp. <sup>b</sup> (°C)	Time (hours)		
1	H	H	H	50	95 ~ 100	24	48	46
2	H	H	H	5	95 ~ 100	24	89	77
3	H	H	H	—	140 ~ 150	24	100	0
4	Me	H	H	5	95 ~ 100	24	56	49
5	Me	H	H	—	140 ~ 145	24	100	37
6	H	Me	H	5	95 ~ 100	6	91	84
7	H	Me	H	—	140 ~ 145	24	100	0
8	H	H	Me	5	95 ~ 100	24	0	—
9	H	H	Me	—	95 ~ 100	6	71	69
10	H	H	Me	—	140 ~ 145	24	100	0
11	H	H	CH <sub>2</sub> CO <sub>2</sub> Et	—	140 ~ 150	12	30	21
12	H	H	CH <sub>2</sub> CO <sub>2</sub> H	—	140 ~ 150	6	34	17
13	H	H	CH <sub>2</sub> CH <sub>2</sub> OAc	—	140 ~ 150	12	44	23
14	H	H	CH <sub>2</sub> CH <sub>2</sub> OH	—	140 ~ 150	24	40	trace

<sup>a</sup> A mixture of the indole (20 mmol) and TFAE (22 mmol) was heated under argon.<sup>b</sup> Oil bath temperature

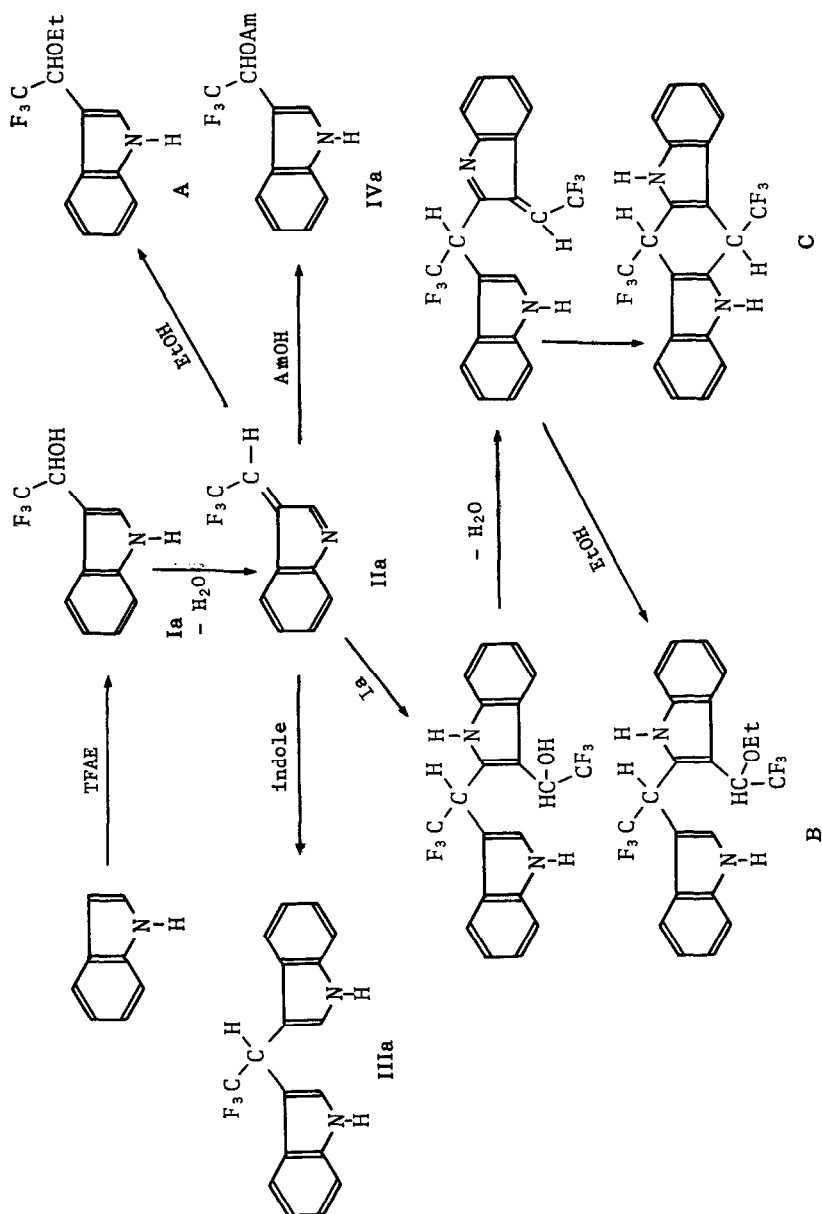
are coupled to one another and correspond to the four protons on the benzene ring of indole. The  $\delta$  value of another doublet (7.44 ppm) is consistent with that of the C-2 ring proton [5]. This proton is coupled ( $J = 4$  Hz) to the adjacent proton at N-1 and becomes a singlet when the NH is converted to ND in methanol- $d_6$ . The hydroxyl proton signal also appears as a AB doublet ( $J = 5$  Hz) coupled to the methine proton. Apparently, intermolecular exchange of the hydroxyl hydrogen is slow enough to be detectable by NMR in acetone solution at 35°C.

Under the mildest conditions (run 1, 0.4 M reactants at reflux in ethanol), Ia was obtained as the only product in 46% yield. When reactant concentrations were increased 10-fold (run 2), the yield of Ia was increased to 76% while IIIa was also found in 11% yield. Finally, equimolar reactants were heated without solvent (run 3, bath temperature 140-150°C) and gave neither Ia nor IIIa, but tarry oligomers together with small amounts of three products (A, B, C) whose NMR and mass spectra suggest the structures shown.

The generation of IIa in run 2 (as the precursor of IIIa) is apparently the result of a higher reaction temperature than in run 1. Reflux of a solution of Ia in 1-butanol (bp. 118°C) was uneventful, whereas reflux in 1-pentanol (bp. 137°C) gave IVa in 97% yield. We have no direct information on the behavior of I ( $R = R' = CF_3$ ) under similar reaction conditions. The indole-hexafluoroacetone adduct was distilled intact at 137°C [3]; on the other hand, the analogous adduct of hexafluoroacetone with oxyindole underwent dehydration upon reflux with phosphorus trichloride [6].

The effectiveness of indole as a trapping agent for IIa was demonstrated by reflux of a solution of equimolar amounts of Ia and indole in 1-pentanol. Bisindole IIIa was obtained in 90% yield and IVa in 6% yield.

Although the condensation of indoles with nonfluorinated aldehydes usually yields bis(3-indole)alkanes, intermediate II can be intercepted by nucleophiles other than indole. Thus, condensation has been achieved with amines (Mannich reaction) [7], alcohols [8], and malonic acid acetonide [9]. In the case of trifluoroacetaldehyde, adduct Ia is stable and can be isolated readily; at elevated temperature, however, Ia is converted to IIa which then reacts with nucleophiles. Thus, Ia may be a useful synthon for trifluoromethylated indole derivatives and investigation of the scope of its reactions is in progress.



Thermal condensation of 1-methylindole and 2-methylindole

TFAE also condensed at C-3 of 1-methylindole and 2-methylindole to give Ib (49% yield) and Ic (84% yield), respectively. Under comparable conditions (run 4 vs run 2), 1-methylindole is less reactive than indole

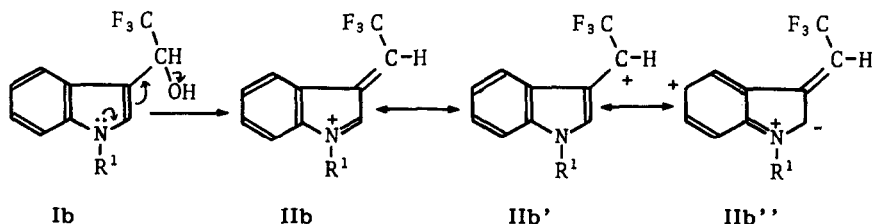


Ib,c

b)  $R^1 = \text{CH}_3$ ,  $R^2 = \text{H}$

c)  $R^1 = \text{H}$ ,  $R^2 = \text{CH}_3$

in forming I; no other products (such as IIIb) were detected by direct  $^{19}\text{F}$  NMR analysis. The structure of Ib was elucidated from its  $^1\text{H}$  NMR spectrum: a singlet at 7.27 ppm was assigned to H-2 by analogy with the spectrum of Ia and on the basis of literature data [5]. At higher temperature (run 5), 1-methylindole gave a mixture of Ib (37%) and three by-products, which appear to be analogous to those obtained from indole in run 3. In the light of our earlier discussion regarding the severe destabilization of trifluoromethyl-substituted carbocation, the apparent conversion of Ib to transient IIb is unexpected, particularly since IIb' should contribute to the resonance hybrid. This inconsistency, however, may be overcome by invoking participation of forms such as IIb'' [10].

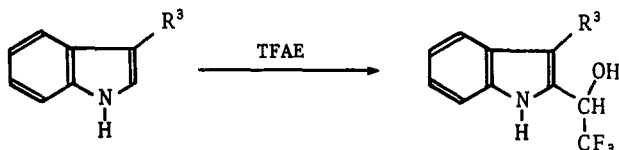


As seen from run 6, 2-methylindole proved significantly more reactive than indole in forming Ic, but gave no evidence for IIIc. Although IIc cannot form termination products analogous to those formed from IIa (B,C), reaction at higher temperature (run 7) gave mainly polymerized products which showed almost equal intensity for two doublets at 13.5 and 13.7 ppm in direct  $^{19}\text{F}$  NMR analysis.

### Thermal condensation of 3-substituted indoles

When 3-methylindole was heated with TFAE in ethanol, no reaction occurred (run 8); however, at somewhat higher temperature (run 9, no solvent), Id was obtained in 69% yield. According to  $^{19}\text{F}$  NMR analysis, condensation occurred exclusively at C-2. As in the case of 2-methylindole, reaction at  $140\sim 145^\circ\text{C}$  led to polymerization.

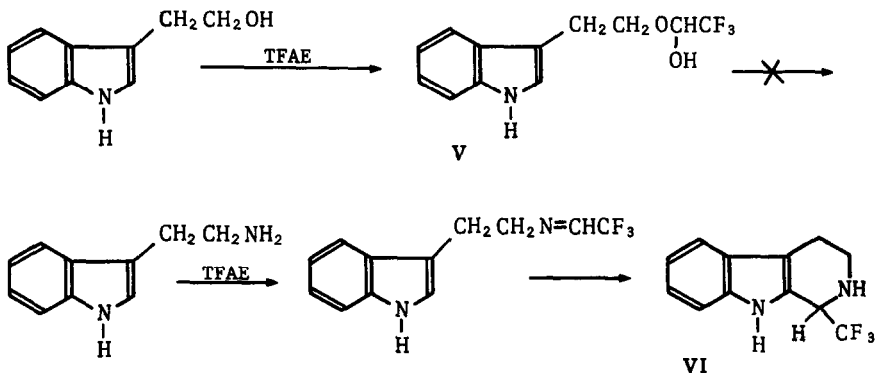
Condensation of indole-3-acetic acid with TFAE gave 17% of the esterified product Ie. Ethyl indole-3-acetate also gave Ie in 20% yield. The low reactivity of both the free acid and the ethyl ester is evident from the



Id, e, f

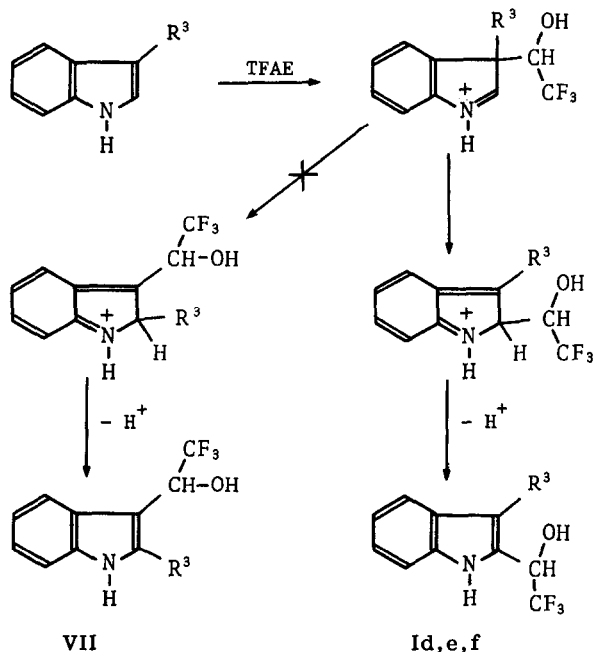
d)  $\text{R}^3 = \text{CH}_3$ , e)  $\text{R}^3 = \text{CH}_2\text{CO}_2\text{Et}$ , f)  $\text{R}^3 = \text{CH}_2\text{CH}_2\text{OAc}$

low conversions (34% and 30%, respectively), despite a higher reaction temperature (runs 11 and 12). In the case of indole-3-ethanol, only a trace of a 1 : 1 adduct was detected by  $^{19}\text{F}$  NMR (as a doublet at 0.0 ppm) and MS ( $m/e$  259  $\text{M}^+$ ), while the compound was partially converted to the hemiacetal V. The  $^{19}\text{F}$  NMR spectrum of V shows a doublet at - 6.0 ppm, close to that of TFAE at - 6.2 ppm. In contrast to tryptamine, which



provides a cyclic product VI with TFAE [11], hemiacetal V does not condense further at C-2. Interestingly, the acetate of indole-3-ethanol condensed normally with TFAE to give If in 23% yield.

Electronic considerations suggest that electrophilic trifluoroacetaldehyde should condense at the 3-position of 3-substituted indoles; the intermediate indolenine then rearranges spontaneously to Id~If. Since the migrating group moves as a virtual anion, it should not be surprising that the more



electronegative group moves preferentially [12], and that no products corresponding to VII have been found.

#### Evaluation for agricultural chemicals

The phytohormonal activities of the products, Ia and Ie, were evaluated for three plants: a Japanese millet (*Echinochloa frumentacea*), a brown mustard (*Brassica juncea*) and a cucumber (*Cucutnis satirus*). As in the case of its parent compound, indole-3-acetic acid, Ie behaves as an auxin for all the plants tested. The auxin activity of Ia is weak for the Japanese millet and the brown mustard, and zero for the cucumber. Both compounds show weak activity as herbicides, but no activity as insecticides or fungicides.



## EXPERIMENTAL

### Materials

TFAE was obtained from Central Glass Co., Ltd., and was distilled prior to use. Ethyl indole-3-acetate and indole-3-ethyl acetate were prepared by common esterification methods. Other indoles were obtained from various commercial sources.

### Analytical methods and instrumentation

Analytical methods and instrumentation have been described previously [1].  $^1\text{H}$  NMR spectra were recorded in acetone- $d_6$  with TMS as internal reference;  $^{19}\text{F}$  NMR spectra are reported with positive  $\delta$  values downfield from the external reference, trifluoroacetic acid. The homogeneity and identity of each product were verified by NMR, IR, MS and TLC. Melting points are uncorrected.

### Thermal condensation of indole with TFAE (Run 1)

A solution of indole (2.34 g, 20 mmol) and TFAE (3.17 g, 22 mmol) in ethanol (50 ml) was heated at reflux under argon for 24 hours. The reaction mixture was analyzed directly by  $^{19}\text{F}$  NMR, showing a doublet at - 0.53 ppm together with the larger signal of TFAE at - 6.4 ppm. The solvent and TFAE were removed by evaporation, and the residual material was fractionated on a silica gel column (180 ml) by elution with (a) dichloro-methane and (b) ether-dichloromethane, 1 : 3. Solvent (a) gave indole (1.22 g, 52% recovery) and solvent (b) gave 3-(1'-hydroxy-2',2',2'-trifluoroethyl)indole (1.98 g, 46% yield, Ia) as colorless needles from chloroform-cyclohexane, mp. 109~111°C; MS m/e (relative intensity) 215 (100)  $\text{M}^+$ , 146 (92)  $\text{M}^+ - \text{CF}_3$ , 117 (66), 91 (17);  $^1\text{H}$  NMR  $\delta$  10.3 (broad d, 1, 1-NH), 7.44 (d, 1,  $J = 4$  Hz, 2-H), 5.45 (AB-q, 1,  $J = 5$  Hz and 7 Hz, 3-(1'-CH)), 5.41 (AB, 1,  $J = 5$  Hz, 3-(1'-OH)), 7.79 (m, 1, 4-H), 7.37 (m, 1, 5-H), 7.03 (AB-d, 1,  $J = 7$  Hz and 4 Hz, 6-H), 7.15 (AB-d, 1,  $J = 7$  Hz and 2 Hz, 7-H);  $^{19}\text{F}$  NMR  $\delta$  - 0.36 (d,  $J = 7$  Hz,  $\text{CF}_3$ ). Analysis: Found: C, 55.60; H, 3.75; N, 6.51%; Calcd. for  $\text{C}_{10}\text{H}_7\text{F}_3\text{NO}$ : C, 55.82; H, 3.28; N, 6.51%.

### Thermal condensation of indole with TFAE (Run 2)

A solution of indole (2.34 g, 20 mmol) and TFAE (3.17 g, 22 mmol) in ethanol (5 ml) was heated under argon in an oil bath (95~100°C) for 24

hours. Direct  $^{19}\text{F}$  NMR analysis showed doublets at 0.3 and 10.4 ppm, in addition to the TFAE signal at - 5.7 ppm. After removal of ethanol and TFAE by evaporation, the residual material was crystallized from chloroform. Colorless needles (1.72 g, Ia) were collected and washed with chloroform. The filtrate and washings were combined and evaporated to dryness. The residual solid was resolved on silica gel by elution with (a) hexane-dichloromethane, 1 : 1, (b) dichloromethane and (c) ether-dichloromethane, 1 : 4. Solvent (a) eluted indole (0.26 g, 11% recovery); solvent (b) gave 1,1-bis(3'-indole)-2,2,2-trifluoroethane (IIIa, 0.34 g, 11% yield) as colorless grains from chloroform-cyclohexane, mp. 152~153°C; MS m/e (relative intensity) 314 (67)  $\text{M}^+$ , 245 (100)  $\text{M}^+ - \text{CF}_3$ , 243 (16)  $\text{M}^+ - \text{CF}_3 - 2\text{H}$ ;  $^1\text{H}$  NMR  $\delta$  5.50 (q, 1,  $J = 10$  Hz, 1-CH), 7.40 (d, 2,  $J = 2$  Hz, 2'-H), 7.61 (m, 2, 4'-H), 7.34 (m, 2, 5'-H), 6.9~7.2 (m, 4, 6'- and 7'-H);  $^{19}\text{F}$  NMR  $\delta$  10.1 (d,  $J = 10$  Hz,  $\text{CF}_3$ ). Analysis: Found: C, 68.62; H, 4.21; N, 8.90%; Calcd. for  $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2$ : C, 68.78; H, 4.17; N, 8.91%. An additional 1.57 g of Ia was eluted with solvent (c) to give a total yield of 77%.

#### Thermal condensation of indole with TFAE (Run 3)

A mixture of indole (2.34 g, 20 mmol) and TFAE (3.17 g, 22 mmol) was heated under argon for 10 hours in an oil bath (140~150°C). The viscous reaction mixture was dissolved in ethanol and was analyzed by  $^{19}\text{F}$  NMR. A large broad peak was found at 11.2 ppm, together with several small peaks at 1~3 ppm and the unreacted TFAE doublet at - 5.7 ppm. Ethanol and TFAE were removed by evaporation and the residual material was resolved on silica gel (100 ml) by elution with (a) dichloromethane and (b) ether-dichloromethane, 1 : 1. Solvent (a) gave a colorless solid (0.23 g) whose MS showed three molecular ion peaks, 243, 394 and 440;  $^{19}\text{F}$  NMR showed three doublets at 1.4, 2.3 and 10.7 ppm. Solvent (b) gave a colorless amorphous solid (4.72 g) whose MS showed no definite peaks at 200°C,  $2 \times 10^{-7}$  Torr;  $^{19}\text{F}$  NMR showed a broad peak at 10.9 ppm.

#### Thermal condensation of other indoles with TFAE

The condensations of 1-methylindole, 2-methylindole, 3-methylindole, indole-3-acetic acid, ethyl indole-3-acetate, indole-3-ethanol and indole-3-ethyl acetate were performed by procedures similar to those described above. Specific reaction conditions are given in the Table. The following products were obtained:

3-(1'-hydroxy-2',2',2'-trifluoroethyl)-1-methylindole (Ib): colorless viscous liquid; MS m/e (relative intensity) 229 (98)  $M^+$ , 160 (100)  $M^+ - CF_3$ , 132 (49), 117 (28);  $^1H$  NMR  $\delta$  3.68 (s, 3, 1- $CH_3$ ), 7.27 (s, 1, 2-H), 5.41 (AB-q, 1,  $J = 3$  Hz and 7 Hz, 3-(1'-CH)), 5.46 (AB, 1,  $J = 3$  Hz, 3-(1'-OH)), 7.68 (m, 1, 4-H), 6.9~7.4 (m, 3, 5-, 6- and 7-H);  $^{19}F$  NMR  $\delta$  - 0.4 (d,  $J = 7$  Hz,  $CF_3$ ).

3-(1'-hydroxy-2',2',2'-trifluoroethyl)-2-methylindole (Ic): colorless columns, mp. 121~122°C from chloroform; MS m/e (relative intensity) 229 (98)  $M^+$ , 160 (100)  $M^+ - CF_3$ , 132 (60), 115 (23);  $^1H$  NMR  $\delta$  2.43 (s, 3, 2- $CH_3$ ), 5.43 (AB-q, 1,  $J = 4$  Hz and 7 Hz, 3-(1'-CH)), 5.33 (AB, 1,  $J = 4$  Hz, 3-(1'-OH)), 7.67 (m, 1, 4-H), 7.24 (m, 1, 5-H), 6.8~7.1 (m, 2, 6- and 7-H);  $^{19}F$  NMR  $\delta$  0.01 (d,  $J = 7$  Hz,  $CF_3$ ); Analysis: Found: C, 57.62; H, 4.43; N, 6.11%; Calcd. as  $C_{11}H_{10}F_3NO$ : C, 57.64; H, 4.40; N, 6.11%.

2-(1'-hydroxy-2',2',2'-trifluoroethyl)-3-methylindole (Id): colorless needles, mp. 111~112°C from cyclohexane; MS m/e (relative intensity) 229 (93)  $M^+$ , 160 (100)  $M^+ - CF_3$ , 132 (15), 130 (15), 117 (18);  $^1H$  NMR  $\delta$  5.52 (q-d, 1,  $J = 7$  Hz and 6 Hz, 2-(1'-CH)), 5.96 (d, 1,  $J = 6$  Hz, 2-(1'-OH)), 2.29 (s, 3, 3- $CH_3$ ), 6.9~7.7 (m, 4, 4-H to 7-H);  $^{19}F$  NMR  $\delta$  - 0.31 (d, 3,  $J = 7$  Hz,  $CF_3$ ); Analysis: Found: C, 57.56; H, 4.38; N, 6.02%; Calcd. as  $C_{11}H_{10}F_3NO$ : C, 57.64; H, 4.40; N, 6.11%.

Ethyl 2-(1'-hydroxy-2',2',2'-trifluoroethyl)indole-3-acetate (Ie): colorless plates, mp. 114~117°C from chloroform; MS m/e 301 (56)  $M^+$ , 228 (100)  $M^+ - COOEt$ , 175 (22), 130 (56);  $^1H$  NMR  $\delta$  1.15 (t, 3,  $J = 7$  Hz,  $CH_3CH_2O$ ), 4.05 (q, 2,  $J = 7$  Hz,  $CH_3CH_2O$ ), 3.81 (s, 2,  $CH_2COO-$ ), 5.60 (q-d, 1,  $J = 7$  Hz and 4 Hz, 2-(1'-CH)), 6.01 (d, 1,  $J = 4$  Hz, 2-(1'-OH)), 7.3~7.6 (m, 2, 4- and 5-H), 6.9~7.2 (m, 2, 6- and 7-H);  $^{19}F$  NMR  $\delta$  0.0 (d,  $J = 7$  Hz,  $CF_3$ ); Analysis: Found: C, 55.82; H, 4.73; N, 4.32%; Calcd. as  $C_{14}H_{14}F_3NO_3$ : C, 55.82; H, 4.68; N, 4.64%.

2-(1'-hydroxy-2',2',2'-trifluoroethyl)indole-3-ethyl acetate (If): colorless plates, mp. 83~85°C from chloroform; MS m/e (relative intensity) 301 (17)  $M^+$ , 241 (100)  $M^+ - CH_3COOH$ , 228 (31), 173 (29), 143 (23), 130 (32);  $^1H$  NMR  $\delta$  1.93 (s, 3,  $CH_3$ ), 3.04 (t, 2,  $J = 7$  Hz, 3-(2'- $CH_2$ )),

4.27 (t, 2,  $J = 7$  Hz, 3-(1'-CH<sub>2</sub>)), 6.46 (q, 1,  $J = 5$  Hz, 2-(1'-CH)), 7.31 (s, 1, 2-(1'-OH)), 7.0~7.2 (m, 2, 6- and 7-H), 7.5~7.7 (m, 2, 4- and 5-H); <sup>19</sup>F NMR  $\delta$  0.1 (d,  $J = 5$  Hz, CF<sub>3</sub>); Analysis: Found: C, 55.76; H, 4.71; N, 4.68%; Calcd. as C<sub>14</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>3</sub> C, 55.82; H, 4.68; N, 4.64%.

#### Reaction of Ia and 1-pentanol

A solution of Ia (646 mg, 3 mmol) in 1-pentanol (5 ml) was heated at reflux under argon (oil bath 140~145°C) for 24 hours. Direct <sup>19</sup>F NMR analysis showed only one signal, a doublet at 1.83 ppm. The solvent was removed by evaporation under reduced pressure and the residual material was recrystallized from cyclohexane to give 3-(1'-pentoxy-2',2',2'-trifluoroethyl)indole (IVa, 0.83 g, 97% yield) as colorless plates, mp. 54~55°C; MS *m/e* (relative intensity) 285 (60) M<sup>+</sup>, 216 (83) M<sup>+</sup> - CF<sub>3</sub>, 198 (44) M<sup>+</sup> - OC<sub>5</sub>H<sub>11</sub>, 146 (100) M<sup>+</sup> - CF<sub>3</sub> - C<sub>5</sub>H<sub>11</sub>, 118 (23); <sup>1</sup>H NMR  $\delta$  0.83 (t, 3,  $J = 5$  Hz, CH<sub>3</sub>), 1.1~1.7 (m, 6, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 3.51 (t, 2,  $J = 6$  Hz, OCH<sub>2</sub>), 10.40 (broad, 1, 1-H), 7.49 (d, 1,  $J = 3$  Hz, 2-H), 5.17 (q, 1,  $J = 8$  Hz, 3-(1'-CH)), 7.76 (m, 1, 4-H), 7.43 (m, 1, 5-H), 7.06 (AB-d, 1,  $J = 6$  Hz and 4 Hz, 6-H), 7.18 (AB-d, 1,  $J = 6$  Hz and 2 Hz, 7-H); <sup>19</sup>F NMR  $\delta$  1.42 (d,  $J = 8$  Hz, CF<sub>3</sub>); Analysis: Found: C, 63.13; H, 6.41; N, 4.85%; Calcd. as C<sub>15</sub>H<sub>18</sub>F<sub>3</sub>NO: C, 63.15; H, 6.36; N, 4.91%.

#### Reaction of Ia and indole

A solution of Ia (646 mg, 3 mmol) and indole (351 mg, 3 mmol) in 1-pentanol (5 ml) was heated at reflux in an oil bath (140~145°C) for 24 hours. Direct <sup>19</sup>F NMR analysis showed two doublets at 2.0 ppm and 10.5 ppm in the ratio 1 : 12. The solvent was removed by evaporation and the residual material was resolved on silica gel (100 ml) by elution with hexane-dichloromethane, 1 : 1. There were obtained IIa (0.85 g, 90% yield) and IIIa (0.05 g, 6% yield).

All the products synthesized in this work are new compounds.

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