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PRACTICAL SYNTHESES OF 5-TRIFLUOROMETHYL-1*H*-INDOLES

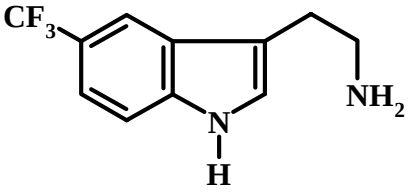
Jean-Gilles Parmentier, Guillaume Poissonnet, and Solo Goldstein*

Chemistry Research Division A, Institut de Recherches Servier
11 rue des Moulineaux, 92150 Suresnes, France
e-mail: solo.goldstein@fr.netgrs.com

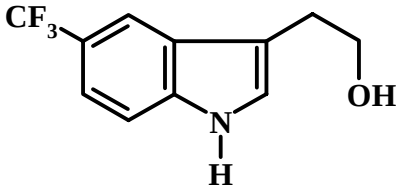
Abstract - Short and convenient syntheses of 5-trifluoromethyltryptamine and 5-trifluoromethyltryptophole have been realized *via* a regioselective, palladium catalyzed, coupling/annulation method involving functionalized alkynes and 2-iodo-4-trifluoromethylaniline. A new and improved approach for the preparation of 5-trifluoromethyl-1*H*-indole is also described.

The indole nucleus is part of numerous natural compounds possessing biological activities.[1] Substituted indoles are used as starting materials for many such compounds and therefore it is important to have access to these synthons in an easy and practical manner. Thus in the course of a project aiming to prepare new ligands for the serotoninergic receptors,[2] multigrams quantities of 5-trifluoromethyl-tryptamine **(1)** and 5-trifluoromethyltryptophole **(2)** (Figure 1) were needed.

Figure 1



1



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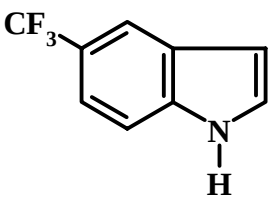


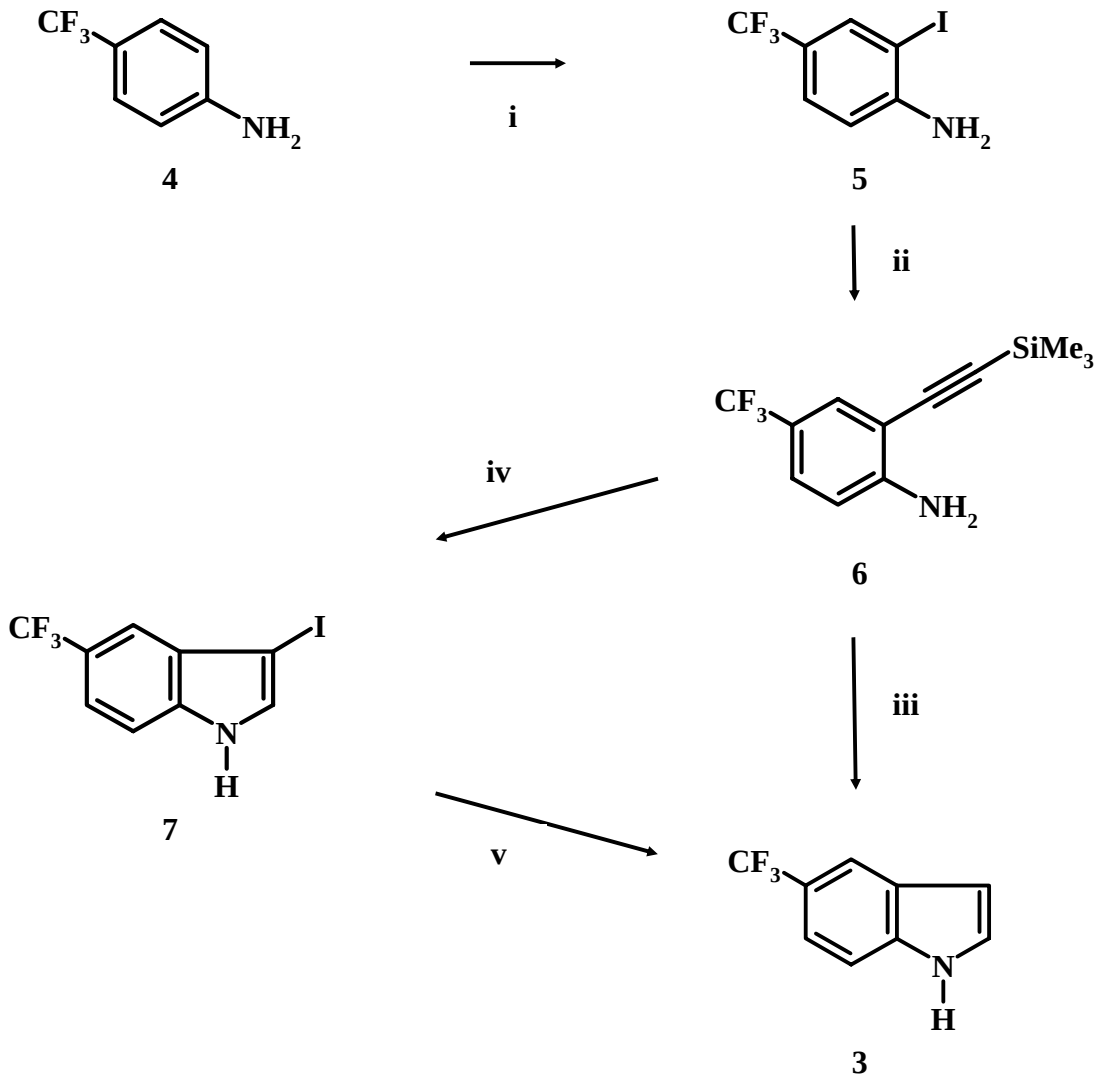
3

However, it was rather surprising that such simple substituted indoles have not yet been prepared, the 5-trifluoromethyl-1*H*-indole **(3)** being the only compound of this type known in the literature.[3,4]

Two procedures have been employed for the preparation of **3**. The first one, a three step synthesis starting from commercially available 5-bromo-1*H*-indole, requires high temperatures and affords low yields of end-product,[3] while the second of these methods involves a multistep process including a Nordlander type reaction.[4] We first tried to apply these methodologies to our targets but in our hands both ways were not satisfactory.

Despite limitations that were pointed out, these results prompted us to try the indole synthesis described by Barluenga,[5a] which makes use of an *ortho*-substituted aniline intermediate.

Scheme 1



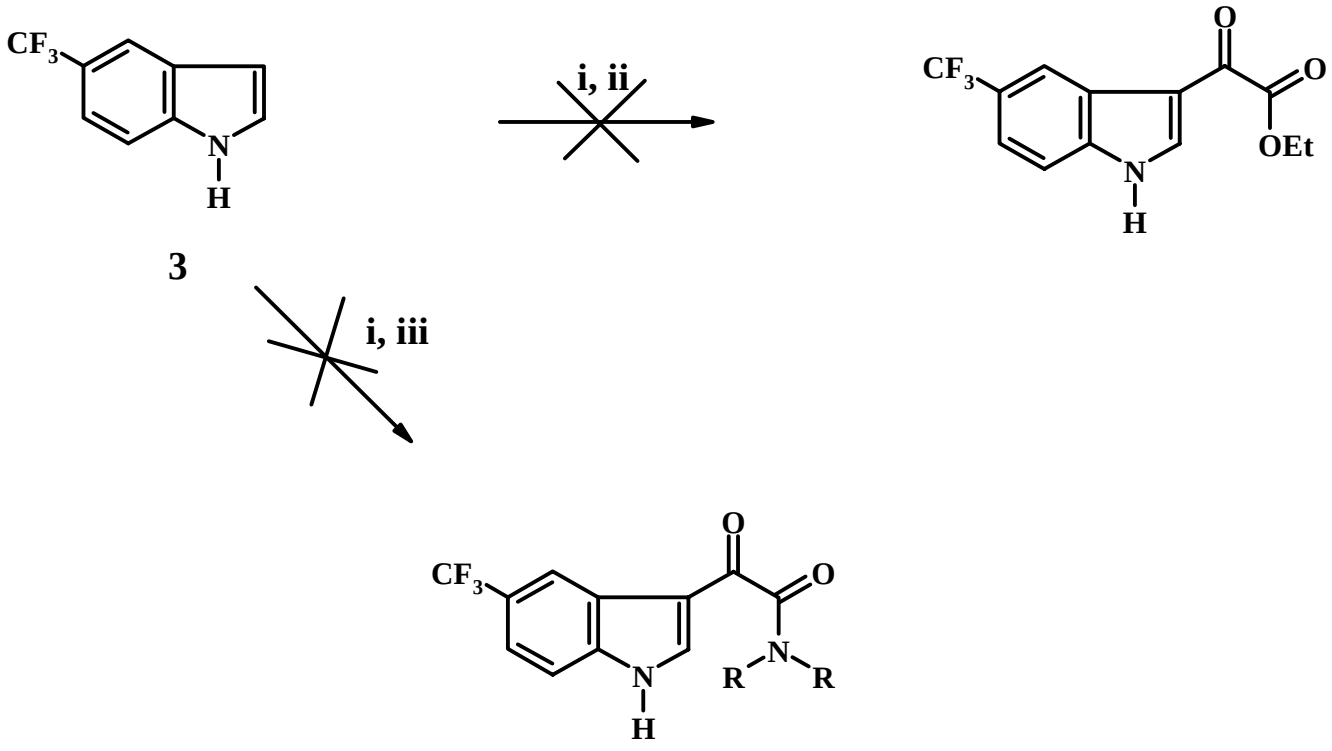
i) $BTMAICl_2$ / $CaCO_3$ / MeOH / 95%
ii) $Pd(OAc)_2$ / $Me_3SiC{\equiv}CH$ / Et_3N / 100%
iii) CuI (1 equivalent) / DMF / 64%
iv) CuI (2 equivalents) / DMF / 80%
v) 10% Pd/C / EtOH / 65%

Thus, a palladium(II) acetate catalyzed Sonogashira coupling[5b] between **5** (itself obtained by *ortho* iodation of **4**)[6] and trimethylsilylacetylene in the presence of CuI *(one equivalent)*, in triethylamine afforded **6** in good yield. Subsequently the ring closure of **6** using an additional *equivalent* of CuI in DMF at 100°C afforded **3** in moderate yield.

Rather surprisingly, the strict application of Barluenga's conditions, using *two or more equivalents of CuI (vide infra)*, led to the exclusive formation of 3-iodo-5-trifluoromethylindole **(7)** in good yield. Despite its relative instability this compound could be used to prepare **3** by treatment with palladium on charcoal (Scheme 1).

Unfortunately, all attempts to introduce further functionality on the 3-position of the indole nucleus resulted in recovery of starting materials only (Scheme 2).

Scheme 2

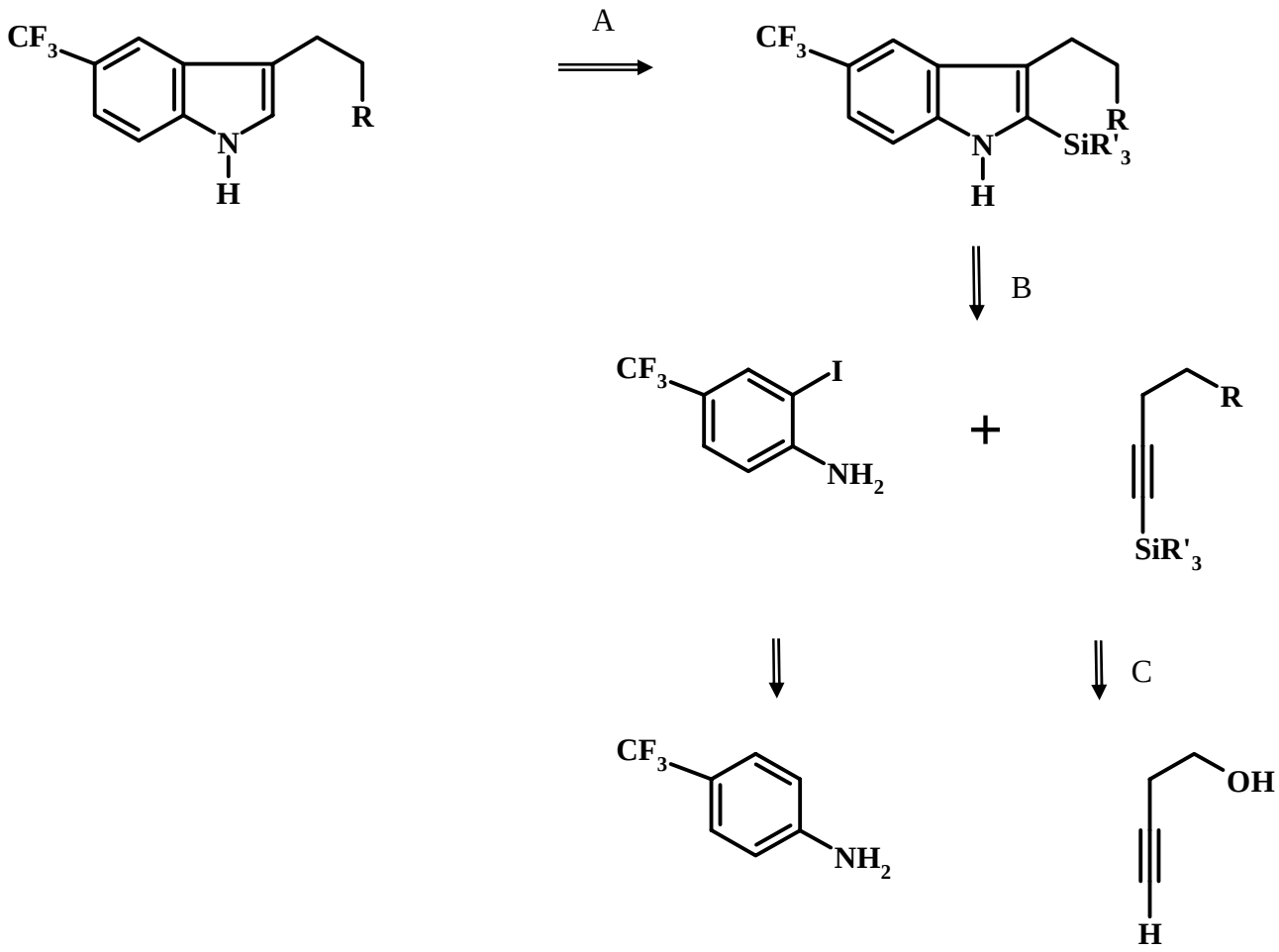


R = H, H or Bz, Bz

i) ClCOCOCl / Et_2O; ii) EtOH; iii) R_2NH

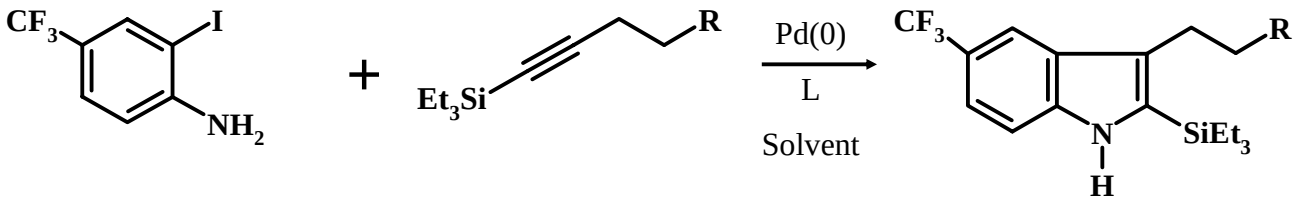
We therefore turned our attention to the synthesis of 3-substituted indoles *via* the palladium catalyzed heteroannulation of difunctionalized alkynes described by Larock and Yum.[7] This strategy, recently improved and extended by Gronowitz,[8] Ujjainwalla,[9] Guillaumet[10] and Cook[11] is depicted for our target molecules in Figure 2 (retrosynthetic scheme).

Figure 2



The regioselectivity of the reaction (step B) should be controlled by the size of the organosilyl substituent while the R group represents a protected amino or hydroxyl group (Scheme 3).

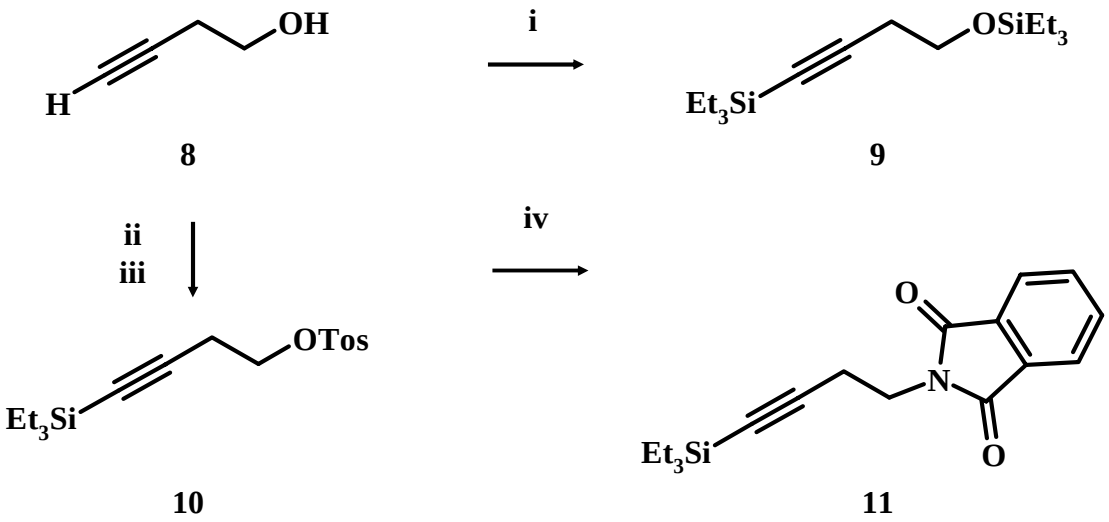
Scheme 3



5		R=OSiEt$_3$	**9**	R=OSiEt$_3$	**12**
		R = NPht	**11**	R=NPht	**13**

The preparation of the two propargyl derivatives **(9)** and **(11)** was first undertaken (Scheme 4).

Scheme 4



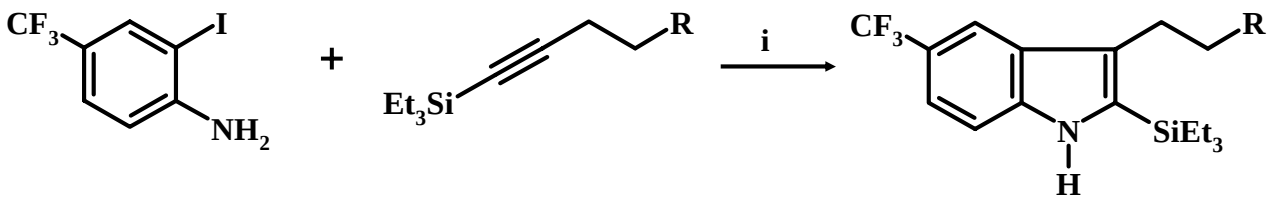
i) *n*BuLi / THF / Et_3SiCl (2 equivalents) / 96% ii) TosCl / Et_3N / CH_2Cl_2 (100%)

iii) *n*BuLi / THF / Et_3SiCl (1 equivalent) / 79% iv) DMF / Potassium Phthalimidate / 81%

It was found that the phthalimido and triethylsilyl ether fulfilled the requirement of stability and ease of deprotection. The silyl ether **(9)** was obtained in a nearly quantitative yield by a one pot bis-silylation of the propargyl alcohol **(8)** in THF at –78°C, using *n*BuLi and two equivalents of triethylsilyl chloride. On the other hand, the phthalimido derivative **(11)** was synthesized by a three step sequence, namely tosylation of the propargyl alcohol **(8)**, followed by silylation of the terminal alkyne with triethylsilyl chloride (*n*BuLi, THF, –78°C) to afford compound **(10)**, and then reaction with potassium phthalimidate in DMF to afford **11** in excellent yield.

Next the heteroannulation of **5** with **9** and **11** was investigated (Scheme 5, Table 1).

Scheme 5



5	R=OSiEt$_3$	**9**	R=OSiEt$_3$	**12**
	R = NPht	**11**	R=NPht	**13**

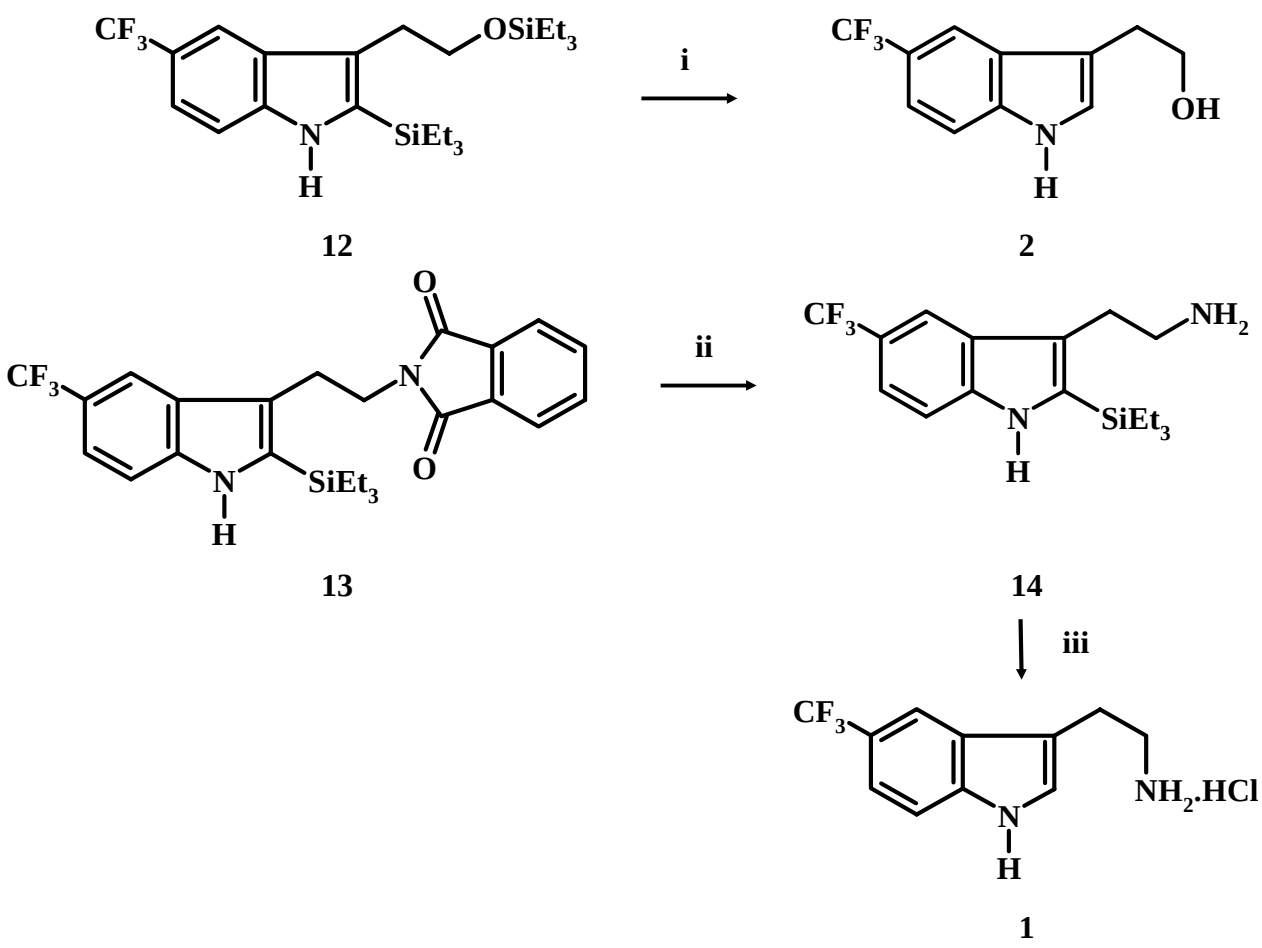
i) $PdCl_2$(dppf) 5% mol / DMF 100°C / LiCl (1 equivalent) / Na_2CO_3 (2 equivalents).

Table 1

Entry	R	Ratio Alkyne/**5**	Reaction Time (h)	Yield (%)
1	$OSiEt_3$	1	18	44
2	$OSiEt_3$	2	14	43
3	$OSiEt_3$	3	12	40
4	NPht	2	18	83
5	NPht	1	20	78

As already indicated by Ujjainwalla,[9] in our hands too, the use of $PdCl_2$(dppf) proved to be far better than $Pd(OAc)_2$ and PPh_3. We also found that an one or two ratio of **11/5** provided excellent yields of **13** (Entries 4 and 5, Table 1), while moderate yields of **12** (Entries 1-3, Table 1) were obtained with **9**/**5** ratios of one to three.

Scheme 6



i) 1N (nBu)$_4$NF / THF /82%

ii) 98% $NH_2NH_2.H_2O$ / EtOH / HCl / 87%

iii) 1N (nBu)$_4$NF / THF / Molecular sieves 3Å / 78%

Deprotection of **12** occurred smoothly upon treatment with 1N (nBu)$_4$NF in THF to afford **2** in 82% yield (Scheme 6). However removal of the C-2 triethylsilyl group in compound **(13)** proved to be unexpectedly problematic. Thus while regeneration of the amino group was easily achieved using the common Gabriel conditions to give **14**, no standard C-desilylating agents (e.g. HCl/MeOH, $AlCl_3$/dichloromethane, aqueous 2N KOH, 1N (nBu)$_4$NF) succeeded in producing the desired target **(1)**.

This transformation was finally achieved by treatment in THF with a stoichiometric amount of 1N (nBu)$_4$NF, in the presence of molecular sieves 3Å (48 h at room temperature), affording after addition of ethanolic HCl, the hydrochloride salt of **1**.

In conclusion, the synthetic approaches described above allowed the first preparation of 5-trifluoromethyltryptamine **(1)** and 5-trifluoromethyltryptophole **(2)** which are important pharmaceutical intermediates. In addition a new and improved approach for the preparation of 5-trifluoromethyl-1*H*-indole was also described. These syntheses can be readily scaled up to multigram quantities and are therefore practical ways for preparing 5-trifluoromethyl-1*H*-indoles.

EXPERIMENTAL

Melting Points were measured on a Tottoli Büchi 535 apparatus and are uncorrected. ^{1}H and ^{13}C NMR were recorded on Bruker 300 MHz or 500 MHz spectrometers. The chemical shifts are reported in ppm (δ value) downfield from tetramethylsilane (TMS), which was used as an internal standard. FT-IR spectra were measured on Fourrier Transform Bruker IFS 48 and IFS 28. MS spectra were recorded on a NERMAG R.10-10 C mass spectrometer (EI and HRMS (m/z)). Reagents and solvents were purchased from Aldrich-Sigma, Riedel-de-Haen, Baker or Acros. Analytical TLC was carried out on precoated plates (silicagel 60 F 254). Flash column chromatography was performed on Kieselgel 60 (230-400 mesh) silica gel (Merck). Solvent mixtures were reported as volume to volume ratios. The elemental analyses were established using Carlo Erba EAS 1108, EAS 1106 or Perkin Elmer 240B apparatuses for carbon, hydrogen, nitrogen and sulfur and a Mettler apparatus for halogens.

5-Trifluoromethyltryptamine (1)

10 mL of a 1N TBAF solution in THF were added to a solution of **14** (3 g, 8.7 mmol) followed by stirring for 72 h with 1 g of molecular sieves 3Å. The THF was removed under vacuum and the residue was dissolved in 100 mL of a 1N HCl solution. The solution was washed three times with 50 mL of ether then brought to basic pH using 2N NaOH and extracted twice with dichloromethane. The organic phases were dried over Na_2SO_4 and evaporated. Treatment with ethanolic HCl afforded the corresponding hydrochloride salt of **1** (2.25 g, 78%) whose crystals were collected and dried: mp > 250°C (ethanol); IR (Nujol) ν: 3298 (NH), 3007 (NH_3^+), 1340-1090 (C-F) cm^{-1}. ^{1}H-NMR (DMSO-d$_6$) δ: 3.08 (4H, s), 7.38

(1H, dd, *J* = 5.5 and 1.2 H_Z), 7.47 (1H, d, *J* = 1.2 H_Z), 7.58 (1H, d, *J* = 5.5 H_Z), 8.00 (1H, s), 8.19 (3H, s large, exchangeable), 11.55 (1H, s, exchangeable). *Anal.* Calcd for $C_{11}H_{11}N_2F_3HCl$: C, 49.92; H, 4.57; N, 10.58; Cl, 13.39. Found: C, 49.66; H, 4.87; N, 10.64; Cl, 13.38.

5-Trifluoromethyltryptophole (2)

10 mL of a 1N TBAF solution in THF were added *via* a syringe and under argon to a solution of **12** (4.5 g, 10 mmol) in 100 mL of THF, followed by stirring for 24 h. The solvent was evaporated and the residue was purified by flash chromatography (eluent: dichloromethane/ethyl acetate, 98/2). Compound **(2)** (1.87 g, 82%) was obtained as a yellow solid: mp 65-67°C (ethyl acetate); IR (Nujol) ν: 3544, 3313, 3263 (NH,OH), 1328, 1105 (C-F) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.90 (2H, t, *J* = 4.9 H_Z), 3.68 (2H, td, *J* = 4.9 and 3.7 H_Z), 4.66 (1H, t, *J* = 3.7 H_Z, exchangeable), 7.35 (2H, dd and s, *J* = 5.5 and 1.2 H_Z), 7.52 (1H, d, *J* = 5.5 H_Z), 7.92 (1H, d, *J* = 1.2 H_Z), 11.28 (1H, s, exchangeable). *Anal.* Calcd for $C_{11}H_{10}NOF_3$: C, 57.64; H, 4.40; N, 6.11. Found: C, 57.86; H, 4.52; N, 6.11.

5-Trifluoromethyl-1*H*-indole (3)

Compound **(6)** (5.2 g, 20 mmol), calcium carbonate (2.4 g, 20 mmol) and CuI (1.9 g, 10 mmol) were heated at 120°C in 100 mL of DMF for 2 h. The solvent was removed under vacuum and the residue was flash chromatographed (eluent: dichloromethane/heptane, 50/50) to afford **3** (2.4 g, 64%). Alternately, a suspension of **7** (3 g, 8 mmol) and 10% Pd on charcoal (0.3 g) in 50 mL of ethanol was hydrogenated under hydrogen pressure (5 bars). The catalyst was filtered off then the solvent was concentrated under vacuum and the residue was flash chromatographed (eluent: dichloromethane/heptane, 50/50) to afford **3** (1.78 g, 65%): mp 67-68°C (heptane) (lit.,[2]: 67-68°C); IR (Nujol) ν: 3433 (NH), 1332, 1162 (C-F) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, s), 7.59 (1H, d, *J* = 5.5 H_Z), 7.53 (1H, d, *J* = 1.2 H_Z), 7.36 (1H, dd, *J* = 5.5 and 1.2 H_Z), 6.60 (1H, s), 11.53 (1H, s, exchangeable). *Anal.* Calcd for $C_9H_6NF_3$: C, 58.39; H, 3.27; N, 7.57. Found: C, 58.20; H, 3.45; N, 7.71.

2-Iodo-5-trifluoromethylaniline (5)

Benzyltrimethylammonium dichloroiodate (12.9 g, 37 mmol) was added portionwise to a suspension of 4-trifluoromethylaniline **(4)** (5.63 g, 35 mmol) and calcium carbonate (3.7 g, 37 mmol) in 50 mL of dichloromethane and 150 mL of methanol. The mixture was stirred for 2 h at rt, filtered and concentrated under vacuum. The brown oil was flash chromatographed (eluent: dichloromethane) to afford **5** (10 g, 100%) as a light sensitive oil: IR (Neat) ν: 3404, 3287, 3193 (NH_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 5.00 (2H, s, exchangeable), 6.82 (1H, d, *J* = 5.5 H_Z), 7.38 (1H, dd, *J* = 5.5 and 1.3 H_Z), 7.79 (1H, d, *J* = 1.3 H_Z).

2-Trimethylsilylethynyl-4-trifluoromethylaniline (6)

A solution of **5** (10 g, 35 mmol) in 10 mL of triethylamine was slowly added at 0°C, to a suspension of CuI (0.6 g, 35 mmol), *bis*(triphenylphosphine)dichloropalladium (200 mg, 0.4 mmol), and trimethylsilylacetylene (5.7 mL, 40 mmol) in 90 mL of triethylamine. The mixture was stirred for 20 h at rt and concentrated under vacuum. Water (100 mL) and dichloromethane (100 mL) were added to the residue followed by filtering on a celite bed. The organic layer was separated, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was flash chromatographed (eluent: dichloromethane/heptane, 1/1) to afford **6** (9g, 100%) as an orange oil: IR (Neat) ν: 2154, 2067 (C≡C), 1625 (NH_2), 1509 (C≡C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.27 (9H, s,), 4.54 (2H, s, exchangeable), 6.70 (1H, d, J = 5.5 H_Z), 7.31 (1H, dd, J = 5.5 and 1.2 H_Z), 7.54 (1H, d, J = 1.2 H_Z).

3-Iodo-5-trifluoromethyl-1*H*-indole (7)

A suspension of **6** (2.57 g, 10 mmol) and CuI (3.8 g, 20 mmol) in 80 mL of DMF was heated for 2 h at 100°C. The solvent was distilled off under reduced pressure and the residue purified by flash chromatography (eluent: dichloromethane) to afford **7** (2.5 g, 80%) as an unstable, light sensitive brown oil: IR (Neat) ν: 1627 (NH), 1329-1115 (C-F) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 7.47 (1H, dd, J = 5.6 and 1.2 H_Z), 7.60 (1H, d, J = 5.6 H_Z), 7.63 (1H, d, J = 1.2 H_Z), 7.78 (1H, s), 12.00 (1H, s, exchangeable).

1-Triethylsilanyl-4-(triethylsilanyloxy)but-1-yne (9)

139 mL of a 1.6 N *n*BuLi solution in hexane was introduced *via* syringe under argon into a flask containing **8** (7.6 mL, 0.1 mol) and 100 mL of THF, followed by cooling to -78°C. The solution was stirred for 1 h and then triethylsilyl chloride (35 mL, 0.21 mol) was added dropwise. The solution was allowed to reach rt and stirring was continued for 24 h. The reaction mixture was poured onto 1 L of ice/water and extracted twice with 500 mL of ether. The combined organic phases were dried over Na_2SO_4 and evaporated to dryness affording **9** (28.5 g, 96%) as a colorless oil: IR (Neat) ν: 2475 (C≡C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.50-0.90 (30H, m), 2.48 (2H, t, J = 4.3 H_Z), 3.70 (2H, t, J = 4.9 H_Z). *Anal.* Calcd for $C_{16}H_{34}OSi_2$: C, 64.36; H, 11.48. Found: C, 64.94; H, 11.52.

4-(Triethylsilanyl)but-3-ynyl-4-methylbenzenesulfonate (10)

A solution of tosyl chloride (104 g, 0.55 mol) in 200 mL of dichloromethane was added dropwise at 0°C to a flask containing **8** (38 mL, 0.5 mol), triethylamine (140 mL, 1mol) and 500 mL of dichloromethane. The reaction mixture was stirred for 2 h, added to 1 L of water followed by separation of phases. The organic layer was dried over Na_2SO_4 and evaporated to dryness affording, after flash chromatography (eluent: dichloromethane/heptane, 1/1), the tosylate (89 g) as a pale yellow oil. This oil was then added to

300 mL of THF in a flask, under argon atmosphere, followed by cooling to -78°C. 250 mL of a 1.6 N *n*BuLi solution in hexane was added *via* syringe, during 15 min. The mixture was stirred for 1 h and then triethylsilyl chloride (85 mL, 0.5 mol) was added and the reaction mixture allowed to reach rt. Water (200 mL) was added forming two phases that were separated. The organic layer was dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford **10** (109 g, 79%) as a pale yellow oil; IR (Neat) ν: 2179 (C≡C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.60-1.00 (15H, m), 2.50 (3H, s), 2.65 (2H, t, *J* = 6.7 H_Z), 4.10 (2H, t, *J* = 7.3 H_Z), 7.20 (2H, d, *J* = 7.9 H_Z), 7.80 (2H, d, *J* = 7.9 H_Z). *Anal.* Calcd for $C_{17}H_{26}O_3SSi$: C, 60.31; H, 7.74; S, 9.47. Found: C, 60.19; H, 8.05; S, 9.15.

2-(4-Triethylsilanylbut-3-ynyl)isoindole-1,3-dione (11)

A solution of **10** (109 g, 0.32 mol) and potassium phtalimidate (72 g, 0.35 mol) in 500 mL of anhydrous DMF was heated at 60°C in a round bottomed flask for 4 h. The DMF was removed under reduced pressure and the residue taken up in 300 mL of water and 500 mL of dichloromethane. After separation, the organic phase was dried over Na_2SO_4, quickly filtered on 200 g of silica gel and evaporated under reduced pressure affording **11** (79 g, 81%) as a colorless oil; IR (Neat) ν : 2177 (C≡C), 1775, 1718 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.45-0.85 (15H, m), 2.65 (2H, t, *J* = 4.3 H_Z), 3.88 (2H, t, *J* = 4.3 H_Z), 7.72 (2H, m), 7.85 (2H, m). *Anal.* Calcd for $C_{18}H_{23}NO_2Si$: C, 68.97; H, 7.40; N, 4.47. Found: C, 69.15; H, 7.58; N, 4.42.

2-Triethylsilanyl-3-(2-triethylsilanyloxyethyl)-5-trifluoromethyl-1*H*-indole (12)

A suspension of **4** (3.4 g, 20 mmol), **9** (6 g, 20 mmol), $PdCl_2$(dppf) (0.25 g, 0.3 mmol), LiCl (0.85 g, 20 mmol), Na_2CO_3 (4.24 g, 40 mmol) in 200 mL of DMF was placed in a round bottomed flask under argon and heated at 100°C during 10 h. The DMF was distilled off, the residue was taken up in dichloromethane, filtered on celite and finally purified by flash chromatography (eluent: heptane) affording **12** (4.1 g, 44%) as a colourless oil: IR (Neat) ν: 3479 (NH); 1330, 1116 (C-F) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.41-1.00 (30H, m), 3.00 (2H, t, *J* = 4.9 H_Z), 3.74 (2H, t, *J* = 4.9 H_Z), 7.40 (2H, s), 7.88 (1H, broad), 8.20 (1H, s, exchangeable). *Anal.* Calcd for $C_{23}H_{38}NOF_3Si_2$: C, 60.35; H, 8.37; N, 3.10. Found: C, 61.13; H, 8.43; N, 3.10.

2-[2-(2-Triethylsilanyl-5-trifluoromethyl-1*H*-indol-3-yl)ethyl]isoindole-1,3-dione (13)

A suspension of **4** (7.2 g, 25 mmol), **11** (16 g, 50 mmol), $PdCl_2$(dppf) (0.4 g, 0.5 mmol), LiCl (1.08 g, 25 mmol), Na_2CO_3 (5.4 g, 50 mmol) in 100 mL of DMF was placed in a round bottomed flask and heated under argon at 100°C for 20 h. The DMF was distilled under vacuum, the residue was taken up in dichloromethane, filtered on celite and finally purified by flash chromatography (eluent:

dichloromethane/heptane, 1/1) to afford **13** (10 g, 83%) as a light yellow oil: IR (Neat) ν: 3470 and 3400 (NH), 1722, 1706 (C=O), 1520 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 0.94 (15H, s), 3.12 (2H, t, *J* = 5.0 H_Z), 3.77 (2H, t, *J* = 4.9 H_Z), 7.35 (1H, dd, *J* = 6.1 and 1.2 H_Z), 7.55 (1H, d, *J* = 6.1 H_Z), 7.84 (4H, m), 7.92 (1H, d, *J* = 1.2 H_Z), 10.97 (1H, s, exchangeable). *Anal.* Calcd for $C_{25}H_{27}N_2O_2F_3Si$: C, 63.54; H, 5.76; N, 5.93. Found: C, 63.77; H, 5.96; N, 5.93.

2-(2-Triethylsilanyl-5-trifluoromethyl-1*H*-indol-3-yl)ethylamine (14)

A solution of **13** (4.7 g, 10 mmol), 98% hydrazine hydrate (3.4 mL, 100 mmol) and 150 mL of ethanol was refluxed for 3 h followed by addition of 20 mL of 1N HCl solution and the mixture was further reflux for 1 h. Water (100 mL) was added and basic pH was reached by addition of a 5% Na_2CO_3 solution. The mixture was extracted twice with 50 mL of dichloromethane. The combined organic layers were dried over Na_2SO_4 and evaporated to dryness. The residue was crystallised from ethanol affording **14** (3 g, 87%) as yellow crystals: mp 56-57°C (ethanol); IR (Neat) ν: 3150 (NH); 1330-1110 (C-F) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (15H, m), 2.70-36.00 (2H, large exchangeable), 2.72 (2H, m), 2.87 (2H, m), 7.33 (1H, dd, *J* = 6.1 and 1.2 H_Z), 7.53 (1H, d, *J* = 6.1 H_Z), 7.92 (1H, d, *J* = 1.2 H_Z), 10.88 (1H, s). *Anal.* Calcd for $C_{17}H_{25}N_2F_3Si$: C, 59.62; H, 7.36; N, 8.18. Found: C, 59.04; H, 7.08; N, 8.06.

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