Synthesis of *N*-Aminoindole Ureas from Ethyl 1-Amino-6-(trifluoromethyl)-1*H*-indole-3-carboxylate

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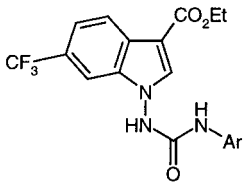
Abstract: Two routes to the synthesis of ethyl 6-(trifluoromethyl)-1*H*-indole-3-carboxylate are described. *N*-Amination of this key intermediate with *O*-(diphenylphosphinyl)hydroxylamine and subsequent reactions with aryl isocyanates, using pyridine as solvent, gave the corresponding *N*-aminoindole ureas **1-4** in good yields.

Key words: aminations, indoles, cyclizations, urea formation, isocyanates

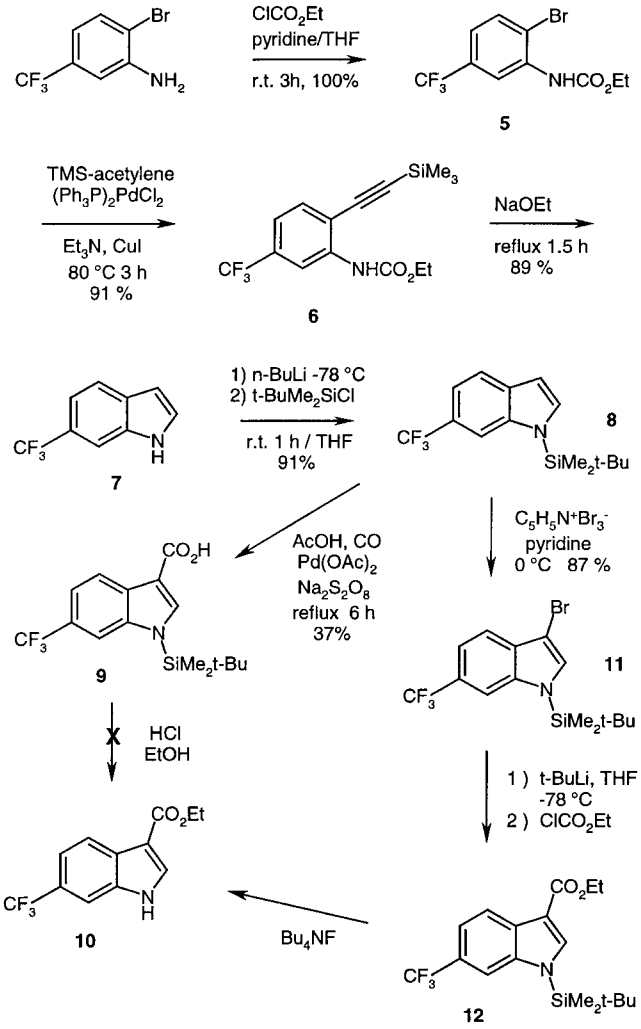
The synthesis of *N*-aminoindoles has been well documented and many of their derivatives have been reported to have interesting biological activities.[1] For example, besipirdine and some of its analogs are potent acetylcholinesterase inhibitors developed for the treatment of Alzheimer's disease.[2] However, the synthesis and pharmacological properties of *N*-aminoindole ureas continues to be virtually unexplored, with only one example cited in the literature.[3] Herein we wish to report a concise synthesis of compounds **1-4** (Figure 1) which are representatives of this new class of *N*-aminoindole ureas.



1 Ar = 4-MePh
2 Ar = 4-ClPh
3 Ar = 4-MeSPh
4 Ar = 2-FPh

Figure 1

The synthesis of ureas **1-4** was initially envisioned to start from commercially available 6-(trifluoromethyl)-1*H*-indole (**7**)[4]. Unfortunately, high costs of the starting material **7** prompted for a more economical preparation, which could be achieved in three steps with an overall yield of 75% (Scheme 1). Thus, 3-amino-4-bromobenzotrifluoride was treated with ethyl chloroformate and pyridine in THF to give the carbamate **5**. Coupling with (trimethylsilyl)acetylene in the presence of bis(triphenylphosphine)palladium dichloride and copper iodide, using the procedure described by Yamanaka,[5] yielded the acetylene derivative **6**, which could be cyclized to **7** with sodium ethoxide in ethanol.[5] The choice of the reaction conditions for this cyclization step is critical. When **6** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in ethanol (reflux, 1 h), only desilylation of **6** to *N*-(ethoxycarbonyl)-5-(trifluoromethyl)-2-ethynylaniline (81% yield) was observed; with DBU in acetonitrile (reflux, 1.5 h), the *N*-(ethoxycarbonyl) derivative of **7** was obtained in 54% yield.

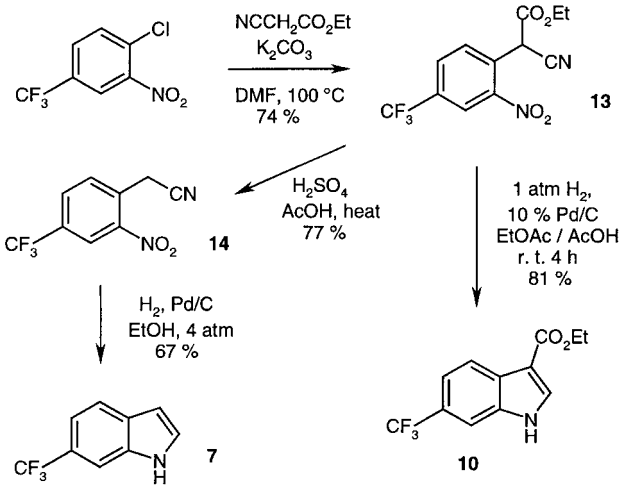


Scheme 1

The indole nitrogen was then protected as a *tert*-butyldimethylsilyl amine[6] to give **8**. Carboxylation in the 3-position using carbon monoxide, palladium acetate and sodium persulfate[7] afforded the acid **9** (37% yield), but subsequent esterification with hydrogen chloride in ethanol failed to give the desired ester **10**.

Ethyl 6-(trifluoromethyl)-1*H*-indole-3-carboxylate **10** was finally obtained using the procedure of Amat[6] with a slight modification (Scheme 1). When the bromination of **8** was performed as described by Amat on a milligram scale with NBS at −78 °C, **11** was obtained in 66% yield. However, upon scaling up, the yield decreased significantly to 20%. Better and reproducible yields could be obtained by performing the brominations with bromine in DMF[8] (71% yield) or with pyridinium bromide perbromide[9] in pyridine at 0 °C (87% yield). Transmetallation of the corresponding bromoindole with *tert*-butyllithium and reverse addition to ethyl chloroformate gave the ester **12** (60% yield), which was noted to slowly hydrolyze to **10** on silica gel or on standing at room temperature. Higher yields of **10** (87%) were possible when the crude reaction mixture containing **12** was treated with tetrabutylammonium fluoride in THF.[10]

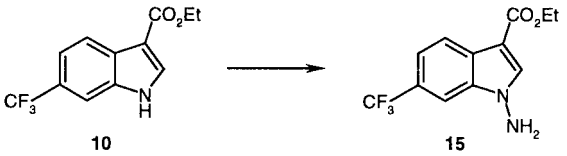
A more expedient route to the indole **10** was subsequently found (Scheme 2). The best-published synthesis of 6-(trifluoromethyl)-1*H*-indole (**7**), described by Kalir and Pelah,[4a] involved an aromatic nucleophilic substitution on 3-nitro-4-chlorobenzotrifluoride by the anion of ethyl cyanoacetate to yield the cyanoester **13**. Ester hydrolysis and decarboxylation of **13** followed by a reductive cyclization afforded **7** in three steps in 38% overall yield. We wondered whether the reductive cyclization could be performed on the intermediate cyanoester **13** directly, thus furnishing **10** in two steps. After much investigation, we found that the best conditions to effect the reductive cyclization of **13** involved the use of AcOH or AcOH:EtOAc mixtures as solvents and an amount of 10% Pd/C corresponding to half the weight of **13**.



Scheme 2

N-Amination of indoles is usually performed using the method of Somei, with hydroxylamine-*O*-sulfonic acid and potassium hydroxide in anhydrous DMF.[1a, 2, 3, 11] Unfortunately, these conditions were found to give poor conversion of the indole **10** to the desired *N*-aminoindole **15** (Table 1). This was not surprising since Somei had previously reported no *N*-amination for 3-acetylindole,[3] probably due to the decreased reactivity of indoles containing an electron-withdrawing substituent in position 3. Better yields for the *N*-amination of **10** were obtained with *O*-(diphenylphosphinyl)hydroxylamine[12] using the procedure of Klotzer.[13] Optimization of the reaction conditions led to the identification of lithium hexamethyldisilazanide as the base of choice for this amination, providing **15** with a reproducible yield of 80%.[14]

Table 1 *N*-Amination of indole **10**



Reagent	Base	Conditions	Ratio **10**:**15**[a]
NH_2OSO_3H	KOH/K_2CO_3	DMF, r.t.	79:21
$Ph_2P(O)ONH_2$	NaH	NMP, r.t.	29:71
$Ph_2P(O)ONH_2$	DBU	NMP, r.t.	48:52
$Ph_2P(O)ONH_2$	KHMDS	NMP, -10 °C to r.t.	40:60
$Ph_2P(O)ONH_2$	LiHMDS	NMP, -10 °C to r.t	20:80

[a] determined by HPLC

The addition reaction between an amine and an isocyanate is the most common method for preparing ureas.[3,15] In an attempt to form the *N*-aminoindole urea of **15**, we initially prepared 1-indole isocyanate **16a** in situ via the treatment of **15** with triphosgene[16] or di-*tert*-butyl dicarbonate.[17] Unfortunately, subsequent reaction of this isocyanate with 4-methylaniline afforded **1** in low yields (maximum 35%), with the two symmetrical ureas **17** and **18** resulting as the major products. Equally disappointing was the reaction between the trichloroacetamide **16b**[18] and 4-methylaniline in the presence of sodium carbonate using Isobe's[19] procedure, where none of the desired urea could be detected.

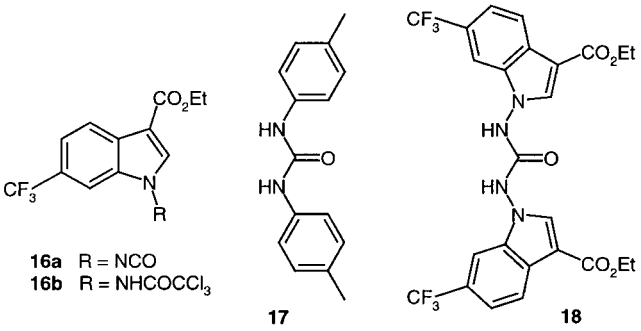
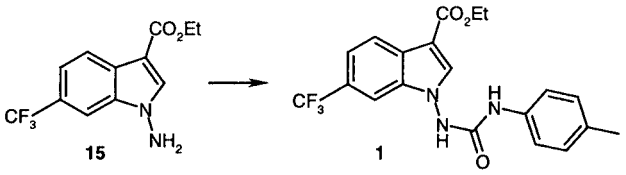


Figure 2

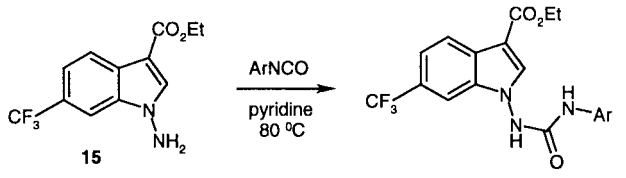
We then turned our attention to the addition of *N*-aminoindole **15** to *p*-tolyl isocyanate. Our initial attempts using this strategy gave very low yields of urea **1**, with *N,N'*-di-*p*-tolyl urea **17** as the major product**.** These poor results could be attributed to the low nucleophilicity of the amino group in **15**. A more thorough examination of the reaction conditions, however, revealed DMF or pyridine as the solvent of choice for this urea formation, with yields above 70% (Table 2). The reaction was found to work well with other aryl isocyanates, giving yields ranging from 60 to 92% in pyridine (Table 3).[20]

Table 2 Preparation of **1** by reaction of aminoindole **15** with *p*-tolyl isocyanate



Entry	Solvent	Conditions	Yield (%)
1	Acetone	56 °C	30
2	CH_2Cl_2	r.t.	<20
3	THF	r.t.	21
4	CH_3CN	r.t.	<20
5	Toluene	140 °C	0
6	Xylene	140 °C	0
7	2-Butanone	110 °C	34
8	$ClCH_2CH_2Cl$	80 °C 16 h	0
9	CH_3CONMe_2	80 °C 16 h	0
10	$MeNO_2$	80 °C 16 h	4
11	DMF	80 °C 16 h	72
12	Pyridine	80 °C 5 h	88

Table 3 Reaction of *N*-aminoindole **15** with isocyanates



Product	ArNCO	Yield (%)
1	4-MePhNCO	88
2	4-ClPhNCO	92
3	4-(MeS)PhNCO	68
4	2-FPhNCO	60

In summary, two synthetic pathways to the *N*-aminoindole ureas **1-4**, from commercially available materials, have been described. The first route, from 6-(trifluoromethyl)-1*H*-indole (**7**), gave **1** in six steps with an overall yield of 46%, while the second route, starting from the less expensive 3-nitro-4-chlorobenzotrifluoride, afforded **1** in four steps in 42% overall yield. The key steps, common to both syntheses, involved the *N*-amination of an indole with *O*-(diphenylphosphinyl)hydroxylamine and its subsequent reaction with an aryl isocyanate in pyridine. The biological profile of these new compounds is currently being investigated.

Experimental procedures

Ethyl 6-(trifluoromethyl)-1*H*-indole-3-carboxylate **10** from **11**: 1.7 M *t*-Butyllithium in pentane (23 mL, 39 mmol) was added dropwise to a solution of 1-(*t*-butyldimethylsilyl)-3-bromo-6-(trifluoromethyl)indole (**11**) (7.0 g, 18.5 mmol) in THF (63 mL) at -78 °C, and the resulting solution was stirred at that temperature for 30 min. It was then cannulated into a solution of ethyl chloroformate (1.86 mL, 19.4 mmol) in THF (63 mL) at -100 °C. The reaction mixture was allowed to warm to 0 °C over an hour, at which point a 1 M solution of tetrabutylammonium fluoride in THF (22 mL) was added. After 15 minutes, the mixture was quenched with sat. NH_4Cl (70 mL) and extracted with *i*-PrOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a green solid. A pink-white solid (3.93 g, 83% yield) was obtained after purification by flash chromatography with EtOAc:toluene 10:90. ^1H NMR (300 MHz, acetone-d_6) δ 11.40 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H), 7.90 (s, 1H), 7.50 (d, J = 8.4 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 164.8, 136.5, 135.3, 129.6, 127.5, 124.8, 122.6, 118.5, 110.6, 109.1, 60.1, 14.8; IR (KBr) 3200, 2980, 1680, 1440, 1330, 1230, 1160, 1120, 1050 cm^{-1}; MS (APCI, neg.) 256 (M-1, 100%), 228, 184; Anal. calcd. for $C_{12}H_{10}NO_2F_3$: C, 56.02; H, 3.92; N, 5.45; found: C, 56.08; H, 4.46; N, 5.47.

Ethyl 6-(trifluoromethyl)-1*H*-indole-3-carboxylate **10** from **13**: To ethyl 2-cyano-2-(2-nitro-4-(trifluoromethyl)phenyl)acetate (**13**) (50 mg; 0.165 mmol) in a 4:1 mixture of EtOAc:AcOH (2.5 ml) was added 25 mg of 10% Pd/C. The solution was stirred at room temperature under 1 atmosphere of H_2 and the reaction was followed by HPLC (Nova Pak C18 column, gradient 20 to 90% CH_3CN in aq. NH_4OAc 2 g/L, 1 mL/min, detection at 239 nm). After 4 hours, the hydrogen was removed and the solution was stirred overnight at room temperature under air. The mixture was filtered through celite, the cake washed with ethanol and the filtrate concentrated under vacuum to give 53 mg of crude product. A trituration in 5% toluene in hexanes gave the desired product (34 mg, 81% yield) as a white solid. Yields on larger scale were slightly lower (66%), principally due to adsorption of compound **10** on Pd/C.

Ethyl 1-amino-6-(trifluoromethyl)-1*H*-indole-3-carboxylate **15**: Lithium hexamethyldisilazanide (4.7 mL, 4.7 mmol) was added dropwise to **10** (1.0 g, 3.9 mmol) in 1-methyl-2-pyrrolidinone (40 mL) at −10 °C, followed by *O*-(diphenylphosphinyl)hydroxylamine (1.09 g, 4.7 mmol) at 0 °C. The reaction was allowed to warm to room temperature and was followed by HPLC (30:70 ethyl acetate:hexane, μ−Porasil column). After 6 hours, the ratio of **10**:**15** remained constant at 1:4. The mixture was then quenched with 2 N HCl (20 mL) and extracted with *i*-PrOAc (200 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The products were purified by flash chromatography on silica gel eluting with EtOAc:hexane 30:70. A yellow-white solid (1.06 g) containing **10** and **15** in a ratio of 1:4 was isolated. Pure **15** was obtained after purification by HPLC on a μ−Porasil column (EtOAc:hexane 30:70). ^1H NMR (300 MHz, acetone-d_6) δ 8.25 (d, J = 8.4 Hz, 1H), 8.08 (s, 1H), 7.94 (s, 1H), 7.49 (dd, J = 1.2, 8.4 Hz, 1H), 6.10 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 164.6, 139.0, 137.5, 133.2, 128.1, 122.8, 122.5, 118.7, 108.8, 105.4, 60.2, 14.8; IR (KBr) 3350, 3310, 3120, 1680, 1520, 1320, 1270, 1200, 1150, 1100, 1040 cm^{-1};

MS (APCI, neg) 184 (100%), 197, 256, 271 (M-1), 331 (M+AcO^-); Anal. calcd. for $C_{12}H_{11}F_3N_2O_2$: C, 52.95; H, 4.07; N, 10.29; found: C, 53.10; H, 4.33; N, 10.06; mp 115.3 °C.

Ethyl 1-((((4-(methylthio)phenyl)amino)carbonyl)amino)-6-(trifluoromethyl)-1*H*-indole-3-carboxylate (**3**): To a solution of the *N*-aminoindole **15** (93 mg, 0.34 mmol) in pyridine (4.5 ml) was added 4-(methylthio)phenyl isocyanate (96 μL, 2.0 eq) and the resulting mixture was stirred at 80 °C under nitrogen for 5 hours. The reaction was quenched with sat. NH_4Cl and the product extracted with ethyl acetate, washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave 214 mg of crude product, which was adsorbed onto 2 g silica gel before purification by flash chromatography on silica gel eluting with EtOAc:toluene 30:70. A second purification, using the same procedure, but with acetone:toluene 10:90, was necessary to provide pure **3** (101 mg, 68% yield) as a yellow solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 9.34 (s, 1H), 8.87 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.25 (s, 1H), 7.83 (s, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 164.1, 154.5, 139.5, 137.5, 137.4, 132.9, 128.5, 127.9, 122.8, 120.5, 119.3, 119.2, 108.1, 108.1, 107.4, 60.3, 16.3, 14.6; IR (KBr) 3270, 1695, 1645, 1535, 1315, 1190, 1035 cm^{-1}; MS (APCI, pos.) 392, 438 (M+1), 455 (100%); Anal. calcd. for $C_{20}H_{18}F_3N_3O_3S$: C, 54.92; H, 4.15; N, 9.61; S, 7.33; found: C, 54.86; H, 4.37; N, 9.32; S, 7.45; mp 226.5 °C.

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(14) When sodium hydride or DBU was used as the base to effect the *N*-amination of **10** with *O*-(diphenylphosphinyl)-hydroxylamine, we found that the aminoindole **15** reverted back to the starting material **10** over time in the reaction mixture. This was not happening with KHMDS or LiHMDS and we are currently investigating the mechanism of this retro-amination. It should also be noted that recycling of the 1:4 mixture did not improved the ratio of **10**:**15**.

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(20) Similar results were also obtained with the 4:1 mixture of **15**:**10** obtained in the previous step, thus avoiding the HPLC purification of **15**.

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