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Synthesis of new trifluoromethylated indole derivatives

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ABSTRACT

New indole trifluoromethyl derivatives have been synthesized using the reaction of indole derivatives with different 2,2,2-trifluoro-*N*-arylacetimidoyl chlorides in the presence of NaH as a base in acetonitrile at room temperature under an N_2 atmosphere. The FT-IR, ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, COSY and HMBC spectra and elemental analysis confirm the structures of the products.

Heterocyclic compounds attract significant attention in the chemical literature due to their abundance in natural products and their diverse biological properties. A large variety of heterocycles are known, and among these, indole and pyran ring systems are of particular importance. A wide spectrum of biological activities have been linked to natural and unnatural compounds possessing a substituted indole nucleus, making it a suitable building block for many therapeutic agents.[1,2]

The indole nucleus is frequently found in natural products, pharmaceuticals, functional materials, and agrochemicals.[2] Indole analogues constitute important therapeutic agents in medicinal chemistry including anticancer,[3] antioxidant,[4] antirheumatoid, and anti-HIV.[5,6] Some indoles inhibit the growth of bladder cancer, cell carcinoma, lung cancer, colon cancer, mammary tumors, prostate cancer, and breast tumor cells.[7] In addition, many indole derivatives are potent scavengers of free radicals.[8]

One particularly important area of medicinal research is the synthesis and application of organofluorine compounds.[9] Organofluorine chemistry represents an expanding and productive area of research, as can be seen by the increasing number of recent publications, reviews, topics, and monographs in this area.[10] Furthermore, organofluorine chemicals have found a wide range of applications in the pharmaceutical industry, materials science, and agriculture due, in part, to the unique biological properties imparted by the fluorine atom.[9,11]

Also, substituted indoles are able to bind many receptors with high affinity. Therefore, the synthesis and selective functionalization of indoles have been the focus of much research.[2,12]

In view of the importance of di- and trifluoromethylated indole derivatives, several methods for their synthesis have been reported in the literature. Intermolecular coupling of a CF_2Br group with the 2-position of indole (or pyrrole), via C–H bond activation with tris(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) provides a useful method for the synthesis of difluoromethyl indole (pyrrole) derivatives. This reaction represents a new way of incorporating difluoromethyl groups into organic compounds.[13] Friedel–Crafts reaction/C–H bond activation of indoles with *N*-(2-iodophenyl)trifluoroacetimidoyl chlorides via addition–elimination/arylation has been used for the synthesis of 6-trifluoromethylindolo[1,2-*c*]quinazolines.[14]

In this research, to combine the interesting and remarkable biological activities of both indole and acetimidoyl groups, we required a synthesis of the indole-annulated trifluoromethyl derivative skeleton **4** (see Scheme 2). Therefore, *N*-aryltrifluoroacetimidoyl chlorides were selected to form a link through carbon or nitrogen to indole.

Trifluoromethylated compounds are of particular interest as the strong electron-withdrawing effect of the CF_3 group contributes to a number of biologically important molecular properties. For example, it results in a significant increase in the lipophilicity of the molecule, which is a very important feature in drug delivery. *N*-Aryltrifluoroacetimidoyl chlorides can be prepared by several procedures.[15,16] In this research, a one-pot synthesis of imidoyl halides is described which involves refluxing a mixture of trifluroacetic acid and a primary amine in carbon tetrachloride in the presence of triethylamine and triphenylphosphine. Work-up and distillation provided the desired imidoyl chlorides in good to excellent yields[16] (Scheme 1).

In an initial study, we examined the reaction of indole (**1a**) with **2a** in presence of K_2CO_3 or NaH in toluene under reflux conditions.

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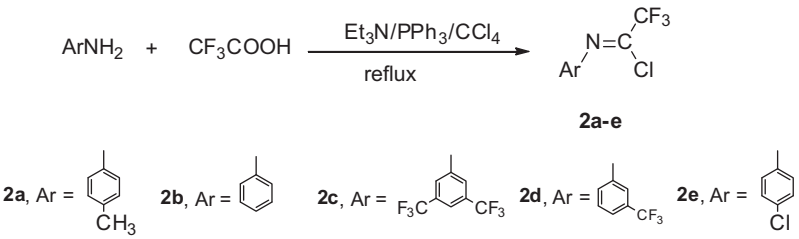
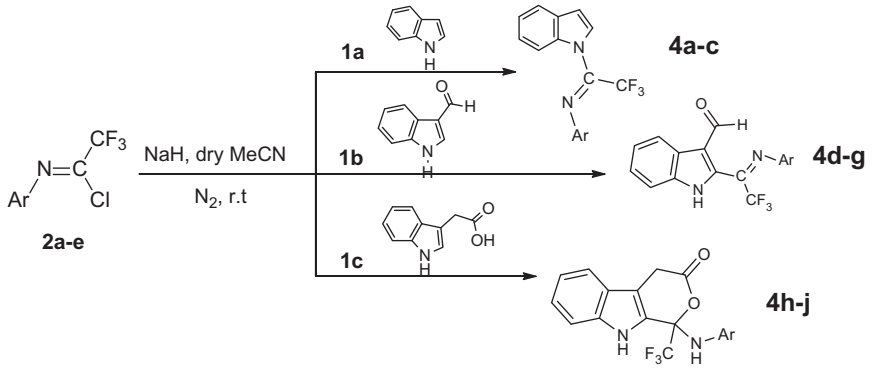


Scheme 1. Preparation of 2,2,2-trifluoroacetimidoyl chloride derivatives.



Scheme 2. Synthesis of new indole trifluoromethyl derivatives.

We faced problems when purifying the products, and the obtained yields were very low. In addition, under these conditions, imidoyl chlorides **2a–c** reacted with indole **1a**, to afford compounds **4a–c** in low yields (10–15%). Further attempts were made to improve the yields. When the reaction was carried out in the presence of NaH in acetonitrile at room temperature under an N_2 atmosphere, it afforded the corresponding products **4a–c** in excellent yields (78–89%) (Scheme 2). In this reaction the pyrrole nitrogen acts as a nucleophile to displace chlorine.

The IR spectrum of *N*-[2,2,2-trifluoro-1-(1*H*-indol-2-yl)ethylidene]aniline (**4a**) showed an absorption band at 1623 cm^{-1}, which corresponds to the C=N moiety. The ^1H NMR spectrum of **4a** exhibited a doublet at δ 7.52 (J = 7.0 Hz) and a doublet at δ 6.88 (J = 6.9 Hz) due to the indole alkylene protons (HC=CH), and three multiplets at δ 7.58–7.60, δ 7.01–7.03, and δ 6.71–6.73, which correspond to six aromatic protons, and a doublet at δ 6.93 (J = 7.2 Hz) which corresponds to two of the aromatic protons present in the molecule. Also the ^1H NMR spectrum of **4a** showed a signal at δ 2.09 corresponding to the CH_3 group. The ^{19}F NMR spectrum of **4a** showed a signal at δ −70.13 corresponding to the CF_3 group. The above spectral data and elemental analysis supported the formation of compound **4a**.[17]

In order to investigate the effect of the substitution on the pyrrole ring on the nucleophilicity, indole-3-carbaldehyde (**1b**), which has proved to be less reactive than indole, was selected. Reaction of imidoyl halides **2a–d** with **1b** using sodium hydride as the base in acetonitrile under an N_2 atmosphere gave the corresponding trifluoromethyl indole derivatives **4d–g** in excellent yields. Spectroscopic data [IR, ^1H NMR, ^{13}C NMR, ^{19}F NMR, 2D-NMR (COSY and HMBC)] and a D_2O exchange experiment showed that, in this reaction, the carbon at the 2-position acted as the nucleophile.

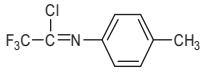
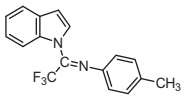
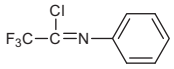
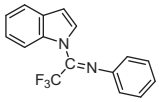
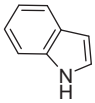
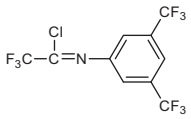
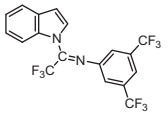
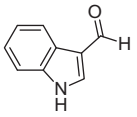
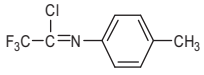
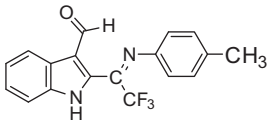
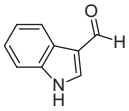
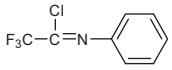
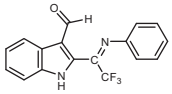
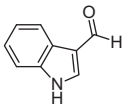
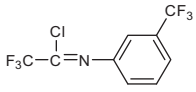
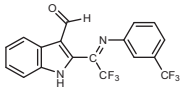
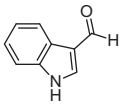
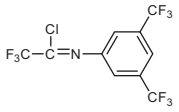
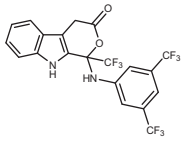
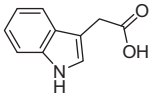
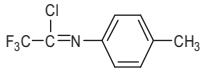
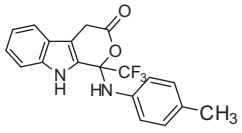
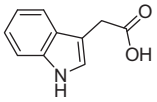
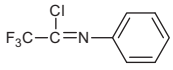
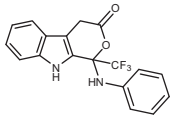
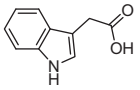
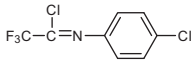
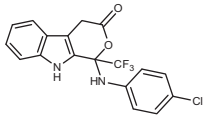
The IR spectrum of 3-[2,2,2-trifluoro-1-(phenylimino)ethyl]-3*H*-indole-3-carbaldehyde (**4e**) showed absorption bands at 1667 cm^{-1} corresponding to carbonyl stretching and at 1453 cm^{-1} corresponding to the C=N moiety. The ^1H NMR spectrum of **4e** exhibited a singlet at δ 10.02 due to the indole NH (D_2O exchangeable) and a signal at δ 8.65 assigned to the aldehyde CH, which were confirmed by 2D-NMR (COSY and HMBC). A doublet at δ 8.03, multiplets at δ 7.18–7.20 and δ 7.06–7.10 and a doublet at δ 6.92 corresponded to the aromatic protons present in the molecule. The ^{13}C NMR spectrum of **4e** displayed a downfield signal at δ 186.76 for the carbonyl group. The ^{19}F NMR spectrum of **4e** showed a signal at δ −70.61 corresponding to the CF_3 group. The above spectral data and elemental analysis results supported the formation of compound **4e**.[17] The spectral data of compounds **4d**, **4f**, and **4g** also supported their structures.

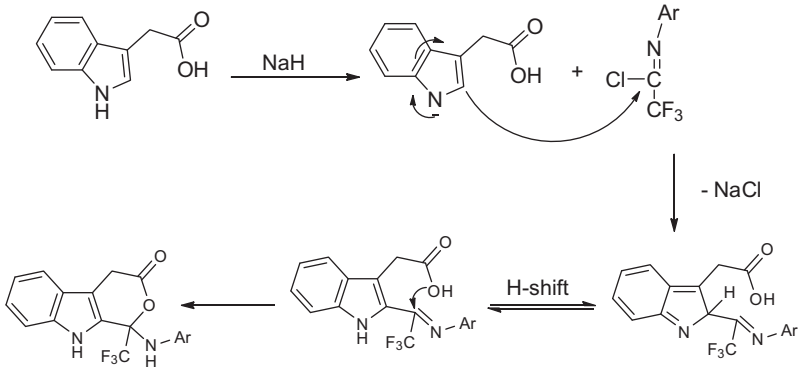
Of particular interest were the reactions of indole-3-carboxylic acid **1c** with various imidoyl chlorides, which gave the corresponding derivatives **4h–j** (Table 1). These products represent a little known class of 1-(arylamino)-1-(trifluoromethyl)-4,9-dihydropyrano[3,4-*b*]indol-3(1*H*)-ones, examples of which are difficult to prepare using conventional procedures. A possible reaction mechanism is illustrated in Scheme 3.

The IR spectrum of 2-(*p*-tolylamino)-2-(trifluoromethyl)-2*H*-spiro[furan-3,3′-indol]-5(4*H*)-one (**4h**) showed a strong absorption at 3415 cm^{-1} corresponding to the NH group. The absorption at 1673 cm^{-1} corresponded to the carbonyl stretching, and the absorptions at 1601 and 1094 cm^{-1} to the C=N and C–O, respectively. The ^1H NMR spectrum of **4h** exhibited a singlet at δ 10.88 and at δ 9.97 due to the NH protons. Doublets at δ 7.57, δ 7.45, and δ 7.32, multiplets at δ 7.21–7.22 and δ 7.01–7.05, and triplet at δ 6.94 correspond to eight aromatic protons present in the molecule. The signals at δ 2.19 and δ 3.67 were assigned to the methyl and methylene protons, respectively. The ^{13}C NMR spectrum of **4h** displayed a downfield signal at δ 169.98 for the carbonyl and at δ 34.25 and δ 20.90 for the CH_2 and methyl carbons, respectively. The ^{19}F NMR spectrum of 4 h showed a peak at δ −73.86 for the CF_3 group. The above spectral and elemental analysis data, the absence of OH absorptions in the IR spectra and ^1H NMR spectra support the formation of compound **4h**.[17] The spectral data of compounds **4i** and **4j** also supported their structures.

A variety of acetymidoyl chloride and indoles were examined to generate the desired coupled products under the optimized conditions (Table 1).

Table 1
Synthesis of 3-(1-nitroalkyl) indoles **4a–j** by reaction of 2,2,2-trifluoro-*N*-arylacetimidoyl chloride derivatives **2a–d** with indoles **1a–c**

Entry	Indole	ArNC(CF_3)Cl	Product	Time (h)	Isolated yield (%)
4a				21	89
4b				20	87
4c				22	78
4d				23	91
4e				20	93
4f				23	78
4g				22	73
4h				24	81
4i				21	78
4j				20	73



Scheme 3. A possible mechanism for the synthesis of 1-(arylamino)-1-(trifluoromethyl)-4,9-dihydropyrano[3,4-*b*]indol-3(1*H*)-ones **4h–j**.

The yields of these reactions were generally excellent. It is important to note that the presence of an electron-withdrawing group had no effect on the yield. Under the optimized conditions, various indoles with electron-donating or electron-withdrawing groups reacted to give the corresponding trifluoromethylated indole products in excellent yields, but in somewhat longer reaction times (20–24 h).

In conclusion, we have successfully synthesized a series of new indole trifluoromethyl derivatives using different 2,2,2-trifluoro-*N*-arylacetimidoyl chlorides under mild conditions via functionalization of indoles. In addition to its efficiency, simplicity, and mild reaction conditions, this method provides high yields of trifluoromethylated indole. Therefore this protocol is efficient and may open up a new area for the functionalization of indoles. Further studies including the pharmacological activities in this area are being carried out in our laboratory.

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17. *Preparation of 4-methyl-N-[2,2,2-trifluoro-1-(1H-indol-1-yl)ethylidene]aniline (**4a**)* In a typical experimental procedure, a dry, two-necked, 50 mL round-bottomed flask equipped with a nitrogen inlet was charged with 5 mL of dry MeCN, 0.117 g (1.0 mmol) of indole and 0.24 g (1.0 mmol) of NaH. The solution was stirred under a nitrogen atmosphere at room temperature for 30 min, then a solution of **2a** (1.0 mmol in 2 mL of dry MeCN) was added dropwise via a syringe. The mixture was stirred at room temperature for 20 h under an N_2 atmosphere and then filtered. After removing the solvent under reduced pressure, the crude product was purified by preparative thin-layer chromatography on silica gel [eluent: *n*-hexane/EtOAC, 4:1] to give the product **4a**. The products obtained from indole-3-carbaldehyde were purified by recrystallization from EtOH (twice). Yield = 89%, yellow oil, FT-IR (neat) ν_{max} = 1623 cm^{-1}, ^1H NMR (DMSO-d_6, 500 MHz) δ = 7.58–7.60 (m, 1H), 7.52 (d, 1H, J = 7.0 Hz), 7.01–7.03 (m, 2H), 6.93 (d, 2H, J = 7.2 Hz), 6.88 (d, 1H, J = 6.9 Hz), 6.71–6.73 (m, 3H), 2.09 (s, 3H, CH_3) ppm. ^{19}F NMR (DMSO-d_6, 475 MHz) δ = −70.13 ppm. Anal. Calcd for $C_{17}H_{13}F_3N_2$ (302.29): C, 67.54; H, 4.33; N, 9.27. Found: C, 67.24; H, 4.11; N, 9.36. *Preparation of 2-[2,2,2-trifluoro-1-(phenylimino)ethyl]-1H-indole-3-carbaldehyde (**4e**):* Similarly, **4e** was prepared from 0.145 g (1.0 mmol) of indole-3-carbaldehyde, 0.24 g (1.0 mmol) of NaH in 5 mL of dry MeCN, and 1.0 mmol of **2b**. This compound was obtained as a white solid. Mp = 114–115 °C, Yield = 93%, FT-IR (KBr) ν_{max} = 1453, 1667 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ = 10.02 (s, 1H), 8.65 (s, 1H), 8.03 (d, 1H, J = 7.3 Hz), 7.18–7.20 (m, 4H), 7.06–7.10 (m, 2H), 6.92 (d, 2H, J = 7.4 Hz) ppm.^{19}F NMR (DMSO-d_6, 475 MHz) δ = −70.61 ppm. ^{13}C NMR (DMSO-d_6, 100.6 MHz); δ (ppm): 112.03, 120.88, 121.23, 121.86, 124.19, 124.44, 125.64, 128.15, 129.68, 135.39, 137.68, 138.06, 139.53, 143.59, 186.76. Anal. Calcd for $C_{17}H_{11}F_3N_2O$ (316.28): C, 64.56; H, 3.51; N, 8.86. Found: C, 64.28; H, 3.34; N, 8.88.
*Preparation of 2-(p-tolylamino)-2-(trifluoromethyl)-2H-spiro[furan-3,3′-indol]-5(4H)-one (**4h**):* Similarly, **4h** was prepared from 0.175 g (1.0 mmol) of indole-3-acetic acid, 0.48 g (2.0 mmol) of NaH in 5 mL of dry MeCN, and 1.0 mmol of **2a**. This compound was obtained as a white solid. Mp = 184 °C, Yield = 81%, FT-IR (KBr) ν_{max} = 3415, 1673, 1601, 1094 cm^{-1}, ^1H NMR (DMSO-d_6, 500 MHz) δ = 10.88 Hz (s, 1H), 9.97 (s, 1H), 7.57 (d, 1H, J = 7.9 Hz), 7.45 (d, 2H, J = 8.3 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.21–7.22 (m, 1H), 7.01–7.05 (m, 2H), 6.94 (t, 1H, J = 7.5, 7.2 Hz), 3.67 (s, 2H), 2.19 (s, 3H) ppm. ^{19}F NMR (DMSO-d_6, 475 MHz) δ = −73.86. ^{13}C NMR (DMSO-d_6, 100.6 MHz); δ (ppm): 20.90, 34.25, 109.13, 111.84, 118.84, 119.19, 119.55, 121.44, 124.35, 127.71, 129.51, 132.35, 136.59, 137.40, 169.98. Anal. Calcd for $C_{19}H_{15}F_3N_2O_2$ (360.33): C, 63.33; H, 4.20; N, 7.77. Found: C, 63.28; H, 4.23; N, 7.71.