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# Synthesis of fused 3-trifluoromethylpyridines

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The synthesis of trifluoromethyl-containing pyridines fused with thiophene and indole has been developed.

The trifluoromethyl group at the β-position to the heterocycle nitrogen atom in azines can be involved in inhibition of enzymes, as was shown by the example of 5-trifluoromethyluracil exhibiting a high antitumor activity. The mechanism of the irreversible enzyme inhibition is determined by the ability of the activated $CF_3$ group to alkylate protein amino groups.[1] Nucleophilic substitution for fluorines in $CF_3$-substituted nitrogen-containing heterocycles by nucleophilic reagents has been well studied.[2] Therefore, the development of synthesis methods for new compounds comprising the 3-trifluoromethylpyridine moiety is of interest for creation of cytotoxic antitumor agents.

The aim of this work was to synthesise 3-trifluoromethyl-substituted fused pyridines. The only known example of obtaining such compounds is the synthesis of isoquinoline derivatives from guaiacol.[3] Using this scheme, we synthesised compounds **1a**,**b**.

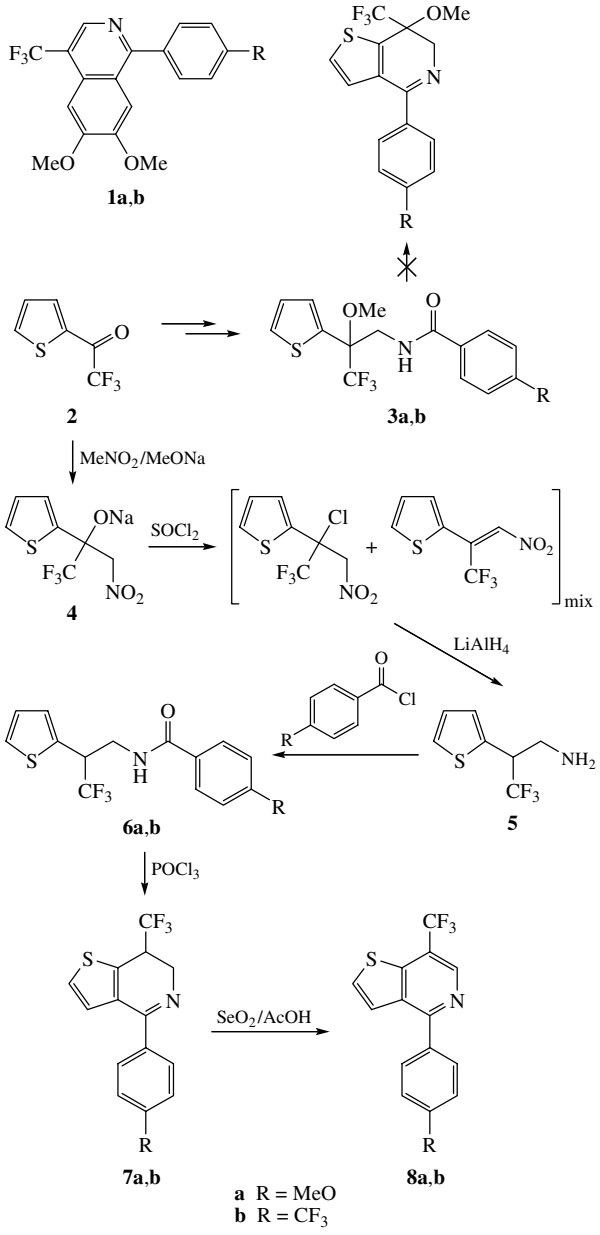
The attempt to spread this scheme to the synthesis of thiophene derivatives has failed. We transformed trifluoroacetylthiophene **2** to key amides **3a**,**b**, but failed to perform cyclization of **3a**,**b** to thienopyridine derivatives even under severe conditions in the presence of Lewis acids ($AlCl_3$, $SnCl_4$, $BF_3$). This could be explained by steric hindrances impeding the formation of the transition state for electrophilic substitution of the rigid five-membered ring. To check this assumption, we needed analogues of **3** containing no methoxy group. For this purpose, we developed the synthesis based on the Henry reaction of 2-trifluoroacetylthiophene with nitromethane in the presence of sodium methoxide (Scheme 1).

The treatment of sodium nitroalkoxide **4** with thionyl chloride gave a mixture of nitrochloride and nitroalkene that was reduced with lithium aluminium hydride to afford 3,3,3-trifluoro-2-(thien-2-yl)propylamine **5**, which was converted into products **6a**,**b** by acylation with benzoic acid chlorides. As expected, amides **6a**,**b** gave heterocycles when boiled in $POCl_3$. The reaction was completed within 8 h to form 6,7-dihydrothieno[3,2-*c*]pyridines **7** in about 70% yield. The further oxidation of **7** with selenium dioxide in boiling glacial acetic acid resulted in target 1-aryl-4-(trifluoromethyl)thieno[3,2-*c*]pyridines **8a**,**b** in 70–80% yield.

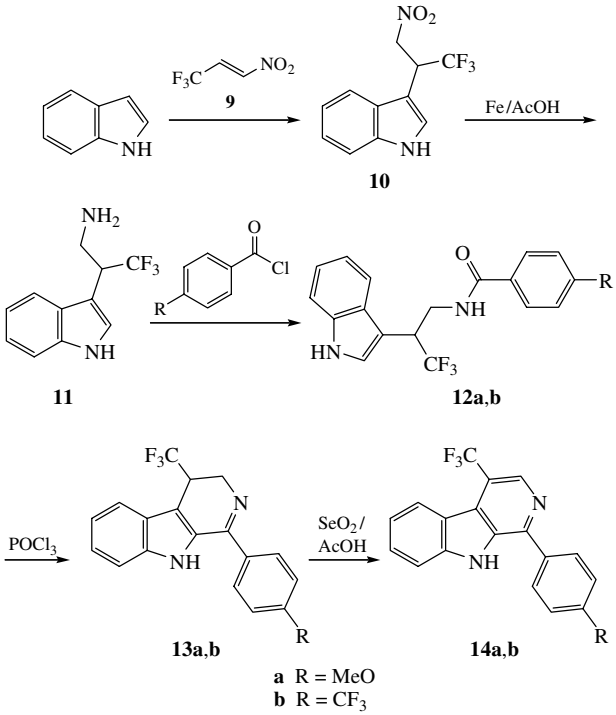
Another challenge of this work was the synthesis of β-carboline derivatives. In this case, the tendency of indole to undergo tautomeric transformations did not allow us to use 3-trifluoroacetylindole in condensation with nitromethane, and the synthesis developed for thieno[3,2-*c*]pyridine derivatives was not suitable. Therefore, a basically new approach to the synthesis of β-carboline derivatives has been developed (Scheme 2).

Initial 3,3,3-trifluoromethyl-2-(indol-3-yl)nitropropane **10** was obtained by reaction of indole with 3,3,3-trifluoromethyl-1-nitropropene **9**.[4] Reduction of **10** with iron in acetic acid gave 3,3,3-trifluoromethyl-2-(indol-3-yl)propylamine **11** in 70% yield. Acylation of amine **11** gave amides **12a**,**b**; the following heterocyclization leading to **13a**,**b** and oxidation of the latter to target 1-aryl-4-trifluoromethyl-β-carbolines **14a**,**b** were carried out under the conditions optimised for thiophene derivatives. The yields were 70 to 80% at heterocyclization and dehydrogenating steps.†

Thus, the key compounds in the synthesis of 3-trifluoromethylpyridines fused with heteroaromatic compounds are 3,3,3-trifluoro-2-(hetaryl)propylamines. Advanced approaches have been developed to the synthesis of such compounds and, therefore, to




**Scheme 1**




**Scheme 2**

the new substituted fused heterocycles whose biological activity is being studied.

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† $^1$H NMR spectra were recorded at 400.13 MHz in $CDCl_3$ solution with TMS used as an internal standard. $^{19}$F NMR spectra were measured at 188.31 MHz in $CDCl_3$ solution with $CF_3COOH$ as an external standard.

**1a**: yield 75%; mp 175–176 °C. $^1$H NMR, $\delta$: 8.77 (s, 1H, CH), 7.67 (d, 2H, CH, $^3J$ 8.4 Hz), 7.50 (s, 1H, CH), 7.41 (s, 1H, CH), 7.08 (d, 2H, CH, $^3J$ 8.4 Hz), 4.09 (s, 3H, MeO), 4.02 (s, 3H, MeO), 3.90 (s, 3H, MeO). $^{19}$F NMR, $\delta$: 17.20 (s, 3F, $CF_3$).

**1b**: yield 80%; mp 187–188 °C. $^1$H NMR, $\delta$: 8.81 (s, 1H, CH), 7.83 (br. s, 4H), 7.44 (br. s, 1H, CH), 7.32 (s, 1H, CH), 4.11 (s, 3H, MeO), 3.90 (s, 3H, MeO). $^{19}$F NMR, $\delta$: 17.11 (s, 3F, $CF_3$), 15.10 (s, 3F, $CF_3$).

**8a**: yield 68%; mp 118–119 °C. $^1$H NMR, $\delta$: 8.80 (s, 1H, CH), 7.83 (d, 2H, CH, $J$ 8.72 Hz), 7.72 (d, 1H, CH, $J$ 5.6 Hz), 7.64 (d, 1H, CH, $^3J$ 5.6 Hz), 7.08 (d, 2H, CH, $J$ 8.72 Hz), 3.91 (s, 3H, MeO). $^{19}$F NMR, $\delta$: 15.24 (s, 3F, $CF_3$).

**8b**: yield 76%, mp 113–114 °C. $^1$H NMR, $\delta$: 8.85 (s, 1H, CH), 7.97 (d, 2H, 2CH, $^3J$ 8.1 Hz), 7.83 (d, 2H, 2CH, $^3J$ 7.8 Hz), 7.72 (d, 1H, CH, $^3J$ 5.3 Hz), 7.66 (d, 1H, CH, $^3J$ 5.6 Hz). $^{19}$F NMR, $\delta$: 14.48 (s, 3F, $CF_3$), 15.00 (s, 3F, $CF_3$).

**14a**: yield 70%; mp 89–90 °C. $^1$H NMR, $\delta$: 8.81 (s, 1H, CH), 8.71 (br. s, 1H, NH), 8.38 (d, 1H, CH, $^3J$ 7.8 Hz), 7.93 (d, 2H, CH, $^3J$ 8.28 Hz), 7.65–7.56 (m, 2H), 7.39 (t, 1H, CH, $^3J$ 7.8 Hz), 7.15 (d, 2H, CH, $^3J$ 8.28 Hz), 3.93 (s, 3H, MeO). $^{19}$F NMR, $\delta$: 15.93 (s, 3F, $CF_3$).

**14b**: yield 75%; mp 86–87 °C. $^1$H NMR, $\delta$: 8.87 (s, 1H, CH), 8.67 (br. s, 1H, NH), 8.40 (d, 1H, CH, $^3J$ 7.2 Hz), 8.11 (d, 2H, CH, $^3J$ 8.08 Hz), 7.91 (d, 2H, CH, $^3J$ 8.08 Hz), 7.69–7.65 (m, 1H, CH), 7.60–7.58 (m, 1H, CH), 7.44–7.40 (m, 1H, CH). $^{19}$F NMR, $\delta$: 15.76 (s, 3F, $CF_3$), 15.02 (s, 3F, $CF_3$).

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