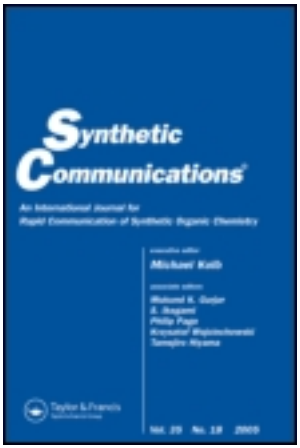


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# Convenient Synthesis of Pyrrole- and Indolecarboxylic Acid *tert*-Butylesters

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## ABSTRACT

The *tert*-butylesters of pyrrole- and indolecarboxylic acids are readily accessed by reacting the appropriate carboxylic acids with *N*,*N*-dimethylformamide di-*tert*-butyl acetal.

*Key Words:* di-*tert*-butyl acetal; *tert*-Butylester; *N*,*N*-Dimethylformamide; Indolecarboxylic acid; Pyrrolecarboxylic acid.

For the synthesis of particular enzyme inhibitors, we needed *tert*-butylesters of pyrrole- and indolecarboxylic acids as starting materials. To our

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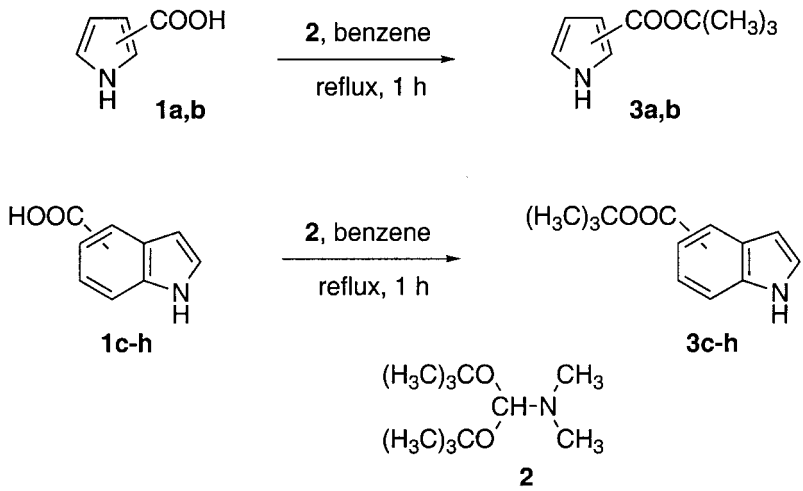
surprise, the simple *tert*-butylesters of pyrrole-3-, indole-4-, indole-5-, and indole-7-carboxylic acid have not been described until now. For the synthesis of the isomeric *tert*-butyl pyrrole-2-, indole-2-, indole-3-, and indole-6-carboxylates, nonuniform methods have been published. *Tert*-butyl pyrrole-2-carboxylate (**3a**) and *tert*-butyl indole-2-carboxylate (**3c**) have been obtained by treatment of the corresponding acid with 2-methylprop-1-en in the presence of sulfuric acid.[1–3] Beside this standard procedure for the synthesis of *tert*-butylesters, *tert*-butyl 2,2,2-trichloroacetimidate/boron trifluoride diethyl etherate was applied for the conversion of pyrrole-2-carboxylate to its *tert*-butyl ester **3a**.[4] Furthermore, indole-2-carboxylic acid *tert*-butyl ester (**3c**) was prepared by thermal cyclization of *tert*-butyl 2-azidocinnamate.[5] Irradiation of 3-diazo-4-oxo-3,4-dihydroquinoline in the presence of *tert*-butanol led to *tert*-butyl indole-3-carboxylate (**3d**).[6] Indole-6-carboxylic acid ester **3g** was afforded in a Leimgruber–Batcho indole synthesis by treatment of 3-nitro-4-methylbenzoic acid *tert*-butylester with dimethylformamide dimethyl acetal/pyrrolidine and subsequent hydrogenation in the presence of palladium on charcoal.[7]

In our efforts to find a general direct route to all isomeric *tert*-butyl pyrrole- and indolecarboxylates starting from the commercially available carboxylic acids **1a–h**, we first reacted indole-2- and -3-carboxylic acid, respectively, with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, *tert*-butanol, 4-dimethylaminopyridine in $CH_2Cl_2$. With this method, the esterification of *N*-protected amino acids had been achieved.[8] Unfortunately, product formation did not occur in our case. The indole-3-carboxylic ester **3d** could be obtained in 78% yield by conversion of indole-3-carboxylic acid into its acid chloride by reaction with thionyl chloride and catalytic amounts of dimethylformamide (DMF) in tetrahydrofuran (THF) at room temperature for 1 h followed by treatment with an excess of *tert*-butanol and triethylamine under reflux for 2 h. However, in the case of the indole-2-carboxylic acid, this reaction did not lead to the desired product.

Applying a method reported by Widmer for the synthesis of several benzoic acid *tert*-butyl ester,[9] all isomeric *tert*-butyl pyrrole- and indolecarboxylates (**3a–h**) could be readily afforded by reacting the carboxylic acids **1a–h** with an excess of *N*,*N*-dimethylformamide di-*tert*-butyl acetal in refluxing benzene (Sch. 1). The yield of the products ranged from 32–89% (Table 1).

In conclusion, *N*,*N*-dimethylformamide di-*tert*-butyl acetal was successfully employed to convert pyrrole- and indolecarboxylic acids into their *tert*-butyl esters. The *tert*-butyl pyrrole-3-, indole-4-, indole-5-, and indole-7-carboxylates synthesized with this method have not been described before.




*Scheme 1.*

## EXPERIMENTAL

Melting points were determined on a Büchi B-540 apparatus and are uncorrected. Hydrogen nuclear magnetic resonance ($^1$H-NMR) spectra were recorded on a Varian Mercury Plus 400 spectrometer (400 MHz). Mass spectra were obtained on a Finnigan EI GCQ system.

***Table 1.*** Preparation of *tert*-butyl pyrrole- and indolecarboxylates employing *N*,*N*-dimethylformamide di-*tert*-butyl acetal.

| Product | Position of the ester moiety | Yield (%) | Melting point | |
|---|---|---|---|---|
| | | | Observed °C | Lit. °C |
| **3a** | 2 | 75 | 87–89 | 49–50[1] |
| **3b** | 3 | 58 | 82–84 | — |
| **3c** | 2 | 89 | 104–105 | 103–105[3]<br>109–110[5] |
| **3d** | 3 | 67 | Oil | Oil[6] |
| **3e** | 4 | 56 | 96 | — |
| **3f** | 5 | 32 | 91–93 | — |
| **3g** | 6 | 57 | 100–101 | Not reported[7] |
| **3h** | 7 | 49 | 65–67 | — |

## Representative Procedure

Pyrrole-3-carboxylic acid (**1b**) (0.50 g, 4.50 mmol) was suspended in dry benzene (15 ml). *N*,*N*-Dimethylformamide di-*tert*-butyl acetal (**2**) (90% purity, 4.07 g, 18 mmol) was added dropwise to the refluxing mixture within 30 min. The solution was refluxed for a further 30 min, cooled, diluted with diethyl ether, and washed with sodium carbonate solution (5%), water, and brine. The organic layer was dried with sodium sulfate, and the solvent was evaporated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate, 9 : 1) and recrystallized from petroleum ether to give **3b** as a white solid.

For the synthesis of the indole derivatives, the amount of solvent was doubled.

## Spectral Data of New Pyrrole- and Indolecarboxylic Acid *tert*-Butylesters

*Tert*-butyl pyrrole-3-carboxylate (**3b**). $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.55 (s, 9H), 6.59 (m, 1H), 6.72 (m, 1H), 7.34 (m, 1H), 8.75 (s, broad, 1H). Mass spectrometry (MS) (EI) $m/z$ (%): 167 $M^+$ (2), 111 (37), 94 (100).

*Tert*-butyl indole-4-carboxylate (**3e**). $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.68 (s, 9H), 7.18 (m, 1H), 7.23 (m, 1H), 7.34 (m, 1H), 7.57 (d, 1H), 7.88 (dd, 1H), 8.39 (s, broad, 1H). MS (EI) $m/z$ (%): 217 $M^+$ (19), 161 (100), 144 (71).

*Tert*-butyl indole-5-carboxylate (**3f**). $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.63 (s, 9H), 6.64 (m, 1H), 7.26 (m, 1H), 7.38 (d, 1H), 7.87 (dd, 1H), 8.36 (m, 1H), 8.40 (s, broad, 1H). MS (EI) $m/z$ (%): 217 $M^+$ (37), 161 (100), 144 (72).

*Tert*-butyl indole-7-carboxylate (**3h**). $^1$H-NMR ($CDCl_3$): $\delta$ (ppm) = 1.66 (s, 9H), 6.59 (m, 1H), 7.14 (t, 1H), 7.30 (m, 1H), 7.84 (m, 2H), 9.88 (s, broad, 1H). MS (EI) $m/z$ (%): 217 $M^+$ (15), 161 (100).

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