# Microwave-Assisted Synthesis of Benzoxazole-7-carboxylate Esters Using Trifluoroacetic Acid and Acetic Acid

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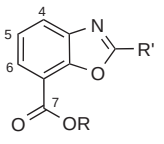
**Abstract:** Existing routes to benzoxazole-7-carboxylates are low-yielding. The following letter describes a new methodology for the synthesis of benzoxazole-7-carboxylates in much improved yield using trifluoroacetic acid–acetic acid and microwave irradiation.

**Key words:** benzoxazoles, heterocycles, cyclisations, acylations, microwave-assisted synthesis, trifluoroacetic acid

The benzoxazole ring system is a feature of several drug molecules e.g. Benoxaprofen (antiinflammatory) and Zoxazolamine (antirheumatic). A one-step synthesis of 4-carboxy-2-substituted benzoxazoles is described in the literature.[1] The synthesis of 5-carboxy-[2] and 6-carboxy-[3] 2-substituted benzoxazoles has been described utilising a two-step procedure starting from the relevant amino phenol.

Our interest was concentrated on the synthesis of the 7-carboxy system **1** (Figure 1). Although a route to these systems has been published[4] utilising an initial coupling of the relevant 2-amino phenol with an acid chloride followed by cyclisation using 4-toluenesulfonic acid in xylene under reflux, the reported yields were poor (11–27%).

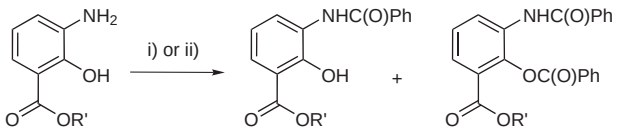



**1**

**Figure 1** Structure of the benzoxazole-7-carboxylate ester system

Initial efforts to synthesise the 2-phenylbenzoxazole-7-carboxylate system from **2a** and benzoyl chloride using a one-step procedure with pyridinium 4-toluenesulfonate, triethylamine in xylene at reflux (Scheme 1), as described in the literature[1] for 4-carboxy derivatives, failed to give any benzoxazole product. Instead, this method gave the amide product **3a** in 81% yield.[5] Use of triethylamine in dichloromethane and benzoyl chloride on **2b** also gave the amide **3b** in good yield (75%). A by-product that was observed during the initial acylation of the amino phenol was the N,O-diacylated material **4b**. The diacylated material was formed in varying yield, depending on the acid chloride used, and was difficult to remove from the monoacylated product. A study of cyclisation conditions was then undertaken for the direct ring synthesis from amino phenol **2b** utilising the Biotage™ Initiator™ microwave to rapidly screen a range of acid catalysts and temperatures. The key challenge was to find suitable acid conditions that would facilitate the dehydration of the amide intermediate and give the desired product (Scheme 2).

Initial reactions using acetic acid as solvent at 200 °C for 15 minutes, gave an indication of product and increasing the temperature to 230 °C for 30 minutes increased the yield to 30%. As this temperature represented the upper limit of what could be achieved with acetic acid, *N*-methyl-2-pyrrolidinone was added as co-solvent and the reaction was heated to 250 °C for 45 minutes. LCMS revealed only trace quantities of starting material remaining, but as well the benzoxazole product, three significant impurity peaks had formed. Ionic liquid (1,3-dibutyl-1*H*-imidazol-3-ium tetrafluoroborate) was also used to increase the temperature of the acetic acid to 250 °C but, again, this gave a number of unidentified products. Cyclisation using acetic acid with two equivalents of 4-toluenesulfonic acid at 225 °C was also attempted. Only trace quantities of the desired product were observed.




**3** **4**

**2a**: R = Et
**2b**: R = Me

**3a**: R = Et, 81%
**3b**: R = Me, 75%

**4a**: R = Et
**4b**: R = Me

Conditions:
i) R' = Et: PhC(O)Cl, pyridinium 4-toluenesulfonate, $Et_3N$, xylene, reflux
ii) R' = Me: PhC(O)Cl, $Et_3N$, $CH_2Cl_2$, r.t.

**Scheme 1** Synthesis of mono- and diacylated amino phenols **3** and **4**

It was reasoned that a stronger acid was required as solvent to enable the dehydration to take place rapidly, and avoid side-products created by elevated temperatures and prolonged reaction times. Trifluoroacetic acid was therefore chosen as co-solvent with acetic acid in a 1:1 ratio and the reaction mixture was heated to 200 °C for 20 minutes.[6] LCMS showed only the desired product peak present and the yield of methyl 2-phenylbenzoxazole-7-

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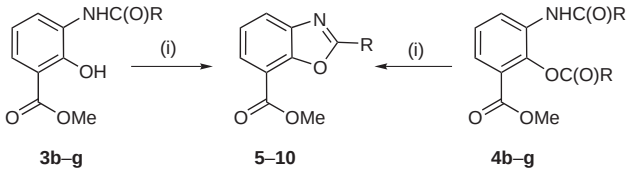
carboxylate (**5**), after evaporation and chromatography was 88%.




**3b–g** **5–10** **4b–g**

(i) TFA –AcOH (1:1), 200 °C, 20 min, microwave

**Scheme 2** Synthesis of 2-arylbenzoxazole-7-carboxylates

**Table 1** Synthesis of Benzoxazoles **5**–**10** from Mono- (**3**) and Diacyl (**4**) Amino Phenols[a,b] (Scheme 2)

| Product | R | **3** | Yield from **3** | **4** | Yield from **4** |
|---|---|---|---|---|---|
| **5** | Ph | **3b** | 88% | **4b** | 84% |
| **6** | 3,5-di$ClC_6H_3$ | **3c** | 88% | **4c** | 95% |
| **7** | 4-$MeOC_6H_4$ | **3d** | 84% | **4d** | 92% |
| **8** | 4-$ClC_6H_4$ | **3e** | 85% | **4e** | 92% |
| **9** | 4-$BrC_6H_4$ | **3f** | 37% | **4f** | 100% |
| **10** | 4-$NO_2C_6H_4$ | **3g** | 95% | **4g** | 93% |

[a] Reactions were carried out using the Biotage™ Initiator™ microwave, TFA–AcOH (1:1), 200 °C, 20 min.
[b] Non-optimised yields based on isolated products.

To demonstrate the utility of the trifluoroacetic acid–acetic acid conditions, a number of mono-acylated amino phenols, **3b**–**g**, were synthesised (by reacting the amino phenol with a range of acid chlorides using standard conditions[5]) and cyclised to give the desired benzoxazoles in good to excellent yield (Scheme 2, Table 1, **5**–**10**) and high purity.

Previous work[7] had shown that it was possible to obtain benzoxazoles by heating amino phenols with excess acid chloride in dioxane at 210 °C and proposed that the reaction proceeded via the diacylated amino phenol.[8] It was reasoned that treatment of the diacyl products with trifluoroacetic acid–acetic acid mixture at 200 °C in the microwave could give the desired benzoxazole products.

The required diacylated compounds, **4b**–**g**, were readily obtained[9] by treatment of the amino phenol **2b** with 2.1 equivalents of acid chloride in the presence of triethylamine in dichloromethane at room temperature followed by aqueous sodium bicarbonate workup, or filtration in cases where the diacyl compound precipitated from the reaction mixture. Subsequent treatment of the diacyl material with trifluoroacetic acid–acetic acid[10] (1:1) at 200 °C for 20 minutes in the microwave (Scheme 2) gave the desired benzoxazoles **5**–**10** in excellent yield after evaporation, workup and chromatography, if required. This methodology proved to be generally applicable to the synthesis of derivatives, incorporating a variety of substituents, including electron-donating and electron-withdrawing groups (Table 1).

In conclusion, a novel method has been developed for the synthesis of 2-arylbenzoxazole-7-carboxylic acid derivatives in excellent yields. The procedure is simple and allows reactions to be performed rapidly in trifluoroacetic acid–acetic acid solvent, utilising microwave heating. Moreover, this approach can be applied to both mono- and diacylated amino phenol precursors.

## Acknowledgment

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## References and Notes

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(5) **General Procedure for Mono-*N*-acyl Compounds 3**: Amino phenol (1.0 equiv), benzoyl chloride (1.1 equiv), pyridinium 4-toluenesulfonate (0.26 equiv) and $Et_3N$ (1.1 equiv) were stirred in xylene (10 mL) and heated at reflux overnight. The reaction mixture was evaporated and purified by chromatography (silica gel; 0–30% EtOAc–pentane). Combined fractions were evaporated and redissolved in EtOAc and washed with aq 2 M aq HCl solution, sat. aq $NaHCO_3$ and brine. The organic solution was dried ($MgSO_4$) and evaporated to give the desired mono-N-acylated product **3b**–**g**.
(6) **Representative Cyclisation Procedure for Mono-N-acylated Precursors; Methyl 2-Phenylbenzoxazole-7-carboxylate (5)**: Methyl-2-hydroxy-3-(phenylamido)-benzoate (0.15 g) was dissolved in TFA–AcOH (1:1, 3 mL), in a 5-mL microwave vial, sealed and irradiated to 200 °C for 20 min in a Biotage™ Initiator™ microwave. The reaction mixture was evaporated to a minimum (co-evaporated with toluene thrice) and purified by flash chromatography [silica gel, 0–30% $Et_2O$–PE (40:60)] and evaporated to give the title compound as a white powder (0.12 g; 88% conversion). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.34 (m, 2 H), 7.99 (m, 2 H), 7.57 (m, 3 H), 7.43 (t, *J* = 7.8 Hz, 1 H), 4.06 (s, 3 H). MS: [ES (Waters Alliance HT LCMS system) (+ve ion)]: *m*/*z* = 254 [$MH^+$].
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(8) Attempted cyclisation using one-pot conditions described by Pottorf did not give any desired product when applied to the synthesis 7-carboxy benzoxazole system.

(9) **General Procedure for Diacylation of Amino Phenol 4**: Amino phenol (1 equiv), aroyl chloride (2.1 equiv), and $Et_3N$ (2.1 equiv) were stirred in $CH_2Cl_2$ for 1–4 d. For **4c**–**g**, diacyl material can be filtered off from reaction mixture as a white precipitate. For phenyl diacyl compound **4b**, the reaction mixture was then diluted with $CH_2Cl_2$ and washed with sat. aq $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated to give the desired material as a white solid.

(10) **General Procedure for Cyclisation of Diacyl Compounds 5–10**: The diacylated amino phenol was suspended in TFA–AcOH in a microwave vial, sealed and irradiated to 200 °C for 20 min in Biotage™ Initiator™ microwave. The reaction mixture was evaporated to a minimum (co-evaporated with toluene thrice), redissolved in $CH_2Cl_2$ and washed with sat. $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), evaporated and purified by chromatography (if required) to give the desired benzoxazole product. $^1H$ NMR and MS (ES) data were consistent with those previously described.