# Reaction of Anthranilic Acid with Orthoesters: a New Facile One-pot Synthesis of 2-Substituted 4*H*-3,1-Benzoxazin-4-ones†

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**Mohammad S. Khajavi,* Nasser Montazari and S. S. Sadat Hosseini**

*Department of Chemistry, Faculty of Science, Shahid Beheshti University, Tehran, Iran*

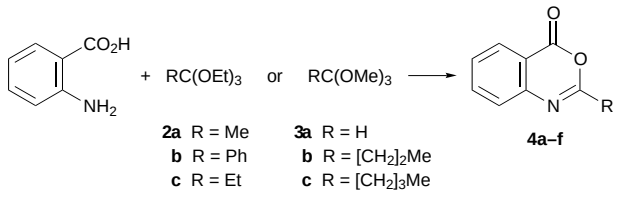
The synthesis of 2-substituted 4*H*-3,1-benzoxazin-4-ones by the condensation of anthranilic acid and orthoesters under classical heating and microwave irradiation is described.



4*H*-3,1-Benzoxazin-4-ones are valuable starting materials for the synthesis of a variety of 2,3-disubstituted quinazolin-4(3*H*)-ones.[1–5] A number of synthetic methods for the preparation of 2-substituted 4*H*-3,1-benzoxazin-4-ones have been described: (i) cyclodehydration of *N*-acylanthranilic acids by acetic anhydride;[6] (ii) reaction of anthranilic acid with acid chlorides in pyridine;[7] (iii) treatment of methyl *N*-aroylanthranilates or methyl 2-ureidobenzoates with concentrated sulfuric acid;[8] (iv) photoisomerization of 2-arylisatogen.[9] Here we report a new general and highly efficient method for the synthesis of benzoxazin-4-ones by the condensation of anthranilic acid with orthoesters under classical heating or microwave irradiation (Scheme 1).

The desired reaction occurs by refluxing a variety of commercially available orthoesters **2a–c** and **3a–c** with anthranilic acid under dry conditions. A number of benzoxazin-4-ones with various substituents were thus prepared in high yield, see Table 1. To the best of our knowledge, there have been no studies on the synthesis of this heterocyclic ring system using anthranilic acid and the orthoester condensation methodology.

In each case, the reaction was carried out using 20 mmol of anthranilic acid and an excess (1.5–4 equiv., Table 1) of the orthoester. In all cases, the products **4a–f** precipitated from the reaction mixtures and were purified by recrystallization.




**Scheme 1**

This reaction proceeds without organic solvent and in the absence of some types of basic or acidic catalyst. Furthermore this method is suitable for the preparation of 2-aryl- and 2-alkyl-4*H*-3,1-benzoxazin-4-one and also for the unsubstituted parent heterocycle **4d**. The reaction seems to proceed through the intermediacy of the imidic ester **5** which undergoes nucleophilic attack by the carboxyl oxygen to produce the cyclized product with the elimination of a molecule of alcohol.

Furthermore, we examined this reaction under microwave irradiation and it was found that the condensation of anthranilic acid with the orthoesters **2a–c** or **3a–c** results in the rapid formation of the benzoxazin-4-ones **4a–f** in high yield when the reactions were conducted in open vessels in a microwave oven. The reaction was performed in a beaker covered with a stemless funnel and to control the reaction the irradiation was carried out in two stages with a cooling period

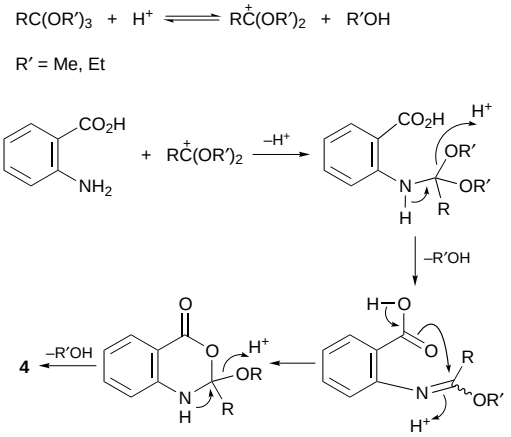



**Table 1** Reactions of anthranilic acid with orthoesters

| Entry | Product **4** | R | Orthoester (equiv.) | Classical heating | | Irradiation conditions[b] | | | | | Mp (*T*/°C) | Lit. mp (*T*/°C) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *t*/min | Yield (%)[a] | (1) *P*/W | *t*/min | (2) *P*/W | *t*/min | Yield (%)[a] | | |
| 1 | **a** | Me | 2 | 90 | 87 | 210 | 3 | 210 | 3 | 90 | 80–82 | 80–81[6] |
| 2 | **b** | Ph | 1.5 | 60 | 91 | 210 | 2 | 385 | 4 | 94 | 123–124 | 124–125[10] 123–124[6] |
| 3 | **c** | Et | 2 | 90 | 83 | 210 | 3 | 210 | 3 | 82 | 84–86 | 85–86[6] |
| 4 | **d** | H | 4 | 120 | 80 | 210 | 5 | 385 | 1 | 76 | 43–44 | 43–44.4[6] 43–45[11] |
| 5 | **e** | Pr | 2 | 90 | 78 | 210 | 3 | 210 | 3 | 80 | 58.5–60 | 59–60[6] |
| 6 | **f** | Bu | 2 | 90 | 75 | 210 | 4 | 210 | 5 | 83 | 41–42 | — |

[a]Yield of pure, isolated product based on anthranilic acid. [b]To control the reaction the irradiation was carried out in two stages, with a cooling time between each stage.

between each irradiation. In some cases, to optimize the yield for each irradiation sequence, a different power was used (Table 1). In general, the reaction in the microwave oven was highly accelerated. The results are summarized in Table 1.

*To receive any correspondence.

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**Table 2** Physical data for compounds **4–f**

| Compound **4** | $\nu_{max}$(KBr)/cm$^{-1}$ C=O | | $\delta$ (ppm) ($CDCl_3$–TMS) |
|---|---|---|---|
| **a** | 1762 | $^1$H | 2.46 (s, 3 H, $CH_3$), 7.42–8.31 (m, 4 H, Ar-H) |
| | | $^{13}$C | 20.85 ($CH_3$), 116.21, 125.90, 127.65, 127.86 (4 CH), 135.96 (C10), 145.98 (C5), 158.97 (CO), 159.74 (C2) |
| **b** | 1768 | $^1$H | 7.24–8.35 (m, 9 H, Ar-H) |
| | | $^{13}$C | 116.62, 126.80, 127.73, 127.86, 128.02, 128.26, 129.81 (9 CH), 132.13 (C-Ph), 135.96 (C10), 146.46 (C5), 156.52 (C2), 158.80 (CO) |
| **c** | 1758 | $^1$H | 1.38 (t, 3 H, $CH_3$), 2.77 (q, 2 H, $CH_2$), 7.38–8.21 (m, 4 H, Ar-H) |
| | | $^{13}$C | 9.44 ($CH_3$), 27.36 ($CH_2$), 116.17, 125.82, 127.29, 127.49 (4 CH), 135.55 (C10), 145.73 (C5), 158.68 (CO), 163.08 (C2) |
| **d** | 1755 | $^1$H | 7.45–8.42 (m, 5 H, $C_2$-H, Ar-H) |
| | | $^{13}$C | 118.86, 127.08, 128.64, 129.20 (4 CH), 136.61 (C10), 145.45 (C5), 149.73 (C2), 158.36 (CO) |
| **e** | 1762 | $^1$H | 1.24 (t, 3 H, $CH_3$), 1.83 (sextet, 2 H, $CH_2$), 2.72 (t, 2 H, $CH_2$), 7.32–8.28 (m, 4 H, Ar-H) |
| | | $^{13}$C | 13.47, 19.50, 36.52 (3C-aliphatic), 116.78, 126.43, 127.98, 128.26 (4 CH), 136.28 (C 10), 146.38 (C5), 159.66 (CO), 163.00 (C2) |
| **f** | 1765 | $^1$H | 1.02 (t, 3 H, $CH_3$), 1.22–1.98 (m, 4 H, $2CH_2$), 2.79 (t, 2 H, $CH_2$), 7.38–8.35 (m, 4 H, Ar-H) |
| | | $^{13}$C | 13.72, 22.23, 28.17, 34.49 (4C-aliphatic), 116.90, 126.56, 128.02, 128.31 (4 CH), 136.33 (C10), 146.51 (C5), 159.26 (CO), 163.24 (C2) |

The structures of compounds **4a–f** were confirmed by IR, $^1$H and $^{13}$C NMR spectral analyses (Table 2) and their physical properties were identical with those of authentic samples prepared by reported procedures.[6]

In conclusion, we have demonstrated that orthoesters and anthranilic acid condense under conventional thermal heating or microwave irradiation, providing an efficient and convenient synthesis of 2-substituted 3,1-benzoxazin-4-ones. In this method, orthoesters serve as a 'one-atom linchpin' to form the corresponding benzoxazin-4-one. The extension of this reaction to the synthesis of other heterocycles is currently under investiation.

## Experimental

IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a JEOL-EX-90 instrument at 90 MHz and 22.63 MHz for $^1$H and $^{13}$C, respectively. Microwave irradiations were carried out in a National oven, Model 5250, at 2450 MHz. Melting points are uncorrected. For safety reasons all the experiments with microwave ovens should be performed in an efficient hood in order to avoid contact with vapours. All products (except **4f**) are known compounds and their physical data, infrared and NMR spectra were identical with those of authentic samples.

*Preparation of* 2-*Substituted* 4H-3,1-*benzoxazin*-4-*ones under Classical Heating. General Procedure with* 2-n-*Butyl*-4H-3,1-benzoxazin-4-*one* (**4f**).—A stirred mixture of anthranilic acid (2.74 g, 20 mmol) and trimethyl orthovalerate (6.49 g, 40 mmol) was heated under reflux for 1.5 h. After this time the reaction mixture was cooled to 0 °C and the white precipitate thus obtained was filtered off and recrystallized from heptane to give colourless needles of **4f** in 75% yield.

*General Procedure under Microwave Irradiation with* 4H-3,1-*Benzoxazin*-4-*one* (**4d**).—A mixture of anthranilic acid (2.74 g, 20 mmol) and trimethyl orthoformate (8.49 g, 80 mmol) contained in a tall beaker was placed in the microwave oven and the beaker was covered with a stemless funnel and irradiated for 5 min at 210 W and then for 1 min at 385 W. The reaction mixture was allowed to cool to room temperature and the resultant residue recrystallised from dry heptane to afford the pure 4*H*-3,1-benzoxazin-4-one (moisture sensitive, very hygroscopic) in 76% yield.

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