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Solvent-free microwave synthesis of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones and variants using activated arylmalonates

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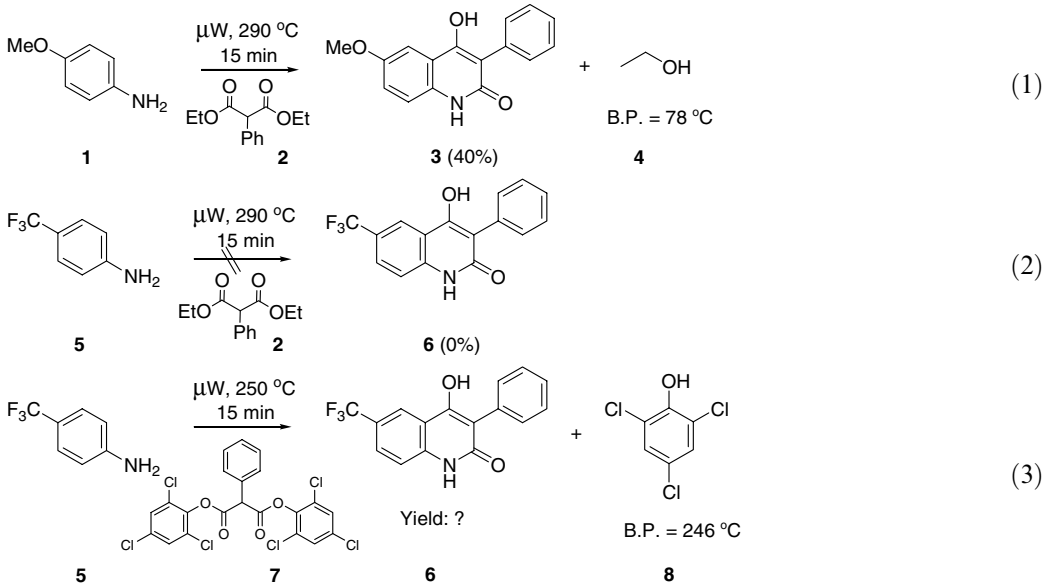
Abstract—The disclosure herein describes the rapid synthesis of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones and variants via a solvent-free microwave cyclocondensation reaction using di-(2,4,6-trichlorophenyl)-2-phenylmalonate, which improves the general scope of this reaction.

Derivatives of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones have been shown to be promising pharmaceutical agents for the treatment of central nervous system disorders,[1] sex hormone-related conditions,[2] the stimulation of bone formation,[3] and the suppression of allergy associated inflammations.[4] As a result of these therapeutic properties, interest has grown in the development of methodology for the rapid synthesis of derivatives of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones.[2a,5]

In an ongoing medicinal chemistry program we required the synthesis of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones



(1)

(2)

(3)

Keywords: Microwave reaction; 4-Hydroxyquinolin-2(1*H*)-ones; 4-Hydroxy-2(1*H*)-pyridones; Di-(2,4,6-trichlorophenyl)-2-phenylmalonate; Pharmaceutical agents.
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and related variants. One of the methods we used to rapidly prepare these compounds was a microwave reaction that was recently reported by Lange et al.[5b] An example of this microwave reaction is shown in Eq. 1. It was reported that irradiation of a mixture of 4-methoxyaniline (**1**) and diethyl-2-phenylmalonate (**2**) in a open reaction vessel afforded quinolinone **3** in 40% yield. This microwave reaction proved to be very practical for the synthesis of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones, and we therefore sought to explore the reaction scope further.

After performing the microwave reaction, under Lange's conditions, with a variety of anilines and diethyl-2-phenylmalonate, two important limitations became apparent. The first limitation was that the reaction did not proceed well or at all with electron deficient anilines (e.g., **5**→**6**, Eq. 2). The second limitation was that the microwave reaction had to be conducted in an open vessel so that the ethanol by-product could escape during the reaction. When we carried out the microwave reaction in a closed vessel, the internal pressure, due to the ethanol by-product, reached dangerous levels and the yields decreased dramatically. Since most bench top microwaves used for rapid parallel synthesis are closed systems, the utility of this microwave reaction is limited.

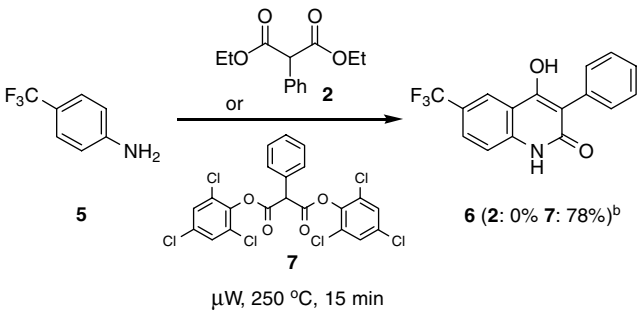
We reasoned that these reaction limitations could be avoided and the scope improved by using commercially available activated di-(2,4,6-trichlorophenyl)-2-phenylmalonate (**7**)[6] instead of malonate **2** (Eq. 3). Activated malonate **7** would likely form the intermediate anilide and undergo electrophilic aromatic cyclization more efficiently than malonate **2**. Furthermore, the by-product from the microwave reaction would be 2,4,6-trichlorophenol, which would reduce, relative to ethanol, the internal pressure in a closed reaction vessel and allow the reaction to proceed efficiently.

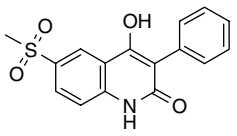
Herein, we report the scope and the yields of the microwave cyclocondensation reactions to prepare 4-hydroxy-3-phenylquinolin-2(1*H*)-ones and variants by using activated malonate **7**.

The results from Table 1 show that malonate **7** reacted efficiently with a variety of commercially available electron-deficient anilines and N-substituted anilines to provide the desired products (**6** and **9**–**12**) in good yields. In contrast, malonate **2**, under the same reaction conditions (vide infra) provided very little or none of the desired products. In the cases of **13** and **14**, both malonate **2** and malonate **7** reacted efficiently to give the products, with **7** providing significantly higher yields. Substitution of the electron deficient aniline was well tolerated, affording N-alkylated quinolinone (e.g., **15**) in good yield. With 3,4-disubstituted anilines, these microwave reactions were also found to be regioselective providing only regioisomers **16**, **17**, and **18**.

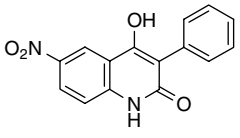
In a typical solvent-free microwave reaction, a mixture of the aniline and malonate **2** or **7** in a 1:2 ratio, respectively, was heated at 250 °C for 15 min. In the case of reactions with malonate **7**, the internal pressure of the reaction vessel never surpassed 1 bar, whereas with malonate **2** the internal pressure often ranged between 3 and 15 bar due to the ethanol formation. Upon completion, the reaction was allowed to reach room temperature and diluted with diethyl ether and the precipitate, 4-hydroxy-3-phenylquinolin-2(1*H*)-ones, collected by filtration. The purity of products **6** and **9**–**18**, as deter-

Table 1. Microwave reactions of anilines with malonates[a]

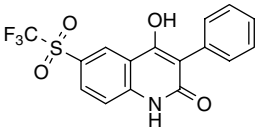




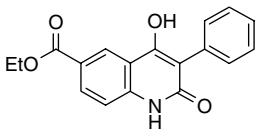
9 (**2**: 0% **7**: 74%)



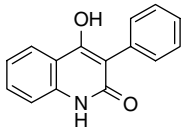
10 (**2**: 0% **7**: 67%)



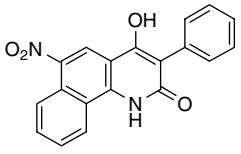
11 (**2**: 0% **7**: 71%)



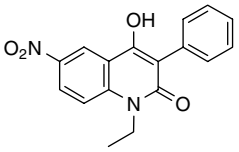
12 (**2**: 15% **7**: 93%)



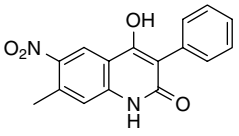
13 (**2**: 54% **7**: 93%)



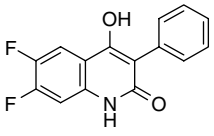
14 (**2**: 51% **7**: 91%)



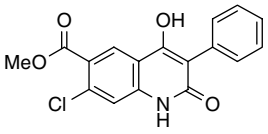
15 (**2**: 0% **7**: 81%)



16 (**2**: 0% **7**: 74%)



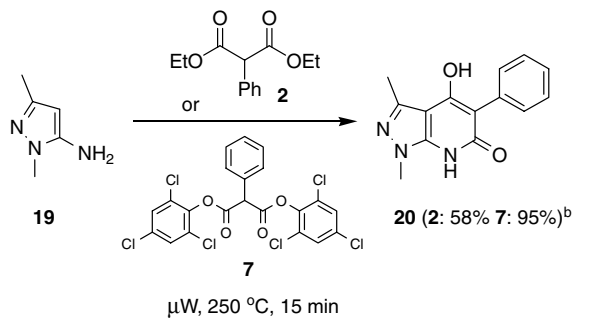
17 (**2**: 15% **7**: 95%)

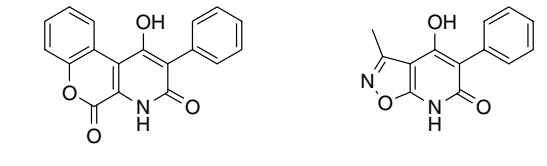


18 (**2**: 6% **7**: 89%)

[a] Microwave irradiations with **2** and **7** were conducted under the same conditions (see text and Supporting information).
[b] Isolated yields of compounds, which were characterized by ^{1}H NMR, ^{13}C NMR, and LCMS.

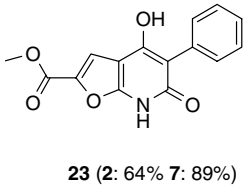
Table 2. Microwave reactions of anilines with malonates[a]



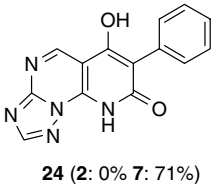


21 (**2**: 20% **7**: 83%)

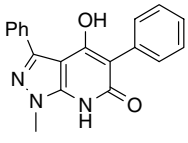
22 (**2**: 0% **7**: 71%)



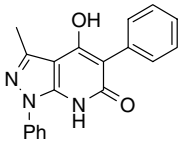
23 (**2**: 64% **7**: 89%)



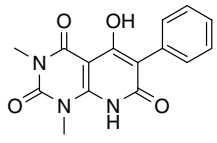
24 (**2**: 0% **7**: 71%)



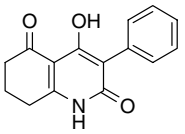
25 (**2**: 48% **7**: 87%)



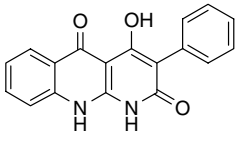
26 (**2**: 56% **7**: 91%)



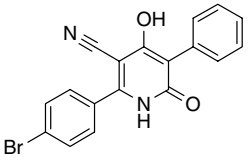
27 (**2**: 63% **7**: 92%)



28 (**2**: 58% **7**: 87%)



29 (**2**: 36% **7**: 80%)



30 (**2**: 61% **7**: 86%)[c]

[a] Microwave irradiations with **2** and **7** were conducted under the same conditions (see text and Supporting information).

[b] Isolated yields of compounds, which were characterized by ^{1}H NMR, ^{13}C NMR, and LCMS.

[c] The starting material is (*E*)-3-amino-3-(4-bromophenyl)-2-propenenitrile.

mined by LCMS and NMR, was 95–99% when malonate **7** was used and no additional purification was required. In contrast, reactions with malonate **2** gave, following filtration, products that were impure and required further purification via reverse phase liquid chromatography.

Given the simplicity and potential generality of this microwave reaction, we investigated the scope for the synthesis of a variety of derivatives of 4-hydroxy-3-phenylpyridin-2(1*H*)-one as shown in Table 2. The results show that a variety of commercially available heterocyclic amines, aminocrotononitrile, and aminocyclohexenone reacted efficiently with activated malonate **7** to provide the desired corresponding products **20**–**30** in high yields and purity (90–99%). In most cases, malonate **2** also provided products **20**–**30**, albeit in lower yields. These products were purified via precipitation with diethyl ether and filtration.

In summary, we have shown that activated malonate **7** is superior to malonate **2**, with respect to the scope of the microwave reaction to form 4-hydroxy-3-phenylpyridin-2(1*H*)-one derivatives. The yields and purification of the products are also improved by use of malonate **7**. In addition, using activated malonate **7** allows for the reaction to proceed efficiently in closed vessel microwave systems, which are commonly used by medicinal chemists. The short reaction time, in combination with the high yields and minimal purification of the products, makes this microwave reaction with activated malonate **7** ideal for the rapid preparation of libraries of 4-hydroxy-3-phenylquinolin-2(1*H*)-ones and related products. Further investigations of the scope of this microwave reaction with di-(2,4,6-trichlorophenyl)-2-phenylmalonate are currently underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.01.148.

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