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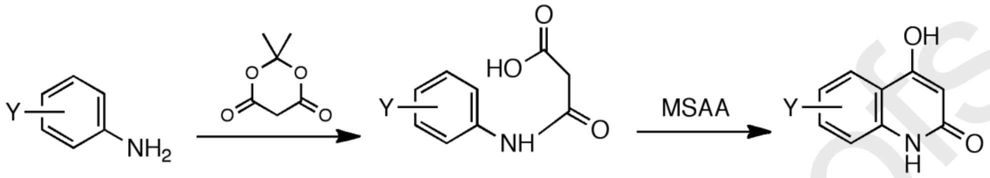

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ABSTRACT

Malonic acid monoanilides were obtained in excellent yield from the reaction of anilines with Meldrum's acid under solvent-free conditions. The malonic acid monoanilide intermediates were then treated with methanesulfonic acid anhydride (MSAA) to produce 4-hydroxy-2-quinolinones in excellent yield. It should be noted that both reactions had to be run under mild conditions to avoid the decarboxylation of the malonic acid monoanilide intermediate.

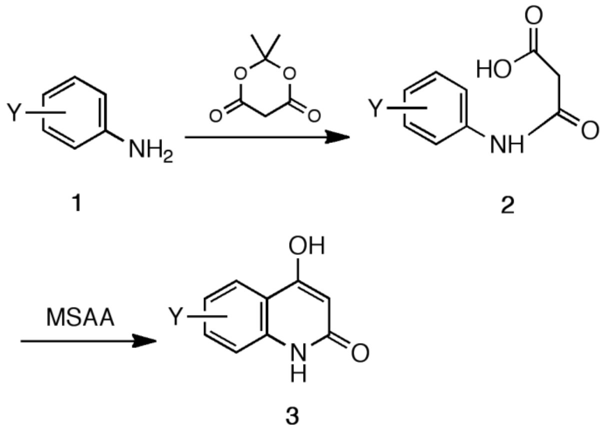
1. Introduction

4-Hydroxy-2-quinolinones are important molecules due to their presence in a number of natural products and their pharmacological activities.[1-5] These molecules are reported to show a variety of biological functions such as antibacterial, antifungal, antimalarial, and anti-inflammatory activities.[1-5] Therefore, the synthesis 4-hydroxy-2-quinolinones are of interest to chemists.[6-15]

In our attempt to synthesize 4-hydroxy-2-quinolinones as part of our research to elucidate the structures of some natural products, we have found that the reported procedures resulted in the decarboxylation of the intermediates and very little 4-hydroxy-2-quinolinone product was obtained.[2,16] We have therefore revisited the synthetic procedures for the title compounds and were able to develop the optimal reaction conditions and reagents that produce the desired products in excellent yields. In this Letter, we report the efficient synthesis of 4-hydroxy-2-quinolinones from aniline and its substituted derivatives under mild and solvent-free conditions.

2. Results and Discussion

The synthesis started with substituted anilines **1**, which were treated with Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) to give malonic acid monoanilide **2** as shown in Scheme 1. The reactions were carried out without solvent at 60 °C for four hours. The reaction mixture was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The aqueous layer was acidified and extracted with ethyl acetate to produce malonic acid monoanilides **2** in excellent yield.



Scheme 1

It is important to note that the reaction temperature needed to be kept below 70 °C at which the monoanilide intermediates started to undergo decarboxylation, as is typical of β-ketoacids. This is in contrast to reported procedures in which the reactions were run at 80-100 °C.[2,6]

The conversion of the malonic acid monoanilide intermediates (**2**) to 4-hydroxy-2-quinolinones products (**3**) were attempted with

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reagents that have been reported to initiate Friedel-Crafts acylation of carboxylic acids such as polyphosphoric acid (PPA) and Eaton's reagent (a solution of phosphorus pentoxide solution in methanesulfonic acid).[2,5,16] PPA-initiated reactions required high temperatures at 120-140 °C and at those temperatures the monoanilide intermediate **2** underwent rapid decarboxylation. In the case of Eaton's reagent, the reactions were hard to carry out under mild conditions due to its high viscosity, and temperatures higher than 70 °C resulted in the decarboxylation of intermediate **2**. Reagents such as acetic anhydride and methanesulfonic acid did not yield any product. However, when the reaction was run in a mixture of acetic anhydride and methanesulfonic acid, the product was obtained in low yield. Fortunately, methanesulfonic acid anhydride (MSAA) was reported as an efficient reagent for the Friedel-Crafts acylation of aromatic compounds using carboxylic acids as acyl donor and was found to successfully promote the cyclization of malonic acid monoanilides to 4-hydroxy-2-quinolinones.[17] The solvent-free reactions were carried out for a few hours as specified in Table 1 at 60 °C (conversion of **2e** to **3e** was sluggish and was run at 70 °C) using 2 equivalents of MSAA. The product was isolated by trituration with ethyl acetate in a dry ice-acetone bath and then washed with cold water and ethyl acetate. The reaction yields were excellent as seen in Table 1.[18]

The products were characterized using NMR spectroscopy as compared to those reported in literature.[2] In the case of quinolinone **3f**, two products were formed because the acylation could occur at either one of the two positions adjacent to the amide group and the product ratio (approximately 1.6:1 in favor of the isomer from the less sterically hindered pathway) was determined by NMR signal integration.

Table 1. Yields for the conversion of anilines **1** to malonic acid monoanilides **2** and their subsequent conversion to 4-hydroxy-2-quinolinones **3**

Entry	Anilines(**1**, Y =)	Yield (**2**, isolated) (%)	Reaction time to form **3** (hours)	Yield (**3**, isolated) (%)
a	H	78	3	90
b	2-methyl	70	6	90
c	4-methoxy	77	3	91
d	4-fluoro	76	10	71
e	4-chloro	75	13	52
f	3,4-dimethyl	72	3	83[a]

[a] Two regioisomers formed in approximately 1.6:1 ratio as determined by NMR signal integration.

The reaction sequence gave excellent yields for anilines with electron-donating and moderately electron-withdrawing groups. However, the synthetic scheme did not work for aniline with strong electron-withdrawing groups. When the strong electron-withdrawing groups such as the cyano or nitro groups were at the 4-position, the malonic acid monoanilide did not form or was formed in poor yields. When the strong electron-withdrawing groups were at the 3-position, the malonic acid monoanilides were formed but failed to undergo Friedel-Crafts acylation.

3. Conclusions

The synthetic route for 4-hydroxy-2-quinolinones through malonic acid monoanilide intermediates was re-examined and the intermediates were observed to readily undergo decarboxylation under reported conditions. Mild reaction conditions for the N-acylation and an efficient reagent (MSAA) for the intramolecular Friedel-Crafts cyclization steps were found to give 4-hydroxy-2-quinolinones in excellent yields. The reaction sequence worked well for substrates with electron-donating and moderately electron-withdrawing groups but not those with strong electron-withdrawing groups.

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18. Experimental details: All reagents were obtained from commercial sources and used without further purification. Typical experimental procedures for the conversion of anilines 1 to malonic acid monoanilides **2** and from **2** to quinolinones **3** are described below using the syntheses 4-hydroxy-2-quinolinone (**3a**) as an example.
    A mixture of aniline (**1a**, 500 mg, 5.4 mmol) and Meldrum's acid (774 mg, 5.4 mmol) in a test tube was heated for 4 hours at 60 °C (reaction was complete as monitored by TLC). The reaction mixture was partitioned between aqueous sodium bicarbonate solution and ethyl acetate. The aqueous layer was acidified with concentrated HCl to pH 1 and extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and the solvent was removed to yield malonic acid monoanilide **2a** as a white solid (746 mg, 78%).
    A 25mL two-necked round-bottom flask was flame dried, charged with MSAA (587 mg, 3.4 mmol) , flushed with nitrogen gas, and fitted with a drying tube containing $CaCl_2$. The flask was heated at 60 °C until MSAA melted. Monoanilide **2a** (300 mg, 1.7 mmol) was added and the flask was flushed with nitrogen gas again. The reaction was complete after three hours (verified by TLC). The reaction was placed in a dry ice bath and triturated with ethyl acetate. The solid that formed was filtered and the solid was washed with cold water and ethyl acetate to produce quinolinone **3a** as an off-white solid (244 mg, 90%).

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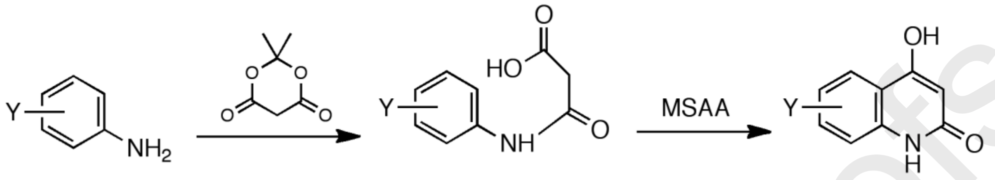

Highlights

- Anilines are converted to malonic acid monoanilides by reacting with Meldrum's acid.
- Malonic acid monoanilides are converted to 4-hydroxy-2-quinolinones by MSAA.
- Malonic acid monoanilides are prone to decarboxylation above 70 °C.
- The reactions require mild conditions (70 °C or lower).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: