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A Practical Method for Preparation of 4-Hydroxyquinolinone Esters

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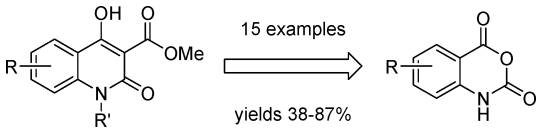

4-Hydroxyquinolinone esters are a common motif for many medicinal agents. Several methods exist for preparation of these compounds, generally involving the use of sodium hydride, which raises significant safety issues and limits their application to large-scale synthesis. In this note a practical, safe, and general method that employs a combination of diisopropylethylamine and sodium *tert*-butoxide is described. This allows for the synthesis of 4-hydroxyquinolinone esters and amides in good yields.

4-Hydroxyquinolinone esters of type **1** represent the core structure of several natural products[1] and are the central pharmacophore found in a number of medicinal agents. Compounds of general subclass **1** have found numerous applications as antimicrobial agents,[2] antiangiogenics,[3] antimalarial agents,[4] aldose reductase inhibitors,[5] anticonvulsants,[6] multiple sclerosis therapies,[7] and RNA polymerase inhibitors for the treatment of Hepatitis C.[8] A variety of synthetic methods exist which allow access to highly functionalized 4-hydroxyquinolinone esters, facilitating library synthesis and drug discovery (Figure 1). For example, substituted anilines **2** can be directly converted into 4-hydroxyquinolinone esters **1** by heating in the presence of methanetricarboxylates (Route A).[9] Difluorobenzonitriles **3** can be elaborated to 4-hydroxyquinolinone esters via a double S_NAr pathway (Route B).[7a] Anthranilic esters **4** can be acylated with malonyl chlorides and cyclized to the 4-hydroxyquinolinone esters under acidic conditions (Route C).[10] Anthranilic acids react with phosgene to form 2*H*-3,1-benzoxazine-2,4(1*H*)-diones **5** (isatoic anhydrides),[11] which can then be transformed into 4-hydroxyquinolinone esters via reaction with malonates (Route D).[12] Although each of these methods offers certain advantages, the high reaction temperatures (>200 °C) for the conversion of **2** to **1** (Route A), the limited availability of a broad range of suitably substituted starting materials (Route B), and the need to isolate the acylated intermediate prior to cyclization to **1** (Route C) have limited the widespread application of these methods. Route D is perhaps the most general protocol for the preparation of **1** starting from an isatoic anhydride **5** and involves an *N*-alkylation-malonate addition-intramolecular cyclization sequence.

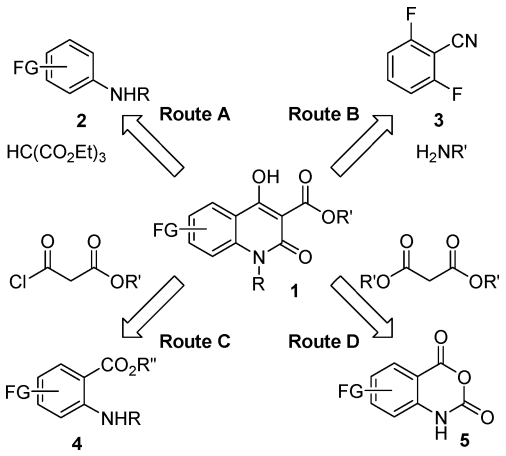

FIGURE 1. Synthesis of 4-hydroxyquinolinone esters.

The most commonly employed base to effect both the *N*-alkylation of the isatoic anhydride and the subsequent

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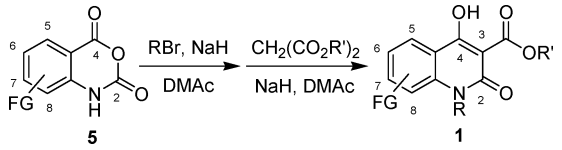
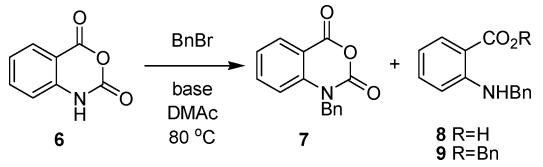
SCHEME 1



SCHEME 2

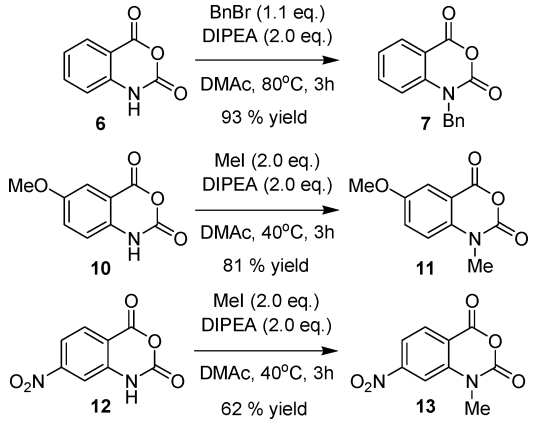


deprotonation of the malonate prior to cyclization to **1** is NaH in either DMF or *N*,*N*-dimethylacetamide (DMAc) at elevated temperatures (~120 °C) (Scheme 1). While suitable for small-scale development, these conditions raise serious concerns in terms of safety associated with scaleup due to reports of thermal runaway in large-scale processes, the pyrophoric nature of NaH, and issues associated with rapid release of hydrogen gas upon deprotonation.[13]

Although alternative bases such as Na_2CO_3,[14] Mitsunobu conditions for the *N*-alkylation of isatoic anhydrides,[15] and succinate esters[16] have been investigated for the conversion of **5** to **1**, several issues still remain. Either sodium metal or sodium hydride is required for the malonate addition or the procedure calls for numerous synthetic manipulations. Studies aimed at the synthesis of NH or *N*-acyl 4-hydroxyquinolinone esters starting from benzoxazin-4-ones have been described which employ sodium *tert*-butoxide, but these are limited in terms of the scope of nitrogen substituents which can be installed.[17] Therefore, there remains a need for an alternative protocol that would not only address the safety limitations of current methodologies, but also be amenable to the large-scale synthesis of 4-hydroxyquinolinone esters **1**. In this note, we document such a strategy that provides access to compounds of the general type **1** in good yields and has significant advantages when compared to existing methods for the preparation of 4-hydroxyquinolinone esters in terms of safety and practicality.

Initial studies focused on the choice of base for the *N*-alkylation of isatoic anhydride **6** with benzyl bromide (Scheme 2). Examination of Na_2CO_3, Cs_2CO_3, and sodium alkoxides (i.e., NaO*t*-Bu and $NaOC(CH_3)_2CH_2CH_3$) revealed that opening of the *N*-alkylated species **7** by either water or the alcohol (*t*-BuOH or $HOC(CH_3)_2CH_2CH_3$) generated during the reaction was competitive and significant amounts of anthranilic acid **8** or the corresponding benzyl ester **9** were observed. Grignard reagents

SCHEME 3



(*i*-PrMgBr and *t*-BuMgCl) were also examined but were found to be ineffective bases for the alkylation resulting in poor conversion to **7**. Even when a large excess of Grignard reagent was employed, a level of conversion to **7** greater than 40% was not achieved. A survey of amine bases revealed that *N*,*N*′-diisopropylethylamine (DIPEA) resulted in extremely efficient formation of *N*-benzylated isatoic anhydride **7** without significant formation of **8** or **9**. Although 1.1 equiv of DIPEA was sufficient, the use of 2 equiv proved more reliable for routinely obtaining high conversion to **7**. The reaction was performed by the addition of DIPEA to a mixture of **6** and benzyl bromide followed by heating at 80 °C for 3 h. The only observed byproduct under these conditions was benzyl ester **9** (<5%). Other amine bases, such as pyridine, DBU, and 2,6-dimethylpyridine were examined but gave substantially lower conversions (<50%).

Compound **7** was surprisingly stable and was easily isolated directly from the reaction mixture in 93% yield by the addition of water (Scheme 3). In similar fashion, alkylated isatoic anhydrides **11** and **13** were obtained in analytically pure form by crystallization from the crude reaction mixture in 81% and 62% yields, respectively.

Having identified DIPEA as a viable base for the *N*-alkylation of isatoic anhydrides, the choice of base for the malonate addition−intramolecular cyclization leading to **1** was examined. The direct addition of dimethyl malonate to **7** in the presence of an excess of DIPEA followed by heating to 95 °C did not afford **14**. The use of inorganic bases such as Na_2CO_3 or K_2CO_3 resulted in significant hydrolysis of **7** to **8**, as noted above. Deprotonation of dimethyl malonate with sodium hexamethyldisilazide (NaHMDS) followed by addition of the resulting sodium salt to **7** afforded only small amounts of **14**. Instead, multiple unidentified byproducts arising from apparent ring opening of **7** by HMDS were observed. In contrast, deprotonation of dimethyl malonate with NaO*t*-Bu followed by addition of a solution of the sodium salt to a crude solution of **7** and warming to 95 °C led to clean formation of **14**. Optimal conditions involved deprotonation of 2 equiv of dimethyl malonate with 2 equiv of NaO*t*-Bu in DMAc followed by addition of this solution in one portion to crude **7** and warming to 95 °C for 1 h (Scheme 4). These conditions resulted in an improved reaction profile and greatly minimized the formation of the anthranilic acid **8** (<5%), the methyl ester **15** (<5%), and the *tert*-butyl ester **16** (<5%). It was found that slow addition of the solution of the sodium salt led to significant amounts of **15**. Use of 1 equiv of the malonate salt and 1 equiv

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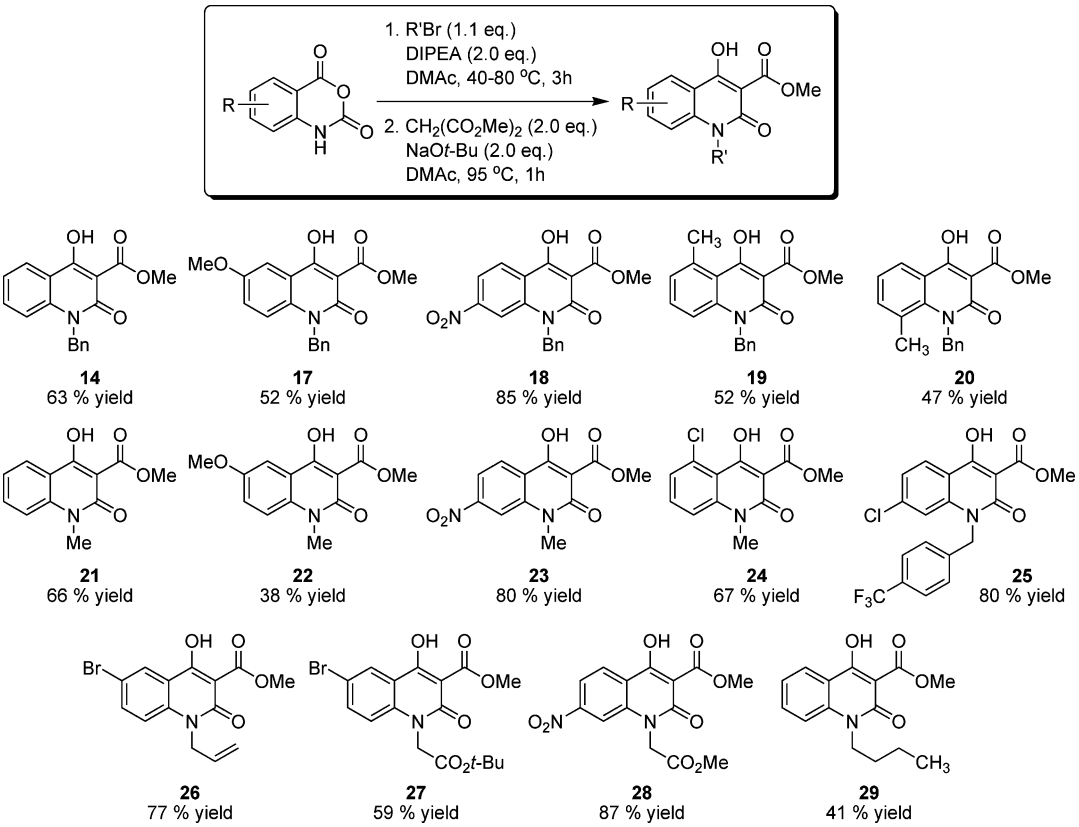
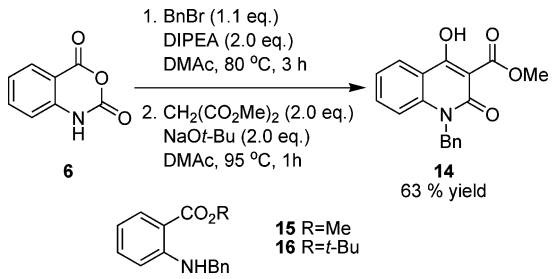
TABLE 1. Synthesis of 4-Hydroxyquinolinone Esters



SCHEME 4



of NaO*t*-Bu also led to lower yields of **14** and the formation of significant amounts of **16**. Two equivalents of the malonate salt were required in order to obtain high conversions since 1 equiv of base was consumed in the neutralization of the diisopropylethylamine hydrobromide formed during the *N*-alkylation. 4-Hydroxyquinolinone ester **14** was isolated in analytically pure form and in 63% overall yield after the addition of 2 N HCl. The use of aqueous HCl in the isolation step not only allowed for the crystallization of **14**, but effectively quenched any excess base and facilitated the removal of potential amine impurities.

The presence of *tert*-butanol appeared to have a beneficial effect on the yield of this reaction. When a combination of DIPEA and NaH was used, large amounts of the methyl ester **15** could be observed in the crude reaction mixture (up to 30%) and a lower yield (40%) and purity of **14** were obtained. Clearly, under the basic conditions of the malonate addition, **7** was highly susceptible to attack by any nucleophile, including *tert*-butanol, as evidenced by the observation of **16**. It is proposed that the methanol released during the cyclization of the quinolinone ring acts as a competitive nucleophile for **7**, leading to formation of **15**. The presence of *tert*-butanol, formed during the deprotonation of dimethyl malonate, suppressed this process. It is unclear at this point if the presence of *tert*-butanol attenuates the nucleophilicity of methanol through a medium effect[18] or by promoting the formation of an unreactive carbonate anion by trapping CO_2 liberated during the reaction.[19]

Having identified DIPEA/NaO*t*-Bu as an effective combination for the *N*-alkylation−malonate addition, the scope of the reaction was explored (Table 1). Variation in the structure of both the isatoic anhydride and the alkylating reagent revealed that the method was general. Both electron-rich and electron-poor isatoic anhydrides gave the desired products in good yields (**17**−**18**). Substitution was tolerated at both the 3- and 6-positions of the isatoic anhydride without compromising reactivity (**19** and **20**). A variety of *N*-substituents could also be introduced by this method, further expanding the scope of the methodology. Methylation was performed with 2 equiv of methyl iodide at 40 °C, yielding the *N*-methyl 4-hydroxyquinolinone esters in good yields after reaction with dimethyl malonate (**21**−**24**). Compound **24**, an important intermediate in the synthesis of Laquinimod,[7] was rapidly assembled in good yield with this method. Other electrophiles including substituted benzyl bromides (**25**), allyl halides (**26**), and α-halo esters (**27** and **28**) were also employed, providing access to more highly functionalized products with potential for further manipulation. Alkyl halides which are prone to elimination, such as *n*-butyl bromide, were also examined (**29**). But in order to obtain a synthetically

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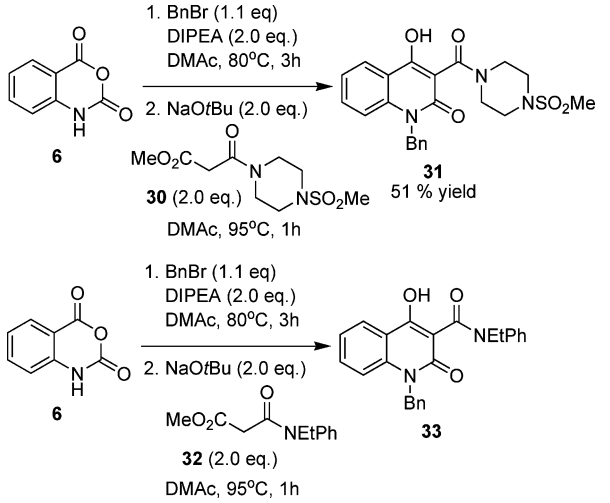
SCHEME 5



useful yield of **29**, significantly longer reaction times were required for the *N*-alkylation step (22 h).

4-Hydroxyquinolinone amides are another class of structures which are common to many interesting medicinal agents.[3,6,7] Although they are generally prepared via direct reaction of a 4-hydroxyquinolinone ester with an amine, it was envisioned that the use of a half malonic amide might allow for direct access to 4-hydroxyquinolinone amides. There are a limited number of examples of such a transformation in the literature.[12d] Therefore, this method was examined with some malonic amides (Scheme 5).

The desired 4-hydroxyquinolinone amide **31** could be obtained in good yield in the case of the substrate **30** but none of the desired product **33** was observed when **32** was employed. In the case of **32**, only small amounts of the corresponding 4-hydroxyquinolinone ester **14** were observed by HPLC. A possible explanation for this product distribution comes from the relative reactivity of the ester and the amide groups in **30** and **32**. In the case of more basic piperazine contained in **30**, methoxide was a better leaving group and selectivity for the 4-hydroxyquinolinone amide was high. Therefore, this method represents a viable option for the one-step preparation of certain 4-hydroxyquinolinone amides.

In summary, an efficient and practical method for the preparation of 4-hydroxyquinolinone esters and amides has been developed. This procedure is a significant extension of existing methodology in that it provides a safer protocol that can be employed on a kilogram scale, requires no chromatography, and allows for the preparation of highly functionalized pharmacophores in a single synthetic transformation from readily available bulk chemicals. Application of this method to the preparation of 4-hydroxyquinolinone esters and amides should facilitate further discovery efforts as well as efforts directed toward large-scale preparation of these compounds.

Experimental Section

Preparation of 1-Benzyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Methyl Ester (14). To a solution of isatoic anhydride **6** (1.0 g, 6.1 mmol) in 5 mL of *N*,*N*-dimethylacetamide was added 2.12 mL of diisopropylethylamine (12.2 mmol, 2.0 equiv) and the solution was stirred for 10 min. To this mixture was added 802 μL of benzyl bromide (6.7 mmol, 1.1 equiv) and the mixture was heated at 80 °C for 3 h. The reaction was then allowed to cool to room temperature and a solution of the sodium salt of dimethyl malonate formed by mixing 1.38 mL of dimethyl malonate (12.2 mmol, 2.0 equiv) and 1.17 g of sodium *tert*-butoxide (12.2 mmol, 2.0 equiv) in 5 mL of *N*,*N*-dimethylacetamide was added in a single portion. The reaction mixture was heated at 95 °C for 1 h and allowed to cool to room temperature. A thick precipitate had formed. To this suspension was added 12 mL of 2 M HCl and the mixture was stirred vigorously for 30 min. The resulting suspension was filtered and washed with 20 mL of water. After slurry washing in 20 mL 2:1 heptane:MTBE and drying under a vacuum/N_2 sweep, 1.17 g (63% yield) of **14** was obtained as a tan solid. Data for **14**: mp 149−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.22 (s, 1H), 8.20 (d, 1H, J = 8.2 Hz), 7.55 (dt, 1H, J = 1.4, 8.5 Hz), 7.3−7.2 (m, 7H), 5.51 (br s, 2H), 4.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 172.1, 159.9, 141.0, 136.6, 134.5, 128.9, 127.3, 126.7, 125.9, 122.2, 115.2, 115.1, 97.7, 53.1, 45.9. Anal. calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.72; H, 4.89; N, 4.48.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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