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A simple and efficient one-step synthesis of 3-substituted-4-hydroxyquinolin-2-one derivatives

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ABSTRACT

A new simple and efficient one-step procedure for the preparation of 3-substituted-4-hydroxyquinolin-2-one derivatives was developed. Product isolation is simple, isolated yields are good to excellent and this method tolerates a variety of substitution patterns.

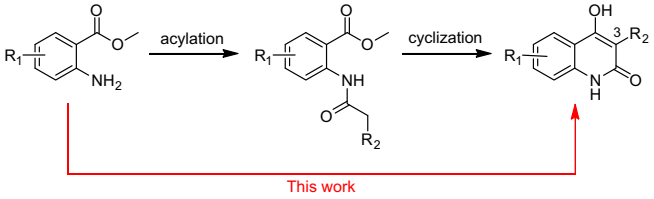
The 4-hydroxyquinolin-2-one motif is found in a variety of biologically active compounds and in particular, 3-substituted-4-hydroxyquinolin-2-one derivatives are known as selective non-competitive agonists of NMDA receptors[1,2] and antagonists of AMPA receptors.[3,4] Some compounds are of utility in the treatment of convulsions, schizophrenia and in the prevention of neurodegenerative disorders, such as Alzheimer's disease, Huntington's disease and Parkinsonism.[5] Recently, this scaffold was also described as type I fatty acid synthase inhibitors.[6]

There are several approaches for the preparation of these compounds all of which require a multistep synthesis. The most commonly found routes used in the literature is a two-step procedure involving acylation reaction of an anthranilic ester derivative with substituted acetate followed by the formation of the pyridinone via an intramolecular Claisen condensation in the presence of a base. (Scheme 1).[6,7]

Several literature references describe the synthesis of 4-hydroxyquinolin-2-one with diverse substitutions at the C3-position. Carbonyl, phenyl, and alkyl groups are common but there are very few reports describing O-substitution.[8] To the best of our knowledge, a convenient and high-yielding method for the synthesis of N-unsubstituted 4-hydroxyquinolin-2-ones with C3 O-substitution[8] is still lacking. Herein, we report a simple one-step synthesis of these compounds of interest from commercially available starting materials (Scheme 1).

Initially, the quinoline-2-one derivatives were prepared following a classical two-step synthesis[6,7] shown in Scheme 1. Acylation in the presence of HATU in DCM at rt was followed by cyclization induced by either LiHMDS at −78 °C or KHMDS at rt in THF. In general, the overall yields over two steps were moderate, especially when R_2 was an *O*-alkyl group. Although these conditions allowed us to generate a number of 3-O-substituted quinolinones, we speculated that it might be possible to improve this synthesis by combining the two reactions in a single step.

As a model system, we investigated the reaction of methyl 2-amino-4-chlorobenzoate and methyl 2-(2-methoxyethoxy) acetate. Table 1 describes the conditions used for the direct cyclization reaction. These results revealed that there were substantial differences between the conditions used. Among the bases utilized, KHMDS was superior to some other bases such as ^{t}BuOK, LDA, or NaH and even better than LiHMDS under the same reaction conditions. In addition, THF appeared to be the solvent of choice. The use of KHMDS in THF at room temperature provided the intended quinolinone in a high yield with no detectable trace of by-products.



Scheme 1. Synthesis of 3-substituted-4-hydroxyquinolin-2-one derivatives.

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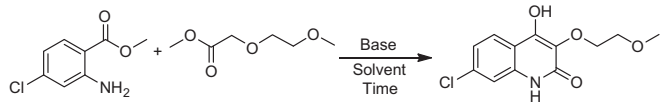
Table 1
Optimization of a one-step quinolinone synthesis[a]



Entry	Base	Solvent	Time	Conv./intended product[b] (%)
1	^{t}BuOK	DMSO	2 h	100/0
2	Cs_2CO_3	DMSO	2 h	100/0
3	NaH	THF	2 h	100/0
4	LDA	THF	3 h	100/0
5	LiHMDS	THF	3 h	82/30
6	LiHMDS	THF	24 h	87/30
7	KHMDS	Toluene	2 h	100/15
8	KHMDS	THF	20 min	100/100 (67%)[c]

[a] Reaction conditions: 1.0:1.2 equiv anthranilic ester/acetate, 3.0 equiv base, 0.13 M solvent, rt (reaction with Cs_2CO_3 was performed at 90 °C).
[b] Determined by HPLC.
[c] Isolated yield.

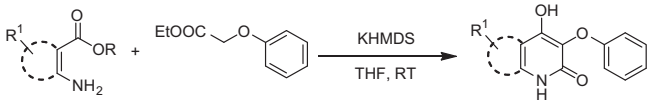
Noteworthy, the difference between the conversion and the isolated yield (entry 8) is certainly due to the loss of material during isolation and purification.

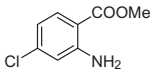
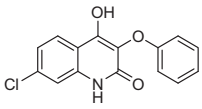
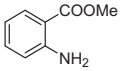
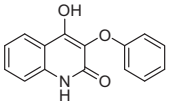
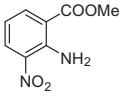
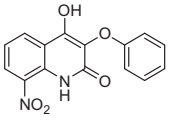
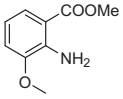
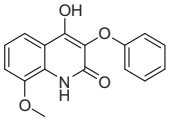
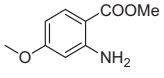
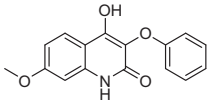
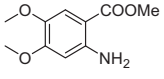
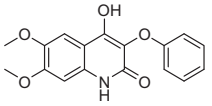
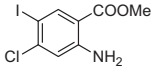
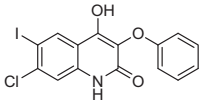
The feasibility of the one-step reaction is being now demonstrated, this procedure was further evaluated for its scope and general applicability. To this end, a variety of anthranilic esters were examined and the results are presented in Table 2.

Firstly the protocol was repeated with ethyl 2-phenoxyacetate (entry 1). As expected, the quinolinone was isolated in excellent yield within 10 min after simple work-up. It turned out that, as outlined in the examples of Table 2, the electronic nature of the substituents on the phenyl ring played a limited role on the reaction outcome. Thus for anthranilic ester bearing mildly electron-withdrawing groups (entries 1, 7, 8, 10) or those with electron-donating substituents (entries 5, 6, 9) the reactions were completed within 30 min. A slight adjustment of the reaction conditions was required in some cases in which more KHMDS was added to achieve full conversion (entries 5, 6, 9, 12). However, the reaction yield with phenyl substituted at the C3-position suggests a marked role of steric factors on the completion of the reaction. In these specific cases, microwave irradiation was used. While no reaction occurred with nitro moiety (entry 3), these stronger conditions allowed us to get the 8-OMe substituted compound (entry 4) in a moderate yield. The anthranilic ester could also be replaced by certain heterocycles (entries 11–13). Even though longer reaction time was required, the protocol allowed us to generate the desired products in every cases, either in a low yield for thiophene moiety (entry 13) or in good yields for pyridine and tetrahydropyridine starting materials (entries 11 and 12).

The scope of this methodology to other substitutions at C-3 on the pyridinone was then enlarged. Examples in Table 3 show that *N*-phenyl (entry 2), *S*-phenyl (entry 3), *O*-alkyl (entry 4), or *O*-pyridyl acetates (entry 1) are tolerated.

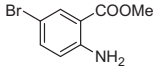
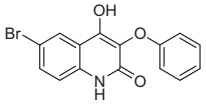
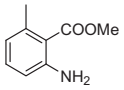
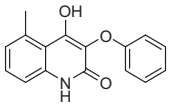
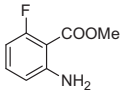
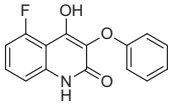
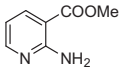
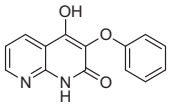
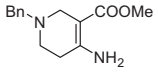
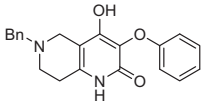
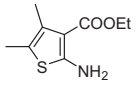
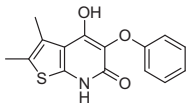
Table 2
Synthesis of quinolinone from various anthranilic esters[a]



Entry	Anthranilic ester	Product	Time (min)	Yield[b] (%)
1			10	92
2			10	91
3			120 15[c]	– –
4			15[c]	33
5			30[d]	79
6			30[d]	80
7			20	98

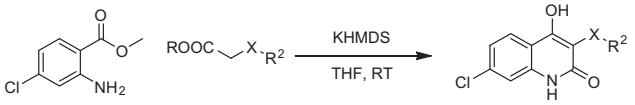
(*continued on next page*)

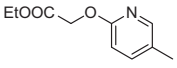
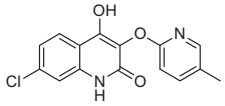
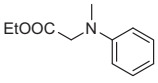
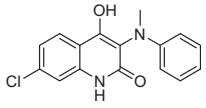
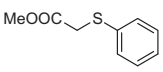
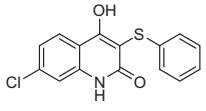
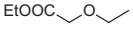
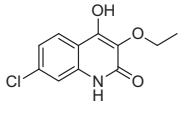
Table 2 (*continued*)

Entry	Anthranilic ester	Product	Time (min)	Yield[b] (%)
8			10	80
9			60[e]	96
10			60	68
11			20	67
12			60[f]	76
13			10[c]	25

[a] Reaction conditions: 1.0:1.2 equiv anthranilic ester/acetate, 3.0 equiv KHMDS 1.0 M in THF, 0.13 M THF, rt.
[b] Isolated yields.
[c] Microwave irradiation, 130 °C.
[d] 0.5 equiv of KHMDS was added after 20 min.
[e] 0.5 equiv of KHMDS was added after 60 min.
[f] Reaction performed at 60 °C. 1 equiv of KHMDS was added after 60 min.

Table 3
Heteroatom and phenyl replacement[a]



Entry	Acetate	Product	Time (min)	Yield[b] (%)
1			20	66
2			20	67
3			10[c]	24
4			40[d]	81

[a] Reaction conditions: 1:1.2 equiv anthranilic ester/acetate, 3 equiv KHMDS 1.0 M in THF, 0.13 M THF, rt.
[b] Isolated yields.
[c] Microwave irradiation, 130 °C.
[d] 1 equiv of KHMDS was added after 40 min.

In conclusion we have developed an efficient and high yielding one-step synthesis of 4-hydroxyquinolin-2-one substituted at the 3-position by a heteroatom directly from anthranilic esters and heteroatom-substituted acetates. The short reaction time, mild

reaction conditions, and high isolated yields render this method more attractive in comparison to the existing synthetic route currently found in the literature.

Typical procedure

To a solution of methyl 2-amino-4-chlorobenzoate (300 mg, 1.6 mmol) and ethyl 2-phenoxyacetate (320 mg, 1.8 mmol) in anhydrous THF (9 mL) was added KHMDS (4.8 mL, 1.0 M in THF, 4.8 mmol) in one portion with vigorous stirring under a nitrogen atmosphere. The reaction mixture was stirred at rt until completion of the reaction (10 min) then MeOH was added. The reaction mixture was concentrated under reduced pressure and the resulting residue was taken up in water and acidified with 1 N HCl until precipitation occurred. The precipitate was filtered, washed with EtOH then dried to give 7-chloro-4-hydroxy-3-phenoxyquinolin-2(1*H*)-one (Table 2, entry 1) as a pale pink powder (449 mg, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 11.37 (s, 1H), 7.88 (s, 1H), 7.49–7.13 (m, 4H), 7.10–6.78 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.8 (s), 157.4 (s), 152.2 (s), 137.2 (s), 134.4 (s), 129.2 (d), 125.3 (s), 124.8 (d), 121.7 (d), 121.6 (d), 115.2 (d), 114.3 (s and d). MS(EI) *m/z* 288 (MH^+).

Acknowledgments

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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.2012.01.140. These data include MOL files and InChiKeys of the most important compounds described in this article.

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