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A Concise and Versatile Synthesis of Viridicatin Alkaloids from Cyanoacetanilides

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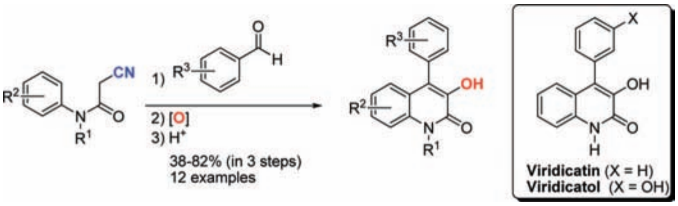
ABSTRACT



The efficient synthesis of 3-hydroxy-4-arylquinolin-2(1*H*)-ones through one-pot Knoevenagel condensation/epoxidation of cyanoacetanilides followed by decyanative epoxide−arene cyclization is described. A convergent assembly with functionalized aldehydes allows for rapid synthesis with diverse substitution patterns. Isolation of 3-hydroxy-4-arylquinolin-2(1*H*)-ones is readily accomplished by precipitation and filtration.

Functionalized 4-arylquinolin-2(1*H*)-ones **1** (Figure 1) constitute a valuable class of biologically active molecules,[1−3] including an orally active antitumor agent[1] that is currently undergoing human clinical trials. In particular, the biological activities of 3-hydroxy-4-arylquinolin-2(1*H*)-one derivatives **2**, including several natural products such as viridicatin (**3**),[4] viridicatol (**4**),[5] and 3-*O*-methylviridicatin (**5**),[6] have attracted much attention in recent years.[7−9] Compounds **3**−**5** were first isolated as fungal metabolites in the 1950s and 1960s,[4−6] but their biological activities remained unexplored until 1998, when Heguy and co-workers reported that **5** inhibits the replication of human immunodeficiency virus (HIV) induced by tumor necrosis factor (TNF-α) with an IC_{50} of 2.5 μM.[7] More recently, Desaubry and co-workers reported on the structure−activity relationships of **5**.[8] In addition, a series of 3-hydroxy-4-arylquinolin-2(1*H*)-ones **2** have been found to act as maxi-K channel openers with antibacterial activity.[9] However, surprisingly, the synthesis of derivatives **2** has

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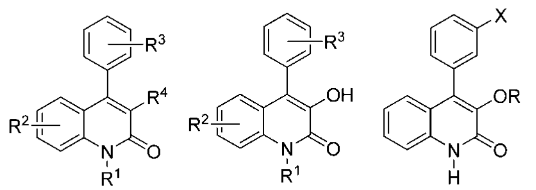


1

2

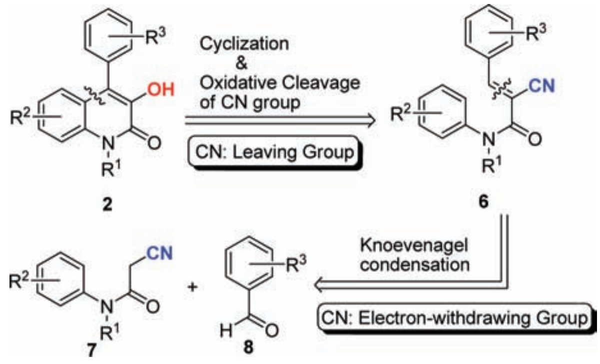
Viridicatin (3) (R = H, X = H)
Viridicatol (4) (R = H, X = OH)
3-*O*-Methylviridicatin (5)
(R = Me, X = H)

Figure 1. Biologically active 4-arylquinolin-2(1*H*)-one derivatives.

remained largely unexplored: only a few methods have been reported, including the condensation of aryldiazomethanes with isatins,[10] transformation of cyclopenin,[11] Friedländer-type condensations,[1−3,12] and Pd-catalyzed coupling reactions.[13,14] These strategies, unfortunately, suffer from the disadvantages that the starting materials are only available in limited supply and that the process of varying the R^2 and R^3 groups of **2** is cumbersome and lengthy. The development of a novel method for the synthesis of derivatives **2** with complete control over both R^2 and R^3 substituents would therefore be of significant value.

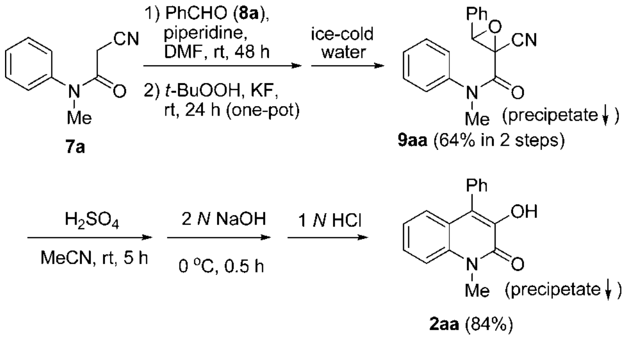
Our strategy for the synthesis of **2** is outlined in Scheme 1, where **2** is obtained from **6** via oxidative cyclizations. In turn, **6** can be readily prepared by Knoevenagel condensation of cyanoacetanilides[15] **7** with aldehydes **8**. We hypothesized that the CN groups would function not only as electron-withdrawing groups at the condensation step (**7** + **8** → **6**) but also as leaving groups at the cyclization step (**6** → **2**). Here, we describe a novel and flexible protocol for the synthesis of functionalized 3-hydroxy-4-arylquinolin-2(1*H*)-ones **2**. The salient features of our method are as follows: (1) a variety of cyanoacetanilides **7** and aldehydes **8** are readily available; (2) only three steps are required beginning from the starting materials, and the rapid synthesis of **2** with diverse substitution patterns is possible; (3) facile isolation of **2** is accomplished by a simple aqueous workup.

Scheme 1. Strategy for the Synthesis of 3-Hydroxy-4-arylquinolin-2(1*H*)-ones **2**



We first examined the reaction between cyanoacetanilide (**7a**) and benzaldehyde (**8a**) (Scheme 2). After a brief survey of reaction conditions, we found that the desired 3-hydroxy-4-arylquinolin-2(1*H*)-one **2aa**[16] was obtained in 84% yield by the H_2SO_4-mediated cyclization of epoxide **9aa**,[17−19] which was, in turn, synthesized from **7a** in good yield by the one-pot Knoevenagel condensation/epoxidation. Knoevenagel condensation was best performed under mild conditions using piperidine as the catalyst (10−15 mol % of piperidine, DMF, rt, 48 h), and one-pot epoxidation proceeded efficiently under optimized conditions[20] (*t*-BuOOH, KF, rt, 24 h). It was noted that both **9aa** and **2aa** were

Scheme 2. Optimized Conditions for the Synthesis of 3-Hydroxy-4-arylquinolin-2(1*H*)-ones **2**



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(15) Cyanoacetanilides (**7a**−**f**) were prepared by reacting cyanoacetic acid with the corresponding aniline up to a 20-g scale (77−96% yields). For experimental details, see the Supporting Information.

(16) All spectral data were in full accord with those reported in the literature; see the Supporting Information.

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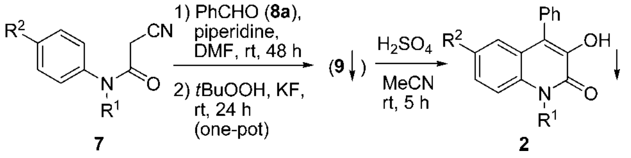
(20) When H_2O_2 was used as the oxidant instead of *t*-BuOOH, we observed partial hydrolysis of the CN group of **9aa**.

obtained as precipitates by simple aqueous workup and could be purified by recrystallization.

With the optimized conditions identified, we examined the substrate scope of the reaction with respect to both the nitrogen (R^1) and the aromatic (R^2) substituents of cyanoacetanilides **7** (Table 1).[21] The reaction showed remarkable tolerance to a range of substituents with markedly different steric and electronic properties (entries 1−6). We first examined the reactions of the more readily deprotected *N*-Bn and *N*-PMB derivatives **7b** and **7c** (entries 1 and 2). Although the one-pot reactions of **7b** and **7c** worked equally well, we could not obtain the corresponding epoxides **9** as precipitates. However, by telescoping[22] the reaction sequence (**7** → **9** → **2**), **2ba** and **2ca** were obtained as white solids in 40% and 72% overall yields, respectively. Notably, the large-scale reactions can be conducted easily and inexpensively. For example, the reactions proceeded cleanly and efficiently to afford 8.7 g of **2ca** when carried out with 30 mmol (8.4 g) of **7c** (entry 3). To expand the utility of this reaction, we next examined the effect of the substituents R^2 on the aromatic rings (entries 4−6). The substituents R^2 were found to have little effect on the one-pot Knoevenagel condensation/epoxidation, and the desired epoxides **9da**−**9fa** were obtained as white solids in moderate-to-good yields. Subsequent epoxide-arene cyclization of epoxide **9da** bearing an electron-rich aryl group took place smoothly to afford the desired quinolinone **2da** in 99% yield (entry 4). In contrast to this result, the reactions of **9ea** and **9fa**, which have electron-withdrawing groups such as Br and Cl on the aromatic rings, proceeded slowly at room temperature; however, the reactions were completed within 24 h to afford the corresponding quinolinones **2ea** and **2fa** in respective yields of 85% and 92% (entries 5 and 6). These halogenated products could in principle be further functionalized by way of transition-metal-catalyzed coupling reactions. As we expected, the isolation of all products **2ba**−**2fa** was readily accomplished by precipitation and filtration.

Table 1. Substrate Scope of Cyanoacetanilides **7**[a]

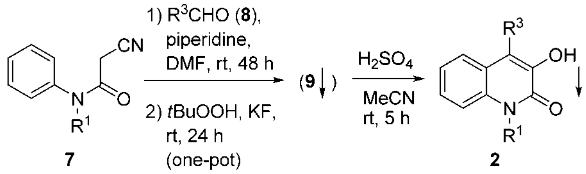


entry	**7** (R^1, R^2)	**9** (yield,[b] %)	**2** (yield, %)
1	**7b** (Bn, H)		**2ba** (40[c])
2	**7c** (PMB,[d] H)		**2ca** (72[c])
3[e]	**7c**		**2ca** (82[c])
4	**7d** (PMB, Me)	**9da** (49)	**2da** (99[f])
5	**7e** (PMB, Br)	**9ea** (88)	**2ea** (85[f,g])
6	**7f** (Me, Cl)	**9fa** (69)	**2fa** (92[f,g])

[a] Unless otherwise noted, all reactions were carried out with 3.0 mmol of **7**. [b] Isolated yields in two steps from **7**. [c] Isolated yields in three steps from **7**. [d] PMB = 4-methoxybenzyl. [e] Carried out with 30 mmol of **7c**. [f] Isolated yields from **9**. [g] **9ea** and **9fa** were consumed in 24 h.

We used the same strategy, one-pot Knoevenagel/epoxidation followed by epoxide-arene cyclization, to synthesize a variety of 3-hydroxy-4-arylquinolin-2(1*H*)-ones **2** by varying the R^3 groups (Table 2). One-pot reactions of cyanoacetanilides **7** with substituted arylaldehydes (**8b**−**g**) generally produced good-to-excellent yields. The subsequent cyclizations of epoxides having electron-rich aromatic rings were found to have beneficial effects on rate, affording the corresponding quinolinones in 59−78% overall yields (entries 1−3). It should be noted that no protection was required for the phenolic −OH in H_2SO_4-mediated epoxide-arene cyclization (entry 1). In contrast, epoxides **9ae** and **9af** bearing electron-withdrawing substituents R^3 proved less reactive (entries 4−6). For example, when **9af** was treated with 10 equiv of H_2SO_4 for 24 h, cyclization did not proceed at all (entry 5), suggesting such substituents inhibit the generation of carbocation species at benzylic positions. Its efficient conversion, however, could be achieved by refluxing in trifluoroacetic acid for 24 h (entry 6). Moreover, this methodology could be applied to the heteroaromatic aldehyde **8g**, and the desired quinolinone **2ag** was obtained, albeit in somewhat lower yield (entry 7).

Table 2. Substrate Scope of Aldehydes **8**



entry	**7** (R^1)	**8** (R^3)	**9** (yield[a])	**2** (yield, %)
1	**7c** (PMB[d])	**8b** (3-HOC_6H_4)		**2cb** (59[b])
2	**7a** (Me)	**8c** (4-$MeOC_6H_4$)	**9ac** (70)	**2ac** (89[c])
3	**7a**	**8d** (1-naphthyl)	**9ad** (87)	**2ad** (90[c])
4	**7a**	**8e** (4-BrC_6H_4)	**9ac** (86)	**2ae** (86[c,e])
5	**7a**	**8f** (4-$CF_3C_6H_4$)	**9ac** (78)	**2af** (0[c])
6	**7a**	**8f**	**9af**	**2af** (71[c,f])
7	**7a**	**8g** (2-thienyl)		**2ag** (38[b])

[a] Isolated yields in two steps from **7**. [b] Isolated yields in three steps from **7**. [c] Isolated yields from **9**. [d] PMB = 4-methoxybenzyl. [e] **9ae** was consumed in 24 h. [f] **9af** was treated in trifluoroacetic acid at 100 °C (reflux) for 24 h.

Finally, the conversion of the resulting *N*-PMB derivatives to quinolinones with free *N*-H functions was examined (Scheme 3). Under acidic conditions, **2ca** and **2cb** were

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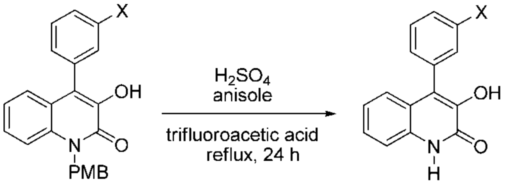
(21) Note that a tertiary anilide must be used to ensure a smooth annulation reaction. This is because the reaction of the secondary anilide (R1 = H) does not proceed at all, most probably due to conformational reasons; see: (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965**, 2995. (b) Nanjan, M. J.; Kannappan, V.; Ganesan, R. *Indian J. Chem.* **1979**, *18B*, 461. (c) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177.

(22) The term "telescoping" has been used before to describe sequential multistep/multipot processes with shortened or omitted isolation procedures for the involved intermediates; see, e.g.: Dale, D. J.; Draper, J.; Dunn, P. J.; Hughes, M. L.; Hussain, F.; Levett, P. C.; Ward, G. B.; Wood, A. S. *Org. Process Res. Dev.* **2002**, *6*, 767.

Scheme 3. Deprotection of *N*-PMB Derivatives



2ca (X = H)
2cb (X = OH)

Viridicatin (**3**), 73%
Viridicatol (**4**), 64%

readily deprotected to afford **3** and **4** in 73% and 64% yields, respectively.

In summary, we have demonstrated an efficient approach to the synthesis of the biologically active 3-hydroxy-4-arylquinolin-2(1*H*)-ones **2** by fully exploiting the CN groups[23] of the cyanoacetanilides **7**. Substrates for the reactions are widely available or can be readily prepared, thus greatly enhancing the synthetic potential of the method. The development of synthetic applications is under investigation and will be reported in due course.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Young Scientists (Start-up) (Y.K.) from Japan Society for the Promotion of Science.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] For recent examples of other reactions fully exploiting the CN groups, see: (a) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *Tetrahedron* **2007**, *63*, 2978. (b) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874.