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One-Step Synthesis for the Preparation of Quinoline Alkaloid Analogues

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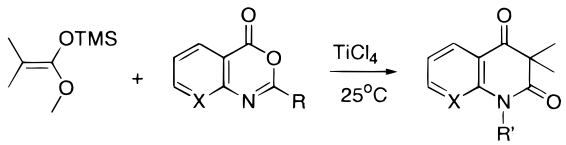
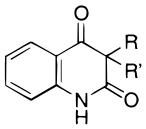
ABSTRACT



A new one-step methodology has been introduced for the synthesis of quinoline alkaloid analogues. The reaction is based on a modification of the Mukaiyama aldol condensation, making use of the high reactivity of lactones or anhydrides. The reaction is general and allows for the construction of new hetero polycondenced molecules in a one-step synthesis.

In the past decade, several scientific groups have managed to isolate a large number of alkaloids that belong to the quinoline class of compounds.[1−7] Isolable natural products of this class constitute two large groups of quinoline derivatives, the 3,3-disubstituted quinoline-2,4-diones (**1**) and the 2-substituted quinoline-4-ones (**2**), pertaining to the antibacterials collectively known as "quinolones".[8] Quinoline



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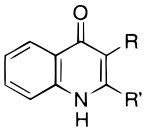

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alkaloids of the first group have been isolated from different species of plants, such as *Haplophyllum tuberculatum*[3] and *Esenbeckia flava*.[2] On the other hand, isolation of active agents from *Pseudomonas* sp.[6,7] gave a large number of 2,3-substituted quinoline derivatives (**2**).

Recently, 3,3-disubstituted quinoline-2,4-dione derivatives have been proven to be capable of protecting CEM-SS cells from the cytopathic effects of HIV-1 in vitro.[5] In addition, they have been identified as novel antibacterials, as they present strong antibacterial effects on *Staphylococcus aureus* and *Escherichia coli*.[3]

The continuous increase of isolable natural products as well as the pharmacological action of these quinolinediones has generated significant synthetic interest.[9−11] Simple analogues of these products can be suitable as precursors in the total synthesis of natural products as well as compounds with important biological properties. In this Letter we wish to report a simple, general, one-step method for the preparation of 3,3-disubstituted quinoline-2,4-diones to simplify routes to total synthesis of quinolinedione natural products.

Retrosynthetic analysis of 3,3(*R*,*R*′)-quinoline-2,4-diones leads to disconnections as shown in Scheme 1. Route B can only be used when the enol hydroxyl and amido functional groups are suitably protected. This demands several steps

(1) Chamberlain, R. T.; Grundon, F. M. *J. Chem. Soc. C* **1971**, 910.
(2) Dreyer, L. D. *Phytochemistry* **1980**, *19*, 941.
(3) Sheriha, M. G.; Abouamer, K.; Elshataiwi, Z. B. *Phytochemistry* **1987**, *26*, 3339.
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(8) *Quinolones*; Andriole T. V., Ed.; Academic Press: New York, 1988.
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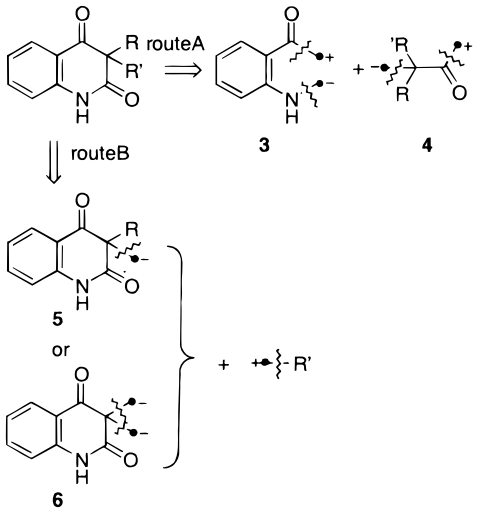
Scheme 1

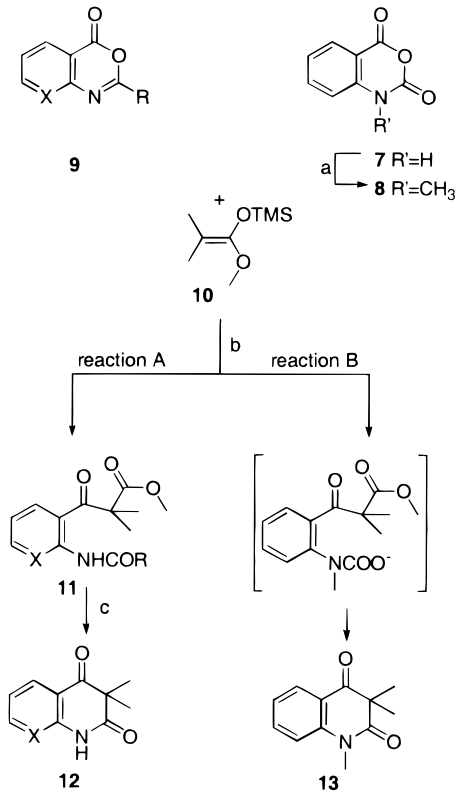


of masking and unmasking of these groups. Considering route A, isatoic anhydride derivatives (**7**, **8**) or 4*H*-3,1-benzoxazin-4-ones[12] (**9**) would be suitable precursors of synthon **3**.

At first, our team focused on preparing the simplest member of the target molecules, 3,3-dimethylquinoline-2,4-dione (**1**, R = R′ = Me). A rather complex method for preparing this compound was proposed by Evans et al. in 1987 using strong reaction conditions to cyclize the corresponding anilide by phosphorus pentoxide.[13] Our first attempt was based on the reaction between 2-methyl-4*H*-3,1-benzoxazin-4-one and an appropriate precursor of **4** such as ethyl isobutyrate. The reaction was unsuccessful when lithium diisopropylamide or lithium bis(trimethylsilyl)amide was employed as the required base, resulting the hydrolyzed benzoxazinone, 2-acetamidobenzoic acid, in quantitative yield.

Because of the sensitivity of this procedure to basic reaction conditions, our attention turned to the use of acidic conditions in order to initiate the reaction. In accordance with route A, an appropriate silyl ketene acetal[14] could be used as the precursor of synthon **4**. Thus, reaction of 1-methoxy-2-methyl-1-trimethylsiloxypropene (**10**) with methyl isatoic anhydride (**8**) or benzo[3,1]-4*H*-oxazin-4-ones (**9**, X = CH) in the presence of Lewis acid, as catalyst, gave the desired products **12** and **13** (Scheme 2). Treatment of 4*H*-3,1-benzoxazin-4-ones (**9**) with silyl ketene acetal offers the advantage of the isolation of the indermediates (**11**) which are stable using these reaction conditions. Variation of substituent R from phenyl to methyl (Scheme 2) resulted the formation of the final product (**12**) rather than the intermediate (**11**). This could be explained by the removal of the acetyl group due to the acidic conditions. The reaction proceeds smoothly under argon at room temperature and gives moderate yields (reaction A = 58−67%, reaction B = 48%) of the disubstituted quinolinediones, in a 3 h reaction time.

Scheme 2[a]



[a] (a) NaH, MeI, DMF; (b) $TiCl_4$, CH_2Cl_2, 25 °C; (c) 6 N HCl, reflux 48 h, R = Me, Ph; X = CH, N.

This is the first time that a reaction using modified Mukaiyama conditions[15−17] has been employed for lactones or anhydrides. This modification is based on the increase in the temperature to 25 °C in combination with the use of titanium tetrachloride as a catalyst.[18]

The mechanism of reaction B is shown in Scheme 3. Attempts to generate the desired products using other Lewis acids such as $AlCl_3$, $SnCl_2$, and $SnCl_4$ yielded only starting material. Attempts to react the isatoic anhydride (**7**) without

(12) For the preparation of benzo- or pyrido[3,1]oxazin-4-ones, see: (a) Krantz A.; Spencer W. R.; Tam F. T. *J. Med. Chem.* **1990**, *33*, 464. (b) Hund C.; Bethune V. *J. Org. Chem.* **1970**, *35*, 1471.

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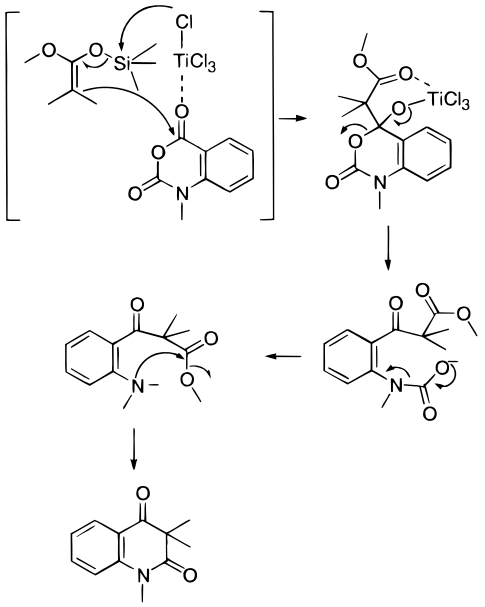
(16) For a review, see: Mukaiyama, T. *Angew. Chem., Ind. Ed. Engl.* **1977**, *16*, 817.

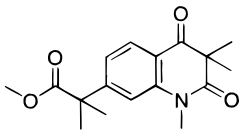
(17) Nelson, G. S. *Tetrahedron: Asymmetry* **1998**, *9*, 357.

(18) **General Procedure.** In a solution of **7** or **8** (1.5 mmol) in anhydrous dichloromethane, silyl ketene acetal (1.5 mmol) was added. The mixture was stirred at room temperature under argon, after which titanium tetrachloride was added in a dropwise manner. Stirring continued for 3 h. The mixture was quenced by water and extracted with dichlomethane. The dichloromethane extracts were evaporated in vacuo, and the residue was purified by column chromatography (chloroform−methanol 5:0.15) to afford the desired product.

Scheme 3



prior *N*-methylation were unsussessful due to its insolubility. As byproducts, we should underline the observation of small amount of product **14** (12%) formed by Friedel−Crafts alkylation of the target molecule by silyl ketene acetal.



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A simple modification that proves the generality of this method was to employ the suggested route to analogues such as 4*H*-pyrido[2,3-*d*][3,1]oxazin-4-ones (**9**, X = N) to obtain 3,3-disubstituted 1,8-naphthyridine-2,4-diones, a new class of molecules (Scheme 2, reaction A).

In conlusion, a new methodology has been introduced for the synthesis of 3,3-disubstituted quinoline-2,4-diones or 3,3-disubstituted 1,8-naphthyridine-2,4-diones, forwarding a new method for the preparation of natural products of this class.

Supporting Information Available: Experimental procedure and NMR characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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