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A Convenient One-Pot Synthesis of 1,8-Naphthyridones

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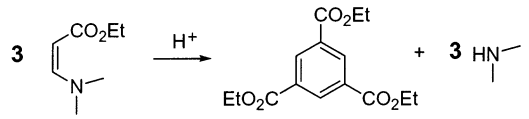
Abstract: In this paper, we disclose an efficient one-pot procedure for the preparation of substituted 1,8-naphthyridin-4-one analogues. Previous efforts to effect this type of transformation were complicated by the formation of benzene tricarboxylate. Via the use of excess base, the impurity formation was completely inhibited. This allowed for the clean preparation of the desired intermediate and subsequent formation of naphthyridone analogues in a single flask, which could then be crystallized directly from the reaction mixture in good yield and high purity.

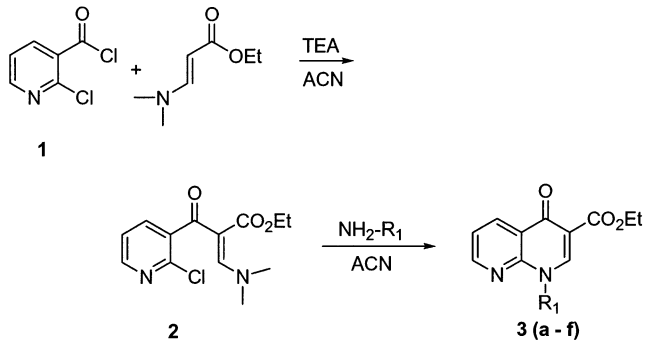
1,8-Naphthyridin-4-ones are a group of heterocycles that demonstrate biological activity toward numerous important targets. As a result there are many recent examples of preparing these compounds.[1]

Most of the documented chemistry for the formation of this particular class of naphthyridones utilizes one of two common approaches toward their synthesis. The first method involves the preparation of an alkyl 1-substituted-2-[2-substituted nicotinyl]acrylic acid ethyl ester intermediate (**2**), followed by base-catalyzed ring closure to form the desired naphthyridone. Of the several ways of preparing this intermediate many are labor intensive. They require the formation of a 2-substituted pyridinyl acetate typically prepared via malonic ester acylation with 2-chloronicotinoyl chloride, followed by decarboxylation and then subsequent reaction with either dimethylamino dimethyl acetal, triethylorthoformate/acetic anhydride, or an iminochlorothioformate.[2−6] A second option is to employ the use of a thermal rearrangement/cyclization that requires temperatures as high as 350 °C.[7−9] In this paper, we disclose a new, one-pot method

SCHEME 1



SCHEME 2



that involves the condensation of 2-chloronicotinoyl chloride with ethyl-3,3-dimethylaminoacrylate followed by in situ reaction with a variety of anilines to provide the desired 1,8-naphthyridone in a single flask.

We recently required a facile method for the preparation of 1,8-naphthyridone analogues on a large scale. While the existing methodology allowed access to a variety of these compounds, they suffered from high temperatures and or messy reaction mixtures that required tedious purification and were not immediately amenable to multi-kilogram scale. We envisioned a one-pot process that would allow for a convenient way of varying substitution, while providing pure material in good yield by direct crystallization of the product from the crude reaction mixture.

Our initial experiments involved heating 2-chloronicotinoyl chloride with dimethylamino acrylate in acetonitrile to provide the desired intermediate (**2**).[10] These reactions were complicated by the excessive formation of the corresponding triethyl 1,3,5-benzenetricarboxylate from trimerization of the acrylate (Scheme 1). We reasoned that this reaction was acid catalyzed and investigated the effect of base on the yield of the proposed reaction. It was found that the amount of trimer was inversely proportional to the amount of base. By taking advantage of this observation and using 4 equiv of base, the trimerization was completely inhibited in acetonitrile and the 3,3-(dimethylamino)-2-[2-chloronicotinyl]acrylic acid ethyl ester intermediate (**2**) was formed in high purity without the need to isolate. This allowed for the

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(9) Hirose, T.; Mishio, S.; Matsumoto, J.-I.; Minami, S. *Chem. Pharm. Bull.* **1982**, *30*, 2399.
(10) Chemistry involving the use of 3,3-dimethylaminoacrylate to form a 2-benzoylacrylic carboxylate was demonstrated in the following: Grohe, K. U.S. Patent 2 699 992, 1987. Bose, P.; Kumar, N.; Kiyoto, T. W.O. Patent 01 66512 A1, 2001. Neither utilized this chemistry for preparing 1,8-naphthyridin-4-ones.
(11) HPLC samples were quenched with *n*-propylamine, and consumption of starting material was considered complete when less than 3 liquid chromatography area percent *n*-propyl-2-chloronicotinamide was detected.

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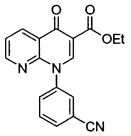
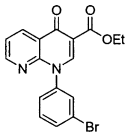
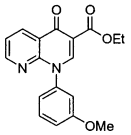
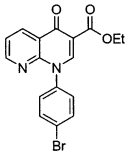
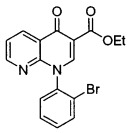
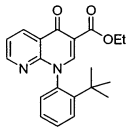
TABLE 1

Entry	Amine	Reaction Time	Product	Yield
a		18 h		67%
b		18 h		67%
c		18 h		64%
d		18 h		62%
e		24 h		43%
f		7days		26%

in situ addition of a given aniline to prepare the desired 1,8-naphthyridone.

With a successful one-pot method in hand, we next decided to investigate the scope of the reaction with respect to the nature and structure of the aniline (Table 1). Entries **a** and **c** demonstrate that both the electron-poor and electron-rich anilines behaved similarly. Thus, the electronic nature of the aniline does not seem to affect the reaction. However, the steric nature of the substituted anilines affected both reaction rate and yield. Differentially substituted bromoanilines were investigated in this reaction (entries **b**, **d**, and **e**). While 3- and 4-substitution gave similar yields within ordinary reaction times (~18 h), the analogous *o*-bromoaniline, entry **e**, which should be electronically similar, required more time to completely react (~24 h) and provided a lower yield. This observation was further supported by the results of the *o*-*tert*-butylaniline, entry **f**, which gave only a 26% isolated yield and required more then a week to completely react.

In conclusion, we have developed a synthetically useful, operationally simple and general synthesis of 1,8-naphthyridin-4-ones that allows for the preparation of a variety of important naphthyridone intermediates. Important to the success of this methodology was the observation of the acid-catalyzed trimerization of the aminoacrylate, and the need for excess base to inhibit the formation of this impurity to effect the desired transformation cleanly. The products were prepared from readily available starting materials in one pot and were isolated directly from the reaction mixture in high purity and in good to moderate yield.

Supporting Information Available: General procedure for the preparation of compound **3a** and characterization data for compounds **3a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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