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# A new approach to the facile synthesis of mono- and disubstituted quinazolin-4(3*H*)-ones under solvent-free conditions

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**Abstract**—Quinazolin-4(3*H*)-one derivatives were synthesized successfully via a one-pot, three component reaction of isatoic anhydride and an orthoester with ammonium acetate or a primary amine catalyzed by silica sulfuric acid under solvent-free conditions. This is the first report on the synthesis of 2-substituted quinazolin-4(3*H*)-ones by this procedure.
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## 1. Introduction

Quinazolin-4(3*H*)-one derivatives **1** possess a broad spectrum of biological and pharmaceutical activities,[1] such as antidiabetic,[2] anticonvulsant,[3] analgesic,[4] antibacterial,[5] phosphorylation inhibition,[6] EGFR inhibition,[7] PDGFR phosphorylation inhibition,[8] CNS depressant,[9] antitumor,[10] and diuretic activity.[11] Also quinazolinones are present in a wide variety of natural products[12] (Fig. 1). The most common approach toward quinazolinones involves the amidation of 2-aminobenzonitrile, 2-aminobenzoic acid, or its derivatives followed by oxidative ring closure under basic conditions.[13,14] This approach, however, is limited by low chemical yields. Recently, a synthesis of 2-substituted quinazolin-4(3*H*)-ones based on the oxidative cyclization of anthranilamide with aldehydes was reported.[15] However, the method suffers from the use of a toxic catalyst. Reports on solid phase synthesis of related quinazolinones are an additional impetus to explore their multifaceted importance.[16] As mentioned above, several methods have been reported for the construction of the quinazolin-4(3*H*)-one skeleton and new efforts have improved the yields and reaction time.[17]

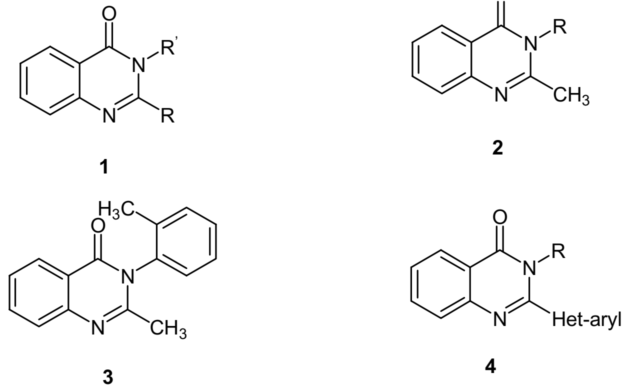

**Figure 1.**

In continuation of our efforts to develop more versatile methodologies for the synthesis of quinazolinone compounds,[18] herein, we report a simple and straightforward method for the one-pot preparation of mono- and disubstituted quinazolin-4(3*H*)-ones. Toward this goal, the solvent-free, three component reactions of isatoic anhydride, ammonium acetate, and different orthoesters, in the presence of catalytic amounts of silica sulfuric acid as a solid acidic catalyst,[19,20] were investigated (Scheme 1).

To the best of our knowledge, there is no report on the synthesis of mono-2-substituted quinazolin-4(3*H*)-ones

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*Keywords*: Quinazolin-4(3*H*)-ones; Silica sulfuric acid; Catalysis; Solvent free.

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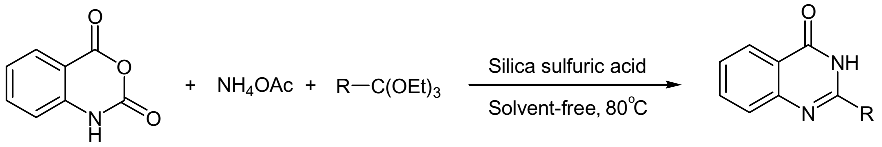


**Scheme 1.**

**Table 1.** Synthesis of 2-substituted quinazolin-4(3*H*)-ones by the reaction of isatoic anhydride, ammonium acetate and different orthoesters under solvent-free conditions

| Entry | R | Yield[a] (%) | Mp[b] (°C) |
|---|---|---|---|
| 1 | Me | 82 | 238–239[18b] |
| 2 | Et | 81 | 235–236[18b] |
| 3 | *n*-Pr | 86 | 206–207[18b] |
| 4 | *n*-Bu | 80 | 157–159[18b] |
| 5 | Ph | 78 | 236–237[18b] |

[a] Isolated yield.

[b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the reported procedures.

**Table 2.** Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones by the reaction of isatoic anhydride, primary amines, and different orthoesters under solvent free conditions

| Entry | R | R′ | Yield[a] (%) | Mp[b] (°C) |
|---|---|---|---|---|
| 1 | $CH_3$ | $4\text{-}ClC_6H_4$ | 78 | 156–158[18d] |
| 2 | $CH_3$ | $4\text{-}CH_3C_6H_4$ | 80 | 148–149[18d] |
| 3 | $CH_3$ | $C_6H_5$ | 81 | 145–146[18d] |
| 4 | $CH_3$ | $4\text{-}CH_3CH_2C_6H_4$ | 80 | 151–152[18a] |
| 5 | $CH_3$ | $C_6H_5CH_2$ | 85 | 230–231[18a] |
| 6 | $CH_3$ | $C_6H_5CH_2CH_2$ | 83 | 100–101[18a] |
| 7 | $CH_3$ | $CH_3CH_2$ | 87 | 64–66[18d] |
| 8 | $CH_3$ | $2\text{-}CH_3C_6H_4$ | 81 | 113–115[18a] |
| 9 | $CH_3CH_2$ | $CH_3CH_2$ | 86 | 96–97[18b] |
| 10 | $CH_3CH_2$ | $4\text{-}CH_3C_6H_4$ | 81 | 162–163[18d] |
| 11 | $CH_3CH_2$ | $4\text{-}BrC_6H_4$ | 78 | 170–172[18d] |
| 12 | $CH_3CH_2CH_2$ | $4\text{-}CH_3C_6H_4$ | 84 | 145–147[18d] |
| 13 | $CH_3CH_2CH_2$ | $C_6H_5CH_2CH_2$ | 81 | 105–106[18a] |
| 14 | $CH_3CH_2CH_2$ | $4\text{-}BrC_6H_4$ | 77 | 138–140[18a] |
| 15 | $CH_3CH_2CH_2$ | $C_6H_5$ | 80 | 120–121[18d] |
| 16 | $CH_3CH_2CH_2$ | $4\text{-}CH_3C_6H_4$ | 79 | 145–146[18d] |
| 17 | $CH_3CH_2CH_2CH_2$ | $C_6H_5CH_2CH_2$ | 79 | 109–110[18a] |
| 18 | $C_6H_5$ | $C_6H_5$ | 79 | 157–159[18d] |
| 19 | $C_6H_5$ | $4\text{-}CH_3C_6H_4$ | 78 | 179–180[18d] |
| 20 | $C_6H_5$ | $4\text{-}ClC_6H_4$ | 75 | 190–192[18d] |
| 21 | $C_6H_5$ | $C_6H_5CH_2CH_2$ | 80 | 175–176[18a] |

[a] Isolated yield.

[b] The products were characterized by comparison of their spectroscopic and physical data with authentic samples synthesized by the reported procedures.

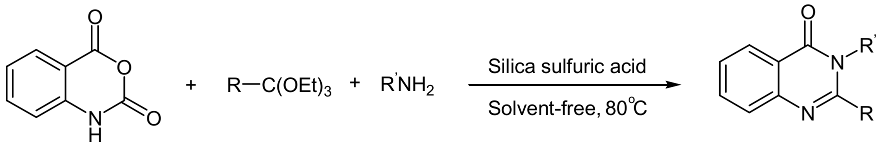
via a one-pot procedure. As shown in Table 1, the target compounds were successfully synthesized in high yields. In this method, ammonium acetate was used as a cheap and safe source of ammonia for manipulation of N-3 in the quinazolin-4(3*H*)-one ring (**1**) (Fig. 1). Orthoesters, which install C-2 in the product, were chosen with aliphatic and aromatic substituents in order to show the versatility of the method. In each case, the product was obtained in good yield.

The synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones was another goal of this study. When isatoic anhydride, a primary amine, and an orthoester, were mixed in the presence of catalytic amounts of silica sulfuric acid under solvent-free conditions, the expected products were obtained satisfactorily (Scheme 2). The results are summarized in Table 2.

Several aliphatic and aromatic amines with different substituents gave the corresponding products in high yields in all cases. 2-Methyl quinazolinone derivatives **2** (Table 2, entries 1–8) (valuable intermediates for the synthesis of 2-heteroaryl quinazolinone compounds **4** with special importance in drug discovery)[21] were synthesized successfully (Fig. 1). Methaqualone (**3**), which has been known as a sedative-hypnotic[1a] compound for a long time, was synthesized by the present method in 81% yield after 4 h (Table 2, entry 8).

The recyclability of the catalyst was investigated using a model reaction of isatoic anhydride, ethylamine, and triethyl orthoacetate in the presence of 30 mol % of the catalyst. After completion of the reaction, ethanol was added and the mixture was filtered to separate the catalyst. The separated catalyst was used for further runs. The activity of the catalyst did not show any significant decrease even after five runs (Table 3).

In summary, we have developed an efficient and versatile method for the preparation of a series of 2-mono- and 2,3-disubstituted quinazolin-4(3*H*)-ones via a one-pot three component reaction of commercially available starting materials. The reusability of the catalyst together with elimination of toxic organic solvents make the procedure green and environmentally friendly. We hope that because of the diversity of this method, it



**Scheme 2.**

**Table 3.** Recycling of silica sulfuric acid for the reaction of isatoic anhydride, triethyl orthoacetate, and ethylamine under solvent-free conditions

| Run no. | Yield[a] (%) | Time (h) |
|---|---|---|
| 1 | 87 | 4 |
| 2 | 85 | 4.5 |
| 3 | 86 | 5 |
| 4 | 84 | 6.5 |
| 5 | 86 | 6 |

[a] Isolated yield.

can be adopted in combinatorial chemistry to synthesize and screen libraries of related important quinazolin-4(3*H*)-ones.

## 2. General procedure for the synthesis of mono-substituted quinazolin-4(3*H*)-ones

Isatoic anhydride (1 mmol), ammonium acetate (1.2 mmol), and the orthoester (1 mmol) were mixed thoroughly with silica sulfuric acid and heated at 80 °C for 4 h. After completion of the reaction, hot ethanol was added to the mixture, which was then filtered. The solvent was evaporated and the crude product was recrystallized from ethanol.

## 3. General procedure for the synthesis of disubstituted quinazolin-4(3*H*)-ones

A mixture of silica sulfuric acid (0.3 mmol, 0.11 g), isatoic anhydride (1 mmol), the primary amine (1.2 mmol), and the orthoester (1 mmol) were heated for 4 h at 80 °C. Work-up as above, afforded the disubstituted product.

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