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Original article

T3P catalyzed one pot three-component synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones

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ABSTRACT

An efficient methodology for the synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones is described *via* one-pot three component reaction from anthranilic acid using T3P as catalyst. Mild reaction conditions, short reaction time, broad functional group tolerance, easy isolation of products and good yields are main advantages of this protocol.

1. Introduction

Multi-component reactions (MCR) have emerged as a powerful strategy in the preparation of heterocyclic compounds due to the advantages compared to conventional linear-type multi-step synthesis [1–4]. Major advantages of MCR include lower cost, shorter reaction time and overcoming time consuming and sparing of purification process. It is established that MCRs are in general much more environment friendly and offer rapid access to large compound libraries with diverse functionalities [5]. The quinazolinone moiety is a building block for many naturally occurring alkaloids [3] such as chloroqualone [6,7], deoxyvasicinone [8], rutaecarpine [9] and bioactive molecules like methaqualone [10] (Fig. 1).

Quinazolinone alkaloids and substituted quinazolinones are a class of natural drugs which display a variety of phormocological and therapeutic activities [11–18], such as anti-inflamatory, anticonvulsant, antiulcer and antimalerial. Number of synthetic routes have been developed for the synthesis of 4(3*H*)-quinazolinones, which include copper-catalyzed *N*-arylation of *o*-bromobenzoic acid derivatives with amidines and subsequent intramolecular condensation affording 2 and 2,3-disubstituted quinazolinones [19], Liu *et al.*, and Ioannis *et al.*, reported a microwave assisted synthesis of 2,3-disubstituted quinazolinones [20,21], Adib *et al.*, reported the K_2CO_3 catalyzed reaction of isatoic anhydride, benzyl halides and amines [22] (Scheme 1).

Several reports available for the synthesis of 2,3-disubstituted quinazolinones, however, some of these multistep procedures have significant drawbacks such as long reaction times, low yield, harsh reaction conditions and use of expensive reagents [23–26]. Development of simple and efficient methods for the synthesis of 2,3-disubstituted quinazolinones are more desirable. T3P was initially employed as peptide coupling agent and water scavenger with low toxicity and less allergic [27,28]. Its utility has been successfully demonstrated in rearrangement reactions [29–31], heterocyclic synthesis [32] and its shows versatile catalytic property [33]. In continuation of our work on synthetic applications of T3P [34–36], here in, we report the synthesis of various disubstituted 3*H*-quinazolin-4-ones which involving an *in situ* coupling of amines with anthranilic acid followed by the cyclocondensation of anthranilamide intermediate with different aldehydes, and further dehydrogenation gives 2,3-disubstituted quinazolinones.

2. Experimental

All of the reagents were used directly as obtained commercially. Column chromatography was performed with silica gel (100–200

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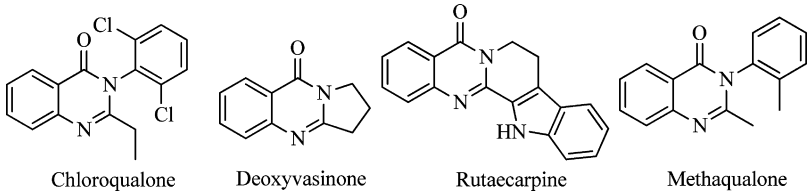
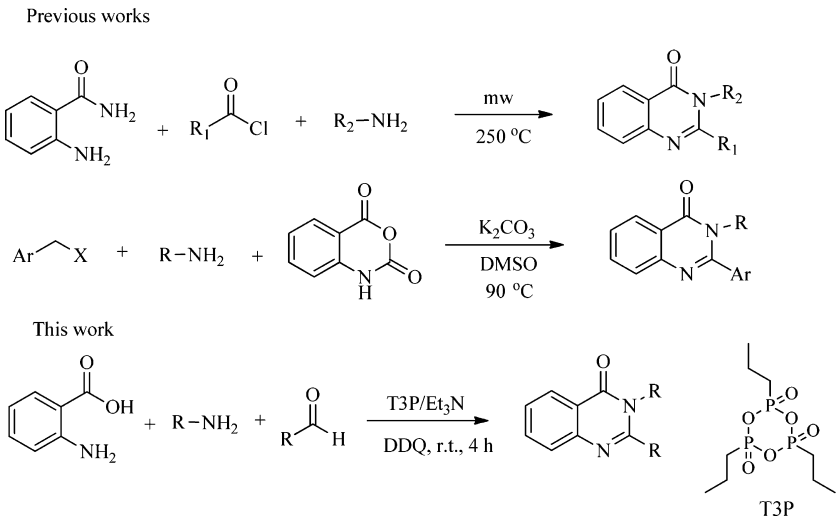


Fig. 1. Representative examples of bioactive compounds containing quinazolinone motif.



Scheme 1. General approaches for the Synthesis of 2,3-di substituted quinazolinones.

mesh) and analytical TLC on silica 60-F24. ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-d_6 on a Bruker Fourier 300 MHz spectrometer (or Bruker Avance III 400 MHz) and chemical shifts (δ) reported relative to internal TMS.

General procedure: To a solution of anthranilic acid (1 mmol) in ethyl acetate (3 mL) solvent, triethyl amine (1.5 mmol) and T3P (2 mmol) was added and the resulting reaction mixture was stirred at room temperature for 1–2 h. Then, aldehyde (1 mmol) was added and stirred for another 1–2 h. The reaction was monitored by TLC. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1 mmol) was added to the reaction mixture and further stirred for 30 min. After completion of the reaction, the mixture is diluted with (20 mL) water and neutralized with 10% $NaHCO_3$ solution. The product was extracted with ethyl acetate (10 mL) and the combined organic phase was washed with water (10 mL) and brine solution. The organic phase was dried over anhydrous Na_2SO_4. The solvent was dried under reduced pressure to afford a crude product, which was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to provide the desired product. 2,3-Disubstituted 3*H*-quinazolin-4-ones **4a–4p** are characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis and LCMS, the detail please see Supporting information.

3. Results and discussion

Initial investigations involved to determine the scope and optimal conditions for T3P/DDQ catalyzed synthesis of 2,3-disubstituted quinazolinones. Anthranilic acid **1a** was selected as a model (Table 1), the reaction of **1a** (1.1 equiv.), **2a** (1.0 equiv.), Et_3N (1.5 equiv.) and T3P (2.0 equiv., 50% solution in EtOAc) in 10 volume of EtOAc at 25 °C for 2 h yielded an amide intermediate, which was then treated with an aldehyde **3d** and DDQ were stirred for additional 2 h to gave a dihydro 2,3-disubstituted quinazolinone. Remarkably, the reaction proceeded efficiently even at room temperature. In fact, high yield of **4d** was observed in this instance (Table 1, entry 4). A reduction in the loading of T3P to 1.5 equiv. showed negative effect on the yield of **4d** (Table 1, entry 2), whereas increasing to 2.5 equiv. did not offer any significant advantage over the 2 equiv. catalyst loading (entry 3). Further screening of appropriate oxidants indicated that DDQ is superior to iodine, iron chloride ($FeCl_3$), *tert*-butyl hydroperoxide (TBHP) were less effective in this oxidative dehydrogenation reaction. In the absence of DDQ, 2,3-dihydroquinazolinone-4(1*H*)-one was formed and the results are summarized in Table 1.

The influence of various solvents on the synthesis of 2,3-disubstituted quinazolinone **4d** was studied in which ethyl acetate was chosen as the appropriate solvent with consideration of yield and the results are summarized in Table 1 (entry 4–10).

Under the established conditions, we evaluated the reactions of anthranilic acids (**1a–c**), amine (**2a–f**), and aldehydes (**3a–g**). In all cases, products were obtained in good yield at room temperature. Finally, benzylic amines, allylamines, amino esters also underwent the title reaction under equally mild conditions. Furthermore, we found that the reaction showed good tolerance to the electronic properties of the substituents on the benzene ring of aldehydes. The target quinzolinones **4(a–p)** were all formed in excellent yields, regardless of whether the aldehyde containing electron-withdrawing or electron-donating substituent's (Table 2).

A possible mechanism of the coupling cyclization to get di-substituted quinazolinones suggested in Scheme 2. The catalytic reaction involves the activation of anthranilic acid **1a** by T3P followed by reaction with amine to give anthranilamide. The second step in the probable mechanism of T3P catalyzed condensation of anthranilamide with aldehyde to afford an intermediate **E,** which generates an imine intermediate **F**. The byproduct P,P′,P″-tripropyl triphosphonic acid **C** protonates imine to give protonated imine **G.** The next step involves intramolecualr cycloaddition to yield the key intermediate **H**, and the subsequent