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# A new approach to the facile synthesis of 2-substituted-quinazolin-4(3*H*)-ones

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**Abstract**

A new approach to the facile synthesis of 2-substituted-quinazolin-4(3*H*)-ones and its derivatives using the condensation reaction of substituted 2-aminobenzamide and orthoesters is reported.


*Keywords:* Quinazolin-4(3*H*)-ones; Synthesis; Aminobenzamide; Orthoester

Quinazolin-4(3*H*)-one derivatives possess a broad spectrum of biological and pharmaceutical activities. Several successfully clinical drugs are based on this scaffold. In particular, the 2-substituted quinazolinones have been utilized as peptidomimetic scaffolds with specificity for cholecystokinin, angiotensin and cell adhesion receptors [1–6]. Therefore, considerable efforts have been made to explore simple and direct approaches for the construction of 4(3*H*)-quinazolinone skeletons [7].

The most common approach for quinazolinones involves the amidation of 2-aminobenzonitrile, 2-aminobenzoic acid, or its derivatives followed by oxidative ring closure under basic conditions. Among them, the main synthetic routes employ 2-aminobenzoic acid, isatoic anhydride, *N*-arylnitrilium salts and 3,1-benzoxazinones as appropriate precursors [8–15]. In addition to the reactions mentioned above, quinazolinones have been obtained by the reaction of 2-aminobenzonitrile and orthoesters catalyzed by Keggin-type heteropolyacids or under basic conditions in different solvent [16–18]. However, most of these reported methods suffer from low yields or tedious procedures. Herein, we report a facile synthesis of 2-substituted quinazolin-4(3*H*)-ones and its derivates in high yields using condensation reaction of substituted 2-aminobenzamide and orthoesters (Scheme 1).

In the present study, the target compounds were successfully synthesized within 1.5–3 h via condensation of 2-aminobenzamide or 2-amino-5-nitrobenzamide with the corresponding variety of commercially available orthoesters under mild conditions (Table 1). In addition to **3a**, this reaction proceeds without organic solvent and in the absence of some types of basic or acidic catalyst. In all cases, the crude products precipitated from the reaction mixtures after

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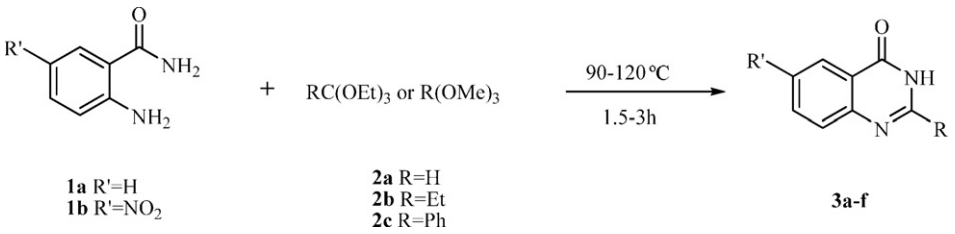
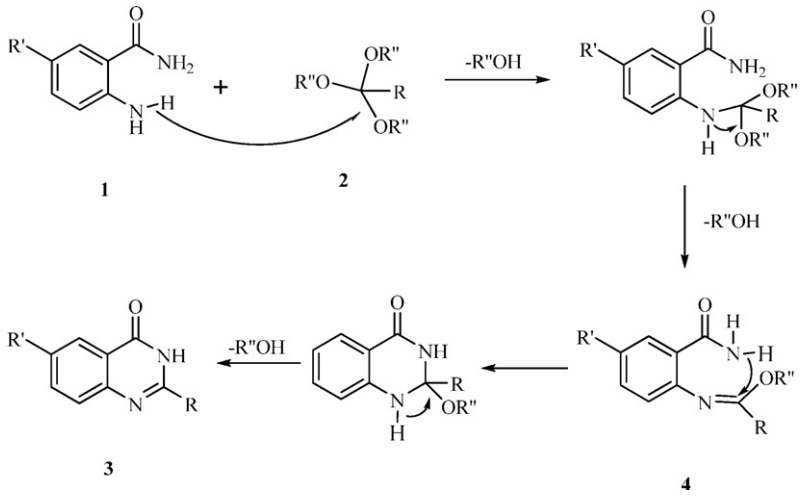



Scheme 1. Synthesis of 2-substituted-quinazolin-4(3*H*)-ones.

Table 1
Reaction conditions and results.

| Entry | Product | R | R′ | Time (h) | Yield (%) | Mp (°C) |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | H | 1.5 | 61 | 215–216 |
| 2 | **3b** | H | Et | 1.5 | 84 | 235–237 |
| 3 | **3c** | H | Ph | 2 | 97 | 237–238 |
| 4 | **3d** | $NO_2$ | H | 1.5 | 81 | 275–276 |
| 5 | **3e** | $NO_2$ | Et | 3 | 80 | 278–279 |
| 6 | **3f** | $NO_2$ | Ph | 3 | 86 | 297–299 |




Scheme 2. The cyclization mechanism of 2-substituted-quinazolin-4(3*H*)-ones.

cooling were purified by recrystallization with high yield. Furthermore, this method is suitable for the preparation of 2-substituted-quinazolin-4(3*H*)-ones and its derivatives.

The reaction may proceed through the intermediacy of the imidicester **4** which undergoes nucleophilic attack by the carboxyl oxygen to produce the cyclized product with the elimination of a molecule of alcohol (Scheme 2).

The structures of compounds **3a–f** were confirmed by $^{1}H$, $^{13}C$ NMR and MS spectral analysis and their physical properties were identical with those of authentic samples prepared by reported procedures (see Supplementary data).

In conclusion, we have developed a simple and highly efficient practical method for one-pot synthesis of the title compounds without solvent under classical heating. Due to the simplicity of the procedure which is eco-friendly, and can be expected to find utility in the construction of 4(3*H*)-quinazolinone skeletons.

## 1. Experimental

$^{1}H$ and $^{13}C$ NMR spectra were recorded using TMS as the internal standard in DMSO-$d_6$ with a Bruker BioSpin GmbH spectrometer at 400.132 MHz and 100.614 MHz, respectively; MS spectra were recorded on a Shimadzu

LCMS-2010A instrument with an ESI or ACPI mass selective detector. Melting points were determined using an SRS-OptiMelt automated melting point instrument without correction.

*Procedures for preparation of 4(3H)-quinazolinone **3a***: A mixture of 2-aminobenzamide (2 mmol) and triethyl orthoacetate (2 mmol) in ethanol (10 mL) was stirred at room temperature for 1.5 h. The reaction was monitored by TLC. The reaction mixture was then allowed to cool to 0 °C and the precipitate thus, obtained was filtered off and recrystallized from ethanol to give white needles of **3a**.

*General procedure for preparation of 2-substituted quinazolin-4(3H)-ones and its derivates **3b–f***: A stirred mixture of 2-aminobenzamide or 2-amino-5-nitrobenzamide (20 mmol) and the orthoester (40 mmol) was heated under reflux for 1.5–3 h. The reaction was monitored by TLC. The reaction mixture was cooled to 0 °C and the white or buff precipitate thus obtained was filtered off and recrystallized from ethanol to give white or buff needles of **3b–f**.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2011.01.034.

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