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Three-component one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives in 2,2,2-trifluoroethanol

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ABSTRACT

Trifluoroethanol (TFE) is found to be an efficient and recyclable medium in promoting one-pot, three-component coupling reactions of isatoic anhydride, aldehyde and ammonium acetate or primary amine to afford the corresponding 2,3-dihydroquinazolin-4(1*H*)-one derivatives in high yields. The solvent (TFE) can be readily separated from reaction products and recovered in excellent purity for direct reuse.

1. Introduction

Fluorinated solvents have recently received a great deal of attention as potential new media for organic synthesis [1]. Owing to their unique physicochemical properties (high hydrogen bonding donor ability, nonvolatility, nonflammability, polarity, high ionizing power, and low nucleophilicity), fluorinated alcohols modify the course of reactions when they are used as solvents, allowing reactions which usually require the use of added reagents or metal catalysts to be carried out under neutral and mild conditions [2–16]. Therefore, today they have marched far beyond this border, showing their significant role in controlling the reaction as powerful reaction media. Reactions in fluorinated solvents are generally selective and without effluents, allowing thus a facile isolation of the product and a recovery of the solvent by distillation. In order to take advantage of these properties, we have studied bond cleavage and formation reactions facilitated by the acidic character and strong hydrogen bond donor ability of fluorinated alcohols. In a continuation of our work on the application of fluorinated alcohols in several organic transformations [17–22], we have developed an efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives under reflux conditions in 2,2,2-trifluoroethanol without the use of a catalyst or any other additives. 2,3-dihydroquinazolinones are very important compounds partially because of their pharmacological properties which include wide applications in medicinal chemistry; notable among them are antifertility, antibacterial, antitumor, antitremor, antifungle, and mono-amine oxidize inhibition [23–26]. In addition, 2,3-dihydroquinazolinone derivatives have recently been evaluated as antagonists of various biological receptors, such as 5-HT_{5A} related diseases [27], calcitonin gene-related peptide [28], and vasopressin V3 receptors [29]. Despite 2,3-dihydroquinazolinone usage in pharmaceutical and other industries, comparatively few methods for their preparation have been reported. In accordance with the significance of 2,3-dihydroquinazolinone, several synthetic methods have been developed for the construction of this kind of fused heterocycles from suitable precursors [30–45]. Very recently, Lee et al. reported a one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using ethylenediamine diacetate in aqueous media under reflux condition [46]. However, some of these procedures have certain limitations such as harsh reaction conditions, use of expensive acid catalysts in organic solvents, long reaction time, tedious work-up, and low yields. Thus, the development of novel methods for the

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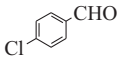
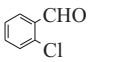
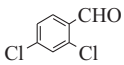
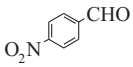
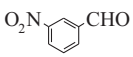
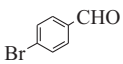
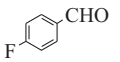
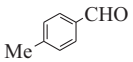
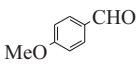
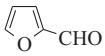
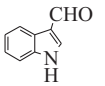
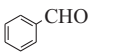
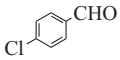
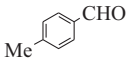
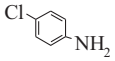
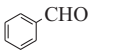
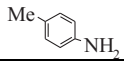
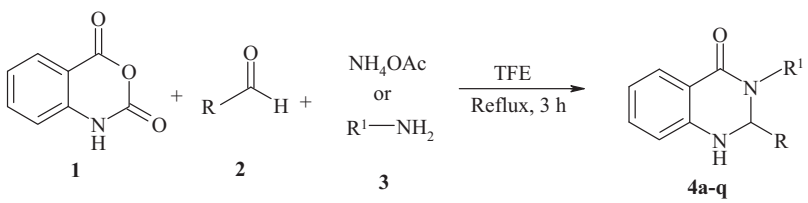
Table 1
Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in TFE.

Entry	Aldehyde	Amine	Product	Yield %
1		NH_4OAc	**4a**	95
2		NH_4OAc	**4b**	97
3		NH_4OAc	**4c**	80
4		NH_4OAc	**4d**	85
5		NH_4OAc	**4e**	92
6		NH_4OAc	**4f**	90
7		NH_4OAc	**4g**	90
8		NH_4OAc	**4h**	95
9		NH_4OAc	**4i**	90
10		NH_4OAc	**4j**	85
11		NH_4OAc	**4k**	92
12		NH_4OAc	**4l**	85
13			**4m**	85
14			**4n**	90
15			**4o**	85
16			**4p**	85
17			**4p**	90

synthesis of dihydroquinazolin-4(1*H*)-ones is of great importance because of their potential biological and pharmaceutical activities. The present investigation describes a facile preparation of 2,3-dihydroquinazolinone derivatives via one-pot condensation of isatoic anhydride and aldehydes with NH_4OAc or primary amine in Trifluoroethanol (TFE) (Scheme 1).

2. Results and discussion

In an initial endeavor, the reaction was carried out by simply mixing isatoic anhydride, benzaldehyde and NH_4OAc (Table 1, entry 1) in trifluoroethanol and refluxing the resulting mixture for 3 hours. The corresponding 2,3-dihydroquinazolin-4(1*H*)-one **4a** was



Scheme 1. One-pot three-component condensation of isatoic anhydride, aldehydes and NH_4OAc or primary amine in TFE.