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FULL-LENGTH PAPER

An efficient, multicomponent approach for solvent-free synthesis of 2-amino-4*H*-chromene scaffold

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Abstract Solvent-free one-pot synthesis of 2-amino-4*H*-chromene scaffold is described in a very simple, efficient, and environmentally benign method using sodium carbonate as a cheap and non-toxic catalyst with up to excellent yields.

Keywords 2-Amino-4*H*-chromenes · Solvent-free · Multicomponent reactions · Domino reactions · *Knoevenagel–Michael* addition

Introduction

The chromene moiety is an important structural component of many naturally occurring compounds. A particularly interesting group of chromenes are 2-amino-4*H*-chromenes (or 2-amino-4*H*-benzo[*b*]pyrans), since they are used as cosmetics and pigments [1,2], spasmolytic, diuretic, anticoagulant, antianaphylactic [3,4], antibacterial [5], anticancer agents [6], and as potent apoptosis inducers [7].

A multicomponent reaction (MCR) is a one-pot reaction in which three or more reactants are combined together to generate a desired product without the isolation of any intermediate [8,9]. The MCR strategy has gained increasing attention in the past decade because of its capability to prepare compound libraries in the field of modern medicinal and combinatorial chemistry [10–12]. The combination of solvent-free and MCR reactions represents a very powerful method from both economical and synthetic points of view since the isolation of the intermediates is skipped, the overall reaction time is significantly decreased, higher yields of products are obtained, and due to less use of solvents and reagents the costs are lowered.

2-Amino-4*H*-chromenes are generally prepared by refluxing active methylene compounds (e.g., malononitrile and cyanoacetic acid esters), with an aldehyde and an activated phenol in organic solvents such as ethanol and acetonitrile, and in the presence of organic bases such as piperidine for several hours [13–16]. Recently, several modified catalysts such as cetyltrimethylammonium chloride [17], cetyltrimethylammonium bromide under ultrasound irradiation [18], KSF clay [19], KF/Al_2O_3 [20], $TiCl_4$ [21], triethylamine [22], basic γ-alumina [23], MgO [24], heteropolyacids [25], basic ionic liquids [26], iodine/K_2CO_3 [27], and DABCO [28] have been used in this reaction. However, only a few of these catalysts (e.g., MgO, basic alumina) are suitable to catalyze the reaction of malononitrile with aromatic aldehydes with active α-naphthol (but not suitable for less active β-naphthols), whereas some others require longer reaction times, difficult workup procedures and afford only moderate yields.

For these reasons and in our continuing interest in the development of environmental friendly protocols for one-pot solvent-free multi-component reactions [29–35], we report herein our results for the synthesis of 2-amino-4*H*-chromene scaffold using Na_2CO_3 as an efficient catalyst for the three-component solvent-free condensation of an aldehyde, malononitrile and an activated phenol with excellent yields.

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