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$Bi(TFA)_3$–[nbp]$FeCl_4$: a new, efficient and reusable promoter system for the synthesis of 4(3*H*)-quinazolinone derivatives

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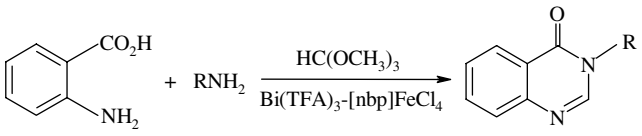
Abstract—4(3*H*)-Quinazolinones have been synthesized in high to excellent yields through the one-pot condensation of anthranilic acid, trimethyl orthoformate and primary amines in the presence of 5 mol % of $Bi(TFA)_3$ immobilized on [nbp]$FeCl_4$ as a room temperature ionic liquid.

1. Introduction

4(3*H*)-Quinazolinones have emerged as an important class of nitrogenated heterocycles that have attracted significant synthetic interest because of their pharmacological and therapeutic properties such as antibacterial, antifungal, antimalarial, antihypertensive, anticonvulsant, anti-Parkinsonism, antihistaminic and local anaesthetic, analgesic, anti-inflammatory antiviral and anticancer activities.[1] A small number of quinazolinones have been reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example, 3-aryl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4(3*H*)-diones and 3-arylquinazoline-2,4(1*H*,3*H*)-diones as antimycobacterial agents[2] and quinazolinone derivatives as antitubercular agents.[3] The antihyperlipidemic activities of these compounds were also investigated.[4] There are several methods for the synthesis of 4(3*H*)-quinazolinones.[5] However, most of these procedures have significant drawbacks such as long reaction times, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. Recently, Das et al., have demonstrated a green process for the synthesis of 4(3*H*)-quinazolinones, which is limited in that only phenyl R groups are tolerated.[6] More recently, Liu et al. reported another procedure for the synthesis of these compounds through a two-step reaction in the presence of $P(PhO)_3$/anhydrous pyridine under microwave irradiation at 250 °C.[7] The second strategy seems to be more flexible but needs toxic reagents and harsh reaction conditions are required.

The demand for increasingly clean and efficient chemical synthesis is important from both economic and environmental points of view.[8] One commonly used method is the immobilization of Lewis acids on ionic liquids. Several catalysts have been immobilized on ionic liquids and successfully recycled as a result of the involatile nature of these media.[9] These ionic catalytic systems gave much higher reaction rates and selectivities than those performed in classical organic solvents.[10] In recent years, we have reported that bismuth(III) trifluoroacetate is a mild and non-toxic catalyst that is stable in water and is reusable.[11] Also, we have examined some important transformations in the presence of Lewis acids immobilized on ionic liquids.[12] In continuation of our work to develop new synthetic methodologies, we report a facile and efficient method for the synthesis of 4(3*H*)-quinazolinone derivatives by the condensation reaction of anthranilic acid, trimethyl orthoformate and primary amines in the presence of a catalytic amount of $Bi(TFA)_3$ in *n*-butylpyridinium tetrachloroferrate ([nbp]$FeCl_4$)[13] as a room temperature ionic liquid (Scheme 1).



Scheme 1.

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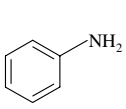
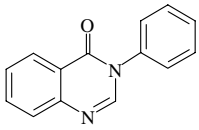
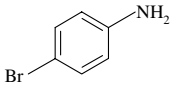
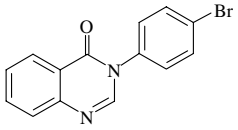
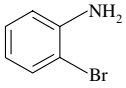
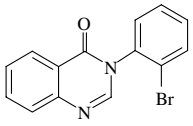
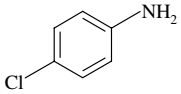
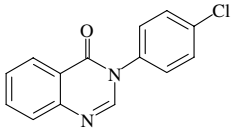
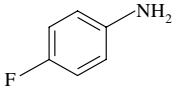
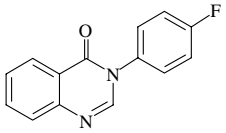
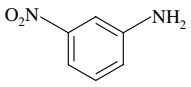
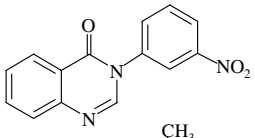
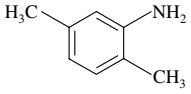
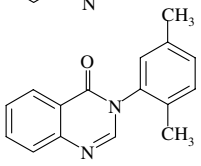
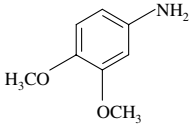
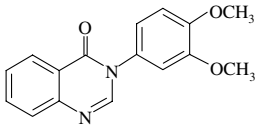
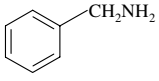
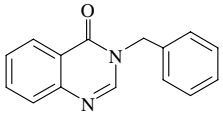
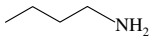
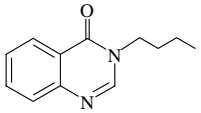
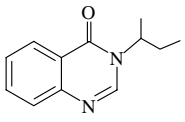
The experimental procedure is simple. The reactions were carried out at 60 °C for 5–20 min by reacting a 1:1.2:1.2 mole ratio mixture of anthranilic acid, trimethyl orthoformate and primary amine in the presence of 5 mol % of $Bi(TFA)_3$ in [nbp]$FeCl_4$ to give the desired products in high to excellent yields. As shown in Table 1, both aniline derivatives and primary aliphatic amines react without any significant difference to give the corresponding 4(3*H*)-quinazolinones. The reaction is fairly general, clean, rapid and efficient. Significant amounts of undesirable side products were not formed. Unlike previously reported methods, the present method does

Table 1. Synthesis of 4(3*H*)-quinazolinones in the presence of $Bi(TFA)_3$ immoblized on [nbp]$FeCl_4$ as a room temperature ionic liquid

Entry	Amine	Quinazolinone	Time (min)	Yield (%)[a]
1			10	94
2			15	90
3			15	83
4			15	92
5			15	90
6			20	79
7			15	93
8			10	95
9			5	91
10			5	98
11			10	97

[a] Yields refer to isolated pure products characterized by NMR and MS spectra.

not require toxic or anhydrous organic solvents. All the products were characterized by NMR, IR and mass spectroscopy and also by comparison with authentic samples.

Interestingly, we observed that the combination of $Bi(TFA)_3$–[nbp]$FeCl_4$ was essential for this transformation. Attempts to carry out the reaction in the absence of each of these did not yield the products and only the starting materials were isolated. On the other hand, trimethyl and triethyl orthoformate reacted similarly these reaction conditions. Another advantage of this method for this is the recyclability of this promoter system. Since $Bi(TFA)_3$–[nbp]$FeCl_4$ was weakly soluble in Et_2O, it could be separated by washing with Et_2O and dried at 80 °C under reduced pressure and reused in three runs without any loss of activity.

In conclusion, we have demonstrated an efficient procedure for the synthesis of 4(3*H*)-quinazolinones. The notable features of this procedure are mild reaction conditions, clear reaction profiles, improved yields for both anilines and primary amines, enhanced rates and simplicity in operation, which make it a useful and attractive process for the synthesis of 4(3*H*)-quinazolinones. Moreover, the reusability, stability and non-toxicity of the catalyst and ionic liquid are other noteworthy advantages of this method.

2. Typical procedure for the synthesis of 3-(4-bromophenyl)-4(3*H*)-quinazolinone (Table 1, entry 2)

To a mixture of anthranilic acid (1 mmol), trimethyl orthoformate (1.2 mmol) and 4-bromoaniline (1.2 mmol) in [nbp]$FeCl_4$ (1 mmol), $Bi(TFA)_3$ (0.05 mmol) was added. The reaction mixture was stirred at 60 °C for 15 min. After completion of the reaction (monitored by TLC) the mixture was washed with Et_2O (3×10 ml) filtered and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-heptane/ethyl acetate 5:1 as eluent) to afford the pure product in 90% yield.

2.1. Data for 3-(4-bromophenyl)-4(3*H*)-quinazolinone (Table 1, entry 2)

Mp 185 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.43 (d, 1H, $J = 8.6$ Hz), 8.12 (s, 1H), 7.95–7.21 (m, 7H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.3, 134.6, 133.4, 132.7, 131.4, 130.7, 128.5, 128.1, 127.7, 127.68, 127.6, 127.1; EIMS *m*/*z* 302, 300 (M^+).

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13. The ionic liquid, *n*-butylpyridinium tetrachloroferrate [nbp]$FeCl_4$ was prepared by the reaction of *n*-butyl pyridinium chloride (1 mmol) with $FeCl_3$ (1 mmol) for 1 h at room temperature.