ABSTRACT: Quinazolinone derivatives are essential units in a wide range of relevant pharmacophores with a broad spectrum of abilities. Due to their wide range of pharmacological and therapeutic activities including anti-inflammatory, hypolipidemic, anticancer, and anti-ulcer, the synthesis of quinazolinone moieties as a privileged class of fused heterocyclic compounds, have received much attention. An efficient and one-pot three components route was developed for the synthesis of 4(3H)-quinazolinones using commercially available starting materials. In order to synthesis of target compounds in good to excellent yields, a reaction between isoanhydride, acylchlorides, and amines in the presence of propylsulfamic acid functionalized magnetic hydroxyapatite nanoparticle $\gamma$-$\text{Fe}_2\text{O}_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H, as a highly efficient and magnetically separable Brønsted acid catalyst, was performed. The organic layer was dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated under vacuum and the residue was recrystallized from 96% EtOH to give 2, 3-disubstituted 4-(3H)-quinazolinone derivatives in high yield. The reaction condition including the solvents, the amount of $\gamma$-$\text{Fe}_2\text{O}_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H, reaction time and required temperature was optimized.

Keywords: Amines; Hydroxyapatite nanoparticles; Isatoic anhydride; 4(3H)-Quinazolinones; Multicomponent reactions; Propylsulfamic acid.

INTRODUCTION

Quinazolinone derivatives are essential units in a wide range of relevant pharmacophores with a broad spectrum of abilities [1-3]. Due to their wide range of pharmacological and therapeutic activities including anticonvulsant [4], anti-inflammatory [5], hypolipidemic [6], anticancer [7], and anti-ulcer [8], the synthesis of quinazolinone moieties as a privileged class of fused heterocyclic compounds [9], have received much attention. In recent years, several synthetic methods have been applied for the synthesis of 4(3H)-quinazolinone derivatives in which the condensation of a 2-aminobenzoic acid or its derivatives with amides has been mentioned as the most common synthetic approach. Various methods which have been recently applied for the synthesis of target compounds involve the cyclocondensation of different substrates [10], multi-step reactions under microwave irradiation [11] or in ionic liquids [12, 13], and also there are some reports on metal catalyzed examples [14, 15]. Meanwhile, there are some methods have been reported for the one-pot synthesis of 4(3H)-quinazolinone derivatives using isoanhydride–anthranilic acid, ortho esters and amines [16]. Based on our knowledge, a few reports has been reported on the one-pot synthesis of 4(3H)-quinazolinones using acyl halides as a starting material [17-22]. However, some of the reported pathways have some drawbacks such as low yields, long reaction times, high temperature and harsh reaction conditions, difficult and time consuming work-up, and use of expensive reagents and catalysts. Therefore, the development of a novel and efficient methodology for the synthesis of 4(3H)-quinazolinelines is in demand. Recently, metal nanoparticles have
received much attention and they have been applied in many fields of sciences [23-25]. Additionally, due to both economic and environmental reasons, magnetic nanoparticles have taken up a special position in organic syntheses either as support or catalyst [26-29].

Using them as support to prepare heterogeneous catalyst, results in the straightforward separation of catalyst from the reaction mixture. We have therefore turned our attention to these systems [30]. Focusing on the pharmacological importance of 4(3H)-quinazolinones, and wide application of metallic nanoparticles in different fields [31-33], we wish to introduce a novel n-propylsulfamic acid functionalized magnetic hydroxyapatite nanoparticle [γ-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H].

**EXPERIMENTAL**

**General**

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. $^1$H- and $^{13}$C-NMR spectrum was recorded on Bruker FT-500, using TMS as an internal standard. The elemental analysis was performed with an Elementar Analysen system GmbH VarioEL CHNS mode. All reagents and solvents were purchased from Aldrich and Merck, and used without any purification.

**Synthesis of nanocatalyst n-propylsulfamic acid supported on HAp-encapsulated-γ-Fe$_2$O$_3$ [γ-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H]**

To manufacture the catalyst, first HAp-encapsulated γ-Fe$_2$O$_3$ was prepared according to the previously reported method [30]. A mixture of FeCl$_2$·4H$_2$O (368 mg, 1.85 mmol) and FeCl$_3$·6H$_2$O (1 g, 3.7 mmol) were dissolved in 30 mL deionized water (DW) under Ar atmosphere at r.t, then a 25% NH$_4$OH solution (10 mL of dry toluene and 3-aminopropyltrimethoxysilane (92 mg, 0.5 mmol). The mixture was refluxed under Ar atmosphere at 100°C for 48 h. The solid residue was separated by an external magnet, washed with EtOH, and dried under vacuum for 24 h after soxhlet extraction by hot EtOH to give the solid surface bonded amine group [γ-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NH$_2$] at a loading ~ 0.75 mmolg$^{-1}$ (calculated by the back-titration analysis). Next, chlorosulfonic acid (CISO$_3$H) (8.6 mmol, 1 g) was added to 10g of [γ-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NH$_2$] at r.t over 30 min. The mixture was stirred vigorously for 6 h. The resulted magnetic nanoparticles were separated by an external magnet and washed with hot EtOH, deionized water, and diethyl ether and then dried under vacuum at r.t. to give [γ-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H] at a loading 0.75 mmolg$^{-1}$ (calculated back-titration and ion exchange pH analysis).

**Typical Procedure for preparation of 4(3H)-Quinazolinones**

A mixture of isatoic anhydride (1) (2.0 mmol), amine (2a-c) (2.2 mmol), acylchloride (3a-g) (2.2 mmol), and [γ-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H] (10 mg, 0.75 mol%) in DCM (1 mL) were stirred at 40°C until completion (2 h). In all cases, the progress of the reaction was monitored by TLC. After 2 h, the reaction mixture was diluted with DCM. The catalyst separated by a magnet device, washed with diethyl ether and dried to reuse in the next runs. The organic layer was washed with the saturated aqueous NaCl solution (5 mL), and water (10 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated under vacuum and the residue was recrystallized from 96% EtOH to give 2, 3-disubstituted 4-(3H)-quinazolinone derivatives in high yield.

2,3-Diphenyl-3,4-Dihydroquinazolin-4-one (4a)

$^1$HNMR (400 MHz, CDCl$_3$, ppm) δ=7.13-7.16 (m, 2H) 7.20-7.24 (m, 2H), 7.27-7.34 (m, 6H), 7.50-7.53 (m, 1H), 7.81-7.85 (m, 2H), 8.22 (d, $J$ = 7.5 Hz, 1H).

$^{13}$CNMR (100 MHz, CDCl$_3$, ppm) δ=122.1, 128.3, 128.4, 128.9, 129.1, 129.5, 130.1, 130.3, 130.5, 135.8, 136.2, 138.9, 148.6, 154.3, 163.5.

2-Phenyl-3-(p-tolyl)-Quinazoline-4(3H)-one (4b)

$^1$HNMR (400 MHz, CDCl$_3$, ppm) δ=2.18 (s, 3H), 7.02-7.05 (m, 2H), 7.11-7.15 (m, 2H), 7.21-7.25 (m, 3H), 7.33-7.38 (m, 2H), 7.50-7.53 (m, 1H), 7.73 (s, 2H), 8.31 (d, $J$ = 7.5 Hz, 1H).

$^{13}$CNMR (100 MHz, CDCl$_3$, ppm) δ=20.1, 120.3, 126.1, 127.5, 127.7, 128.4, 128.6, 129.0, 129.1, 129.5, 130.1, 130.3, 130.5, 135.8, 136.2, 138.9, 148.6, 154.3, 161.8.

2-(p-Tolyl)-3-Phenyl-Quinazoline-4(3H)-one (4c)

$^1$HNMR (400 MHz, CDCl$_3$, ppm) δ=2.18 (s, 3H), 7.02-7.05 (m, 2H), 7.11-7.15 (m, 2H), 7.21-7.25 (m, 3H), 7.33-7.38 (m, 2H), 7.50-7.53 (m, 1H), 7.73 (s, 2H), 8.31 (d, $J$ = 7.5 Hz, 1H); $^{13}$CNMR (100 MHz, CDCl$_3$, ppm) δ=20.1, 120.3, 126.1, 127.5, 127.7, 128.4, 128.6, 129.0, 129.2, 129.5, 134.5, 135.4, 135.9, 138.1, 146.2, 154.2, 161.8.

2-(p-Tolyl)-3-Phenyl-Quinazoline-4(3H)-one (4d)

$^1$HNMR (400 MHz, CDCl$_3$, ppm) δ=2.25 (s, 3H), 7.11 (d, $J$ = 7.5 Hz, 2H), 7.18 (d, $J$ = 8 Hz, 2H), 7.25 (d, $J$ = 8 Hz, 2H), 7.32-7.38 (m, 3H), 7.55 (s, 1H), 7.88 (s, 2H), 8.39 (d, $J$ = 7.5 Hz, 1H); $^{13}$CNMR (100 MHz, CDCl$_3$, ppm) δ=20.5, 122.2, 126.4, 126.8, 127.5, 128.4, 128.8, 129.0, 129.3, 133.8, 134.6, 136.7, 140.5, 146.8, 156.5, 162.1.
RESULTS AND DISCUSSION

Silica-coated uniform maghemite $\gamma$-Fe$_2$O$_3$ core-shell particles were synthesized by a chemical co-precipitation technique of Fe$^{2+}$ and Fe$^{3+}$ ions in alkaline solution and tetraethyl orthosilicate (TEOS), then propyl sulfamic acid functionalization was achieved by surface modification of $\gamma$-Fe$_2$O$_3$@SiO$_2$ using aminopropyl trimethoxy silane, subsequently by chlorosulfonic acid. The transmission electron microscopy (TEM) image of the synthesized nanocatalyst $[\gamma$-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H] was shown in Fig. 1.

Amides are attractive starting materials because they are easily available, but amides themselves are rarely used as precursors in organic synthesis due to their relative stability. The nitrogen atom in amide functional group, donates its lone pair electrons to carbon-nitrogen bond, which leads to decrease the electrophilicity of carbonyl group and nucleophilicity of nitrogen group. Due to this fact, there are several reports to activate the amide moiety [34]. We believed that $[\gamma$-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H] was found to be useful for our purpose. The three component one-pot condensation of isatoic anhydride 1, benzoyl chloride 2a, and aniline 3a was selected as a model reaction. The reaction condition including the solvents, the amount of $[\gamma$-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H], reaction time and required temperature was optimized. As shown in Table 1, among three different solvents and conditions, CH$_2$Cl$_2$, 40 °C, and 10 mg (0.75 mol%) leads to the best results. It was observed that no quinazolinone 4a is formed in the absence of $[\gamma$-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H], and also using the higher amounts of $[\gamma$-Fe$_2$O$_3$-HAp-(CH$_2$)$_3$-NHSO$_3$H] show no significant improvement in this reaction.

Then, a wide range of structurally diverse acyl chlorides 2, amines 3, and isatoic anhydrides 1 were reacted under the optimum conditions (Fig. 2) and the results are summarized in Table 2.

In all cases, the three component reaction proceeded smoothly to afford the corresponding 4(3H)-quinazolinone derivatives in good to excellent yields. The results also showed that aliphatic and aromatic amines reacted to give the corresponding quinazolinones in good yields. Also it is found that amines or acyl halides having an electron-donating or electron withdrawing group tolerated the cyclization reaction to give the corresponding quinazolinone in satisfactory yields.

It is concluded that this procedure is an efficient method for the preparation of quinazolinone derivatives from isatoic anhydride, acylhalides and amines under mild conditions. The observed and literature melting points are in Table 2.
Finally, the reusability of the catalyst was explored. To this purpose, after reaction completion, the catalyst was recovered using an external magnet, washed with H₂O and EtOH and then oven-dried at 80 °C overnight. A new reaction was then performed with fresh reactants under identical conditions. Using this approach, our catalyst was reused for at least 3 times without any further treatment while no appreciable loss in the catalytic activity was observed (Fig. 3).

CONCLUSION

In conclusion, we have developed a convenient one-pot approach for the synthesis of 4(3H)-quinazolinone derivatives from isatoic anhydride, different amines and
Table 2: Synthesis of Quinazolinone derivatives.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R</th>
<th>Yield</th>
<th>Observed Temperature</th>
<th>Literature reference</th>
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<tr>
<td>4a</td>
<td>C_6H_5</td>
<td>C_6H_5</td>
<td>94</td>
<td>159-160</td>
<td>[35,36]</td>
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<tr>
<td>4b</td>
<td>4-Me C_6H_5</td>
<td>4-Me C_6H_5</td>
<td>78</td>
<td>178-179</td>
<td>[35,36]</td>
</tr>
<tr>
<td>4c</td>
<td>4-C_1C_6H_5</td>
<td>C_6H_5</td>
<td>80</td>
<td>173-175</td>
<td>[35,36]</td>
</tr>
<tr>
<td>4d</td>
<td>4-MeO C_6H_5</td>
<td>C_6H_5</td>
<td>85</td>
<td>198-200</td>
<td>[35,36]</td>
</tr>
<tr>
<td>4e</td>
<td>4-MeO C_6H_5</td>
<td>4-MeO C_6H_5</td>
<td>88</td>
<td>178-180</td>
<td>[35,36]</td>
</tr>
<tr>
<td>4f</td>
<td>2-Cl C_6H_5</td>
<td>C_6H_5</td>
<td>89</td>
<td>172-175</td>
<td>[35,36]</td>
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</table>

REFERENCES


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