Synthesis and Insecticide Activity of Octahydroquinazolinone derivatives

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Abstract
A simple method for the synthesis of octahydroquinazolinone derivatives in the presence of BF₃·SiO₂ and Insecticide activity of these compounds against Spodoptera litura was investigated to be comparable to commercial pyrethroid insecticides, Cypermethrin and Cyhalothrin. The structure of the isolated compounds was characterized by ¹H NMR and FT-IR spectroscopy. The proposed method had some advantages such as high yield, mild reaction condition, ease of operation and workup, high product purity and green process.

Key words: Insecticidal activity, BF₃·SiO₂, Octahydroquinazolinone.

Introduction
Octahydroquinazolinone derivatives are an important class of the organic compounds which due to their molecular structure, have important biological activities such as antibacterial activity [1,2] and calcium antagonist activity [3,4]. Several methods have been developed for the preparation of Octahydroquinazolinone derivatives. In general, simple procedures have been employed for the synthesis of dihydropyrimidinones using dimedone, aromatic aldehydes and urea/thiourea, in the present of catalysts such as Zn(OTf)₂ [2] Nafion-H [4], TMSCl [5], Conc.H₂SO₄ [6], lanthanum oxide [7], ZrOCl₂.8H₂O [8], silica sulfuric acid [9], ionic liquid [tbmim]Cl₂/AlCl₃ [10], Phosphotungstic Acid Nanoclusters [11] and ammonium metavanadate [12]. Silica supported boron trifluoride, BF₃·SiO₂, which is easy to prepare, shows unusually high acidity which can be controlled by activation temperature, and exhibits considerable catalytic activity [13], enables
better accessibility of the reactants to the active sites. The BF$_3$SiO$_2$ is used in several organic transformations, such as in Claisen-Schmidt condensations [14], in syntheses of 14-aryl or alkyl-14H-dibenzo[a,j] xanthenes [15], 1,2,4,5-tetrasubstituted imidazoles [16], tetrahydrobenzo[a]xanthenes-11-one [17], in the polymerization of styrene [18], the preparation of polyfunctionalized piperidin-4-ones [19], α-amino phosphonates [20], quinoxalines [21], and 3,4-dihydropyrimidin-2(1H)-ones [22].

Spodoptera litura is a serious pest causing enormous losses to many economically important cultivated crops such as cotton, soybean, groundnut, tobacco and vegetables [23]. Sometimes it has been found to cause 26–100% yield loss in the field [24]. Its control has depended mostly on application of various insecticides. As a result, many field populations of this pest have developed multiple resistances and field control failure has been observed very frequently [25-29].

Materials and methods

General

The materials were purchased from Sigma–Aldrich and Merck and were used without any additional purification. Products were characterized by FT-IR, $^1$H-NMR and comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-500 Avanes) NMR was used to record the $^1$H NMR spectra.

Preparation of BF$_3$SiO$_2$

3.7 g of BF$_3$ (7.0 ml of BF$_3$.Et$_2$O) was added dropwise to a mixture of 6.3 gr of silicagel and 10 ml of chloroform. The mixture was stirred for 1 h at room temperature. The resulted suspension was filtered. The obtained solid was washed by chloroform and dried in a domestic microwave oven for 20 min in power 100 [30].

General procedure for the synthesis of octahydroquinazolinone derivatives in solvent condition

A mixture of aldehydes (10 mmol), dimedone (10 mmol) and urea/thiourea (15 mmol) with the BF$_3$.SiO$_2$ (10 mol%) in 1,2-dichloroethanesolvent at the reflux. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer was then washed by deionized water and dried over anhydrous Na$_2$SO$_4$. Organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to afford the pure corresponding octahydroquinazolinone derivatives in excellent yields. All products were identified by comparison of their physical and spectral data with those of authentic samples.
In vitro insecticidal activity

The biological assay was conducted against third-instar larvae of *S. litura* (7 ± 1 day old) using the feeding method and topical treatment [31].

Feeding method

The castor leaf was dipped in a 0.1% solution of synthesized compounds for 2 s and then air-dried. Moist filter paper was placed in glass Petri plates (9 cm diameter) on which treated leaf disks were kept. Larvae of *S. litura* preserved for 4h were released individually into each Petri plate. Thirty replications were kept for each treatment. Solvent was used as control. Mortality was observed after 24h.

Topical treatment

The 0.1% stock solution of various compounds was prepared in dichloromethane. 2 mL of each compound was applied on the ventral side of the *S. litura* larvae. Ten treated larvae were released in glass bottles, and fresh tender castor leaves were given as food. Each treatment was kept in triplicate, and solvent was used as control. Mortality was observed after 24h.

Insect growth regulatory activity (IGR)

The IGR activity of the above synthesized compounds was evaluated against *S. litura* following the test procedure. Third Instar larvae (*S. litura*) reared on the artificial diet was used for IGR activity. The 0.1% stock solution of test compounds was prepared using appropriate solvent. Newly mold pre-weighed (30-40 mg) 3rd instar larvae were treated through leaf dip method with different concentrations of the compounds. Individual leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with ten third-instar larvae. Each treatment was performed in triplicate. Controls were treated with carrier solvent alone. After 24h, treated larvae were observed for larval weight, larval mortality, percentage pupation, deformed pupae, larval-pupal and pupil-adult intermediates, percentage adult emergence and deformed adults and the same were recorded.

Results and discussion

In our continuing search for insecticidal activity of substances and in connection with our efforts towards the study of synthesis of octahydroquinazolinone, we initiated an investigation on the insecticidal activity of these compound adducts against insecticidal. First, we described an efficient synthetic protocol for the preparation of these compounds that were shown to be active against *Spodoptera litura*

Initially, we investigated the synthesis of 4-(4-nitro-phenyl)-7,7-Dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline - 2, 5 - dione
using 4-nitrobenzaldehyde (10 mmol, 1.55 g),
dimedone (10 mmol, 1.50 g), urea (15 mmol,
0.9 g) and BF$_3$.SiO$_2$ as the catalyst under
various conditions (Scheme 1, Table 1). The
best conditions were obtained for BF$_3$.SiO$_2$(10
mol%) in 1,2-dichloroethane solvent at the
reflux (Table 1, entry 10).

Next, the synthesis of octahydroquinazolinone
derivatives were studied and summarized in
Table 2. In all cases, the three-component
reaction proceeded smoothly to give the
corresponding octahydroquinazolinone in
moderate to good yields. In brief, in this
studyBF$_3$.SiO$_2$ is introduced as an efficient,
catalyst for synthesis of octahydroquinazolinone
derivatives. All of products were characterized
by FT-IR and $^1$H-NMR.

Table 1. The synthesis of 4-(4-nitro-phenyl)-7,7-Dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Time (min)</th>
<th>Yield$^a$ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Chloroform</td>
<td>r.t.</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Chloroform</td>
<td>Reflux</td>
<td>25</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Ethanol</td>
<td>r.t.</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Ethanol</td>
<td>Reflux</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Water</td>
<td>r.t.</td>
<td>25</td>
<td>scarce</td>
</tr>
<tr>
<td>7</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Solvent-free</td>
<td>r.t.</td>
<td>25</td>
<td>36</td>
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<tr>
<td>8</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>Solvent-free</td>
<td>80°C</td>
<td>25</td>
<td>65</td>
</tr>
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<td>9</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>r.t.</td>
<td>25</td>
<td>59</td>
</tr>
<tr>
<td>10</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>Reflux</td>
<td>25</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>Reflux</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>BF$_3$.SiO$_2$(5)</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>Reflux</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>13</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>2nd run</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>Reflux</td>
<td>15</td>
</tr>
<tr>
<td>14</td>
<td>BF$_3$.SiO$_2$(10)</td>
<td>2nd run</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>Reflux</td>
<td>15</td>
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</table>

$^a$ Isolated yield
All the octahydroquinazolinone derivatives were also evaluated for insecticide activity as well as insect growth regulatory activity against lepidopteran insect pest namely, *Spodoptera litura* (third instar larvae) at 0.1% dose by both contact and feeding method [30]. The results obtained as insecticidal activities against *Spodoptera litura* at 0.1% through both contact and stomach feeding technique are presented in Table 3 and IGR (insect growth regulator) activities of octahydroquinazolinone derivatives against *Spodoptera litura* at 0.1% are presented in Table 4. Figure 1 shows the insecticide activities of all compounds. In this figure the percent of inhibition of all compounds versus Spodoptera litura at 0.1% through both contact and feeding technique is presented. The contact and stomach Insecticidal activities of compound increase as 2-thioxo replace 2,5-dione and also the insecticidal activities of the compound increase with increasing the number of hydroxyl and methoxy groups in the molecule. For instance, compound 8 shows only moderate activities owing to 1-hydroxyl groups and methoxy group in its structure. Figure 2 illustrates IGR (insect growth regulator) activities of all compounds by means of the percent of growth inhibition index of all compounds versus *Spodoptera litura* at 0.1%. The increase of the IGR (insect growth regulator) activities of compounds increase by replacing 2-thioxo with 2,5-dione.
Table 3. Insecticidal activities against *Spodoptera litura* at 0.1% through both contact and feeding technique.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Insect mortality (S. litura)</th>
</tr>
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<tr>
<td></td>
<td>Contact</td>
</tr>
<tr>
<td>1</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
</tr>
<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
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<td>12</td>
<td>55</td>
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<tr>
<td>13</td>
<td>47</td>
</tr>
<tr>
<td>14</td>
<td>58</td>
</tr>
<tr>
<td>Cypermethrin</td>
<td>93</td>
</tr>
<tr>
<td>Cyhalothrin</td>
<td>80</td>
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</tbody>
</table>

Table 4. IGR (insect growth regulator) activities of all compounds against *Spodoptera litura* at 0.1%.

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Mortality</th>
<th>% Abnormal larva/dead larva</th>
<th>% Abnormal pupa/dead pupa</th>
<th>% Normal adult</th>
<th>% Growth inhibition index</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>8</td>
<td>12</td>
<td>20</td>
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<tr>
<td>2</td>
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</table>

Figure 1. Insecticidal activities of all compounds.
In conclusion, we demonstrated a simple method for the synthesis of octahydroquinazolinone derivatives using BF$_3$·SiO$_2$, as an eco-friendly, inexpensive and efficient reagent. Short reaction times, high yield and simplicity of operation are the main advantages of the present method. These promising results suggest that the evaluation of insecticidal activity should be extended to other structural types of octahydroquinazolinone derivatives.

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