An effective synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1H indazole derivatives

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ABSTRACT

A simple synthesis of 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1H indazole derivatives by the condensation of 1H indazole-3-carboxylic acid hydrazide and aromatic acids in the presence of phosphorus oxychloride under microwave irradiation in excellent yields. © 2009 Trade Science Inc. - INDIA

INTRODUCTION

The substituted oxadiazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores and many are key elements with potential biological activities such as pesticidal, anti-peripheral vasomotility, CNS stimulant, anti-inflammatory, hypotensive, insecticidal, bactericidal, hypoglycemic, analgesic, anticonvulsive, antiemetic, diuretic, muscle relaxant, and fungicidal activities. Indazoles constitute an important class of heterocycles that display interesting biological properties such as anti-depressant, anti-inflammatory, analgesic and antipyretic, dopamine antagonistic, anti-tumor, anti-emetic and anti-HIV activities. The indazole ring system is also present in many other compounds such as herbicides, dyes or sweeteners like guanidine-1Hindazole.

The application of microwave as an efficient heating source for organic reactions. The advantage of microwave assisted organic synthesis is the shorter reaction time using only small amount of energy. Simple experimental procedure, very high yields and clean reaction of many microwave assisted transformations offers additional convenience in the field of organic synthesis. Microwave assisted clays or solid supported reactions and solvent-free reactions have been extensively employed in organic synthesis. The solvent-free technique has been claimed economical and particularly environment friendly, since it avoids the use of solvents and offers a simpler method of workup. Biological properties associated with oxadiazole and indazole moieties and importance of solvent-free microwave irradiation technique promoted us to synthesize some oxadiazoles with indazole nucleus under microwave irradiation.

EXPERIMENTAL

Apparatus and reagents
All the melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. Do-
A domestic Microwave oven (frequency 2450 MHz and 900 W output power) was used for microwave irradiation. The progress of reaction was monitored by TLC. The IR spectra were recorded on Perkin-Elmer spectro-photometer in KBr disc. The 1H NMR spectra were recorded on Varian 300 MHz spectrometer in DMSO-d$_6$ as a solvent and TMS as an internal standard. The chemical shifts values are shown in δ ppm scale. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique.

**TABLE 1: Characterization data of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1H indazole (3a-g)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Conventional</th>
<th>Microwave</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>(3a)</td>
<td>C$_6$H$_5$</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>(3b)</td>
<td>2-ClC$_6$H$_4$</td>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>(3c)</td>
<td>3-ClC$_6$H$_4$</td>
<td>7</td>
<td>72</td>
</tr>
<tr>
<td>(3d)</td>
<td>2-OHC$_6$H$_4$</td>
<td>9</td>
<td>69</td>
</tr>
<tr>
<td>(3e)</td>
<td>2,4-(2,4,6$_3$C$_6$H$_3$</td>
<td>9</td>
<td>67</td>
</tr>
<tr>
<td>(3f)</td>
<td>4-OCH$_3$C$_6$H$_4$</td>
<td>9</td>
<td>71</td>
</tr>
<tr>
<td>(3g)</td>
<td>CH=CH-C$_6$H$_5$</td>
<td>8</td>
<td>68</td>
</tr>
</tbody>
</table>

*Isolated yields

**RESULT AND DISCUSSION**

In this paper we would like to report an efficient synthesis of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1H indazole derivatives by the reaction of 1H-indazole-3-carboxylic acid hydrazide with the aromatic acids in the presence of phosphorus oxychloride (SCHEME 1).

The titled compounds were synthesized successfully according to reported procedure used for the synthesis of other 1,3,4-oxadiazoles by both conventional[26] and microwave irradiation method[27]. In the conventional method 1H-indazole-3-carboxylic acid hydrazide (1) was treated with aromatic acids (2a-g) in presence of phosphorus oxychloride to afford the 5-substituted indazolyl oxadiazole derivatives (3a-g) in 6-9 h with good yields (65-76%). The reaction was found to proceed smoothly under reflux condition (TABLE 1).

Microwave assisted synthesis of 3-(5-aryl-[1,3,4]oxadiazol-2yl)-1H indazole derivatives (3a-g) were carried out by the reaction of 1H-indazole-3-carboxylic acid hydrazide (1) with the aromatic acids (2a-g) in the presence of phosphorus oxychloride using alumina as a solid support. The reaction was completed within 10-15 min with excellent product yields (80-90%) (TABLE 1).

To establish the generality with respect to carboxylic acid; acid hydrazide were treated with various substituted aromatic acids under the influence of microwave irradiation to get the corresponding oxadiazoles in excellent yields. The product was confirmed by IR, 1H NMR and Mass spectroscopic analysis technique[28].
In conclusion we have synthesized various 3-(5-aryl-[1,3,4]oxadiazole-2-yl)-1H indazole derivatives under microwave irradiation. The remarkable advantages of this method are short reaction times, solvent-free reaction conditions, ease of isolation, excellent yields of product.

ACKNOWLEDGEMENTS

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[28] (3g) IR (KBr, cm⁻¹): 3402, 1670, 1592, 1249, 887. ¹H NMR (DMSO, 300MHz): δ 3.90 (s, 3H, OCH₃), 7.50-7.90 (m, 7H, ArH), 8.22 (d, 1H, ArH), 8.52 (d, 1H, ArH). ES-MS: 293 (M+1).