Note

Ecofriendly synthesis of quinazolin-4(3H)-ones

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Several substituted quinazolin-4(3H)-ones are synthesized using environmentally benign procedure. Neat reactants on subjecting to microwave irradiation (MWI) in the presence of dicyclohexylcarbodimide (DCC) as a condensing agent give the required products more quickly and in better yields in comparison to traditional methodologies. The observed yields and enhancement in reaction rates are due to the solvent free conditions coupled with microwave usage.

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Quinazolin-4(3H)-ones moiety is known for diverse biological activities. Some of them possess several pharmacological properties including anticonvulsant activities. These are prepared generally in three steps requiring longer reaction time and poor yield.

Usage of microwave irradiation (MWI) is well known for the synthesis of variety of compounds wherein chemical reactions are accelerated because of selective absorption of microwave by polar molecules. The coupling of MWI with solid supported reagents under solvent free conditions provides unique chemical processes with special attribute such as enhanced reaction rate, higher yield, greater selectivity and ease of manipulation. But the above technique requires an appreciable amount of solvent for adsorption of reactants and elution of products. In the view of our ongoing research on neat synthesis, which aims at complete elimination of the solvent as well as solid support from the reaction, these no solvent reactions, when coupled with microwave radiation prove to be advantageous for environmental reasons as well due to their uniform heating effect and shorter reaction times.

In continuation of our interest in the development of environmentally benign protocols and the bioactivity of quinazolin-4(3H)-ones, we herein describe microwave assisted neat synthesis of quinazolin-4(3H)-one derivatives.

Result and Discussion

The o-(phenylacetyl)-aminobenzoic acid I and o-(benzoyl)-aminobenzoic acid I were synthesized from their corresponding anthranilic acid and benzoyl

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>R'</th>
<th>Yield (%)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>-CH₃Ph</td>
<td>-C₆H₅</td>
<td>80</td>
<td>8</td>
<td>92</td>
<td>2.5</td>
</tr>
<tr>
<td>4b</td>
<td>-CH₃Ph</td>
<td>p-C₆H₄NO₂</td>
<td>82</td>
<td>7</td>
<td>93</td>
<td>3.0</td>
</tr>
<tr>
<td>4c</td>
<td>-Ph</td>
<td>p-C₆H₄OMe</td>
<td>81</td>
<td>8</td>
<td>91</td>
<td>2.0</td>
</tr>
<tr>
<td>4d</td>
<td>-Ph</td>
<td>80</td>
<td>6</td>
<td>90</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>4e</td>
<td>-Ph</td>
<td>85</td>
<td>7</td>
<td>95</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>4f</td>
<td>-Ph</td>
<td>84</td>
<td>8</td>
<td>96</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>4g</td>
<td>-Ph</td>
<td>83</td>
<td>8</td>
<td>94</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>
chloride or phenylacetyl chloride according to the
literature method.4,5

Conventional synthesis of quinazolin-4(3H)-ones 4 from
2-aryl-3,1-benzoxazin-4-ones 2 requires glacial
acetic acid. The products were obtained in moderate
yield, but when the above reaction was carried out
over acidic alumina, the products were obtained within
several minutes in good yield (Table 1). The reaction
was also carried out over neutral alumina which gave
appreciable yield in the same reaction time. An
attempted conventional reaction for the synthesis of 4
from 1 and 3 in ethanol in absence of glacial acetic acid
yielded no product while the same reaction in presence
of DCC gave product in poor yield. This prompted us
to carry out the neat synthesis of 4 from 1 and 3 in
the presence of DCC as a condensing agent (Scheme I)
without using any solid support or solvent or an acid
which gave very good yield in shorter reaction time
(Table I).

The structure of compounds were confirmed on the
basis of spectroscopic data (Table II) Appearance of
IR band in the region of 1670-1645 (-N-C=O) and
1600-1500 (C=N) cm\(^{-1}\), also in \(\text{\textsuperscript{13}}\text{C}\) NMR spectrum,
signal at 159.5-161.8 due to C\(_2\) and 165.2-165.9 \(\delta\) due
to C\(_4\) (carbonyl carbon) of pyrimidine ring confirmed
the formation of products 4a-g.

Reactions under neat conditions gave better yields
with not much change in reaction time when compared
with solid support synthesis. Furthermore, the
usage of several heterocyclic amines led to synthesis
of novel quinazolin-4(3H)-ones derivatives.

Experimental Section

Physical and spectral data for the new compounds
are listed in Table II. Melting points were taken on
electrothermal apparatus and are uncorrected. IR
(KBr) were recorded on a model 599 Perkin-Elmer
Spectrophotometer, \(\text{\textsuperscript{1}}\)H NMR Hitachi R-600 at 300
MHz using TMS as internal standard. \(\text{\textsuperscript{13}}\text{C}\) NMR
spectra were recorded 300 MHz on a Bruker advance
spectrometer. The purity of compounds was checked
on silica gel coated aluminium plates (Merk). A ken-

![Scheme I](image)

**Table II—Physical and spectral data of compounds 4a-g**

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. (°C)</th>
<th>IR (KBr) cm(^{-1})</th>
<th>(\text{\textsuperscript{1}})H NMR</th>
<th>(\text{\textsuperscript{13}}\text{C}) NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>160(^t)</td>
<td>1670 1600</td>
<td>7.5-8.0 (m, 14H, Ar-H), 3.1 (s, 2H, CH(_2))</td>
<td>159.5 (C(_2)), 165.6 (C(_4)), 31.6 (C(_1) of C(_2))</td>
</tr>
<tr>
<td>4b</td>
<td>168(^t)</td>
<td>1672 1590</td>
<td>7.6-8.1 (m, 14H, Ar-H), 3.5 (s, 2H, CH(_2))</td>
<td>159.7 (C(_2)), 165.8 (C(_4)), 31.8 (C(_1) of C(_2))</td>
</tr>
<tr>
<td>4c</td>
<td>169(^t)</td>
<td>1665 1595</td>
<td>7.8-8.1 (m, 9H, Ar-H), 1.5-1.8 (s, 3H, CH(_3))</td>
<td>159.4 (C(_2)), 165.9 (C(_4)), 31.2 (C(_1) of C(_2))</td>
</tr>
<tr>
<td>4d</td>
<td>162</td>
<td>1660 1600</td>
<td>7.8-8.0 (m, 14H, Ar-H)</td>
<td>161.5 (C(_2)), 165.2 (C(_4)), 168.8 (C(_4) of C(_2)), 153.8 (C(_5) of C(_2))</td>
</tr>
<tr>
<td>4e</td>
<td>165</td>
<td>1650 1600</td>
<td>7.2-7.5 (m, 13H, Ar-H)</td>
<td>161.6 (C(_2)), 165.6 (C(_4)), 168.9 (C(_5)), 156.4 (C(_4) of C(_2))</td>
</tr>
<tr>
<td>4f</td>
<td>164</td>
<td>1645 1600</td>
<td>7.2-7.5 (m, 13H, Ar-H)</td>
<td>161.8 (C(_2)), 165.8 (C(_4)), 169.2 (C(_5) of C(_2)), 156.6 (C(_4) of C(_2))</td>
</tr>
<tr>
<td>4g</td>
<td>161</td>
<td>1670 1590</td>
<td>7.6-7.8 (m, 12H, Ar-H)</td>
<td>161.2 (C(_2)), 165.3 (C(_4)), 168.4 (C(_4) of C(_2)), 157.4 (C(_5) of C(_2))</td>
</tr>
</tbody>
</table>
star microwave oven at 2450 MHz was used for MWI.

General procedure for the synthesis of quinazolin-4(3H)-one derivatives 4a-g

Method A

Equimolar amount of 1 and 3 were condensed in the presence of DCC in 250 mL Erlenmeyer flask. The reaction mixture was irradiated for (2-4 minutes), reaction mixture was cooled, ice cold water was added and the solid separated was filtered off, washed with cold ethanol and recrystallized from ethanol.

Method B

Acidic alumina\(^6\) (20 g) was added to the equimolar mixture of 2 and 3 in ethanol (10 mL) at room temperature. The reaction mixture was thoroughly mixed and dried in air. It was then placed in an alumina bath\(^1\) and subjected to MWI. Upon completion of reaction as monitored by TLC, the reaction mixture was cooled and the product was extracted into ethanol (3 x 10 mL). Removal of solvent under reduced pressure afforded compounds 4a-g which were recrystallized from ethanol.

References

16. Aluminium oxide, acidic Brokman I, 150, mesh, 58 A CAMAG 506-1, Surface area 155 m\(^2\)/g, pH = 6.0.