One pot facile synthesis of 5-alkyl-1,2-dihydro-spiro[4H-3,1-benzoxazine-2,3’[3H]indol]-4,2’-diones under microwave irradiation

Anjali Saxena, Pankaj Khanna, Sunita Bhagat, Archana Gupta & Subhash C Jain

Department of Chemistry, University of Delhi, Delhi 110 007, India

E-mail: jainsc48@hotmail.com

Received 6 October 2005; accepted (revised) 9 January 2006

A facile synthesis of some novel 5-alkyl-1,2-dihydro-spiro[4H-3,1-benzoxazine-2,3’[3H]indol]-4,2’-diones, in high yields, has been carried out classically as well as under microwave irradiation in solvent free conditions. Microwave irradiation offers tremendous advantages in the form of shorter reaction time, operational simplicity, cleaner reaction, easy work-up and better yields as compared to the classical method. Besides this, some novel 6-alkylanthranilic acids required for the synthesis of new spiro compounds have also been synthesized. The importance of alkyl substituent at C-6 position in anthranilic acid has been recognized again in such a cyclocondensation reaction, even when it is carried out under microwave irradiation. This is also supported by molecular modeling.

Keywords: 5-Alkyl-1,2-dihydro-spiro[4H-3,1-benzoxazine-2,3’[3H]indol]-4,2’-diones, 6-alkylanthranilic acids, cyclocondensation, microwave, molecular modeling

IPC: Int.Cl. C07D

Microwave dielectric heating is rapidly gaining popularity in organic synthesis, as a source of thermal energy, for reactions in organic solvents as well as in dry media\(^1\). Microwave induced organic reactions, under solvent free conditions, have been extensively studied earlier in case of pyrroles\(^2,3\), \(\beta\)-lactams\(^4\) and indoles\(^5\). The resulting products such as spirobenzoxazine and spiro[benzoxazine-indol] are biologically important as they exhibit potent hypotensive, bactericidal and CNS depressant activity\(^6,7\).

Earlier, the cyclocondensation of indole-2,3-diones 4a-j with 6-methylanthranilic acid 3a in absolute ethanol has been achieved by a classical method\(^8\). 6-Alkylanthranilic acids used in these reactions are known for their biological importance\(^9\) and some of these have been used in the treatment of auto-immune diseases such as arthritis. In continuation of the ongoing search for novel bioactive heterocyclic pharmacophores\(^10-13\), the synthesis of some hitherto unknown title compounds starting from isatins 4a-j and novel 6-alkylanthranilic acids 3b-e under classical conditions as well as under microwave irradiation has been carried out. The compounds 3b-e required for the synthesis were obtained from methyl-2-nitro-6-(phenylsulfonylmethyl)-benzoate 1\(^14\) (Scheme I).

The present work describes the synthesis of a few known compounds 5a-j and some novel 5-alkyl-1,2-dihydro-spiro[4H-3,1-benzoxazine-2,3’[3H]indol]-4,2’-diones 5k-n under microwave irradiation in dry media. A comparative study of results obtained from conventional and microwave methods is briefly discussed. Microwave approach provides a faster, cleaner and simpler process for the synthesis of compounds 5a-n via cyclocondensation of indole-2,3-diones 4a-j with 6-alkylanthranilic acids 3a-e in dry media.

This method offers tremendous advantages in the form of reduction in reaction time, operational simplicity, cleaner reaction, easy work-up and better yields as compared to the conventional methods. Further, the method does not require any solid support for the reaction to occur. The cyclocondensation of indole-2,3-diones 4a-j and 6-alkylanthranilic acid 3a-e using microwave irradiation led to the formation of 5-alkyl-1,2-dihydro-spiro[4H-3,1-benzoxazine-2,3’[3H] indol]-4,2’-diones 5a-n in excellent yields within 2-6 min (Scheme II). For this purpose, several 6-alkylanthranilic acids 3a-e were mixed with indole-2,3-diones 4a-j thoroughly and the mixture was then separately subjected to microwave irradiation for 2-6 min to give the corresponding 5-alkyl-1,2-dihydrospiro[4H-3,1-benzoxazine-2,3’[3H]indol]-4,2’-diones...
5a-n (Table I). The structures of all the new products 2b-e, 3b-e, 5k-n were established from their physical and spectral characterization data and for known compounds 5a-j by comparison with authentic samples (Table II).

Results and Discussion

6-Alkylantranilic acids 3b-e required for the synthesis of the desired novel 5-alkyl-1,2-dihydrospiro[4H-3,1-benzoaxazine-2,3′[3H]indol]-4,2′-diones 5k-n have been prepared starting from methyl 2-nitro-
Table I — Comparison of reaction time for product formation and yields of compounds 5a-n using microwave and conventional method

<table>
<thead>
<tr>
<th>Compd</th>
<th>Conventional method</th>
<th>Microwave method (at 200 W power)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t_(min)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>5a</td>
<td>180</td>
<td>95</td>
</tr>
<tr>
<td>5b</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td>5c</td>
<td>120</td>
<td>96</td>
</tr>
<tr>
<td>5d</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td>5e</td>
<td>120</td>
<td>90</td>
</tr>
<tr>
<td>5f</td>
<td>180</td>
<td>94</td>
</tr>
<tr>
<td>5g</td>
<td>180</td>
<td>92</td>
</tr>
<tr>
<td>5h</td>
<td>240</td>
<td>95</td>
</tr>
<tr>
<td>5i</td>
<td>120</td>
<td>91</td>
</tr>
<tr>
<td>5j</td>
<td>240</td>
<td>93</td>
</tr>
<tr>
<td>5k</td>
<td>180</td>
<td>94</td>
</tr>
<tr>
<td>5l</td>
<td>120</td>
<td>96</td>
</tr>
<tr>
<td>5m</td>
<td>240</td>
<td>96</td>
</tr>
<tr>
<td>5n</td>
<td>180</td>
<td>97</td>
</tr>
</tbody>
</table>

Table II — Physical and spectral characterization data for 2b-e, 3b-e, 5k-n

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. °C</th>
<th>H NMR (δ, ppm)</th>
<th>C NMR (δ, ppm)</th>
<th>MS m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>59</td>
<td>0.86 (t, 3H, J = 6.4 Hz, -CH3), 1.18 (brs, 16H, 8 x CH2-), 2.34 (m, 2H, H-2'), 3.71 (s, 3H, -COOCH3), 4.48 (dd, 1H, J = 3.8 Hz and 11.2 Hz, H-1'), 7.43 (m, 2H), 7.53-7.70 (m, 4H), 8.08 (m, 2H).</td>
<td>13.9, 22.6, 26.3, 28.7, 29.0, 29.1, 29.3, 29.4, 31.7, 53.2 (C-1'), 65.8 (-COOCH3), 124.4, 128.7, 128.7, 129.6, 130.1, 130.3, 133.5, 136.4, 137.3, 149.1, 166.7 (-CO-).</td>
<td>587 (M+, 20), 445 (38), 263 (25), 245 (15), 215 (15), 189 (48), 169 (17), 155 (24).</td>
</tr>
<tr>
<td>3e</td>
<td>-</td>
<td>0.84 (t, 3H, J = 6.4 Hz, -CH3), 1.21 (brs, 10H, 5x-CH2-), 1.92 (t, 2H, J = 5.6 Hz, H-5'), 3.11 (m, 2H, H-2'), 3.71 (s, 3H, -COOCH3), 4.40 (dd, 1H, J = 3.8 Hz &amp; 11.2 Hz, H-1'), 7.43 (m, 2H), 7.53-7.70 (m, 4H), 8.08 (m, 2H).</td>
<td>14.1, 18.3, 20.1, 20.8, 22.5, 28.3, 28.5, 31.6, 53.2 (C-1'), 64.1 (-COOCH3), 73.1, 84.5, 124.5, 128.8, 129.1, 130.3, 130.5, 133.8, 134.1, 137.2, 147.8, 164.8 (-CO-).</td>
<td>471 (M+, 7), 412 (20), 329 (24), 279 (15), 213 (22), 180 (16), 151 (21).</td>
</tr>
<tr>
<td>3b</td>
<td>115</td>
<td>0.86 (t, 3H, J = 6.2 Hz, -CH3), 1.24 (brs, 16H, 8 x CH2-), 1.59 (m, 2H, H-2'), 2.87 (t, 2H, J = 7.2 Hz, H-1'), 6.52 (t, 2H, J = 8.0 Hz, H-3, H-5), 7.14 (brs, 4H, H-4, -NH2-).</td>
<td>16.3, 20.7, 22.3, 28.8, 29.0, 29.1, 29.7, 29.8, 30.0, 32.2, 53.1 (C-1'), 64.2 (-COOCH3), 124.1, 128.6, 128.9, 129.3, 129.6, 130.3, 130.6, 133.8, 133.9, 147.3, 149.8, 165.1 (-CO-).</td>
<td>585 (M+, 27), 554 (16), 444 (38), 428 (35), 345 (30), 331 (41), 326 (43).</td>
</tr>
</tbody>
</table>

(Contd)
6-(phenylsulfonylmethyl)-benzoate (Scheme I). Methyl 2-nitro-6-(phenylsulfonylmethyl)-benzoate 1 was coupled with the desired alkyl/alkenyl/alkynyl bromide to give the corresponding alkylated sulfones 2b-e. Desulfonation, deesterification and reduction of nitro to amino group, were all carried out in a single step by treating the alkylated sulfones 2b-e with 10% sodium amalgam in absolute ethanol to yield the corresponding 6-alkyl/alkenyl/alkynyl anthranilic acids 3b-e in 70-80% yield. The structures of these intermediates and of the final compounds have been established from their spectral characterization data as given in Table II.
Alkyl/alkenyl/alkynyl bromides required for the coupling reactions are either commercially available or have been prepared using the literature method\textsuperscript{15,16}. The synthesized alkylated/alkenylated/alkynylated compounds 2b-e were fully identified from their $^1$H NMR spectra, which showed a characteristic double doublet for -CH(SO$_2$Ph) in the region $\delta$ 4.47-4.80 (dd, 1H, $J$ = 3.8 and 11.2 Hz) along with other expected signals for aromatic and methyl ester protons.

The structures of 6-alkylanthranilic acids 3b-e were also established from their respective spectral characterization data before being taken up for the next step.

$^1$H NMR spectrum of 3b exhibited two aromatic resonances at $\delta$ 6.55 (t, 2H, $J$ = 8.0 Hz, H-3 and H-5) and $\delta$ 7.14 (brs, 4H, H-4 and N$^+\text{H}$), showing thereby a distinctive 1,2,3-substitution pattern. The signals indicating the presence of a terminal methyl group at $\delta$ 0.86 (t, 3H, $J$ = 6.2 Hz), number of methylene protons at $\delta$ 1.24 (brs, 16H), $\delta$ 1.59 (m, 2H) and for two benzylic protons at $\delta$ 2.87 (t, 2H, $J$ = 7.2 Hz) showed the presence of an alkyl side chain on an aromatic ring. Its IR spectrum showed the presence of two absorption bands at 3423 (N$^+\text{H}$) and 1601 (COO) cm$^{-1}$ suggesting thereby that these alkylated amino acids exist in zwitter-ionic form.

The physical and spectral characterization data of all these compounds are given in Table II.

Stirring of indole-2,3-diones 4a-j with 6-alkylanthranilic acids 3a-e in absolute ethanol, at RT, for about 2-4 hr furnished 5a-n. Alternatively, when an equimolar mixture of 3a-e and compound 4a-j was subjected to microwave irradiation at 200 W power level in an open vessel for 2-6 min, it furnished 5a-n in good yield. It is worth noting here that the reaction time reduced drastically when the reaction was carried out under microwave irradiation. For example, it has been reported\textsuperscript{5} earlier that this reaction takes 2-4 hr to be completed under classical conditions whereas under microwave irradiation, the reaction went to completion in 2-6 min. The results are tabulated in Table II. A comparison between the two methods clearly indicates that the microwave technique is much superior as it does not compromise with the yield while achieving desired results in extremely short times. The compounds 5a-j were characterized by direct comparison with the authentic samples and also by comparing their physical and spectral characterization data with those reported in the literature\textsuperscript{5}. The structures of novel compounds 5k-n were established from their spectral data.

The $^1$H NMR spectrum of 5k showed signals as expected for aromatic protons at $\delta$ 6.74 (d, 2H, $J$ = 7.0 Hz), 6.83 (d, 1H, $J$ = 8.1 Hz), 7.18 (d, 1H, $J$ = 7.8 Hz) and 7.25 (m, 2H). Moreover, imino protons that appeared as broad singlets at $\delta$ 6.70 and 9.22, were found to be D$_2$O exchangeable. $^{13}$C NMR spectrum showed characteristic peaks for carbonyl carbons at $\delta$ 174.2 (C-2') and $\delta$ 162.9 (C-4). It also showed a signal at $\delta$ 111.6 indicating the presence of a spiro carbon. Various aromatic carbons present in the molecule appeared between $\delta$ 112.6 and $\delta$ 149.2. IR spectrum of 5k confirmed the presence of both the carbonyl functionalities at 1723 (lactone carbonyl, C-4) and 1607 cm$^{-1}$ (amidic carbonyl C-2').

The mass spectrum (70eV) of 5k shows the presence of molecular ion peak at m/z (%) 434 (30). The major fragmentation of the molecular ion occurs through the loss of CO molecule and allylic cleavage leading to peaks at m/z 406 (75), 294 (68) and 266 (30). The other pathway involves the cleavage of the lactone ring to give fragmentation at m/z 273 (20) and 160 (48) which on further fragmentation gives m/z at 245 (15) and 105 (42). The probable mode of fragmentation is shown in Chart I.

The earlier observations that methyl group at C-6 position in 6-methylanthranilic acid plays a vital role in the formation of the desired product holds good even under the microwave conditions. In this case also, the reaction of indole-2,3-diones 4a-j with anthranilic acid under varied conditions failed to give the desired spiro compounds. These observations suggest that the presence of C-6 methyl is crucial for the reaction to take place. To confirm this hypothesis, this reaction was carried out with different 6-alkylanthranilic acids 3b-e, in order to study the effect of alkyl group, with different chain lengths and unsaturation site at C-6 position in the anthranilic acid. Here also, the corresponding spiro compounds were obtained but having much shorter reaction time. This observation was also supported by molecular modeling which suggested that as the size of the alkyl chain increases, the reaction gets completed in shorter time, which may be due to the better alignment of carboxyl and amino group for the intramolecular cyclization to take place.

The above reaction, in all probability, has proceeded via nucleophilic attack by the amino group at the free carboxyl in indole-2,3-dione at C-3 position, followed by the simultaneous cyclization with the loss of water molecule to give the desired spiro compound.
Some of the synthesized spiro compounds and others\textsuperscript{8,10} have displayed moderate to strong antibacterial activity against \textit{E. coli}, the details of which will be published later.

**Experimental Section**

Cyclocondensation reactions leading to the formation of the title compounds were carried out at RT. The melting points were taken in open glass capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer IR spectrometer Model BX-II in KBr pellets and \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Bruker 300 MHz and 74.7 MHz model in CDCl\textsubscript{3} and CD\textsubscript{3}COCD\textsubscript{3}. All chemical shifts are reported in \( \delta \) (ppm) downfield from tetramethylsilane. Mass spectra were recorded on a Jeol JMS-DX 303 and KC 455 instrument by using Electron Ionization at 70eV and only major peaks are quoted.
General procedure for alkylation of methyl 2-nitro-6-(phenylsulfonyl)methyl)benzoate 1: Alkylation of methyl 2-nitro-6-(phenylsulfonyl)methyl)benzoate 1 (5.0 mmole) with the alkyl/alkenyl/alkynyl bromide (6.0 mmole) in presence of NaH (14.3 mmole) gave compounds 2b-e in 75-80% yield. The physical and spectral characterization data of the compounds 2b-e are given in Table II.

General procedure for the preparation of 6-alkylanthranilic acids 3b-e: Methyl 2-nitro-6-(1-phenylsulfonylalkyl)benzoate 2b-e (3.49 mmole) was reduced with 10% Na-Hg (6.0 g) in absolute ethanol to give 6-alkylbenzoic acids 3b-e in 70-80% yield. Melting points and spectral characterization data of the synthesized compounds 3b-e are listed in Table II.

General procedure for the preparation of 5-alkyl-1,2-dihydro-spiro[4H-3,1-benzoxazine-2,3'[3H]indol]-4,2'-diones 5a-n: These have been prepared by two methods, A and B.

Method A: An equimolar mixture of 4a-j (0.01 mole) and 3a-e (0.01 mole) in 30 mL of absolute ethanol was stirred at RT for 2-4 hr. A colourless solid that precipitated was filtered off and purified by recrystallization from chloroform/methanol to obtain the corresponding spiro compounds 5a-n.

Method B: An equimolar mixture of 4a-j (0.1 mmole) and 3a-e (0.1 mmole) was mixed thoroughly and then subjected to microwave irradiation in domestic MW oven at 200 W power level in an open vessel for 2-6 min. Reaction mixture was eluted with chloroform/methanol to obtain the crude product which was purified by recrystallization from chloroform/methanol to obtain the desired spiro compounds 5a-n.

The physical and spectral characterization data of all the synthesized compounds are summarized in Table II. A comparative study of the two methods is briefly included in Table I.

Conclusion

Microwave irradiation for synthesis of title compounds offers tremendous reduction in reaction time, operational simplicity, cleaner reaction, easy work-up and improved yields as compared to the classical method. The importance of alkyl substituent at C-6 position in anthranilic acid has been highlighted in such cyclocondensation reactions, which was supported by molecular modeling studies. Reactions have been successfully carried out with different hitherto unknown saturated and unsaturated 6-alkyl substituted anthranilic acids, which further signifies the role of C-6 alkyl substituent. Some of these spiro compounds and others have displayed promising antibacterial activity against E. coli, the details of which will be published later. The one pot reaction is of great importance because of its environmentally benign character as non-toxic chemicals are used and no effluents are generated.

Acknowledgements

Authors (AS and PK) are thankful to UGC and CSIR respectively for award of Senior Research Fellowships and (SB and AG) for DST support.

References