FACILE AND EXPEDITIOUS CONVENTIONAL AND MICROWAVE ASSISTED SYNTHESIS OF CURCUMIN-4-ARYLIDENE AND ANALOGUES

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ABSTRACT
Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione) -4-arylidene synthesis describe with conventional and microwave irradiation method. In first scheme equimolar Curcumin and aromatic aldehydes in presence of Alum (KAl(SO₄)₂·12H₂O), ammonium acetate in DMF reflux to obtained product in good yields, six derivatives (3a-f) was prepared with better yield. Second attempt was, reacting three moles of aromatic aldehydes and one mole of acetylacetone, acetic acid in PEG-400 irraditate in MW obtained satisfactory yields, six derivatives (6a-f) was obtained by this method with satisfactory yield. Representative product were characterized for spectral analysis and found good agreement with reported.

Keywords: Curcumin-4-arylidene, One pot reaction, methodology, Claisen-schmidt condensation

INTRODUCTION
The Latin word ‘Curcuma’ came from Arabic ‘Kourkoum’ means saffron, with respect to its yellow colour appearance and similar taste. Curcumin commonly known as turmeric, obtained from the rhizomes of Curcuma longa, one of the species from Zingiberaceae family and exhibits characteristic
golden yellow colour. Today there are some 120 known species of turmeric. Curcumin used as yellow colour curry pigment in all over Indian subcontinent. Several research groups have investigated and compare their activity as antioxidant, cardio-protective, neuro-protective, antidiabetic, antitumor and chemopreventive activities, either as pure compound or as mixtures [1-4]. It helps prevent cell weakening and rebuild the cellular genetic codes to life levels [5-8]. Curcumin found useful in human prostate cancer cells [9], and release of cytochrome [10, 11]. On the other hand, one of the predominant targets of curcumin is the NF-kB cell signalling pathway [12, 13], curcumin has found active to proteasomes 26S [14, 15]. Curcumin has been introduced to many clinical trials in different human cancer therapy [16-18], the clinical potential of curcumin remains limited because of its relatively poor bioavailability [19].

Curcumin consisting central methylene moiety with most reactive proton held by carbon atom. Aromatic benzaldehyde in presence of ethanolic sodium hydroxide offers 4-arylidene substituted curcumin. Pharmaceutically these analogues were synthesized and found more active than curcumin [20, 21]. Replacement of an acidic proton from the central methylene with benzylidene derivatives proved to be as effective antimalarial as curcumin. The 4-hydroxy-3-methoxy-benzylidene derivative of curcumin was more active than curcumin. This suggested that the presence of electron donating group (-OMe) at meta position of 4-hydroxy-3-methoxy-benzylidene derivative of curcumin appears to play an important role for the potency of antimalarial compounds. [20, 21].

RESULTS AND DISCUSSIONS

Describe new methods for the synthesis of 4-arylidene curcumin and 4-arylidine curcumin analogues (Reaction Scheme 1). For synthesis of 4-arylidene curcumin analogues, alum (KAl(SO$_4$)$_2$·12H$_2$O), ammonium acetate and DMF used as catalyst-solvent and reflux condition. Whereas, curcumin 4-arylidene analogues catalytic Acetic acid in PEG-400 when introduce microwave irradiation at power 600W for 2 minutes, offers satisfactory yield. Both described methods are productive.

A model reaction was performed to optimized reaction condition. Curcumin and 4-methoxy benzaldehyde were kept as fixed reacting partner. Various reaction conditions were tried including non-conventional techniques like Microwave irradiation and solvent free method. 4-methoxy benzaldehyde was preferred as one fix component to avoid workup difficulties after completion of
reaction, which usually occurs with free hydroxyl (–OH) aldehydes. Addition preference does not show any significant effect on yield of product. Alum is naturally occurring substance exhibiting versatile catalytic properties. Table 1 shows numbers of solvent catalyst combinations were used to achieve optimum yield of reaction. Curcumin is unstable in alkaline p\(\text{H}\) [25]. Two phenolic –OH and one enolic –OH susceptible for alkaline p\(\text{H}\), KOH catalyzed reaction, not surprisingly, gave low productivity.

**Reaction Scheme 1**

**Synthesis of 4-arylidine curcumin analogues from Curcumin and aromatic aldehydes**

![Reaction Scheme 1](image)

**Table 1**  Optimization of reaction condition for Scheme 1, Curcumin and 4-methoxy benzaldehyde as model reaction.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction condition</th>
<th>Time</th>
<th>Yield(^a) of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH, KOH, rt.</td>
<td>12 hours</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>Toluene, pyridine, reflux</td>
<td>18 hours</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>Toluene, NaH, stirred at rt</td>
<td>12 hours</td>
<td>17 %</td>
</tr>
<tr>
<td>4</td>
<td>DMF, AcOH, pyridine, stirred at rt</td>
<td>24 hours</td>
<td>27%</td>
</tr>
<tr>
<td>5</td>
<td>DMF, AcOH, AcONa, reflux</td>
<td>12 hours</td>
<td>49%</td>
</tr>
<tr>
<td>6</td>
<td>DMF, Alum, CH(_3)CO(_2)NH(_4), reflux</td>
<td>4 hours, 8 hours</td>
<td>73%, 89%</td>
</tr>
<tr>
<td>7</td>
<td>DMF, AcOH, CH(_3)CO(_2)NH(_4), reflux</td>
<td>9 hours</td>
<td>68%</td>
</tr>
<tr>
<td>8</td>
<td>Toluene, pyridine, MWI</td>
<td>2 min.</td>
<td>Sticky mass</td>
</tr>
<tr>
<td>9</td>
<td>DMF, Alum, CH(_3)CO(_2)NH(_4), MWI</td>
<td>2 min.</td>
<td>53%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield
This explanation for low productivity may extend up to workup stage, after product formation, pour to ice-water and neutralized, this water-alcohol solvent mixture not allowed all products to precipitate out. Workup procedure for alcoholic KOH when was modified with evaporation of alcohol from reaction mixture in reduce pressure, offers dark red-brown coloured sticky product. So, overall requirement was aprotic-polar solvent, non-alkaline condition and easy water workup, all this was achieved by using DMF as solvent Alum and ammonium acetate as catalyst. (Table 1; Entry 6) Series of reactions were performed with applying optimized reaction condition (Table 2; 3a-f). Describe method is productive with simple handling procedure, use of naturally occurring Alum enhance green impact of present methodology. Dimethyl formamide aprotic polar solvent allowed reaction contains to attain much higher temperature.

Present methodology consists of one fix component as curcumin hence resultant diarylheptanoid back-bone was fixed and unaltered throughout the derivatisation.

Second methodology describes offers choice of diarylheptanoid backbone selection. Three moles of Aromatic aldehydes and one mole of acetylacetone (Scheme 2) react to obtain desired curcumin-4-
arylidine analogues. 4-methoxy benzaldehyde and acetylacetone was taken as fix starting materials for model reaction. Various reaction conditions were applied to optimized reaction condition with respect to yield, easy handling procedure and time. Reaction conditions were applied as shown in Table 2. Base catalyzed reactions (Table 2; Entry 1, 2, 3, 4)

Reaction Scheme 2

Synthesis of 4-arylidine curcumin analogues from aromatic aldehydes and acetylacetone

![Reaction Scheme 2](image)

and 5) exhibits related low yield than acid catalyzed reaction (Table 2; Entry 6), this may be explain with respect to structure of acetylacetone as more numbers of acidic proton (three sets) and couple of carbonyl functionality may increases self condensation probability during strong pH change reaction. Microwave technique was used and found productive (Table 2; Entry 6). As microwave methods found more fruitful used further for derivatisation reactions. As continuation of previous research work [25], developed new methods consisting more green impact in form of using Alum as catalyst with salt (ammonium acetate), PEG-400 as solvent with non-conventional method.

Table 2 Optimization of reaction condition, 4-methoxy benzaldehyde and acetyl acetone used as model reaction.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Reaction condition</th>
<th>Time</th>
<th>Yield(^a) of products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EtOH, KOH, stirred at 5° to rt.</td>
<td>8 hours</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>DMC, Piperidine, rt</td>
<td>8 hours</td>
<td>57%</td>
</tr>
<tr>
<td></td>
<td>EtOH, NaOEt, 5°-rt.</td>
<td>7 hours</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>DMF, KOH, stirred at rt</td>
<td>8 hours</td>
<td>64%</td>
</tr>
</tbody>
</table>
PEG, KOH, stirred at rt 8 hours 67%

AcOH, HCl, reflux 6 hours 71%

PEG, AcOH, MWI 2 min. 91%

PEG, KOH, MWI 2 min. 59%

\(^a\) Isolated yield

![Figure 2. Structure of 4-arylidene-1,7-bis(4-methoxyphenyl)hepta-1,6-diene-3,5-dione derivatives.](image)

![Table 2. Showing reaction condition and yield of product by using optimized reaction condition](table)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Products No.</th>
<th>Alum, CH(_3)CO(_2)NH(_4), DMF, Reflux</th>
<th>Time in hr.</th>
<th>Yield (%)</th>
<th>Sr. No.</th>
<th>Products No.</th>
<th>AcOH, PEG-400, MWI-600W</th>
<th>Time in min.</th>
<th>(Yield (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(3a)</td>
<td></td>
<td>9</td>
<td>89%</td>
<td>7</td>
<td>(6a)</td>
<td></td>
<td>2 min.</td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td>(3b)</td>
<td></td>
<td>12</td>
<td>60%</td>
<td>8</td>
<td>(6b)</td>
<td></td>
<td>2 min.</td>
<td>77%</td>
</tr>
</tbody>
</table>
EXPERIMENTAL

Materials and Methods

All the compounds used in synthesis were of analytical grade; the melting points of the compounds were determined in open head capillary and are uncorrected. $^1$H NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrophotometer in CDCl$_3$ using TMS as Internal standard. Chemical shifts (δ) are reported in ppm. The IR spectra were recorded using Perkin Elmer spectrometer (KBr plates). The reaction was carried out in a scientific microwave oven (Sineo, MASS-II, Microwave Synthetic Workstation, China). All the compounds were checked for purity by thin layer chromatography (TLC). Column chromatographic separation was performed with 60-120 mesh size silica gels. Melting points were recorded in an oil bath with open head capillary and are uncorrected. All products were shown good agreements with reported spectral values and physical constant. [20, 21]

General procedure for synthesis of Curcumin-4-arylidine (3a-f)

Conventional method:
Curcumin (2 mmol), 4-methoxybenzaldehyde (2.2 mmol) was added in DMF containing Alum (5 mmol) and ammonium acetate (5 mmol) in one portion with stirring. Reaction was reflux for appropriate time and progress of reaction was monitor by TLC. After completion of reaction, allowed contain to attained room temperature and pour into crush-ice-water mixture with gentle stirring and left in ice-water bath for next 3 hours. Thus obtained crude product was filter off and purified with column chromatography. (Yield 89%)
contains were irradiated with Microwave at 600W for appropriate time. After each successive 10 sec.
irradiation 5 sec. were set as rest period. Reaction was monitor by TLC and after completion pour to
cool water and left for 3-4 hours without stirring. Thus obtained yellow colour crude product were
filter off and purified by column chromatography. (Yield 91%)

SPECTRAL ANALYSIS

1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(4-methoxybenzylidene)hepta-1,6-diene-3,5-dione: (3a)
Yield 89%; NMR (300MHz, CDCl₃) δ 8.12 (s, 1H), 7.89 (d, 1H), 7.51 (d, 1H), 7.48 (d, 1H), 7.18-
7.23 (d, 2H), 7.09-7.13 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.71-6.68 (d, 2H), 5.87-5.93
(broad, 2H), 3.88 (s, 3H), 3.64 (s, 3H), 3.55 (s, 3H).

4-(4-fluorobenzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione: (3c)
Yield 77%; NMR (300MHz, CDCl₃) δ 8.01 (s, 1H), 7.86 (d, 1H), 7.50 (d, 1H), 7.49 (d, 1H), 7.43 (d,
1H), 7.16-7.20 (d, 2H), 7.01-7.04 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.71-6.68 (d, 2H),
5.87-5.93 (broad, 2H), 3.64 (s, 3H), 3.55 (s, 3H).

1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(4-methoxybenzylidene)hepta-1,6-diene-3,5-dione: (3a)
Yield 89%; NMR (300MHz, CDCl₃) δ 8.12 (s, 1H), 7.89 (d, 1H), 7.51 (d, 1H), 7.48 (d, 1H), 7.18-
7.23 (d, 2H), 7.09-7.13 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.71-6.68 (d, 2H), 5.87-5.93
(broad, 2H), 3.88 (s, 3H), 3.64 (s, 3H), 3.55 (s, 3H).

1,7-bis(4-hydroxy-3-methoxyphenyl)-4-(3-methoxybenzylidene)hepta-1,6-diene-3,5-dione: (3d);
Yield 86%; NMR (300MHz, CDCl₃) δ 8.12 (s, 1H), 7.88 (d, 1H), 7.55 (d, 1H), 7.50 (d, 1H), 7.19-
7.22 (d, 2H), 7.05-7.10 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.71-6.68 (d, 2H), 5.87-5.93
(broad, 2H), 3.87 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H).

4-(4-methoxybenzylidene)-1,7-bis(4-methoxyphenyl)hepta-1,6-diene-3,5-dione: (6a); Yield 91%;
NMR (300MHz, CDCl₃) δ 8.12 (s, 1H), 7.89 (d, 1H), 7.51 (d, 1H), 7.48 (d, 1H), 7.18-7.23 (d, 2H),
7.09-7.13 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.72-6.70 (m, 4H), 3.88 (s, 3H), 3.64 (s,
3H), 3.55 (s, 3H).

4-(4-hydroxy-3-methoxybenzylidene)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-
dione: (6b); Yield 77%; NMR (300MHz, CDCl₃) δ 8.18 (s, 1H), 7.59 (d, 2H), 7.53 (d, 1H), 7.19-
7.22 (d, 2H), 7.09-7.14 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (d, 2H), 6.71-6.68 (d, 2H), 5.79-5.90 (broad, 3H), 3.87 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H).

**4-(4-fluorobenzylidene)-1,7-bis(4-fluorophenyl)hepta-1,6-diene-3,5-dione: (6c); Yield 92%; NMR (300MHz, CDCl₃) δ 8.12 (s, 1H), 7.89 (d, 1H), 7.51 (d, 2H), 7.48 (d, 2H), 7.18-7.23 (d, 2H), 7.09-7.13 (d, 2H), 6.90-6.94 (d, 2H), 6.89-6.77 (m, 3H), 6.72-6.70 (m, 2H)**

**CONCLUSIONS**

Describe methods are simple and productive, easy workup procedure, easily available and cost effective starting materials are significant advantages. Alum and ammonium acetate elevate considerable green impact of present methodology. First conventional method consisting curcumin as fixed backbone, considering this as limitation second microwave assisted methodology describe offers to produce 4-arylidine analogues. We believe that present methodologies could be good replacement traditional one.

**REFERENCES**


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