**SONOCHEMICAL SYNTHESIS OF 2, 4-DISUBSTITUTED QUINOLINES CATALYZED BY PHOSPHOSULFONIC ACID (PSA) UNDER SOLVENT-FREE CONDITIONS**

Kothari Sathish Babu1,4, Jhansi Rani Vangavargan2, Nanda Kumar Yellapu1 and Anindita Chatterjee*1

1 Department of Chemistry, Koneru Lakshmaiah University, Green Fields, Vaddeswaran, Guntur 522502, India
2 Department of Chemistry, Sri Venkateswara University, Tirupati 517502, India
3Division of Animal Biotechnology, Department of Zoology, Sri Venkateswara University, Tirupati 517502, India
4Mylan Laboratories Ltd, CRD, Anrich Industrial Estate, Bollaram, Hyderabad 502325, India

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**Abstract:** A simple, efficient and environment-friendly one-pot multicomponent method has been developed for synthesizing 2, 4-disubstituted quinolones. It uses ultrasound-mediated condensation of aldehydes, amines and anilines in the presence of various catalysts under solvent-free conditions. Phosphosulfonic acid (PSA) was found to be superior to other catalysts for the reaction of 2-methoxybenzaldehyde and ethynylbenzene with 4-methoxyaniline. A series of 2,4-disubstituted quinolones were synthesized in good to excellent yields after short reaction times when compared to the conventional thermal method. This new procedure provides several advantages over current methods, including: simple work-up, cost effectiveness, a wide range of functional group tolerance and use of an inexpensive reusable heterogeneous catalyst. All new compounds were identified and characterized by 1H, 13C NMR and HRMS spectra.

**Key words:** Quinolones, Phosphosulfonic acid, 1H NMR, 13C NMR, HRMS.

**INTRODUCTION**

Quinoline analogues are an important class of natural and synthetic bicyclic nitrogen-containing heterocyclic compounds which have a wide range of applications. These include biological roles as antagonists for the N-methyl-D-aspartate (NMDA) receptor glycine site [1-4] and the Follicle-stimulating hormone (FSH) receptor.[5,6] Some quinolones also have important roles as antimarial[7], anti-bacterial, anti-fungal, anti-inflammatory, antitumor[8], anthelmintic, cardiotoxic, analgesic activity, anticonvulsant, and antioxidant drugs.[9,10] Quinolines and other heterocyclic molecules were also useful ligands for transition-metal complexes[11] and are important building blocks in organic chemistry.[12-16] The inherent fluorescent properties of quinolones make them useful as emitting chromophores.[17,18] There is therefore considerable ongoing interest in improved syntheses of useful quinoline derivatives particularly environmentally-friendly syntheses.[19-25] Most of the present routes to substituted quinolines have environmental drawbacks like using organic solvents, or traditional Lewis and Bronsted acids.[26-28] Most of these synthetic routes also produce a large amount of waste and require long reaction times.[29]

We therefore set out to devise improved synthetic routes to quinoline derivatives. We decided to react various amines and aldehydes with amines using ultrasound irradiation under solvent-free conditions. Additionally, we decided to use solid-supported catalysts because they are cost-effective due to the fact that they are reusable and they also have ecological benefits. Solid acid catalysts are easily handled and have high catalytic activities. Phosphosulfonic acid (PSA) is one of these and it provides easy accessibility of active sites, stability, hygroscopic properties, handling, reusability, and good product yields. Ultrasound-promoted synthesis is known to shorten many reaction times and important heterocycles have been synthesized under solvent-free conditions using this technique.[30-38]

To the best of our knowledge, there are no reports on the synthesis of 2, 4-disubstituted quinolines under solvent-free ultrasound irradiation at 80 °C catalyzed by PSA which should provide a more environmentally friendly route to these compounds. This would be quite desirable if current yields and reaction times were at least maintained. Herein, we report a facile one-pot synthesis of 2,4-disubstituted quinolines via three-component coupling of anilines, aldehydes and amines under solvent-free conditions using solid-supported PSA catalyst and ultrasound irradiation at 80°C (Scheme 1).

**RESULT AND DISCUSSION**

The conventional and ultrasonic synthesis of 4-(2-methoxyphenyl)-2-(4-methoxyphenyl) quinolone (4a) from ethynylbenzene (1), 4-methoxybenzaldehyde (2) and 4-methoxyaniline (3) was used as a model (Table 1) to determine the best experimental conditions. We initially carried out the reactions without any catalyst (Table 1, entry 1). The reaction was then examined utilizing different catalysts under both conventional and ultrasound irradiation without solvent (Table 2, entries 2-10). In every case except one (Table 2, entry 5), ultrasonic conditions produced shorter reaction times and larger yields than conventional conditions.

The reaction produced very low (<40% conventional and < 52% ultrasonic) yields when InF₃, CAN-SiO₂, and ZnCl₂-SiO₂ were used as catalysts (Table 1, entries 2-4). Catalysts such as MnCl₂·4H₂O, Yb (OAc)₃, NbCl₅ and FePO₄ gave larger (45-55% conventional and 55-70% ultrasonic) yields (Table 1, entries 5-8) but these were...
all lower than solid-supported catalysts such as PS/PTSA, MSA, and PSA (Table 1, entries 9–11). Among these solid-supported catalysts, PSA showed the best results under ultrasound irradiation conditions. (Table 1, entry 11). The data in Table 1 reveal that yields increased slightly with mol % PSA up to 5%. Yields at 10% PSA (Table 1, entry 14) were identical to those at 5%. The best results were obtained in the presence of PSA (5 mol %) at 80 °C (Table 1, entry 11) affording 4-(2-methoxyphenyl)-2-(4-methoxyphenyl) quinolone (4a) in 85% yield after 15 min at 80°C. Therefore, 5 mol% of PSA was found necessary and sufficient for the total completion of the reaction under both conventional and ultrasonic conditions.

The superiority of the present methodology over some of the recently reported procedures was established by comparison of the result obtained with the PSA-catalyzed reaction with that of other reported catalysts/systems (Table 1 & 2). Comparison of the Catalytic Efficiency of PSA with Various Catalysts for the Synthesis of 4a.

Table 1: Influence of the catalyst for the synthesis of 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Conventional</th>
<th>Ultrasonic</th>
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<tr>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
<td>Time (min)</td>
</tr>
<tr>
<td>1</td>
<td>160</td>
<td>20</td>
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<tr>
<td>2</td>
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<tr>
<td>14</td>
<td>50</td>
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<td>15</td>
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</tbody>
</table>

*aReaction of ethynylbenzene, (1, 1 mmol), 2-methoxybenzaldehyde (2, 1 mmol) and 4-methoxyaniline (3, 1 mmol) under solvent free condition at 80 °C. Isolated yields. Catalyst was reused three times.

Table 2: Screening of various solvent for the synthesis of 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (5mL)</th>
<th>Conventional</th>
<th>Ultrasonic</th>
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<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
<td>Time (min)</td>
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<tr>
<td>6</td>
<td>48</td>
<td>85</td>
<td>16</td>
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</tbody>
</table>

*aReaction of ethynylbenzene (1, 1 mmol), 3-methoxybenzaldehyde (2, 1 mmol), 4-methoxyaniline (3, 1 mmol), PSA catalyst (5 mol %) at 80 °C. Isolated yields.

We next studied the effect of solvent on the conventional and ultrasonic reaction conducted under the “ideal” conditions at 80 °C using 5 mol % PSA with solvent-free (neat) conditions and in the presence of different solvents. The yield of products was lower (Table 2, entries 1–5) with all solvents relative to solvent-free (neat) conditions (Table 2, entry 6). Poor product yields in solvent may be due to solvation of the substrates in the reaction medium.

The ability to recycle the PSA catalyst was also checked by running the same model reaction in three additional cycles using recovered PS/PTSA. Use of the same PSA catalyst for an initial and three subsequent runs gave 4a yields of 94%, 91%, 90% and 87% (Table 1, entry 11). Thus it appears the catalyst can be used multiple times without much loss of efficiency.

To establish the generality, various aldehydes, amines, and alkynes were subjected to a one-pot reaction catalyzed by PSA (Table 3). Under these optimized set of experimental reaction conditions, the condensation of aldehydes (2) with different alkynes and various amines (3a) was carried out and obtained a variety of 2,4-disubstituted quinolines (4a), and the results were described in Table 3. As shown in Table 3, in all cases, with either electron-donating or electron-withdrawing groups on aldehydes reacted smoothly with alkyn e and amines in the presence of 5% PSA at 80 °C to form the corresponding 2,4-disubstituted quinolines in good to excellent yields without formation of any side products.

We have described herein PSA as a new and extremely efficient catalyst for synthesis of 2,4-disubstituted quinolones by a three-component, one-pot reaction. With the increasing concern for need of green synthetic procedures, the advantages such as the (i) solvent-free reaction, 22 (ii) high yields, (iii) eco-friendly, and (iv) ease of product isolation/purification fulfill the triple bottom line philosophy of green chemistry.23 And make the present methodology environmentally benign. The chemical structures of all the synthesized compounds were characterized by IR, 1H, 13CNMR, and HRMS studies and their data are presented in the experimental section. In the
1H NMR spectra of compounds 4a-4s, the chemical shifts of aromatic hydrogens of the phenyl ring appeared as multiplets in the region δ 6.22–6.87 [39-43]. In 13C NMR chemical shifts for compounds 4i were observed in their expected regions [44-47].

**Conclusion**

In conclusion, we have found an efficient and practical procedure for the preparation of 2,4-disubstituted quinolines from alkynes and different aromatic aldehydes with various aromatic amines in the presence of PSA under ultrasound irradiation at room temperature using solvent-free conditions. Ultrasound irradiation speeds up the reaction compared to traditional (reflux) methods and provides better yields. This protocol provides the advantages of increased yields, shorter reaction times, ecofriendly catalyst and easy workup.

**Materials and Methods**

4-(2-methoxyphenyl)-2-(4-methoxyphenyl) quinoline (4a).

A mixture of ethynylbenzene (1, 1 mmol), 3-methoxybenzaldehyde (2, 1 mmol), 4-methoxyaniline (3, 1 mmol) in the presence of PSA (3 mol %) were placed on a 25 mL beaker and exposed to ultrasound irradiation at room temperature for appropriate time (Table 3) in solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with chloroform and filtered to recover the catalyst. The filtrate was evaporated, and the crude product was recrystallized from ethanol to afford pure 4a in excellent yields.

**Synthesis of Phosphosulfonic acid (PSA)**

25mL reaction flask was equipped with a constant-pressure dropping funnel and the gas outlet which was connected to a vacuum system through an alkali solution trap. DHAMP (1 g, 7.5 mmol) was charged into the flask and chlorosulfonic acid (2.62 g, ca. 1.5 mL, 22.5 mmol) in CH2Cl2 (10 mL) was added drop wise over a period of 15 min at room temperature. After completion of the addition, the reaction mixture was shaken for 2 h, while the residual HCl was eliminated by suction. Then the mixture was washed with excess of CH2Cl2 and obtained the white powder on dried (Scheme 2).

**Scheme 2: Preparation of PSA**

2-(4-Methoxyphenyl)-4-(o-tolyl)quinoline (4b): Yellow solid; 1H NMR (500 MHz, CDCl3): δ = 2.45 (s, 3H), 3.80 (s, 3H), 7.24 (d, J = 10.0 Hz, 2H), 7.29-7.32 (m, 3H), 7.39-7.42 (m, 1H), 7.48-7.58 (m, 6H), 8.13 (d, J = 10.0 Hz, 1H), ppm. 13C NMR (75 MHz, CDCl3): δ: 20.6, 55.4, 103.7, 122.9, 122.9, 126.1, 128.5, 128.8, 129.5, 129.9, 131.0, 131.6, 136.4, 138.7, 140.6, 144.7, 147.4, 154.7, 157.5 ppm. HRMS: calcld. for C25H19NO[M+H]+ 326.1467; found 326.1476.

4-(Isopropylphenyl)-2-(4-fluorophenyl) quinoline (4c): Yellow solid; 1H NMR (500 MHz, CDCl3): δ = 3.86 (s, 3H), 4.06 (s, 3H), 7.15-7.18 (m, 1H), 7.20 (s, 1H), 7.25-7.32 (m, 1H), 7.36-7.40 (m, 1H), 7.48-7.58 (m, 6H), 7.68 (d, J = 3.65 Hz, 1H), 8.04-8.09 (m, 1H), ppm. 13C NMR (75 MHz, CDCl3): δ: 25.6, 56.3, 103.3, 108.8, 116.5, 121.2, 124.5, 128.4, 128.8, 129.5, 130.6, 131.4, 138.9, 146.1, 146.8, 150.2, 152.4 ppm. HRMS: calcld. for C25H18FNO2[M+H]+ 360.1322; found 360.1331.

4-(3,4-Dimethylphenyl)-2-(4-nitrophenyl) quinoline (4d): Yellow solid; 1H NMR (500 MHz, CDCl3): δ: 2.38 (s, 3H), 4.06 (s, 3H), 7.15 (s, 1H), 7.51-7.55 (m, 6H), 6.77 (m, 1H), 8.28 (m, 4H), 7.68 (d, J = 3.65 Hz, 1H), 8.04-8.09 (m, 1H), ppm. 13C NMR (75 MHz, CDCl3): δ: 56.7, 56.9, 103.5, 109.4, 118.9, 122.5, 124.7, 128.5, 129.9, 138.8, 146.4, 148.6, 152.3, 154.5 ppm. HRMS: calcld. for C25H16N2O2[M+H]+ 367.1273.

4-(4-Isopropylphenyl)-2-(4-methoxyphenyl)quinoline (4f): Yellow solid; 1H NMR (500 MHz, CDCl3): δ: 1.28 (d, J = 10.0 Hz, 6H), 2.94-2.98 (m, 1H), 3.84 (s, 3H), 7.05 (d, J = 8.5 Hz, 2H), 7.48 (m, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.62-7.66 (m, 2H), 7.71-7.73 (m, 1H), 7.82 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 8.21-8.26 (m, 2H), ppm. 13C NMR (75 MHz, CDCl3): δ: 24.1, 33.9, 55.8, 115.2, 118.9, 126.5, 127.6, 128.1, 128.9, 129.7, 131.1, 131.6, 132.4, 133.6, 135.3, 149.2, 151.2, 152.7, 157.2, 180.0 ppm. HRMS: calcld. for C25H15NO2[M+H]+ 354.1780; found 354.1789.

4-(4-Chlorophenyl)-2-(3,4-dimethylphenyl) quinoline (4o): Yellow solid; 1H NMR (500 MHz, CDCl3): δ: 3.86 (s, 3H), 4.02 (s, 3H), 7.16 (s, 1H), 7.53-7.57 (m, 6H), 7.64-7.66 (m, 1H), 8.23-8.26 (m, 4H), 7.72 (d, J = 3.65 Hz, 1H), 8.01-8.05 (m, 1H), ppm. 13C NMR (75 MHz, CDCl3): δ: 55.6, 56.2, 104.2, 108.3, 119.6, 123.4, 126.8, 127.4, 129.3, 129.8, 132.6, 145.6, 147.5, 153.2, 153.4 ppm. HRMS: calcld. for C25H18ClNO2[M+H]+ 376.1026; found 376.1031.

4-(4-Methoxyphenyl)-2-(4-fluorophenyl) quinoline (4p): Yellow solid; 1H NMR (500 MHz, CDCl3): δ: 3.86 (s, 3H), 7.04 (d, J = 8.5 Hz, 2H), 7.23-7.26 (m, 1H), 7.36-7.38 (m, 2H), ppm. 13C NMR (75 MHz, CDCl3): δ: 20.6, 55.4, 103.7, 122.9, 122.9, 126.1, 128.5, 128.8, 129.5, 129.9, 131.0, 131.6, 136.4, 138.7, 140.6, 144.7, 147.4, 154.7, 157.5 ppm. HRMS: calcld. for C25H19NO[M+H]+ 326.1467; found 326.1476.

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2H), 7.64-7.69 (m, 2H), 7.93 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 8.08-8.14 (m, 3H), 8.21-8.24 (m, 2H) ppm. 13C NMR (75 MHz, CDCl3): δ = 55.1, 113.2, 118.1, 120.3, 121.2, 123.6, 124.5, 125.9, 128.2, 128.8, 129.3, 131.2, 134.4, 139.3, 145.1, 147.3, 148.4, 150.2, 160.4 ppm; HRMS: calcd. for C22H16ClNO346.0920 [M+H]+, Found: 346.0928.

4-(4-Fluorophenyl)-2-(4-methoxyphenyl) quinoline (4q): Yellow solid; 1H NMR (500 MHz, CDCl3): δ = 3.86 (s, 3H), 7.02-7.04 (m, 2H), 7.22-7.26 (m, 2H), 7.43-7.46 (m, 3H), 7.68-7.70 (m, 1H), 7.78 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 10.0 Hz, 2H), 8.28 (d, J = 8.7 Hz, 1H) ppm; 13C NMR (75 MHz, CDCl3): δ = 55.6, 113.2, 116.4, 116.3, 118.9, 124.3, 127.3, 128.6, 129.5, 130.4, 131.2, 132.1, 132.9, 133.0, 133.7, 149.2, 150.5, 161.5, 164.5 ppm. HRMS: calcd. for C22H16FNO329.1216 [M+H]+, Found: 329.1223.

Table 3: One-pot three-component synthesis of 2,4-disubstituted quinolone analogues (4a-4s).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>R1</th>
<th>R2</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Mp (°C) observed</th>
<th>Literature</th>
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<tr>
<td>4a</td>
<td>2-Methoxy 4-Methoxy</td>
<td>25</td>
<td>85</td>
<td>152–153</td>
<td>4b</td>
<td>2-Methyl        4-Methoxy</td>
<td>28</td>
</tr>
<tr>
<td>4c</td>
<td>4-Isopropyl 4-Methoxy</td>
<td>33</td>
<td>81</td>
<td>165–167</td>
<td>4d</td>
<td>2-fluoro        3,4-dimethoxy</td>
<td>17</td>
</tr>
<tr>
<td>4e</td>
<td>4-nitro 3,4-dimethoxy</td>
<td>31</td>
<td>81</td>
<td>162–163</td>
<td>4e</td>
<td>4-nitro          3,4-dimethoxy</td>
<td>31</td>
</tr>
</tbody>
</table>
4f 4-tert-butyl 4-methoxy 38 92 132–134 (133)[48]

4g 4-methyl 4-methoxy 26 85 116-118 (115–117)[48]

4h 4-nitro 4-methoxy 35 90 138–140

4i 4-tert-butyl 4-methyl 33 81 120–121 (120)[48]

4j -- 4-methoxy 28 88 76–77(75-76)[49]

4k -- 4-methyl 25 85 116-117 (116–117)[50]
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<th>Compound</th>
<th>Functional Groups</th>
<th>IC50</th>
<th>Selectivity</th>
<th>IC50 Range</th>
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<td>4-isopropyl, 4-methoxy</td>
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<tr>
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<td>4-chloro, 3,4-dimethoxy</td>
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<td>81</td>
<td>125–127</td>
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<tr>
<td>4n</td>
<td>3,4-dimethoxy</td>
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<td>88</td>
<td>143-144 (142–144)[51]</td>
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<tr>
<td>4o</td>
<td>4-nitro, 4-chloro</td>
<td>24</td>
<td>85</td>
<td>144-145 (145)[48]</td>
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<tr>
<td>4p</td>
<td>4-chloro, 4-methoxy</td>
<td>22</td>
<td>90</td>
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REFERENCES


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