One-pot Three-component Coupling Reaction: Solvent-free Synthesis of Novel 2-substituted Aryl (amino) Kojic Acid by pTSA-catalyzed

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ABSTRACT

p-toluenesulfonic acid (pTSA) catalyzed one-pot synthesis of 2-substituted aryl (amino) kojic acid have been achieved by three component coupling reaction between aldehydes, aniline and kojic acid under solvent free condition in high.

Key words: Multi-component reactions, Kojic acid, Aniline, Aldehyde, p-toluenesulfonic acid.

INTRODUCTION

Multi-component reactions (MCRs) are powerful strategies for the quick synthesis of diverse and complex organic molecules of potential interest particularly in the area of material science and drug discovery. This methodology allows creation of diversity in addition to molecular complexity by the facile formation of several new covalent bonds in a one-pot transformation. The search and discovery of new MCRs, therefore, have gained tremendous importance.

Kojic acid is a natural pyrone produced by certain filamentous fungi, mainly species of Aspergillus and Penicillium. It is a common by-product in the fermentation of soy sauce, sake and rice wine, and is widely used as a food additive to prevent oxidative browning or in cosmetics as a depigmenting agent. Derivatives of kojic acid also have antimicrobial activity against a variety of other fungi and bacteria, showing its potential as a polyfunctional backbone for new antimicrobial agents. Therefore, the synthesis and selective functionalization of kojic acids have been the focus of active research over the years.

p-Toluenesulfonic acid (pTSA) is environmentally benign, inexpensive, and economically feasible catalyst that offers several advantages. Therefore, organic reactions that exploit pTSA catalyst could prove ideal for industrial synthetic organic chemistry applications provided that the catalyst shows high catalytic activity under solvent-free.
EXPERIMENTAL

Chemicals used in this work were purchased from Aldrich and Merck chemical companies and used without purification. IR spectra were recorded on a Shimadzu 435-U-04 FT spectrometer as KBr pellets. ¹H and ¹³C NMR spectra were measured in DMSO-CDCl₃ with a Bruker DRX-400 Advance instrument at 400 and 100 MHz, respectively, using Me₄Si as internal standard. Mass spectra were recorded with a spectrometer Finnegan-MAT 8430 operating at an ionization potential of 70 eV. Melting points were measured on a SMP1 apparatus.

General procedure for the synthesis of 2-substituted (aryl amino) kojic acid derivative (1a–m)

To a mixture of aldehyde (1 mmol), kojic acid (1 mmol), aniline (1 mmol and pTSA (0.12 mmol) were taken in a 25 mL round-bottomed flask and the mixture was inserted in an oil bath and heated at 95 °C for the appropriate time as mentioned in Table 1. Completion of the reaction was indicated by TLC. After completion of the reaction as monitored by TLC, the mixture was allowed to cool to room temperature and quenched with water and extracted with ethyl acetate (2 × 10 mL).

All the products obtained were fully characterized by spectroscopic methods such as IR, ¹H-NMR, ¹³C-NMR, mass spectroscopy and elemental analysis and have been identified by the comparison of the reported spectral data. The spectral and analytical data for the selected compounds are presented below.

3-Hydroxy-6-hydroxymethyl-2-(phenylphenylamino-methyl)-pyran-4-one (4a)

solid, mp 114–116 °C; ¹H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ/ppm): 8.77 (1H, s, OH), 6.43–7.14 (10H, m, CH₃), 6.31 (1H, s, =CH), 4.59 (1H, s, CH), 4.25 (1H, s, NH), 4.22 (2H, s, CH₂), 3.75 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-δ₆, δ/ppm): 187.1 (CO), 177.5 (C=O), 143.5 (C₆H₅), 142.4 (C₆H₅), 139.0 (C₆H₅), 132.7 (C₆H₅), 131.2 (C₆H₅), 129.4 (C₆H₅), 128.7 (C₆H₅), 127.7 (C₆H₅), 116.9 (C₆H₅), 112.8 (C₆H₅), 111.8 (C₆H₅), 71.3 (CH₂), 55.8 (CH); IR (KBr): v 3372, 2927, 2851, 1712, 1624, 1461, 1208, 747; ESI-MS: m/z [M⁺, 323]. Anal. calcd. For C₁₃H₁₃N₃O₃: C: 70.58, H: 5.30, N: 4.33. Found: C: 70.64, H: 5.21, N: 4.49 %.

3-Hydroxy-6-hydroxymethyl-2-[(4-methoxyphenyl)-phenylamino-methyl]-pyran-4-one (4b)

solid, mp 127–129 °C; ¹H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ/ppm): 8.93 (1H, s, OH), 6.52–7.03 (9H, m, CH₃), 6.38 (1H, s, =CH), 4.61 (1H, s, CH), 4.03 (1H, s, NH), 4.20 (2H, s, CH₂), 3.73 (3H, s, OCH₃), 3.41 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-δ₆, δ/ppm): 187.3 (CO), 177.6 (C₆H₅), 143.4 (C₆H₅), 141.8 (C₆H₅), 138.5 (C₆H₅), 132.3 (C₆H₅), 131.5 (C₆H₅), 130.9 (C₆H₅), 129.2 (C₆H₅), 127.4 (C₆H₅), 116.7 (C₆H₅), 113.6 (C₆H₅), 111.9 (C₆H₅), 71.5 (CH₂), 57.3 (CH₃), 55.7 (CH); IR (KBr): v 3328, 2925, 1701, 1615, 1451, 1317, 1252, 1090, 759, cm⁻¹; ESI-MS: m/z [M⁺, 354]. Anal. calcd. For C₁₇H₁₅N₃O₅: C: 67.79, H: 5.69, N: 3.95. Found: C: 67.68, H: 5.71, N: 4.88 %.

3-Hydroxy-6-hydroxymethyl-2-[(4-chlorophenyl)-phenylamino-methyl]-pyran-4-one (4c)

solid, mp 119–121 °C; ¹H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ/ppm): 8.87 (1H, s, OH), 6.41–7.15 (9H, m, CH₃), 6.29 (1H, s, =CH), 4.58 (1H, s, CH), 4.01 (1H, s, NH), 4.22 (2H, s, CH₂), 3.48 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-δ₆, δ/ppm): 186.9 (CO), 177.2 (C₆H₅), 143.1 (C₆H₅), 141.5 (C₆H₅), 138.4 (C₆H₅), 132.0 (C₆H₅), 131.2 (C₆H₅), 129.7 (C₆H₅), 128.4 (C₆H₅), 127.7 (C₆H₅), 116.9 (C₆H₅), 113.2 (C₆H₅), 112.1 (C₆H₅), 71.6 (CH₂), 55.8 (CH); IR (KBr): v 3358, 2932, 1691, 1627, 1488, 1450, 1221, 996, 741 cm⁻¹; ESI-MS: m/z [M⁺, 357]. Anal. calcd. For C₁₇H₁₄ClN₂O₅: C: 63.78, H: 4.51, N: 3.91. Found: C: 63.83, H: 4.63, N: 3.82 %.

3-Hydroxy-6-hydroxymethyl-2-[(4-bromophenyl)-phenylamino-methyl]-pyran-4-one (4d)

solid, mp 122–125 °C; ¹H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ/ppm): 8.63 (1H, s, OH), 6.52–7.19 (9H, m, CH₃), 6.21 (1H, s, =CH), 4.57 (1H, s, CH), 4.02 (1H, s, NH), 4.21 (2H, s, CH₂), 3.47 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-δ₆, δ/ppm): 186.1 (CO), 176.9 (C₆H₅), 144.3 (C₆H₅), 142.3 (C₆H₅), 138.3 (C₆H₅), 134.3 (C₆H₅), 132.8 (C₆H₅), 128.5 (C₆H₅), 127.5 (C₆H₅), 116.8 (C₆H₅), 114.4 (C₆H₅), 112.3 (C₆H₅), 71.7 (CH₂), 55.7 (CH); IR (KBr): v 3391, 2924, 1713, 1618, 1509, 1456, 1302, 1179, 1030, 860, 745 cm⁻¹; ESI-MS: m/z [M⁺, 402]. Anal. calcd. For C₁₇H₁₁BrN₂O₅: C: 56.73, H: 4.01, N: 3.48. Found: C: 56.29, H: 4.30, N: 3.56 %.
3-Hydroxy-6-hydroxymethyl-2-(naphthenal-1-yl-phenylamino-ethyl)-pyran-4-one (4e)
Solid, mp 108–110 °C; 1H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ / ppm): 7.89 (1H, s, OH), 6.43–7.64 (12H, m, CH₃,CH₂), 6.30 (1H, s, =CH), 4.59 (1H, s, CH), 4.00 (1H, s, NH), 4.20 (2H, s, CH₂), 3.37 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-d₆, δ / ppm): 185.7 (CO), 176.8 (C₂), 144.2 (C₆), 142.5 (C₅), 138.1 (C₄), 134.7 (C₃), 132.5 (C₂), 131.2 (C₁), 129.8 (C₀), 128.5 (C₇), 127.5 (C₆), 125.5 (C₅), 125.2 (C₄), 124.8 (C₃), 123.3 (C₂), 121.1 (C₁), 116.4 (C₀), 114.5 (C₉), 111.8 (C₈), 71.7 (CH₂), 55.6 (CH); IR (KBr): ν 3394, 2928, 1705, 1624, 1581, 1455, 1268, 1163, 748 cm⁻¹; ESI-MS: m/z [M+H]⁺ [M+2H]²⁺ [M+3H]³⁺. Anal. calc’d. For C₉H₇NO₂: C 73.58, H: 5.64, N: 3.73. Found: C 73.32, H: 5.55, N: 3.94 %.

3-Hydroxy-6-hydroxymethyl-2-[(4-hydroxy -phenyl)-phenylamino-methyl]-pyran-4-one (4f)
Solid, mp 99–101 °C; 1H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ / ppm): 8.71 (1H, s, OH), 6.39–7.08 (9H, m, CH₃), 6.22 (1H, s, =CH), 5.03 (1H, s, OH), 4.58 (1H, s, CH), 4.01 (1H, s, NH), 4.22 (2H, s, CH₂), 3.48 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-d₆, δ / ppm): 186.1 (CO), 176.9 (C₂), 155.3 (C₁), 144.5 (C₀), 142.4 (C₉), 138.5 (C₈), 134.4 (C₇), 131.1 (C₆), 128.1 (C₅), 127.4 (C₄), 116.6 (C₃), 114.2 (C₂), 111.6 (C₁), 71.7 (CH₂), 55.6 (CH); IR (KBr): ν 3379, 2954, 2705, 1658, 1624, 1514, 1451, 1195, 1020, 747 cm⁻¹; ESI-MS: m/z [M+H]⁺ [M+2H]²⁺ [M+3H]³⁺. Anal. calc’d. For C₉H₇NO₂: C 67.25, H: 5.05, N: 4.13. Found: C 67.32, H: 5.21, N: 4.33 %.

3-Hydroxy-6-hydroxymethyl-2-[(2-chloro-phenyl)-phenylamino-methyl]-pyran-4-one (4g)
Solid, mp 103–105 °C; ¹H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ / ppm): 8.93 (1H, s, OH), 6.72–7.31 (9H, m, CH₃), 6.32 (1H, s, =CH), 4.59 (1H, s, CH), 4.02 (1H, s, NH), 4.23 (2H, s, CH₂), 3.47 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-d₆, δ / ppm): 187.5 (CO), 177.2 (C₂), 143.2 (C₁), 141.6 (C₀), 138.4 (C₉), 132.0 (C₈), 131.5 (C₇), 130.7 (C₆), 129.7 (C₅), 128.4 (C₄), 127.6 (C₃), 121.5 (C₂), 116.9 (C₁), 113.3 (C₀), 112.1 (C₉), 71.6 (CH₂), 55.7 (CH); IR (KBr): ν 3387, 2927, 1707, 1650, 1576, 1457, 1310, 1208, 1071, 833, 748 cm⁻¹; ESI-MS: m/z [M+H]⁺ [M+2H]²⁺ [M+3H]³⁺. Anal. calc’d. For C₉H₇ClNO₂: C 63.78, H: 4.51, N: 3.91. Found: C 63.53, H: 4.67, N: 3.75 %.

3-Hydroxy-6-hydroxymethyl-2-[(2-bromo-phenyl)-phenylamino-methyl]-pyran-4-one (4h)
Solid, mp 96–98 °C; ¹H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ / ppm): 8.81 (1H, s, OH), 6.54–7.23 (9H, m, CH₃), 6.22 (1H, s, =CH), 4.57 (1H, s, CH), 4.02 (1H, s, NH), 4.21 (2H, s, CH₂), 3.47 (1H, s, CH₂), 130.5 (C₀), 127.5 (C₉), 127.1 (C₈), 116.1 (C₇), 71.7 (CH₂), 55.7 (CH); IR (KBr): ν 3355, 2930, 1621, 1578, 1459, 1249, 1181, 763 cm⁻¹; ESI-MS: m/z [M+H]⁺ [M+2H]²⁺ [M+3H]³⁺. Anal. calc’d. For C₉H₇BrNO₂: C 71.20, H: 5.68, N: 4.15. Found: C 71.31, H: 5.57, N: 4.28 %.
3-Hydroxy-6-hydroxymethyl-2-[(2-methyl-phenyl)-phenylamino-methyl]-pyran-4-one (4k)

Viscous liquid; 'H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ / ppm): 8.45 (1H, s, OH), 6.42–7.05 (9H, m, CH₆₇, m, CH, 6.38 (1H, s, =CH), 4.52 (1H, s, CH₂), 4.01 (1H, s, NH), 4.20 (2H, s, CH₂), 3.41 (1H, s, CH₂OH), 2.38 (3H, s, CH₃); ¹³C-NMR (100 MHz, DMSO-d₆, δ / ppm): 187.0 (CO), 177.4 (C₁), 143.1 (C₂), 138.7 (C₃), 136.6 (C₄), 127.6 (C₅), 126.9 (C₆), 126.2 (C₇), 125.8 (C₈), 125.5 (C₉), 125.0 (C₁₀), 121.4 (C₁₁), 116.7 (C₁₂), 112.9 (C₁₃), 111.9 (C₁₄), 71.8 (-CH₂), 55.7 (CH), 14.8 (CH₃); ν 3327, 3058, 2924, 2915, 1669, 1452, 1103, 747 cm⁻¹; ESI-MS: m/z [M+], 337. Anal. calcd. For C₂₁H₁₈N₂O₅: C: 71.20, H: 5.68, N: 4.15. Found: C: 71.25, H: 5.60, N: 4.32 %.

3-Hydroxy-6-hydroxymethyl-2-[(2,4-dichlorophenyl)-phenylamino-methyl]-pyran-4-one (4l)

Solid. mp 87–89 °C; 'H NMR (400 MHz, DMSO + CDCl₃, 1:4, δ / ppm): 8.51 (1H, s, OH), 6.58–7.21 (8H, m, CH₆₇, m, CH, 6.39 (1H, s, =CH), 4.55 (1H, s, CH₂), 4.23 (2H, s, CH₂), 4.03 (1H, s, NH), 3.42 (1H, s, CH₂OH); ¹³C-NMR (100 MHz, DMSO-d₆, δ / ppm): 187.3 (CO), 177.5 (C₁), 143.5 (C₂), 140.1 (C₃), 139.1 (C₄), 133.4 (C₅), 133.1 (C₆), 126.9 (C₇), 126.2 (C₈), 125.7 (C₉), 125.2 (C₁₀), 121.3 (C₁₁), 116.8 (C₁₂), 113.0 (C₁₃), 111.8 (C₁₄), 71.7 (-CH₂), 55.8 (CH); IR (KBr): ν 3307, 2966, 1691, 1634, 1575, 1451, 1207, 1081, 744 cm⁻¹; ESI-MS: m/z [M+], 392. Anal. calcd. For C₂₁H₁₇Cl₂N₂O₅: C: 58.18, H: 3.85, N: 3.57. Found: C: 57.92, H: 3.97, N: 3.61 %.

RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents,10–13 we wish, herein is reported the use of pTSA as a more robust and efficient catalyst in the one-pot synthesis of the 2-substituted aryl (amino) kojic acid derivatives 3a–o by coupling reaction of aniline and kojic acid with different aromatic aldehydes in good yields (90–94 %) under solvent free (Scheme 1, Table 1). As shown in the Table, the reactions occurred excellently within 1.4–2.0 h under solvent free conditions. The experimental results indicate that the most effective conversion occurred when a mole ratio 1:0.12 of substrate/pTSA was used. Longer reaction times were required when lower amounts of pTSA were employed. It is important to

Scheme 1: Synthesis of 2-substituted aryl (amino) kojic acid 4

Scheme 2: A plausible reaction mechanism
<table>
<thead>
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<th>Entry</th>
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<th>Time (h)</th>
<th>Yields (%)</th>
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</table>

*) All products were characterized by $^1$H NMR, IR, mass spectroscopy and elemental analysis. *) Isolated yields.
note that no 2-substituted aryl (amino) kojic acid derivatives were afforded when the reactions were performed in the absence of pTSA in the reaction mixture.

Mechanistically, we presume that when aniline is treated with aldehyde in the presence of pTSA, an iminium ion intermediate is formed which is attacked by kojic acid to get the 2-substituted aryl (amino) kojic acid (Scheme 2).

CONCLUSION

We have described an efficient and environmentally benign method for the preparation of 2-substituted aryl (amino) kojic acid derivatives. This three-component reaction is efficiently catalyzed by pTSA under solvent-free at 95 °C. Operational simplicity, mild reaction conditions, enhanced rates, and high isolated yields of the pure products are significant advantages of the protocol presented here.

REFERENCES