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# Efficient One-pot pTSA-catalyzed Synthesis of 2-substituted Aryl (indolyl)kojic Acid and Kojyl Thioether Derivatives Under Mild Conditions

Mehdi Forouzani[1,*] and Hassan Ghasemnejad-Bosra[2]

[1]*Department of Chemistry, Payamenoor University, 19395-4697 Tehran, Iran*

[2]*Islamic Azad University-Babol Branch, School of Science, P.O. Box 755, Babol, Iran*

**Abstract:** New and convenient one-pot syntheses of 2-substituted aryl (indolyl) kojyl thioether from 2-substituted aryl (indolyl) kojic acids have been found. Firstly, the 2-substituted aryl (indolyl) kojic acids were readily obtained from coupling of aldehyde, kojic acid and indoles in the presence of *p*-toluenesulfonic acid as catalyst in good yields and with high selectivity. Then, 2-substituted aryl (indolyl) kojic acids were reacted with thionyl chloride to afford corresponding 2-substituted aryl (indolyl) kojic chlorides. Finally, the 2-substituted aryl (indolyl) kojic chloride derivatives were reacted with benzenethiols in presence of triethylamine in tetrahydrofurane to afford the corresponding thioether derivatives in good yields.

**Keywords**: The one-pot synthesis, 2-substituted aryl (indolyl) kojic acids, 2-substituted aryl (indolyl) kojic chlorides, *p*-toluenesulfonic acid, kojyl thioether**.**

## INTRODUCTION

Kojic acid [1] 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. [2-4] Kojic acid has chelating activity [5] and inhibits tyrosinase, [6] and polyphenoloxidase (PPO). [7] Based on these effects, kojic acid has been used as a depigmenting agent for cosmetics and as a food additive to prevent enzymatic browning due to PPO. Kojic acid has also been shown to scavenge free radicals and to prevent photodamage [7] However, only a few studies on kojic acid and its derivatives as NO inhibitors have been conducted. The biological activities of kojic acid are due to its γ-pyranone structure having an enolic hydroxyl group. Thus, various kojic acid derivatives, that are modified at the 2-position, have been developed to enhance biological activities [8].

## 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. $^1$H and $^{13}$C NMR spectra were measured in DMSO-$CDCl_3$ with a Bruker DRX-400 Advance instrument at 400 and 100 MHz, respectively, using $Me_4Si$ 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 an SMPI apparatus.

**General procedure of the synthesis of 2-substituted aryl(Indolyl)kojic acid derivative (4a–k):** Aldehyde (1 mmol), kojic acid (1 mmol), indole (1 mmol) and pTSA (0.12 mmol) were taken in a 25 mL round-bottomed flask containing 10 mL of water. The mixture was stirred at 90 $^o$C for an appropriate time as mentioned in Table 1. 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).

The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated in *vacuo* and purified by column chromatography on silica gel (Merck, 60–120 mesh, ethyl acetate/hexane, 3:7) to afford the pure substituted aryl(Indolyl)kojic acid derivative. These products were characterized on the basis of their physical properties and also characterized by $^1$H-NMR, $^{13}$C-NMR, IR spectra and, and by direct comparison with literature data [13].

Typical procedure of the synthesis of 2-((1H-indol-3-yl)-phenyl-methyl)-3-hydroxy-6-(phenylsulfanylmethyl)-4H-pyran-4-one (6a): To a stirred solution of kojyl chloride 5a (4.8 g, 30 mmol) and trietylamine (1.6 g, 4 mmol) in THF (10 mL) under $N_2$ was added benzenethiol (3.7 g, 33 mmol). The reaction mixture was stirred for 8 h at room temperature, after which THF was evaporated in vacuo. The residue was extracted with ethyl acetate (30 mL), washed with water. The organic layer was dried with anhydrous $MgSO_4$ and concentrated to give a crude product. The resultant was purified by

*Address correspondence to this author at the Department of Chemistry, Payamenoor University, 19395-4697 Tehran, Iran; Tel: +98-2415078; Fax: +98-2415026; E-mail: forouzanimehdi@yahoo.com

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crystallization from ethyl acetate-hexane to give 6a (1.5 g) in 87 % yields.

All the products obtained were fully characterized by spectroscopic methods such as IR, $^1$H-NMR, $^{13}$C-NMR, mass spectroscopy and elemental analysis and have been identified by the comparison of the reported spectral data.

**3-Hydroxy-2-[(1*H*-Indol-3-yl)-(phenyl)methyl]-6-phenylsulfanylmethyl-4*H*-pyran-4-one (6a):** solid, Time: 8h; Yield: 87%; M.p. 78–80 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.86 (1H, *s*, O**H**), 7.97 (1H, *s*, N**H**), 6.81–7.31 (14H, *m*, C$\mathbf{H}_{arom.}$), 6.31 (1H, *s*, C$\mathbf{H}_{ind.}$), 5.98 (1H, *s*, C$\mathbf{H}_{coj.}$), 4.48 (1H, *s*, C**H**), 3.42 (2H, *s*, C$\mathbf{H_2}$); $^{13}$C-NMR(100 MHz, DMSO): δ 174.1, 166.9, 159.0, 150.3, 141.8, 138.7, 135.6, 135.3, 132.7, 131.2, 130.5, 128.7, 128.4, 127.7, 126.6, 126.4, 124.9, 121.7, 120.3, 119.1, 118.3, 112.9, 111.1, 109.4, 107.8, 43.5, 38.3; IR (KBr): υ 3331, 2927, 2851, 1712, 1624, 1461, 1208, 747 cm$^{-1}$; ESIMS: m/z [439, M+1]. Anal. calcd. For $C_{27}H_{21}NO_3S$; C: 73.78, H: 4.82, N: 3.19. Found: C: 73.32, H: 5.02, N: 3.24 %.

**3-Hydroxy-2-[(1*H*-Indol-3-yl)-(4-methoxyphenyl) methyl]-6-phenylsulfanyl methyl-4*H*-pyran-4-one (6b):** solid, Time: 7.3h; Yield: 91%; M.p. 97–99 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.27 (1H, *s*, O**H**), 8.02 (1H, *s*, N**H**), 6.77–7.50 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.58 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.01 (1H, *s*, C$\mathbf{H}_{coj.}$), 4.63 (1H, *s*, C**H**), 3.73 (3H, *s*, OC$\mathbf{H_3}$), 3.65 (2H, *s*, C$\mathbf{H_2}$); $^{13}$C-NMR (100 MHz, DMSO): δ 173.8, 165.5, 157.9, 140.5, 136.7, 133.2, 132.8, 130.7, 129.8, 128.8, 128.2, 126.1, 124.9, 124.3, 123.5, 122.7, 120.5, 120.1, 119.1, 118.4, 117.9, 114.2, 111.2, 108.4, 103.1, 57.4, 43.8, 37.2; IR (KBr): υ 3328, 2925, 1701, 1615, 1512, 1511, 1451, 1317, 1252, 1090, 995, 759, 738 cm$^{-1}$; ESI-MS: m/z [470, M+1]. Anal. calcd. For $C_{28}H_{23}NO_4S$; C: 71.47, H: 5.14, N: 2.98. Found: C: 71.22, H: 4.35, N: 3.14 %.

**3-Hydroxy-2-[(1*H*-Indol-3-yl)-(4-methylphenyl) methyl]-6-phenylsulfanyl methyl-4*H*-pyran-4-one (6c):** solid, Time: 9.1h; Yield: 86%; M.p. 94–95 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.35 (1H, *s*, O**H**), 7.80 (1H, *s*, N**H**), 6.63–7.57 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.56 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.03 (1H, *s*, C$\mathbf{H}_{coj.}$), 4.78 (1H, *s*, C**H**), 3.43 (2H, *s*, C$\mathbf{H_2}$), 2.38 (3H, *s*, C$\mathbf{H_3}$); $^{13}$C-NMR (100 MHz, DMSO): δ 174.0, 166.1, 142.1, 141.5, 140.0, 136.4, 130.3, 129.8, 126.3, 125.1, 123.7, 121.4, 122.2, 121.8, 121.3, 120.2, 119.4, 118.5, 118.1, 116.5, 113.6, 112.7, 111.3, 108.9, 103.3, 44.4, 37.2, 20.9; IR (KBr): υ 3358, 2932, 1691, 1627, 1583, 1488, 1450, 1221, 996, 741 cm$^{-1}$; ESI-MS: m/z [453, M+1]. Anal. calcd. For $C_{28}H_{23}NO_3S$; C: 74.15, H: 5.11, N: 3.09. Found: C: 74.21, H: 5.25, N: 2.94 %.

**3-Hydroxy-2-[(1*H*-Indol-3-yl)-(4-chloro phenyl) methyl]-6-phenylsulfanyl methyl-4*H*-pyran-4-one (6d):** solid, Time: 9.4h; Yield: 87%; M.p. 93–95 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.38 (1H, *s*, O**H**), 7.74 (1H, *s*, N**H**), 6.73–7.49 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.64 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.14 (1H, *s*, C$\mathbf{H}_{coj.}$), 5.17 (1H, *s*, C**H**), 3.78 (2H, *s*, C$\mathbf{H_2}$); $^{13}$C-NMR (100 MHz, DMSO): δ 173.6, 167.1, 135.2, 133.4, 130.8, 130.1, 131.7, 129.4, 129.0, 128.7, 127.4, 125.4, 124.1, 120.6, 120.3, 120.0, 119.2, 118.9, 112.8, 112.5, 111.4, 110.5, 108.8, 103.6, 103.4, 43.5, 37.6; IR (KBr): υ 3391, 2924, 1713, 1618, 1576, 1509, 1456, 1302, 1245, 1179, 1030, 860, 828, 745 cm$^{-1}$; ESI-MS: m/z [473, M+1]. Anal. calcd. For $C_{27}H_{20}ClNO_3S$; C: 68.42, H: 4.25, N: 2.96. Found: C: 68.22, H: 4.55, N: 3.18 %.

**3-Hydroxy-2-[(1*H*-Indol-3-yl)-(4-bromophenyl)methyl]-6-phenylsulfanyl methyl-4*H*-pyran-4-one (6e):** solid, Time: 8.3h; Yield: 88%; M.p. 90–92 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.33 (1H, *s*, O**H**), 7.78 (1H, *s*, N**H**), 6.61–7.39 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.54 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.07 (1H, *s*, C$\mathbf{H}_{coj.}$), 5.09 (1H, *s*, C**H**), 3.65 (2H, *s*, C$\mathbf{H_2}$); $^{13}$C-NMR (100 MHz, DMSO): δ 174.1, 170.8, 136.6, 136.1, 135.3, 133.6, 133.0, 132.1, 131.7, 131.2, 130.6, 130.3, 130.1, 128.5, 127.1, 122.8, 121.7, 120.6, 120.3, 119.4, 118.7, 110.6, 108.5, 103.9, 103.7, 43.8, 37.5; IR (KBr): υ 3394, 2928, 1705, 1624, 1581, 4197, 1455, 1268, 1163, 1072, 748 cm$^{-1}$; ESI-MS: m/z [518, M+1]. Anal. calcd. For $C_{27}H_{20}BrNO_3S$; C: 62.55, H: 3.89, N: 2.70. Found: C: 62.17, H: 4.13, N: 2.97 %.

**3-Hydroxy-2-[(1*H*-Indol-3-yl)-(2-methylphenyl)methyl]-6-phenylsulfanyl methyl-4*H*-pyran-4-one (6f):** solid, Time: 8.7h; Yield: 85%; M.p. 86–87 $^o$C; $^1$H NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.27 (1H, *s*, O**H**), 7.89 (1H, *s*, N**H**), 6.93–7.65 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.71 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.14 (1H, *s*, C$\mathbf{H}_{coj.}$), 4.67 (1H, *s*, C**H**), 3.62 (2H, *s*, C$\mathbf{H_2}$), 2.42 (3H, *s*, C$\mathbf{H_3}$); $^{13}$C NMR (100 MHz, DMSO): δ 173.5, 168.3, 139.4, 138.2, 136.5, 135.6, 133.3, 132.4, 131.9, 131.5, 130.7, 129.3, 128.0, 127.2, 126.6, 121.8, 120.2, 119.6, 118.9, 118.4, 115.1, 112.8, 109.5, 108.7, 108.3, 43.6, 30.9, 15.1; IR (KBr): υ 3379, 2954, 2705, 1658, 1624, 1575, 1514, 1451, 1195, 1020, 863, 747 cm$^{-1}$; ESI-MS: m/z [453, M+1]. Anal. calcd. For $C_{28}H_{23}NO_3S$; C: 74.15, H: 5.11, N: 3.09. Found: C: 73.92, H: 5.39, N: 3.25 %.

**3-Hydroxy-2-[(1H-Indol-3-yl)-(4-hydroxy phenyl) methyl]-6-phenylsulfanyl methyl-4H-pyran-4-one (6g):** solid, Time: 7.8h; Yield: 90%; M.p. 89–91 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.25 (1H, *s*, O**H**), 7.79 (1H, *s*, N**H**), 6.92–7.43 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.82 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.57 (1H, *s*, C$\mathbf{H}_{coj.}$), 5.22 (1H, *s*, O**H**), 4.68 (1H, *s*, C**H**), 3.47 (2H, *s*, C$\mathbf{H_2}$); $^{13}$C-NMR (100 MHz, DMSO): δ 173.2, 167.4, 155.8, 150.5, 141.3, 137.9, 135.6, 133.2, 131.0, 130.3, 129.7, 128.3, 127.4, 126.6, 124.9, 121.4, 118.8, 118.0, 115.6, 112.1, 11.0, 110.4, 108.3, 107.6, 103.2, 37.4, 37.5; IR (KBr): υ 3387, 2927, 1707, 1650, 1619, 1576, 1457, 1310, 1208, 1071, 1011, 869, 833, 748 cm$^{-1}$; ESI-MS: m/z [455, M+1]. Anal. calcd. For $C_{27}H_{21}NO_4S$; C: 71.19, H: 4.65, N: 3.07. Found: C: 71.01, H: 4.81, N: 3.29 %.

**3-Hydroxy-2-[(1H-Indol-3-yl)-(2-chloro phenyl) methyl]-6-phenylsulfanyl methyl-4H-pyran-4-one (6h):** solid, Time: 8.9h; Yield: 86%; M.p. 81–83 $^o$C; $^1$H-NMR(400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.26 (1H, *s*, O**H**), 7.95 (1H, *s*, N**H**), 7.02–7.69 (13H, *m*, C$\mathbf{H}_{arom.}$), 6.42 (1H, *s*, C$\mathbf{H}_{ind.}$), 6.25 (1H, *s*, C$\mathbf{H}_{coj.}$), 4.57 (1H, *s*, C**H**), 3.48 (2H, *s*, C$\mathbf{H_2}$); $^{13}$C-NMR (100 MHz, DMSO): δ 174.0, 167.6, 138.1, 137.0, 134.1, 133.2, 132.7, 130.8, 127.8, 126.6, 126.2, 125.1, 122.8, 121.5, 120.4, 119.6, 118.1, 115.6, 113.0, 112.2, 111.3, 110.0, 108.5, 107.4, 103.3, 43.3, 37.4; IR (KBr): υ 3367, 2923, 1703, 1647, 1581, 1453, 1377, 1240, 10514, 989, 822, 753 cm$^{-1}$; ESI-MS: m/z [473, M+1]. Anal. calcd. For $C_{27}H_{20}ClNO_3S$; C: 68.42, H: 4.25, N: 2.96. Found: C: 68.11, H: 4.39, N: 3.19 %.

**2-[(5-Chloro-1H-indol-3-yl)-phenyl-methyl] 3-hydroxy-6-p-tolylsulfanyl methyl- 4H-pyran-4-one (6i):** viscous liquid; Time: 8.5h; Yield: 88%; $^1$H-NMR (400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.41 (1H, *s*, O**H**), 8.21 (1H, *s*, N**H**), 7.10–7.61 (13H, *m*, C**H**$_{arom.}$), 6.78 (1H, *s*, C**H**$_{ind.}$), 6.02 (1H, *s*, C**H**$_{coj.}$), 4.78 (1H, *s*, C**H**), 3.39 (2H, *s*, C**H$_2$**); $^{13}$C-NMR (100 MHz, DMSO): δ 181.4, 174.2, 137.7, 137.4, 135.6, 134.5, 133.0, 131.4, 129.8, 128.8, 128.4, 126.6, 125.7, 123.8, 121.2, 120.7, 120.0, 118.4, 117.8, 113.9, 113.2, 112.2, 108.7, 103.0, 43.6, 37.1; IR (KBr): υ 3355, 2930, 1621, 1578, 1510, 1459, 1249, 1181, 1030, 799, 763 cm$^{-1}$; ESI-MS: m/z [473, M+1]. Anal. calcd. For $C_{27}H_{20}ClNO_3S$; C: 68.42, H: 4.25, N: 2.96. Found: C: 68.10, H: 4.43, N: 3.20 %.

**2-[(5-Chloro-1H-indol-3-yl)-(4-methoxy-phenyl)-methyl]-3-hydroxy-6-p-tolyl sulfanyl methyl- 4H-pyran-4-one (6j):** viscous liquid; Time: 8.3h; Yield: 85%; $^1$H NMR (400 MHz, DMSO + $CDCl_3$, 1:4): δ 10.35 (1H, *s*, O**H**), 8.63 (1H, *s*, N**H**), 6.95–7.60 (11H, *m*, C**H**$_{arom.}$), 6.77 (1H, *s*, C**H**$_{ind.}$), 5.97 (1H, *s*, C**H**$_{coj.}$), 4.79 (1H, *s*, C**H**), 3.71 (3H, *s*, OC**H$_3$**), 3.43 (2H, *s*, C**H$_2$**), 2.31 (3H, *s*, C**H$_3$**); $^{13}$C NMR (100 MHz, DMSO): δ 182.4, 173.1, 159.0, 137.3, 136.3, 134.3, 133.0, 132.1, 129.4, 128.7, 127.8, 127.5, 126.4, 122.4, 122.8, 121.4, 118.3, 114.0, 113.4, 112.1, 111.9, 111.2, 109.3, 108.5, 103.1, 56.0, 43.7, 37.4, 29.2; IR (KBr): υ 3327, 3058, 2924, 1705, 1669, 1452, 1103, 1051, 747 cm$^{-1}$; ESI-MS: m/z [519, M+1]. Anal. calcd. For $C_{29}H_{24}ClNO_4S$; C: 67.24, H: 4.67, N: 2.70. Found: C: 67.39, H: 4.97, N: 2.90 %.

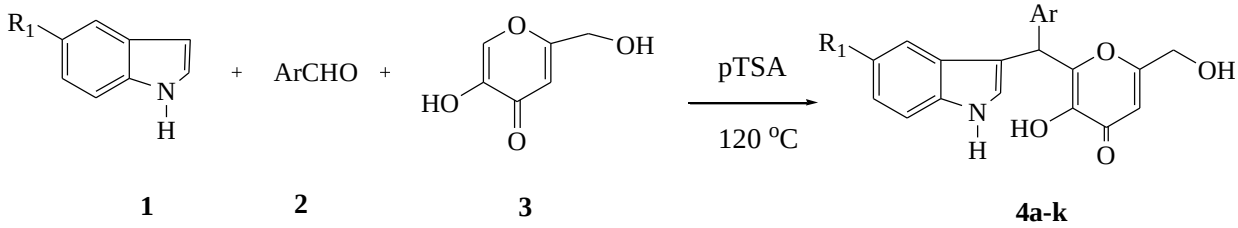
**3-Hydroxy-2-[(5-methoxy-1*H*-indol-3-yl)-(4-methoxy-phenyl)-methyl]-6-*p*-tolyl sulfanyl methyl- 4*H*-pyran-4-one (6k):** Solid, Time: 8.1h; Yield: 89%; M.p. 81-83 °C; $^1$H NMR (400 MHz, DMSO + $CDCl_3$, 1:4): δ 11.03 (1H, *s*, O**H**), 8.71 (1H, *s*, N**H**), 6.70–7.21 (11H, *m*, C**H**$_{arom.}$), 6.49 (1H, *s*, C**H**$_{ind.}$), 6.01 (1H, *s*, C**H**$_{coj.}$), 4.75 (1H, *s*, C**H**), 3.82 (3H, *s*, OC**H$_3$**), 3.75 (3H, *s*, OC**H$_3$**), 3.45 (2H, *s*, C**H$_2$**), 2.45 (3H, *s*, C**H$_3$**); $^{13}$C NMR (100 MHz, DMSO): δ 175.7, 168.6, 159.1, 156.7, 152.5, 141.6, 136.2, 134.8, 134.0, 133.7, 129.6, 128.3, 126.9, 125.3, 122.8, 121.9, 120.1, 119.2, 118.5, 117.6, 114.2, 111.2, 109.7, 104.5, 56.2, 56.0, 43.7, 37.4, 29.2; IR (KBr): υ 3381, 2924, 1694, 1652, 1578, 1509, 1457, 1361, 1194, 1071, 1025, 856, 749 cm$^{-1}$; ESI-MS: m/z [515, M+1]. Anal. calcd. For $C_{30}H_{28}NO_5S$; C: 70.02, H: 5.48, N: 2.72. Found: C: 69.67, H: 5.68, N: 2.86 %.

## RESULTS AND DISCUSSION

In continuation with the search for simple non-hazardous methods for the transformations in organic synthesis using various reagents, [9-13]. we wish, herein, to report on the use of pTSA as a more robust and efficient catalyst in the one-pot synthesis of 2-substituted aryl(indolyl)kojic acid derivatives ( from kojic acid, aryl aldehydes and indoles under neutral conditions in high yields (92-94%) (Scheme **1**, Table **1**).

We propose a mechanism for these reactions in three steps as shown in Scheme (**2**).

Thus, the aldehydes act as Michael acceptors and the kojic acid as the nucleophile resulting in a Michael adduct



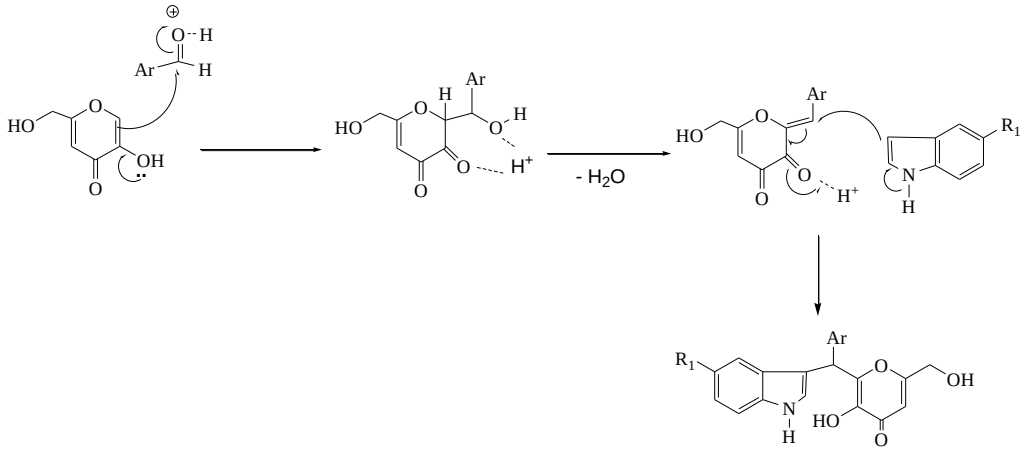

**1** **2** **3** **4a-k**

**Scheme (1).** Synthesis of 2-substituted aryl(indolyl)kojic acid 4.

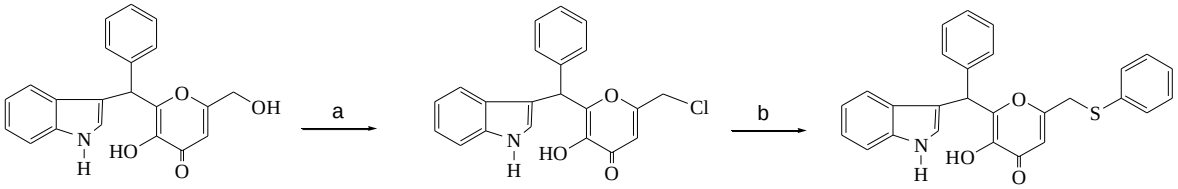
**Table 1. pTSA-Catalyzed Synthesis of 2-substituted Aryl(indolyl)kojic Acid Derivatives (4a-k)**

| Entry | Product [a] | $R_1$ | Ar | Time (min) | Yield (%) [b] |
|---|---|---|---|---|---|
| 1 | 4a | H | $C_6H_5$ | 48 | 93 |
| 2 | 4b | H | 4-OMe$C_6H_5$ | 54 | 92 |
| 3 | 4c | H | 4-Me$C_6H_5$ | 45 | 94 |
| 4 | 4d | H | 4-Cl$C_6H_5$ | 44 | 93 |
| 5 | 4e | H | 4-Br-$C_6H_5$ | 43 | 90 |
| 6 | 4f | H | 2-Me$C_6H_5$ | 45 | 92 |
| 7 | 4g | H | 4-OH$C_6H_5$ | 52 | 93 |
| 8 | 4h | H | 2-Cl$C_6H_5$ | 49 | 90 |
| 9 | 4i | Cl | H | 57 | 91 |
| 10 | 4j | Cl | 4-OMe$C_6H_5$ | 64 | 92 |
| 11 | 4k | OMe | 4-OMe$C_6H_5$ | 67 | 93 |

[a])All products were characterized by $^1$H-NMR, $^{13}$C-NMR, IR spectra and, by direct comparison with literature data [14]. [b])Isolated yields.



**Scheme (2).** A plausible reaction mechanism.



**4a** **5a** **6a**

**Scheme (3).** Reaction conditions; (**a**) $SOCl_2$, DMF, rt; (**b**) benzenethiols, triethylamine, THF, rt.

which, under the influence of pTSA, forms an enone. The resulting enone may undergo conjugate addition with indole to give the desired product as depicted in Scheme (**2**).

In continuous, 2-substituted aryl(indolyl)kojic acid derivatives (**4a-4k**) were reacted with thionyl chloride to afford corresponding 2-substituted aryl(indolyl)kojic chlorides (**5a-5k**). Then, 2-substituted aryl(indolyl)kojic chlorides were reacted with benzenethiols in presence of triethylamine in tetrahydrofuran to afford the corresponding thioether derivatives (**6a-6k**) (Scheme **3**).

## CONCLUSION

In summary, we have described an efficient and environmentally benign method for the preparation of 2-substituted aryl(indolyl)kojic acid derivatives by pTSA-catalyzed reaction in water at 90 $^{o}$C and convert to their corresponding kojyl thioether. Operational simplicity, mild reaction conditions, enhanced rates, and high isolated yields of the pure products are significant advantages of the protocol presented here.

## CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

## ACKNOWLEDGEMENTS

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Evaluation of Health Aspects of Kojic Acid in Food.

## REFERENCES

[1] Burdock, G.A.; Soni, M.G.; Carabin, I.G. Evaluation of health aspects of Kojic acid in food. *Regulat. Toxicol. Pharmacol.*, **2001**, *33*, 80-101; (b) Futamura, T.; Okabe, M.; Tamura, T.; Toda, K.; Matsunobu, T.; Park, Y.S. Improvement of production of Kojic acid by a mutant strain Aspergillus oryzae, MK107-39. *J. Biosci. Bioeng.*, **2001**, *91*, 272-276.

[2] Solano, F.; Briganti, S.; Picardo, M.; Ghanem, G. Hypopigmenting agents: an updated review on biological, chemical and clinical aspects. *Pigment Cell Res.*, **2006**, *19*, 550-571.

[3] Chang, T.S. An updated review of tyrosinase inhibitors**.** *Int. J. Mol. Sci*., **2009**, *10*, 2440-2475.

[4] Leyden, J.J.; Shergill, B.; Micali, G.; Downie, J.; Wallo, W. Natural options for the management of hyperpigmentation. *J. Eur. Acad. Dermatol. Venereol.*, **2011**, *25*, 1140-1145.

[5] Yuen, V.G.; Caravan, P.; Gelmini, L.; Glover, N.; Mcneill, J.H.; Setyawati, I.A.; Zhou, Y.; Orvig, C. Glucose-lowering properties of vanadium compounds: comparison of coordination complexes with maltol or kojic acid as ligands**.** *J. Inorg. Biochem*., **1997**, *73*, 109-116.

[6] Ohyama, Y.; Mishima, Y. Melanosis-inhibitory effect of kojic acid and its action mechanism. *Fragrance J.*, **1990**, *6*, 53-58.

[7] Chen, J.S.; Wei, C.I.; Rolle, R.S.; Otwell, W.S.; Balaban, M.O.; Marshall, M.R.J. Inhibitory effect of kojic acid on some plant and crustacean polyphenol oxidases. *Agric. Food Chem.*, **1991**, *39*, 1396-1401.

[8] Mitani, H.; Koshiishi, I.; Sumita, T.; Imanari, T. Prevention of the photodamage in the hairless mouse dorsal skin by kojic acid as an iron chelator. *Eur. J. Pharmacol.*, **2001**, *411*, 169-174. (a) Kobayashi, Y.; Kayahara, H.; Tasada, K.; Nakamura, T.; Tanaka, H. Synthesis of amino acid derivatives of kojic acid and their tyrosinase inhibitory activity. *Biosci. Biotechnol. Biochem.*, **1995**, *59*, 1745-1746; (b) Kobayashi, Y.; Kayahara, H.; Tadasa, K.; Tanaka, H. Synthesis of *N*-kojic-amino acid and *N*-kojic-amino acid-kojiate and their tyrosinase inhibitory activity. *Bioorg. Med. Chem. Lett.*, **1996**, 6, 1303-1308; (c) Kadokawa, J.; Nishikura, T.; Muraoka, R.; Tagaya, H.; Terada, Y.; Fukuoka, N. Synthesis of Kojic acid derivatives containing phenolic hydroxy groups. *Synth. Commun.*, **2003**, *33*, 1081.

[9] Ghasemnejad-Bosra, H.; Faraje, M.; Habibzadeh, S.; Ramzaniyan-Lehmali, F. An efficient one-pot synthesis of highly substituted furans catalyzed by *N*-bromosuccinimide. *J. Serb. Chem. Soc.*, **2010**, *75*, 299-305.

[10] Ghasemnejad-Bosra, H.; Haghdadi, M.; Gholampour-Azizi, I. *N*-Bromosuccinimide (NBS) as Promoter for Acylation of Sydnones in the Presence of Acetic Anhydride under Neutral Conditions. *Heterocycles*, **2008**, *75*, 391-395.

[11] Ghasemnejad-Bosra, H.; Faraje, M.; Habibzadeh, S. Efficient One-Pot 1,3-Dibromo-5,5-dimethylhydantoin (DBH)-Catalyzed Synthesis of Highly Substituted Furans. *Helv. Chim. Acta.*, **2009**, *92*, 575-578.

[12] Ghasemnejad-Bosra, H.; Forouzani, M. A. A simple and effi cient one-pot bis-bromine-1,4-diazabicyclo [2.2.2]octane (Br 2 - DABCO) catalyzed synthesis of 14-aryl-14*H*dibenzo[*a*,*j*]xanthenes under solvent-free conditions. *Hetrocycl. Commun.*, **2011**, *17* (1-2), 83-85.

[13] Reddy, B. V. S.; Reddy, Reddy, M. R.; Madan, Ch.; Kumar, K. P.; Rao, M. S. Indium(III) chloride catalyzed three-component coupling reaction: A novel synthesis of 2-substituted aryl(indolyl)kojic acid derivatives as potent antifungal and antibacterial agents. *Bioorg Med. Chem. Lett.*, **2010**, *20*, 7507.

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