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One-pot three-component synthesis of 3-[(aryl)-arylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one

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A good yield in the synthesis of 3-[(aryl)-arylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one is described involving the reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with aromatic aldehydes and thiols in the presence of *p*-toluene sulfonic acid (*p*-TSA) under reflux conditions.

Keywords: 4-Hydroxy-6-methyl-2*H*-pyran-2-one, *p*-Toluene sulfonic acid, Thiols, Aromatic aldehydes, Multicomponent reactions

INTRODUCTION

Multicomponent reactions (MCRs), by virtue of their convergence, provide a single purification step, higher yields than stepwise procedure, use of simple and diverse precursors to construct complex molecules and use of only a single promoter or catalyst [1-3]. Multicomponent reactions are useful and efficient methods in organic synthesis. Thus, the development of new multicomponent reactions is a popular area of research in organic chemistry from a green chemistry point of view [4-6].

The reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with aromatic aldehydes and thiol has already been reported [7-9], but there are many limitations, such as long reaction times, hazardous organic solvents and reagents, and low yields. Hence, we have used a novel method to synthesize another class of this derivatives *via* three-component condensation reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with aromatic aldehydes and thiols in the presence of *p*-toluene sulfonic acid (*p*-TSA). We have developed a mild one-pot method, characterized by excellent yield, simple work-up, fast reaction, and employment of the cheap catalyst *p*-TSA.

As part of our current studies on the development of new routes in organic synthesis [10-13], we report the reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one with aromatic aldehydes and thiols in the presence of *p*-toluene sulfonic acid.

EXPERIMENTAL

Instruments

Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-250 Avance spectrometer in DMSO solution using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General experimental procedure

To a mixture of 4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) and aromatic aldehyde (1 mmol) in acetone (10 mL) in the presence of *p*-toluene sulfonic acid (0.1 mmol) as the catalyst, 1 mmol thiol was added under reflux.

The reaction progress was controlled by TLC (*n*-hexane:ethyl acetate=1:1). After 3 h, the reaction was completed and the solvent was removed under reduced pressure, the precipitated product was filtered off, washed with water (5 mL) and crystallised from ethanol.

RESULTS AND DISCUSSION

Reaction between 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** with aromatic aldehydes **2** and thiols **3** in the presence of *p*-toluene sulfonic acid under reflux conditions affords 3-[(aryl)-arylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **4** in good yields. (Scheme 1).

The compounds **4a-d** were characterized by ^{1}H, ^{13}C-NMR and IR spectroscopy and elemental analyses [5-7]. Compounds **4e-n** were new and their structures were deduced by elemental and spectral analysis. The structure of the other products was proved on the basis of ^{1}H, ^{13}C-NMR and IR spectroscopy and elemental analyses. The mass spectra of compounds **4a–n** were fairly similar and displayed molecular ion peaks. For example, the

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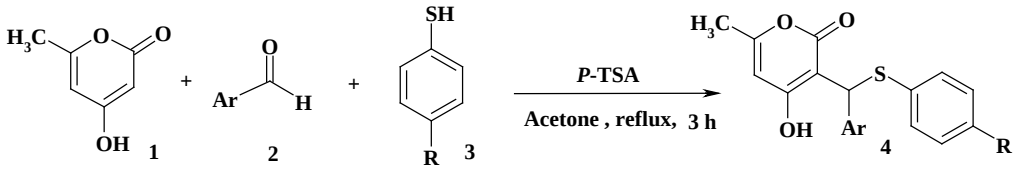


4	Ar	R	%Yield*
a	C_6H_5	H	78
b	4-NO_2 C_6H_4	H	91
c	4-Cl C_6H_4	H	86
d	4-CH_3O C_6H_4	H	75
e	4-Br C_6H_4	H	84
f	4-F C_6H_4	H	80
g	4-CH_3 C_6H_4	H	75
h	2-Cl C_6H_4	H	85
i	2-FC_6H_4	H	87
j	2-O_2N C_6H_4	H	90
k	4-NO_2 C_6H_4	CH_3	87
l	4-Cl C_6H_4	CH_3	83
m	4-CH_3O C_6H_4	CH_3	72
n	2-Cl C_6H_4	CH_3	82

*Isolated yields

Scheme 1

mass spectrum of compound **4e** showing a molecular ion peak at 403 m/z confirmed that compound **4e** is a triadduct of 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-bromobenz-aldehyde and thiol. The ^{1}H-NMR spectrum of compound **4e** displayed a sharp single signal at δ = 5.82 ppm for methine proton, along with charactristic signals at δ = 6.81–7.80 ppm for aromatic protons. A singlet was observed at δ = 9.93 ppm for OH proton, disappeared by addition of D_2O. ^{13}C NMR spectrum of compound **4e** showed 15 distinct signals in agreement with the proposed structure.

A mechanism of reasonable possibility is presented in scheme 2. As can be seen, firstly, Knoevenagel condensation between 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** and aromatic aldehydes **2** in the presence of *p*-toluene sulfonic acid occurs and intermediate **5** is formed. Intermediate **5** reacts with thiols *via* conjugate addition to form product **4.**

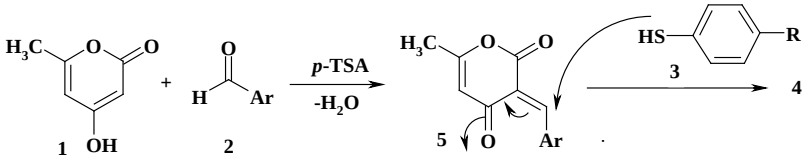
In summary, we have developed a mild, one-pot three-component reaction between 4-hydroxy-6-methyl-2*H*-pyran-2-one, aromatic aldehydes and thiols in the presence of *p*-toluene sulfonic acid under reflux conditions, characterized by excellent yield, simple work-up, fast reaction, and employment of the cheap catalyst *p*-TSA.

3-[(4-Bromophenyl)-phenylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **(4e).**

Brown powder, m.p. 83–85 °C, IR (KBr) (ν_{max} cm^{-1}): 3113 (OH), 1684 (C=O). Analyses: Calcd. for $C_{19}H_{15}BrO_3S$: C, 56.59; H, 3.75%. Found: C, 56.45; H, 3.90. MS (m/z, %): 403 (5). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.13 (3H, s, CH_3), 5.82 (1H, s, CH), 6.07 (1H, s, =CH), 6.81-7.80 (9H, m, arom), 9.93(1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.51 (CH_3), 34.48 (CH), 100.40, 101.58, 119.06, 127.05, 129.11, 129.48, 131.20, 131.63, 132.68, 140.03, 161.70, 164.23, 168.29 ppm.

3-[(4-Fluorophenyl)-phenylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **(4f).**

Yellow powder, m.p. 118–120 °C, IR (KBr) (ν_{max} cm^{-1}): 3427 (OH), 1684 (C=O). Analyses: Calcd. for $C_{19}H_{15}FO_3S$: C, 66.65; H, 4.42%. Found: C, 66.54; H, 4.58. MS (m/z, %): 342 (3). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.28 (3H, s, CH_3), 5.75 (1H, s, CH), 6.07 (1H, s, =CH), 6.96-7.52 (9H, m, arom), 10.90 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.62 (CH_3), 34.20 (CH), 103.19, 115.48, 127.17, 127.53, 128,14, 129.06, 130.32, 131.10, 137.00, 159.66, 161.83, 163.56, 169.60 ppm.



Scheme 2

3-[(4-methylphenyl)-phenylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **(4g).**

Brown powder, m.p. 183–185 °C, IR (KBr) (ν_{max} cm^{-1}): 3125 (OH), 1693 (C=O). Analyses: Calcd. for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36%. Found: C, 80.13; H, 5.21. MS (m/z, %): 338 (4). ^{1}H NMR (250 MHz, d_6-DMSO): δ 1.70 (3H, s, CH_3), 2.21 (3H, s, CH_3), 5.68 (1H, s, CH), 6.11 (1H, s, =CH), 7.13-7.90 (9H, m, arom), 11.18 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.57 (CH_3), 23.36 (CH_3), 35.76 (CH), 100.21, 101.40, 119.15, 123.53, 124.46, 127.17, 127.85, 131.55, 129.32, 143.10, 161.43, 165.61, 167.75 ppm.

3-[(2-Chlorophenyl)-phenylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **(4h).**

Brown powder, m.p. 161–163 °C, IR (KBr) (ν_{max} cm^{-1}): 3115 (OH), 1696 (C=O). Analyses: Calcd. for $C_{19}H_{15}ClO_3S$: C, 63.60; H, 4.21%. Found: C, 63.75; H, 4.012. MS (m/z, %): 358 (5). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.19 (3H, s, CH_3), 5.73 (1H, s, CH), 6.04 (1H, s, =CH), 7.11-7.84 (9H, m, arom), 11.52 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.48 (CH_3), 34.46 (CH), 100.37, 101.71, 125.77, 127.17, 127.88, 128.31, 128.90, 130.48, 131.14, 133.08, 140.35, 143.27, 161.82, 164.37, 166.52 ppm.

3-[(2-Fluorophenyl)-phenylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **(4i).**

Yellow powder, m.p. 103–105 °C, IR (KBr) (ν_{max} cm^{-1}): 3432 (OH), 1691 (C=O). Analyses: Calcd. for $C_{19}H_{15}FO_3S$: C, 66.65; H, 4.42%. Found: C, 66.50; H, 4.60. MS (m/z, %): 342 (5). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.24 (3H, s, CH_3), 5.86 (1H, s, CH), 6.13 (1H, s, =CH), 7.03-7.65 (9H, m, arom), 10.96 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.50 (CH_3), 34.27 (CH), 103.34 115.62, 127.13, 127.67, 128,19, 129.12, 130.45, 131.17, 133.15, 137.06, 140.28, 159.52, 161.77, 163.50, 169.43 ppm.

3-[(2-nitrophenyl)-phenylsulfanyl-methyl]-4-hydroxy-6-methylpyran-2-one **(4j).**

Brown powder, m.p. 201–203°C, IR (KBr) (ν_{max} cm^{-1}): 3418 (OH), 1688 (C=O), 1524 and 1355 (NO_2). Analyses: Calcd. for $C_{19}H_{15}NO_5S$: C, 61.78; H, 4.09; N, 3.79%. Found: C, 61.63; H, 4.27; N, 3.92. MS (m/z, %): 369 (8). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.26 (3H, s, CH_3), 5.74 (1H, s, CH), 6.13 (1H, s, =CH), 7.15-8.46 (9H, m, arom), 11.50 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.57 (CH_3), 35.80 (CH), 100.46, 101.22, 121.20, 122.14, 124.33, 127.13, 127.72, 128.76, 130.55, 133.06, 146.03, 148.71, 161.58, 165.60, 167.43 ppm.

3-[(4-nitrophenyl)(p-tolylsulfanyl)-methyl]-4-hydroxy-6-methylpyran-2-one **(4k).**

Brown powder, m.p. 211–213°C, IR (KBr) (ν_{max} cm^{-1}): 3403 (OH), 1681 (C=O), 1526 and 1345 (NO_2). Analyses: Calcd. for $C_{20}H_{17}NO_5S$: C, 62.65; H, 4.47; N, 3.65%. Found: C, 62.71; H, 4.35; N, 3.80. MS (m/z, %): 383 (8). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.10 (3H, s, CH_3), 2.38 (3H, s, CH_3), 5.72 (1H, s, CH), 6.13 (1H, s, =CH), 7.35-8.28 (8H, m, arom), 11.42 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.43 (CH_3), 21.66 (CH_3), 35.80 (CH), 100.52, 101.22, 123.43, 124.39, 127.07, 127.64, 128.72, 129.26, 146.18, 149.82, 161.73, 165.51 and 168.18 ppm.

3-[(4-Chlorophenyl)(p-tolylsulfanyl)-methyl]-4-hydroxy-6-methylpyran-2-one **(4l).**

Brown powder, m.p. 125–127°C, IR (KBr) (ν_{max} cm^{-1}): 3267 (OH), 1693 (C=O). Analyses: Calcd. for $C_{20}H_{17}ClO_3S$: C, 64.42; H, 4.60%. Found: C, 64.55; H, 4.49. MS (m/z, %): 372 (4). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.18 (3H, s, CH_3), 2.35 (3H, s, CH_3), 5.81 (1H, s, CH), 6.14 (1H, s, =CH), 7.08-7.95 (8H, m, arom), 11.36 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.47 (CH_3), 21.50 (CH_3), 34.46 (CH), 100.42, 101.73, 124.85, 127.16, 127.64, 128.21, 129.10, 130.77, 139.43, 141.32, 161.87, 164.20 and 166.75 ppm.

3-[(4-methoxyphenyl)(p-tolylsulfanyl)-methyl]-4-hydroxy-6-methylpyran-2-one **(4m).**

Brown powder, m.p. 173–175°C, IR (KBr) (ν_{max} cm^{-1}): 3156 (OH), 1681 (C=O). Analyses: Calcd. for $C_{21}H_{20}O_4S$: C, 68.46; H, 5.47%. Found: C, 68.62; H, 5.33. MS (m/z, %): 368 (3). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.22 (3H, s, CH_3), 2.30 (3H, s, CH_3), 3.68 (3H, s, OCH_3), 5.72 (1H, s, CH), 6.15 (1H, s, =CH), 7.11-7.88 (8H, m, arom), 11.21 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.48 (CH_3), 21.52 (CH_3), 35.77 (CH), 56.43 (OCH_3), 100.16, 101.52, 119.22, 123.58, 124.63, 127.16, 127.80, 131.63, 129.35, 143.24, 161.50, 165.39 and 167.52 ppm.

3-[(2-Chlorophenyl)(p-tolylsulfanyl)-methyl]-4-hydroxy-6-methylpyran-2-one **(4n).**

Brown powder, m.p. 150–152°C, IR (KBr) (ν_{max} cm^{-1}): 3293 (OH), 1690 (C=O). Analyses: Calcd. for $C_{20}H_{17}ClO_3S$: C, 64.42; H, 4.60%. Found: C, 64.58; H, 4.43. MS (m/z, %): 372 (7). ^{1}H NMR (250 MHz, d_6-DMSO): δ 2.27 (3H, s, CH_3), 2.30 (3H, s, CH_3), 5.66 (1H, s, CH), 6.09 (1H, s, =CH), 7.08-7.92 (8H, m, arom), 11.33 (1H, s br, OH) ppm. ^{13}C NMR (62.9 MHz, d_6-DMSO): δ 19.50 (CH_3), 21.62 (CH_3), 34.37 (CH), 100.28, 101.69, 125.71, 127.25, 127.76, 128.39, 128.95, 130.53, 131.22, 133.11, 140.30, 143.37, 161.75, 164.34, 166.72 ppm.

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ЕДНОСТАДИЕН ТРИКОМПОНЕНТЕН СИНТЕЗ НА 3-[(АРИЛ)-АРИЛСУЛФАНИЛ-МЕТИЛ]-4-ХИДРОКСИ-6-МЕТИЛПИРАН-2-ОН

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(Резюме)

Описан е синтезът на 3-[(арил)-арилсулфанил-метил]-4-хидрокси-6-метилпиран-2-он с добър добив посредством реакция на 4-хидрокси-6-метил-2*H*-пиран-2-он с ароматни алдехиди и тиоли в присъствие на *p*-толуенсулфонова киселина при температура на кипене.