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Potassium *tert*-Butoxide Catalyzed Synthesis and Characterization of Novel 3-Aryl-3-(phenylthio)-1-(thiophen-3-yl)-propan-1-one Derivatives

Budak, Yakup

Department of Chemistry, Faculty of Arts and Sciences, Gaziosmanpasa University, 60250, Tokat, Turkey

A series of thiophenyl-containing 3-thiophene derivatives (**4a**—**4i**) were prepared via the reaction of chalcone-analogua compounds (**3a**—**3i**) and thiophenol in the presence of catalytic amount of KOBu-*t* in CH_2Cl_2 with moderate to high yields. The mechanistic pathway of the reaction was explained by the Michael-type addition of thiophenol to chalcone derivatives (**3a**—**3i**).

Keywords 1-(thiophen-3-yl)ethanone, Michael addition, potassium*tert*-butoxide, chalcone, catalysis

Introduction

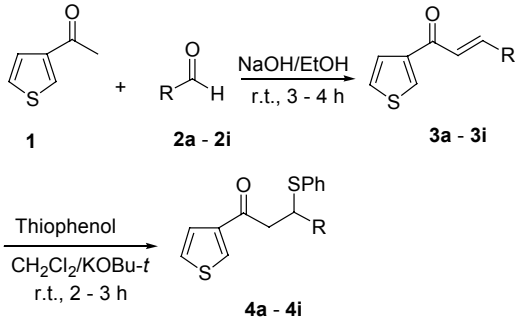
α,*β*-Unsaturated ketones, especially 1,3-diarylprop-2-en-1-ones, are commonly called as chalcones. Chalcones, either natural or synthetic are known to exhibit various biological activities[1] such as antioxidant,[2] anti-inflammatory,[3] antimalaria,[4] antileishmanial,[5] anticancer[6] and antitumor.[7] In addition, chalcones are very important compounds as a Michael acceptor in organic syntheses. The Michael reaction since its discovery in 1889 is one of the most important reactions in organic chemistry.[8] It is well known that conjugate addition to *α*,*β*-unsaturated carbonyl compounds is a useful strategy for the construction of carbon-carbon and carbon-sulfur bonds.[9-11] The carbon-sulfur bond formation by 1,4-addition of thiols to *α*,*β*-unsaturated carbonyl compounds has versatile application in chemistry and biology as it plays critical roles in the biosynthesis, synthesis of bioactive compounds, protection of the olefinic double bond of conjugated enones, and generation of *β*-acylvinyl cation homoenolate anion equivalents.[12-14] The Michael addition of thiols to electron deficient alkenes is a very useful process for making carbon-sulfur bond. This addition to chalcone derivatives is very interesting and challenging as it is less facile compared to the addition to aliphatic acyclic enones and thus it is not always satisfactory with the conventional reagents used for general 1,4-addition.[10]

Numerous methods have been reported in literature regarding the nucleophilic activation of thiols for the desired transformation catalyzed by various organic and inorganic bases.[15] On the other hand, these reactions were also investigated using solid acids such as $HClO_4$-SiO_2,[16] and different Lewis acids, such as $InBr_3$,[17] $Zn(ClO_4)_2 \cdot 6H_2O$,[18] $Hf(OTf)_3$,[19] $Bi(NO_3)_3$,[20] $Bi(OTf)_3$,[21] $Cu(BF_4)_2$.[22] Most of the methods have some disadvantages like long reaction times, high reaction temperature, dry or stringent reaction conditions, complex work-up procedures, and moderate yields. In this study, we reported the potassium *tert*-butoxide catalyzed addition of thiophenol to chalcones under mild conditions in short reaction time, high yield and at room temperature.

Results and Discussion

Firstly, the chalcone derivatives **3a**—**3i** were synthesized employing the traditional method reported in literature.[23-29] As shown in Scheme 1 and Table 1, a series of 9 chalcone derivatives **3a**—**3i** were prepared using the base catalyst. The reaction of 1-(thiophen-3-

Scheme 1



(a) R = Ph, (b) R = *p*-Cl-C_6H_4, (c) R = *p*-Br-C_6H_4, (d) R = *p*-CH_3-C_6H_4, (e) R = *p*-OCH_3-C_6H_4, (f) R = *m*-Br-C_6H_4, (g) R = *m*-CH_3-C_6H_4, (h) R = *o*-OCH_3-C_6H4, (i) R = 2-thiophene (C_4H_3S)

* E-mail: ybudak@gop.edu.tr
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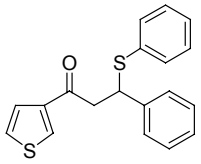
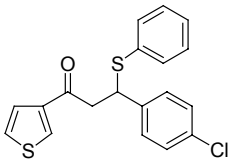
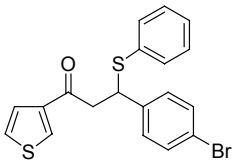
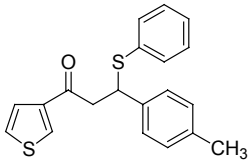
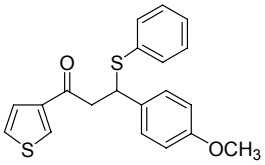
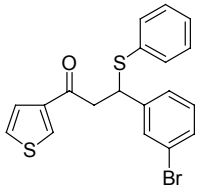
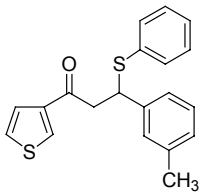
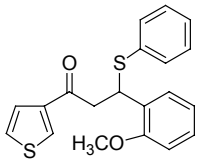
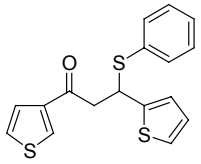
Table 1 Synthesized compounds **4a**—**4i**

Entry	Product	Time/h	m.p./℃	Yield/%
4a		2.5	90—91	93
4b		2.5	87—88	93
4c		2.5	97—98	88
4d		2.5	57—58	94
4e		2.5	Colorless liquid	82
4f		2.5	88-89	85
4g		2.5	Yellowish liquid	81
4h		2.5	Yellowish liquid	86
4i		2.5	Cherry liquid	73

yl)ethanone (**1**) with benzaldehyde derivatives **2a**—**2i** in ethanolic NaOH gave the chalcone derivatives **3a**—**3i** in high yields (93%—99%) (Sheme 1, Table 1). The structures of chalcones (**3a**—**3i**) were established on the basis of spectral data and compared to literature data. The results are in agreement with the proposed structures.

The syntheses of chalcone-like compounds containing thiophenol unit (**4a**—**4i**) were performed by a base-catalyzed additon of thiophenol to compounds **3a**—**3i**.[24] In this synthesis, firstly, various bases (NaOH, KOH, Na_2CO_3, K_2CO_3 and KO*t*-Bu) were tested as catalyst in different solvents (EtOH, MeOH, $CHCl_3$, CH_2Cl_2, *etc*.). Good results were obtained using the catalytic amount of KO*t*-Bu in CH_2Cl_2 as a solvent. The reaction of chalcone-like compounds **3a**—**3i** with thiophenol in the presence of a catalytic amount of KO*t*-Bu in CH_2Cl_2 at room temperature afforded the compounds **4a**—**4i** in yields of 73%—93% (Table1).

The crude products were purified by filtration on a short silica gel column and recrystallized from CH_2Cl_2/*n*-hexane (1∶5). While the compounds **4a**, **4b**, **4c**, **4d** and **4f** were obtained as pure colorless crystals, the others were liquid. In this series, compounds (**4a**—**4i**) are unknown according to our literature survey.

The structures of compounds (**4a**—**4i**) were determined on the basis of spectral data (^{1}H NMR, ^{13}C NMR, IR and elemental analysis).

In summary, nine novel thiophenyl-containing 3-thiophene derivatives (**4a**—**4i**) were easily prepared by the reaction of compounds (**3a**—**3i**) with thiophenol in the presence of catalytic amount of KO*t*-Bu in CH_2CI_2 with good yields and the mild reaction conditions (room temperature and simple operation). Potassium*tert*-butoxide (KO*t*-Bu) was found to be an efficient catalyst for Michael-type addition of thiophenol to chalcone derivatives.

Experimental

General

1-(Thiophene-3-yl)ethanone (**1**) and aldehyde derivatives **2a**—**2i** are commercially available (Merck). All reagents were dried and distilled by standard procedures. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra (KBr or liquid) were recorded on a Jasco FT/IR-430 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 instrument. As internal standards served TMS (δ 0.00) for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR spectroscopy, *J* values are given in Hz. The multiplicities of the signals in the ^{1}H NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quarted), m (multiplet), br (broad) and combinations thereof. Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

General procedure for preparation of thiophenchalcone derivatives 4a—4i[24]

A solution of chalcone derivatives (1 mmol) (**3a**—**3i**)[24] and thiophenol (1 mmol) in CH_2CI_2 (5 mL) was stirred at room temperature for 2—3 h in the presence of a catalytic amount of KO*t*-Bu. After the reaction was completed, the reaction mixture was extracted with

diethyl ether (15 mL×3). The extract was washed with H_2O, and dried (Na_2SO_4). The solvent was evaporated (45 ℃, 20 mmHg). After the crude product was filtrated on a short silica gel column, pure product was obtained by crystallized from *n*-hexane and CH_2Cl_2 (5∶1), yield 73%—93%.

3-Phenyl-3-(phenylthio)-1-(thiophen-3-yl)propan-1-one (4a) Colorless crystals (*n*-hexane∶CH_2Cl_2, 5∶1), yield 93%; m.p. 90—91 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.00—7.99 (m, 1H), 7.49 (d, J=5.2 Hz, 1H), 7.45—7.44 (m, 1H), 7.36—7.33 (m, 4H), 7.29—7.23 (m, 7H), 4.95 (t, J=6.4 Hz, 1H), 3.54 (d, J=6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.2, 142.1, 141.1, 132.7, 132.2, 130.7, 129.0, 128.4, 127.8, 127.6, 127.4, 126.8, 126.5, 48.2, 46.0; IR (KBr) v: 3104, 3056, 3025, 1671, 1509, 1405, 1232, 1072, 794, 736, 692 cm^{-1}. Anal. calcd for $C_{19}H_{16}OS_2$: C 70.33, H 4.97, S 19.77; found C 70.43, H 4.84, S 19.95.

3-(4-Chlorophenyl)-3-(phenylthio)-1-(thiophen-3-yl)propan-1-one (4b) Colorless crystals (*n*-hexane∶CH_2Cl_2, 5∶1), yield 93%; m.p. 87—88 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.01—8.00 (m, 1H), 7.49 (d, J=4.8 Hz, 1H), 7.34—7.31 (m, 4H), 7.26—7.21 (m, 6H), 4.90 (t, J=6.4 Hz, 1H), 3.48 (d, J=6.4 Hz, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.9, 141.9, 139.8, 133.7, 133.2, 133.0, 132.3, 129.2, 129.0, 128.6, 127.8, 126,8, 126.6, 47.6, 45.7; IR (KBr) v: 3102, 1673, 1506, 1405, 1234, 1091, 1012, 823, 796, 690, 617, 547 cm^{-1}. Anal. calcd for $C_{19}H_{15}ClOS_2$: C 63.58, H 4.21, S 17.87; found C 63.65, H 4.29, S 17.94.

3-(4-Bromophenyl)-3-(phenylthio)-1-(thiophen-3-yl)propan-1-one (4c) Colorless crystals (*n*-hexane∶CH_2Cl_2, 5∶1), yield 88%; m..p. 97—98 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.00—7.99 (m, 1H), 7.56 (d, J=8.8 Hz, 1H), 7.51—7.48 (m, 1H), 7.37 (d, J=8.4 Hz, 2H), 7.34—7.28 (m, 3H), 7.19—7.02 (m, 4H), 4.88 (t, J=6.4 Hz, 1H), 3.50 (d, J=6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.8, 141.9, 140.3, 133.6, 132.9, 132.3, 131.6, 129.5, 129.0, 127.8, 127.2, 126.8, 121.2, 47.6, 45.6; IR (KBr) v: 3102, 2896, 2846, 1673, 1506, 1486, 1230, 1172, 1072, 1008, 792, 736, 690, 647, 547 cm^{-1}. Anal. calcd for $C_{19}H_{15}BrOS_2$: C 56.58, H 3.75, S 15.90; found C 56.71, H 3.71, S 15.87.

3-Phenyl-1-(thiophen-3-yl)-3-*p*-tolylpropan-1-one (4d) Colorless crystals (*n*-hexane∶CH_2Cl_2, 5∶1), yield 94%; m.p. 57—58 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.99—7.96 (m, 1H), 7.49—7.48 (m, 1H), 7.36—7.34 (m, 2H), 7.29—7.20 (m, 6H), 7.07 (d, J=8 Hz, 2H), 4.91 (t, J=6.4 Hz, 1H), 3.54 (d, J=6.4 Hz, 4H), 2.30 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.3, 142.1, 138.0, 137.1, 132.5, 132.2, 129.2, 128.8, 127.9, 127.6, 127.4, 126.9, 126.4, 47.8, 46.0, 21.1; IR (KBr) v: 3102, 3052, 2919, 1673, 1509, 1413, 1234, 1020, 900, 788, 686 cm^{-1}. Anal. calcd for $C_{20}H_{18}OS_2$: C 70.97, H 5.36, S 18.95; found C 70.89, H 5.42, S 19.05.

3-(4-Methoxyphenyl)-3-(phenylthio)-1-(thiophen-3-yl) propan-1-one (4e) Colorless liquid, yield 82%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.98—7.97 (m, 1H), 7.44 (d, J=7.6 Hz, 1H), 7.36—7.35 (m, 1H), 7.29—7.21 (m, 5H), 6.80 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.6 Hz, 2H), 4.93 (t, J=6.4 Hz, 1H), 3.76 (s, 3H, OCH_3), 3.54 (d, J=6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.4, 158.8, 142.1, 134.4, 133.1, 132.6, 132.2, 128.9 (2C), 127.5, 126.9, 126.5, 113.9, 55.2, 47.6, 46.1; IR (KBr) v: 3100, 3056, 2927, 2832, 1671, 1509, 1436, 1249, 1029, 1072, 825, 736, 688 cm^{-1}. Anal. calcd for $C_{20}H_{18}O_2S_2$: C 67.76, H 5.12, S 18.09; found C 67.69, H 5.17, S 18.15.

3-(3-Bromophenyl)-3-(phenylthio)-1-(thiophen-3-yl)propan-1-one (4f) Colorless crystals (*n*-hexane∶CH_2Cl_2, 5∶1), yield 85%; m.p. 88—89 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02—8.01 (m, 1H), 7.68 (d, J=4.8 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.67 (d, J=5.1 Hz, 1H), 7.50—7.48 (m, 1H), 7.33—7.30 (m, 3H), 7.26—7.23 (m, 3H), 7.11 (t, J=7.6 Hz, 1H), 4.86 (t, J=6.4 Hz, 1H), 3.50 (d, J=6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.7, 143.6, 133.08, 132.4, 130.7, 130.0, 129.0, 127.9, 127.4, 127.2, 126.8, 126.6, 126.4, 124.4, 122.5, 47.7, 45.6; IR (KBr) v: 3102, 3052, 2896, 1662, 1602, 1506, 1409, 1311, 1226, 1176, 779, 690, 570 cm^{-1}. Anal. calcd for $C_{19}H_{15}BrOS_2$: C 56.58, H 3.75, S 15.90; found C 56.65, H 3.80, S 15.83.

3-(Phenylthio)-1-(thiophen-3-yl)-3-*m*-tolylpropan-1-one (4g) Yellowish liquid, yield 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.99—7.97 (m, 1H), 7.82 (d, J=15,6 Hz, 1H), 7.70 (d, J=6,4 Hz, 1H), 7.50—7.44 (m, 2H), 7.40—7.35 (m, 2H), 7.28—7.24 (m, 3H), 7.16 (d, J=5.6 Hz, 2H), 4.93 (t, J=6.4 Hz, 1H), 3.56 (d, J=6.4 Hz, 2H), 2.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.3, 142.09, 141.0, 138.1, 134.4, 132.6, 132.3, 131.4, 128.9, 128.6, 128.4, 128.3, 126.9, 126.5, 124.8, 48.1, 46.0, 21.5; IR ($CHCl_3$) v: 3100, 3052, 2854, 1656, 1596, 1506, 1409, 1240, 1174, 1029, 981, 779, 736, 700, 638 cm^{-1}. Anal. calcd for $C_{20}H_{18}OS_2$: C 70.97, H 5.36, S 18.95; found C 70.91, H 5.42, S 18.97.

3-(2-Methoxyphenyl)-3-(phenylthio)-1-(thiophen-3-yl) propan-1-one (4h) Yellowish liquid, yield 86%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.01—7.98 (m, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.37—7.34 (m, 3H), 7.28—7.19 (m, 5H), 6.92—6.87 (m, 2H), 5.37 (t, J=6.4 Hz, 1H), 3.81 (s, 3H, OCH_3), 3.55 (d, J=6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 191.6, 156.6, 142.2, 135.1, 132.3, 132,1, 129.3, 129.1, 128.6, 128.1, 127.2, 127.0, 126.3, 120.7, 111.0, 55.6, 45.4, 42.2; IR ($CHCl_3$) v: 3102, 2998, 2834, 1673, 1579, 1506, 1475, 1432, 1322, 1245, 1024, 736, 686, 590 cm^{-1}. Anal. calcd for $C_{20}H_{18}O_2S_2$: C 67.76, H 5.12, S 18.09; found C 67.86, H 5.04, S 18.19.

3-(Phenylthio)-3-(thiophen-2-yl)-1-(thiophen-3-yl)propan-1-one (4i) Cherry liquid, yield 73%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.03—8.02 (m, 1H), 7.52 (d, J=5.2 Hz, 1H), 7.42—7.37 (m, 3H), 7.30—7.26 (m, 4H), 7.16 (d, J=4.8 Hz, 1H), 6.85—6.82 (m, 1H), 5.24 (t, J=6.4 Hz, 1H), 3.54 (d, J=6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 190.7, 145.3, 142.0, 136.5, 133.0, 132.5, 129.0, 128.0, 127.9, 126.7, 126.5, 125.6, 124.6,

46.9, 43.7; IR ($CHCl_3$) *v*: 3106, 3052, 2983, 2846, 1673, 1587, 1513, 1409, 1265, 1234, 1172, 1076, 1027, 788, 736, 701, 586 cm^{-1}. Anal. calcd for $C_{17}H_{14}OS_3$: C 61.78, H 4.27, S 29.11; found C 61.83, H 4.32, S 29.09.

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