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Original article

Solvent-free synthesis of substituted thiopyrans *via* multicomponent reactions of α-haloketones

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ABSTRACT

A straightforward and efficient method for the synthesis of thiopyran derivatives *via* three-component reaction of alkyl propiolate, benzoylisothiocyanate or its derivatives and α-haloketones in the presence of triphenylphosphine under solvent-free conditions at 70 °C without using any catalyst is reported. The method offers several advantages including high yields of products and an easy work-up procedure.

1. Introduction

At present, heterocycles with sulfur atoms, like thiopyrans, have attracted increased attention. These compounds have different biological activities [1] that have been recognized [2]. Thiopyrans are used in medicinal chemistry, but receive relatively less attention [3]. Also, thiopyrans are often in the structure of natural products with different pharmaceutical activities such as anti-bacterial [4], anti-hyperplasia [5], anti-psychiatric [6], and anticancer activities [7]. Investigation of anticancer activity of thiopyran derivatives showed that they have antiproliferative activity against tumor cell lines [8]. It has also been described that substituted thiopyrans are powerful inhibitors of deoxyribonucleic acid-protein kinases [9]. However, the methods for synthesis of these important compounds often feature tedious synthetic routes, long reaction time, harsh reaction conditions, and narrow application scope of substrates. In addition, to the best of our knowledge, there have been few reports about the synthesis of thiopyran derivatives [10–12]. Hence, we describe herein the reaction of alkyl propiolate **1**, benzoylisothiocyanate **2** and α-haloketones **3** in the presence of triphenylphosphine **4** under solvent-free conditions to produce substituted thiopyran derivatives **5** in good yield (Scheme 1).

2. Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1MHz and 125.8 MHz, respectively. ^{1}H NMR and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ using TMS as the internal standard or 85% H_3PO_4 as the external standard.

General procedure for preparation of compounds ***5a–e****.* α-Haloketones (2-mmol) and triphenylphosphine (2 mmol) were stirred at 70 °C for 45 min. After 45 min, triethylamine (2 mmol) and alkyl propiolate (2 mmol) were added to the mixture. Then, arylisothiocyanate (2 mmol) was added after 15 min. The reaction mixture was stirred for 8 h at 70 °C. After completion of reaction (monitored by TLC), 15 mL H_2O was poured into the reaction mixture, and the solid residue was filtered and washed by cold diethylether (Et_2O) to afford **5**.

Methyl 2-(benzoilimino)-6-phenyl-2H-thiopyran-3-carboxylate ***(5a)***: Yellow oil, yield: 0.45 g (65%) IR (KBr, cm^{-1}): ν 1738, 1725, 1695, 1587, 1463, 1348, 1259. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 3.78 (s, 3 H, MeO), 6.37 (d, 1 H, ^3J = 7.8, CH), 7.28 (d, 1 H, ^3J = 7.8,

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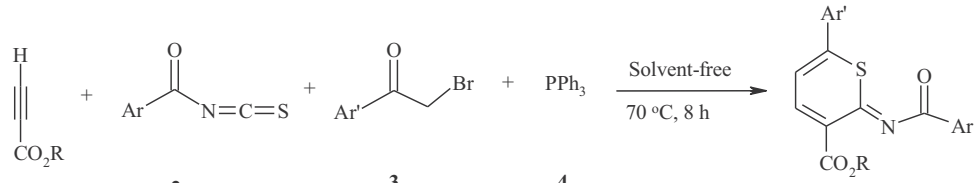


1, 2, 3, 5	R	Ar	Ar'	Yield of **5** (%)
a	Me	Ph	Ph	65
b	Me	4-MeO-C_6H_4	4-MeO-C_6H_4	70
c	Me	4-MeO-C_6H_4	4-Me-C_6H_4	78
d	Me	4-Me-C_6H_4	4-Br-C_6H_4	75
e	Et	4-NO_2-C_6H_4	4-MeO-C_6H_4	60

Scheme 1. Reaction of propiolates, aroyl isothiocyanates and α-halo carbonyl compounds in the presence of triphenylphosphine.

CH), 7.38 (t, 1 H, ^3J = 7.4, CH), 7.56 (m, 3 H, 3 CH), 7.64 (t, 2 H, ^3J = 7.8, 2 CH), 7.78 (d, 2 H, ^3J = 7.6, 2 CH), 8.14 (d, 2 H, ^3J = 7.6, 2 CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 52.4 (MeO), 118.6 (C), 128.2 (CH), 129.4 (CH), 130.2 (2 CH), 130.6 (2 CH), 131.4 (2 CH), 131.8 (2 CH), 133.2 (CH), 134.8 (C), 135.4 (C), 141.7 (C), 143.6 (CH), 160.4 (C=O), 162.7 (C=N), 172.4 (C=O). EI-MS: *m/z* 349 (10, M^+), 318 (86), 105 (100), 77 (88), 31 (100). Anal. Calcd. for $C_{20}H_{15}NO_3S$ (349.40): C 68.75, H 4.33, N 4.01; found C 68.83, H 4.42, N 4.12%.

Methyl 2-(4-methoxybenzoilimino)-6-(4-methoxyphenyl)-2H-thiopyran-3-carboxylate ***(5b)***: Yellow oil, yield: 0.57 g (70%). IR (KBr, cm^{-1}): ν 1735, 1728, 1695, 1654, 1588, 1474, 1357. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 3.75 (s, 3 H, MeO), 3.82 (s, 3 H, MeO), 3.87 (s, 3 H, MeO), 6.29 (d, 1 H, ^3J = 7.5, CH), 7.12 (d, 2 H, ^3J = 7.6, 2 CH), 7.22 (d, 2 H, ^3J = 7.6, 2 CH), 7.30 (d, 1 H, ^3J = 7.5, CH), 7.62 (d, 2 H, ^3J = 7.6, 2 CH), 8.04 (d, 2 H, ^3J = 7.6, 2 CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 51.8 (MeO), 54.5 (MeO), 55.2 (MeO), 115.4 (2 CH), 116.5 (2 CH), 118.3 (C), 128.5 (CH), 129.4 (C), 130.4 (2 CH), 131.2 (2 CH), 142.7 (C), 145.2 (CH), 158.3 (C), 161.4 (C=O), 162.5 (C=N), 164.7 (C), 171.9 (C=O). Anal. Calcd. for $C_{22}H_{19}NO_5S$ (409.45): C 64.54, H 4.68, N 3.42; found: C 64.63, H 4.76, N 3.54%.

Methyl 2-(4-methoxybenzoilimino)-6-(4-methylphenyl)-2H-thiopyran-3-carboxylate ***(5c)***: Yellow oil, yield: 0.61 g (78%). IR (KBr, cm^{-1}): ν 1732, 1712, 1687, 1646, 1547, 1485, 1362, 1295. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.36 (s, 3 H, Me), 3.78 (s, 3 H, MeO), 3.85 (s, 3 H, MeO), 6.19 (d, 1 H, ^3J = 7.4, CH), 7.23 (d, 2 H, ^3J = 7.8, 2 CH), 7.34 (d, 1 H, ^3J = 7.5, CH), 7.38 (d, 2 H, ^3J = 7.5, 2 CH), 7.58 (d, 2 H, ^3J = 7.6, 2 CH), 8.14 (d, 2 H, ^3J = 7.6, 2 CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 22.3 (Me), 51.8 (MeO), 55.4 (MeO), 114.8 (2 CH), 117.8 (C), 127.4 (CH), 129.6 (2 CH), 130.2 (C), 131.4 (2 CH), 132.3 (2 CH), 133.7 (C), 137.6 (C), 141.6 (C), 144.8 (CH), 161.7 (C=O), 162.8 (C=N), 163.8 (C), 175.4 (C=O). Anal. Calcd. for $C_{22}H_{19}NO_4S$ (482.50): C 67.16, H 4.87, N 3.56; found: C 67.04, H 4.76, N 3.45%.

Methyl 2-(4-methylbenzoilimino)-6-(4-bromophenyl)-2H-thiopyran-3-carboxylate ***(5d)***: Yellow oil, yield: 0.66 g (75%). IR (KBr, cm^{-1}): ν 1732, 1715, 1695, 1648, 1537, 1465, 1374, 1283. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.38 (s, 3 H, Me), 3.82 (s, 3 H, MeO), 6.23 (d, 1 H, ^3J = 7.6, CH), 7.35 (d, 1 H, ^3J = 7.6, CH), 7.43 (d, 2 H, ^3J = 7.6, 2 CH), 7.58 (d, 2 H, ^3J = 7.8, 2 CH), 7.63 (d, 2 H, ^3J = 7.6, 2 CH), 7.86 (d, 2 H, ^3J = 7.8, 2 CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 22.5 (Me), 52.3 (MeO), 118.7 (C), 124.3 (C), 126.2 (CH), 128.6 (2 CH), 129.4 (2 CH), 130.7 (2 CH), 135.2 (2 CH), 135.8 (C), 136.2 (C), 136.8 (C), 143.8 (CH), 144.0 (C), 160.6 (C=O), 162.3 (C=N), 174.6 (C=O). Anal. Calcd. for $C_{21}H_{16}BrNO_3S$ (442.32): C 57.02, H 3.65, N 3.17; found: C 57.15, H 3.74, N 3.26%.

Ethyl 2-(4-nitrobenzoilimino)-6-(4-methoxyphenyl)-2H-thiopyran-3-carboxylate ***(5e)***: Yellow oil, yield: 0.53 g (60%). IR (KBr, cm^{-1}): ν 1733, 1716, 1696, 1675, 1578, 1465, 1385, 1263. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 1.27 (t, 3 H, $^3J_{HH}$ = 7.4, Me), 3.86 (s, 3 H, MeO), 4.26 (q, 2 H, ^3J = 7.4, CH_2O), 6.18 (d, 1 H, ^3J = 7.5, CH), 7.14 (d, 2 H, ^3J = 7.6, 2 CH), 7.38 (d, 1H, ^3J = 7.5, CH), 7.56 (d, 2 H, ^3J = 7.6, 2 CH), 7.63 (d, 2 H, ^3J = 7.6, 2 CH), 8.34 (2 H, d, ^3J = 7.8, 2 CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 14.2 (Me), 55.6 (MeO), 61.4 (CH_2O), 114.2 (2 CH), 117.8 (C), 124.8 (2 CH), 127.5 (2 CH), 128.6 (CH), 129.6 (C), 130.2 (2 CH), 138.6 (C), 143.2 (CH), 143.8 (C), 152.4 (C), 161.4 (C=O), 161.8 (C), 162.4 (C=N), 176.8 (C=O). Anal. Calcd. for $C_{22}H_{18}N_2O_6S$ (438.45): C 60.27, H 4.14, N, 6.39; found: C 60.34, H 4.22, N 6.45%.

3. Results and discussion

The reaction of alkyl propiolate **1**, benzoyl isothiocyanate **2** and alkyl bromide **3** in the presence of triphenylphosphine **4** under solvent-free conditions produced substituted thiopyran derivatives **5** in good yield (Scheme 1).

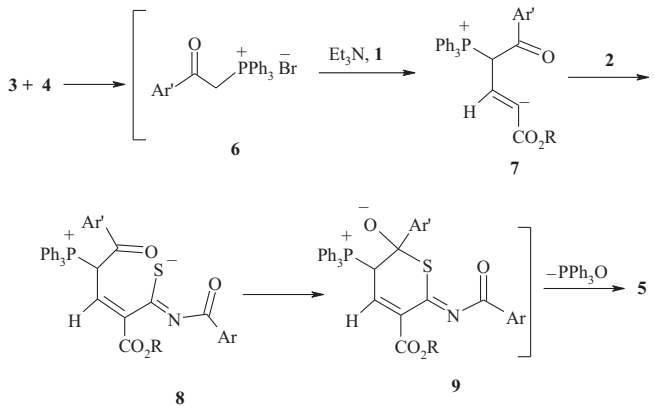
The starting point for our experiments was to optimize the reaction conditions such as solvent and reaction time for the production of 2*H*-thiopyranes which have anti-bacterial [4], anti-hyperplasia [5], anti-psychiatric [6], and anticancer activities [7] (see Table 1).

To achieve suitable conditions for the above transformation, a series of experiments was carried out. First, we investigated the reaction of methyl propiolate, benzoyl isothiocyanate, and phenacyl bromide in the presence of triphenyl phosphine in various solvents, in water and under solvent-free classical heating conditions. The reaction proceeds in organic solvents and water with low yield (Table 1, entries 1–10). In the absence of solvent and at 70 °C, the reaction was performed with good yield after 8 h. Structures of compounds **5a–e** were determined based on their IR,

Table 1
Optimization of reaction conditions of compound **5a**.

Entry	Solvent (5 mL)	*Temp.* (°C)	Time (h)	Yield (%)[a]
1	DMF	90	12	None
2	Toluene	70	15	32
3	Toluene	90	15	40
4	CH_3CN	70	14	45
5	CH_3CN	90	14	45
6	EtOH	90	24	25
7	EtOH	120	24	25
8	H_2O	50	12	Trace
9	H_2O	70	12	Trace
10	H_2O	90	12	15
11	Solvent-free	50	8	58
12	Solvent-free	70	8	65

[a] Isolated yield.



Scheme 2. Proposed mechanism for the synthesis of compound **5**.

^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra. The mass spectra of these compounds show molecular ion peaks at the appropriate *m*/*z* values. In the ^{1}H NMR spectrum of **5a** displayed one singlet at 3.78 for methoxy protons, two doublets at 6.37 (d, ^{3}J = 7.8, CH) and 7.28 (d, ^{3}J = 7.8, CH) for methine protons along with signals for an aromatic moiety. The carbonyl group's resonances in the ^{13}C NMR spectra of **5a** appeared at 160.4 (C=O) and 172.4 (C=O) ppm. Also the mass spectra of **5a** displayed the molecular ion peak at the appropriate *m*/*z* values.

A proposed mechanism for this reaction is shown in Scheme 2. On the basis of phosphorus nucleophile chemistry, it is reasonable to presume that triphenylphosphonium bromide **6** results from initial addition of the triphenylphosphin **4** to α-haloketones **3**. Intermediate **6** is reacted with alkyl propiolate **1** in the presence of triethylamine as the base for production of zwitterionic species **7**. Then, nucleophilic attack of this intermediate on benzoyl isothiocyanate **2** produces intermediate **8**. Finally, by intramolecular cyclization, compound **9** is afforded by elimination of triphenylphosphine oxide, which is converted to **5** as the product.

4. Conclusion

In conclusion, we found that the reaction of alkyl propiolate with benzoyl isothiocyanate and alkyl bromide in the presence of triphenylphosphine leads to a facile synthesis of some functionalized thiopyrans under solvent-free conditions, without using any catalyst.

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