



Application of Green Chemistry in the Synthesis of Thiopyran Derivatives

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Abstract

An efficient synthesis of 2*H*-thiopyran derivatives via three-component reaction of alkyl propiolate, benzoyl isothiocyanate or its derivatives and alkyl bromides in the presence of triphenylphosphine in water at 80°C without using any catalyst in water is described. The method offers several advantages including high yields of products and an easy work-up procedure.

Key words: *Triphenyl Phosphite; Dialkyl Acetylenedicarboxilates; Multicomponent reactions; Triethyl phosphite.*

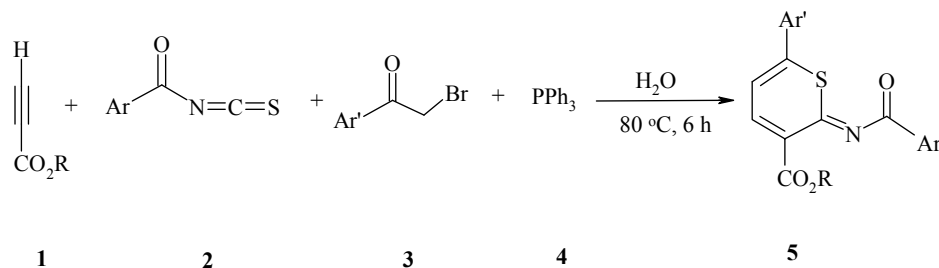
Introduction

At the beginning of the new century, a move in importance in chemistry is obvious with the longing to extend environmentally gentle routes to a numerous of materials [1]. Green chemistry approaches hold out momentous potential not only for reduction of byproducts, a reduction in the waste produced, and lowering of energy costs but also in the development of new methodologies toward previously unobtainable materials, using existing technologies [2]. Of all of the existing areas of chemistry, medicinal and pharmaceutical

chemistry, with their traditionally large volume of waste/product ratio, are maybe the most developed for greening [3]. Thiopyran derivatives have different biological activities [4] that has been recognized [5]. Thiopyrans are used in medicinal chemistry [6]. Also, thiopyrans were commonly used in the structure of natural products with different pharmaceutical activities such as anti-bacteria [7], antihyperplasia [8], anti-psychiatric [9] and anticancer activities [10].

Herein, we describe the reaction of alkyl propiolate **1**, benzoyl isothiocyanate **2** and alkyl bromide **3**

in the presence of triphenylphosphine **4** in water in good yield (Scheme 1).
that produced substituted thiopyran derivatives **5**



1, 2, 3, 5	R	Ar	Ar'	Yield (%) of 5
a	Me	Ph	Ph	78
b	Me	4-MeO-C ₆ H ₄	4-MeO-C ₆ H ₄	85
c	Me	4-MeO-C ₆ H ₄	4-Me-C ₆ H ₄	82
d	Me	4-Me-C ₆ H ₄	4-Br-C ₆ H ₄	80
e	Et	4-NO ₂ -C ₆ H ₄	4-MeO-C ₆ H ₄	75

Scheme 1. The reaction of alkyl propiolate, benzoyl isothiocyanate and alkyl bromide in the presence of triphenylphosphine in water.

Experimental

Materials

All chemicals were obtained from Fluka and were used without further purification. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ¹H and ¹³C NMR spectra were obtained with a Bruker FT-500 spectrometer in CDCl₃, and tetramethylsilane (TMS) was used as an internal standard or 85% H₃PO₄ as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values.

General procedure

To a magnetically solution of alkyl bromide and triphenylphosphine at 80 °C in water (10mL) for 30 min, triethylamine and alkyl propiolate (2 mmol) was added gently. Then arylisothiocyanate was added after 15 min. The reaction mixture was stirred for 5 h at 80 °C. After completion of reaction (monitored by TLC), mixture of reaction was filtered and the solid residue was washed by cold diethylether to afford **5**.

Methyl 2-(benzoilimino)-6-phenyl-2H-thiopyran-3-carboxylate (5a).-Yellow oil, yield: 0.45 g (78 %) IR (KBr): $\nu = 1738, 1725, 1695, 1587, 1463, 1348, 1259\text{ cm}^{-1}$. - EI-MS: $m/z = 349 (10, \text{M}^+), 318 (86), 105 (100), 77 (88), 31 (100)$. - 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 %. - 1H NMR (500.1 Hz, $CDCl_3$): δ 3.78 (3 H, s, MeO), 6.37 (1 H, d, $^3J = 7.8$, CH), 7.28 (1 H, d, $^3J = 7.8$, CH), 7.38 (1 H, t, $^3J = 7.4$, CH), 7.56 (3 H, m, 3 CH), 7.64 (2 H, t, $^3J = 7.8$, 2 CH), 7.78 (2 H, d, $^3J = 7.6$, 2 CH), 8.14 (2 H, d, $^3J = 7.6$, 2 CH) ppm. - ^{13}C NMR (125.7 Hz, $CDCl_3$): $\delta = 52.4$ (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) ppm.

Methyl 2-(4-methoxybenzoilimino)-6-(4-methoxyphenyl)-2H-thiopyran-3-carboxylate (5b). - Yellow oil, yield: 0.57 g (85%) IR (KBr): $\nu = 1735, 1728, 1695, 1654, 1588, 1474, 1357$ cm^{-1} . - 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 %. - 1H NMR (500.1 Hz, $CDCl_3$): δ 3.75 (3 H, s, MeO), 3.82 (3 H, s, MeO), 3.87 (3 H, s, MeO), 6.29 (1 H, d, $^3J = 7.5$, CH), 7.12 (2 H, d, $^3J = 7.6$, 2 CH), 7.22 (2 H, d, $^3J = 7.6$, 2 CH), 7.30 (1 H, d, $^3J = 7.5$, CH), 7.62 (2 H, d, $^3J = 7.6$, 2 CH), 8.04 (2 H, d, $^3J = 7.6$, 2 CH) ppm. - ^{13}C NMR (125.7 Hz, $CDCl_3$): $\delta = 51.8$ (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) ppm.

Methyl 2-(4-methoxybenzoilimino)-6-(4-methylphenyl)-2H-thiopyran-3-carboxylate (5c).

- Yellow oil, yield: 0.61 g (82 %) IR (KBr): $\nu = 1732, 1712, 1687, 1646, 1547, 1485, 1362, 1295$ cm^{-1} . - 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 %. 1H NMR (500.1 Hz, $CDCl_3$): δ 2.36 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 6.19 (1 H, d, $^3J = 7.4$, CH), 7.23 (2 H, d, $^3J = 7.8$, 2 CH), 7.34 (1 H, d, $^3J = 7.5$, CH), 7.38 (2 H, d, $^3J = 7.5$, 2 CH), 7.58 (2 H, d, $^3J = 7.6$, 2 CH), 8.14 (2 H, d, $^3J = 7.6$, 2 CH) ppm. - ^{13}C NMR (125.7 Hz, $CDCl_3$): $\delta = 22.3$ (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) ppm.

Methyl 2-(4-methylbenzoilimino)-6-(4-bromophenyl)-2H-thiopyran-3-carboxylate (5d). - Yellow oil, yield: 0.66 g (80 %) IR (KBr): $\nu = 1732, 1715, 1695, 1648, 1537, 1465, 1374, 1283$ cm^{-1} . - 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 %. 1H NMR (500.1 Hz, $CDCl_3$): δ 2.38 (3 H, s, Me), 3.82 (3 H, s, MeO), 6.23 (1 H, d, $^3J = 7.6$, CH), 7.35 (1 H, d, $^3J = 7.6$, CH), 7.43 (2 H, d, $^3J = 7.6$, 2 CH), 7.58 (2 H, d, $^3J = 7.8$, 2 CH), 7.63 (2 H, d, $^3J = 7.6$, 2 CH), 7.86 (2 H, d, $^3J = 7.8$, 2 CH) ppm. - ^{13}C NMR (125.7 Hz, $CDCl_3$): $\delta = 22.5$ (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) ppm.

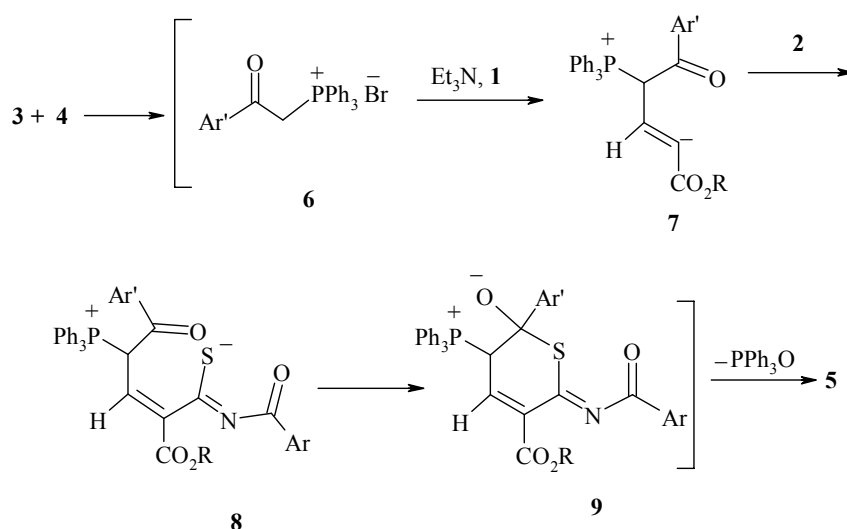
Ethyl 2-(4-nitrobenzoylimino)-6-(4-methoxyphenyl)-l-2H-thiopyran-3-carboxylate (5e). - Yellow oil, yield: 0.53 g (75 %) IR (KBr): $\nu = 1733, 1716, 1696, 1675, 1578, 1465, 1385, 1263 \text{ cm}^{-1}$. - Anal. Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_6\text{S}$ (438.45): C 60.27, H 4.14, N, 6.39; found: C 60.34, H 4.22, N 6.45 %. - ^1H NMR: $\delta = 1.38$ (3 H, t, $^3J_{\text{HH}} = 7.4$, Me), 3.92 (3 H, s, MeO), 4.36 (2 H, q, $^3J = 7.4$, CH_2O), 6.53 (1 H, d, $3J = 7.5$, CH), 7.14 (2 H, d, $^3J = 7.6$, 2 CH), 7.38 (1H, d, $^3J = 7.5$, CH), 7.52 (2 H, d, $^3J = 7.6$, 2 CH), 7.63 (2 H, d, $^3J = 7.6$, 2 CH), 8.34 (2 H, d, $^3J = 7.8$, 2 CH) ppm. - ^{13}C NMR (125.7 Hz, CDCl_3): $\delta = 14.2$ (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) ppm.

Results and discussion

Structures of compounds **5a–e** were determined on the basis of their IR, ^1H NMR, ^{13}C NMR and ^{31}P NMR spectra. The mass spectra of these compounds display molecular ion peaks at the appropriate m/z values. In the ^1H NMR spectrum

of **5a** are displayed one singlet at 3.78 for methoxy protons, two doublets at 6.37 (d, $^3J = 7.8$, CH) and 7.28 (d, $^3J = 7.8$, CH) for methin protons along with signals for aromatic moiety. The carbonyl groups resonances in the ^{13}C NMR spectra of **5a** are appeared at 160.4 (C=O) and 172.4 (C=O) ppm. Also the mass spectra of **5a** displayed the molecular ion peak in the appropriate m/z values.

A proposed mechanism for this reaction to achievement of compound **5** is shown in Scheme 2. On the basis of phosphorus nucleophiles chemistry, it is mentionable to presume that triphenylphosphonium bromide **6** results from initial addition of the triphenylphosphin **4** to alkyl bromide **3**. Intermediate **6** is reacted with alkyl propiolate **1** in the presence of triethylamine as the base to producing of zwitterionic species **7**, and then by the nucleophilic attack of this intermediate to benzoyl isothiocyanate **2** produce intermediate **8**. Finally, by the intramolecular cyclization, compound **9** is afforded that by elimination of triphenylphosphine oxide, is converted to **5** as the product.



Scheme 2. Proposed mechanism for the formation of compound 5.

Conclusion

In conclusion, we found that the reaction of alkyl propiolate with benzoyl isothiocyanate and alkyl bromide in the presence of triphenylphosphine leads to synthesis of some thiopyrans in water as the green conditions, without using any catalyst.

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