Green and practical synthesis of functionalised 2*H*-thiopyrans *via* one-pot multicomponent reactions of aryl isothiocyanates in water

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An efficient synthesis of thiopyran derivatives *via* one-pot reactions between methyl propiolates, aryl isothiocyanates and acetylacetone in water is described.

Keywords: acetylacetone, 2*H*-thiopyrans, aryl isothiocyanate, methyl propiolate, multicomponent reactions

Recently, the need has become apparent to extend environmentally benign routes to synthesise numerous materials.[1] Green chemistry has considerable 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] Medicinal and pharmaceutical chemistry, with their traditionally large waste-to-product ratio, are perhaps the most suitable for greening.[3] Accordingly, there has been a focus on the use of water as a green solvent in organic synthesis. Other than the economic and environmental benefits (abundant, cheap, nontoxic, nonflammable, nonexplosive), water also has unique physical and chemical properties which lead to unique reactivity and selectivity in comparison with organic solvents. Thus, the development of organic reactions in a water medium is of considerable interest.[4–11]

Combinatorial methods using multicomponent reactions (MCRs) have been closely examined as fast and convenient solutions for the synthesis of diverse classes of compounds.[12, 13] MCRs, defined as one-pot reactions in which at least three functional groups join through covalent bonds, have been gaining importance in synthetic organic chemistry.[12–15] Their advantages include atom economy, convergent character, and simplicity of one-pot procedures over other reactions.

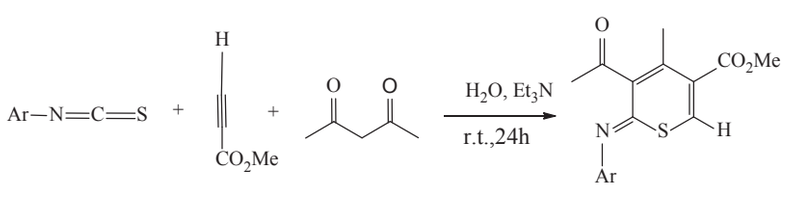
Thiopyrans are heterocycles containing a sulfur atom and are key units in organic synthesis and medicinal chemistry.[16,17] Recently, some MCRs have been applied in the synthesis of thiopyran derivatives, which are compatible with a green chemistry approach.[18–20] For example, the one-pot MCRs of aldehydes, cyanothioacetamide and malononitrile promoted by an ionic liquid proved to be an efficient way to synthesise thiopyran derivatives.[18] Other examples include, a one-pot reaction of aromatic aldehydes, cyanothioacetamide and malononitrile under microwave irradiation to synthesise 2,6-diamino-4-aryl-4*H*-thiopyran-3,5-dicarbonitriles.[21] The imino-2*H*-thiopyrans are useful thiopyran derivatives. Synthesis of 2-imino-2*H*-thiopyrans have been performed by reaction of 1,6-diynes with isothiocyanates and carbon disulfide *via* either Ru or Rh-catalysed [2+2+2] cycloadditions.[22,23] The use of Rh and/or Ru catalysts due to their high cost is one of the disadvantages of those reactions. Derivatives of 2-imino-5,6-dihydro-2H-thiopyran have been obtained in fair to good yields by reaction of 1-heteroalkyl-1,3-butadienes and isothiocyanates and with a calculated amount of dilute aqueous acid.[24]

As part of our continuing studies on the multicomponent area and the synthesis of organosulfur compounds,[25–28] we report an efficient three-component reaction between aryl isothiocyanates **1**, activated esters **2** with acetylacetone **3**, in the presence of triethylamine in water (under green conditions), which produce 2*H*-thiopyran derivatives **4** in good yields (Scheme 1).

Results and discussion

As shown in Scheme 1, aryl isothiocyanates **1**, methyl propiolate **2**, and acetylacetone **3** undergo a 1:1:1 addition reaction in water to produce 2*H*-thiopyrans **4** in 70–78% yields.

The data from elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and mass spectra confirmed the identity of all of the products. The mass spectrum of **4b** exhibited a molecular ion peak at *m/z* 346 and more importantly, an ion peak at *m/z* 303 showed that the acetyl group has been lost and thus the presence of this group on the structure was confirmed. The ^{1}H NMR spectrum



1 **2** **3** **4**

1, 2, 4	R	Ar	Yield % of 4
a	Me	phenyl	75
b	Me	4-nitrophenyl	75
c	Me	4-bromophenyl	70
d	Me	2-chlorophenyl	78
e	Me	3-bromophenyl	70

Scheme 1 The reaction of aryl isothiocyanates, activated esters with acetylacetone in water.

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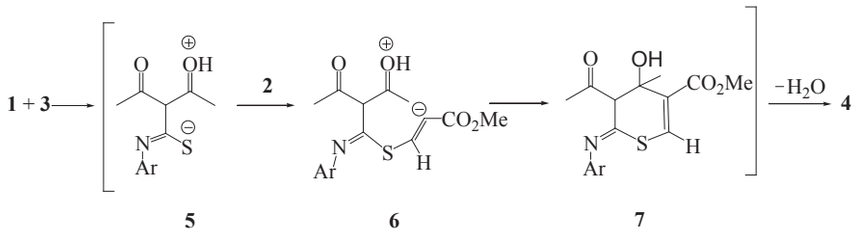

Scheme 2 Proposed mechanism for the formation of compound **4**.

of **4b** clearly showed four sharp singlet signals as arising from methyl, acetyl, methoxy and methine protons (δ_H=2.12, 2.53, and 3.85, 7.16) respectively. Two doublets at 7.02 and 8.14 ppm are attributable to aromatic protons. The ^{13}C NMR spectrum of **4b** showed 14 separate signals, which were in accord with the proposed structure. The ^{13}C chemical shifts for compounds **4a–e** are given in the experimental section.

Although we have not verified the mechanism of our reaction in an experimental manner, a possible explanation is proposed in Scheme 2. It is conceivable that, the reaction involves the initial formation of a 1,3-dipolar intermediate **5** between the enol form of acetylacetone and the aryl isothiocyanate which then reacts with the methyl propiolate to produce **6**. Cyclisation of zwitterionic intermediate **6** leads to the ketol **7**. Subsequent dehydration affords compound **4**.

In summary, we have described an efficient method for the synthesis of 2*H*-thiopyran derivatives in water. The benefits include: (1) The reaction is carried out under green conditions, and in water as the solvent. (2) No catalyst was required. (3) The simplicity of the existing method makes it an appealing alternative to complex multistep procedures.

Experimental

All chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyser. IR spectra were measured on a Shimadzu IR-460 spectrophotometer. Mass spectra were recorded on a Finnigan-MAT 8430 spectrometer operating at an ionisation potential of 70 eV. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-500 Avance spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H, and ^{13}C, spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard.

Synthesis of 2-imino-2H-thiopyran derivatives; general procedure

The mixture of acetylacetone **3** (2 mmol) and triethylamine (2 mmol) was added slowly to a magnetically stirred solution of the appropriate aryl isothiocyanate **1** (2 mmol) and alkyl propiolate **2** (2 mmol) in H_2O and the reaction mixture was stirred for 24H at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 5:1), the reaction mixture was extracted with EtOAc and washed with cold diethyl ether to afford pure title compounds.

*Methyl 3-acetyl-4-methyl-2-(phenylimino)-2*H*-thiopyran-5-carboxylate* (**4a**): Yellow oil, yield 75%. IR (KBr) ν_{max}/cm^{-1}: 1735, 1692, 1576, 1384 and 1257. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.27 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.82 (3H, s, MeO), 7.06 (1H, s, CH), 7.54 (2H, t, *J*=7.2 Hz, 2CH), 7.62 (1H, t, *J*=7.2 Hz, CH), 8.05 (2H, d, *J*=7.3 Hz, 2CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 16.9 (CH_3), 28.5 (CH_3), 52.6 (MeO), 112.3 (CH), 122.5 (2CH), 123.8 (CH), 129.2 (2CH), 133.6 (C), 134.5 (C), 138.8 (C), 148.9 (C–N), 157.6 (C=N), 161.5 (C=O), 207.1 (C=O). MS: *m/z* (%)=301 [M$^+$, 10], 286 (46), 270 (76), 258 (100), 242 (57), 224 (35), 31 (57), 15 (22). Anal. Calcd for $C_{16}H_{15}NO_3S$ (301.36): C, 63.77; H, 5.02; N, 4.65. Found: C, 63.84; H, 5.12; N, 4.73%.

*Methyl 3-acetyl-4-methyl-2-(4-nitrophenylimino)-2*H*-thiopyran-5-carboxylate* (**4b**): Pale yellow oil, yield 75%. IR (KBr) ν_{max}/cm^{-1}: 1740, 1683, 1457, 1368, 1265, 1158 and 1109. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.12 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.85 (3H, s, MeO), 7.02 (2H, d, *J*=7.6 Hz, 2CH), 7.16 (1H, s, CH), 8.14 (2H, d, *J*=7.5 Hz, 2CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 16.7 (CH_3), 31.2 (CH_3), 53.5 (MeO), 112.6 (CH), 120.4 (2CH), 126.7 (2CH), 135.3 (C), 137.3 (C), 140.8 (C), 145.2 (C), 155.0 (C–N), 155.4 (C=N), 161.2 (C=O), 202.3 (C=O). MS, *m/z* (%): 346 (M$^+$, 20), 331 (43), 315 (54), 300 (24), 287 (34), 59 (33), 31 (88). Anal. Calcd for $C_{16}H_{14}N_2O_5S$ (346.35): C, 55.49; H, 4.07; N, 8.09. Found: C, 55.57; H, 4.27; N, 8.16%.

*Methyl 3-acetyl-2-(4-bromophenylimino)-4-methyl-2*H*-thiopyran-5-carboxylate* (**4c**): Orange oil, yield 70%. IR (KBr) ν_{max}/cm^{-1}: 1736, 1685, 1524, 1425, 1268 and 1194. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.05 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.83 (3H, s, MeO), 6.78 (2H, d, *J*=7.5 Hz, 2CH), 7.12 (1H, s, CH), 7.58 (2H, d, *J*=8.2 Hz, 2CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 17.6 (CH_3), 31.2 (CH_3), 53.0 (MeO), 111.7 (CH), 122.4 (2CH), 132.3 (C), 133.4 (2CH), 134.8 (C), 135.8 (C), 140.6 (C), 148.4 (C–N), 154.2 (C=N), 170.3 (C=O), 210.7 (C=O). Anal. Calcd for $C_{16}H_{14}BrNO_3S$ (380.25): C, 50.54; H, 3.71; N, 3.68. Found: C, 50.49; H, 3.67; N, 3.66%.

*Methyl 3-acetyl-2-(2-chlorophenylimino)-4-methyl-2*H*-thiopyran-5-carboxylate* (**4d**): Colourless oil, yield 78%. IR (KBr) ν_{max}/cm^{-1}: 1730, 1695, 1568, 1437 and 1325. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.07 (3H, s, CH_3), 2.55 (3H, s, CH_3), 3.82 (3H, s, MeO), 7.14–7.32 (5H, m, 5 CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 17.5 (CH_3), 31.2 (CH_3), 53.5 (MeO), 112.6 (CH), 117.2 (CH), 125.6 (CH), 126.4 (CH), 129.2 (C), 130.7 (CH), 132.4 (C), 135.7 (C), 136.3 (C), 138.2 (C–N), 152.3 (C), 156.0 (C=N), 170.2 (C=O), 203.4 (C=O). Anal. Calcd for $C_{16}H_{14}ClNO_3S$ (335.80): C, 57.23; H, 4.20; N, 4.17. Found: C, 57.47; H, 4.17; N, 4.16%.

*Methyl 3-acetyl-2-(3-bromophenylimino)-4-methyl-2*H*-thiopyran-5-carboxylate* (**4e**): Colourless oil, yield 70%. IR (KBr) ν_{max}/cm^{-1}: 1742, 1697, 1587, 1464, 1389, 1254 and 1125. ^{1}H NMR (500.1 Hz, $CDCl_3$): δ 2.05 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.85 (3H, s, MeO), 6.83 (1H, t, *J*=7.5 Hz, CH), 7.12 (1H, d, *J*=7.6 Hz, CH), 7.14 (1H, s, CH), 7.27 (1H, d, *J*=7.6 Hz, CH), 7.36 (1H, s, CH). ^{13}C NMR (125.7 Hz, $CDCl_3$): δ 17.5 (CH_3), 31.0 (CH_3), 53.4 (MeO), 110.6 (CH), 118.2 (CH), 122.7 (CH), 128.2 (CH), 129.0 (C), 130.4 (C), 132.2 (CH), 134.7 (C), 136.2 (C), 151.2 (C–N), 154.6 (C=N), 167.2 (C=O), 202.7 (C=O). Anal. Calcd for $C_{16}H_{14}BrNO_3S$ (380.25): C, 50.54; H, 3.71; N, 3.68. Found: C, 50.57; H, 3.37; N, 3.56%.

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