One-pot synthesis of *trans*-4-alkylthio- and 4-arylthio-cinnamic acids from *trans*-4-chlorosulfonylcinnamic acid in an aqueous medium

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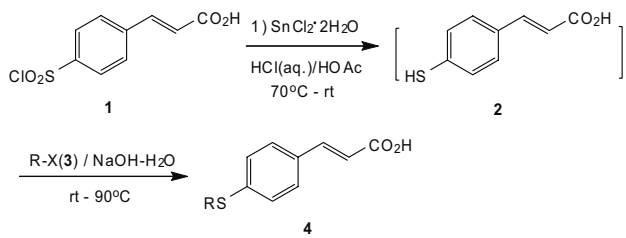
A one-pot syntheses of *trans*-4-alkylthio- and 4-arylthio-cinnamic acids were achieved in high yields by reduction of *trans*-4-chlorosulfonylcinnamic acid with stannous chloride dihydrate followed by alkylation and arylation of the resulting *trans*-4-thiocinnamic acid with various kinds of alkyl and activated aryl halides in an aqueous medium.

Keywords: cinnamic acid, aqueous medium, alkylarylsulfide, diarylsulfide, *trans*-β-arylvinyl bromide, 4-chlorosulforyl-cinnamie acid

Alkyl, aryl and diaryl sulfides are useful synthetic intermediates in organic and medicinal chemistry.[1] In addition, the scope and application of organosulfur chemistry in organic synthetic reactions has increased tremendously since sulfur-containing groups serve as valuable auxiliary functions in synthetic sequences.[2] A variety of synthetic methods has been reported. Among these methods, the synthetic process involving the reaction of thiols and halogens in the presence of a strong base is the most general method.[3] Another important method is the efficient transformation of sulfur-containing compounds mediated by transition-metal catalysts (Pd or Cu).[4-15] However, the use of thiols limits the synthetic scope of these methods. Because thiols are unstable to oxidation and are easily converted into undesirable disulfides (R–S–S–R), many inconvenient procedures are needed in previous synthetic procedures, including storage under an atmosphere of inert gas and keeping the thiols from oxidants or substances that give free radicals. In order to overcome this problem, one-pot procedures for alkyl aryl sulfides by reaction between alkyl halides and lithium arene thiolates or arene thiolate anions prepared *in situ* have recently been reported.[16,17]

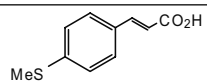
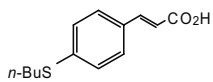
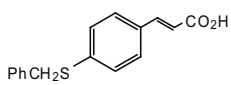
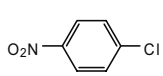
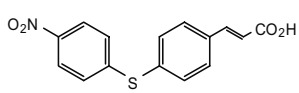
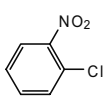
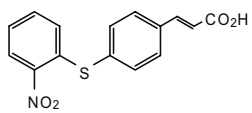
Trans 4-alkylthio- and 4-arylthio-cinnamic acids containing both sulfide and cinnamic acid groups are used as versatile building blocks in the syntheses of various antibacterials, antifungals, compounds with antiparasitical activity, natural products and polymers.[18,19] Here we report a facile strategy to prepare a series of *trans*-4-alkylthio- and 4-arylthio-cinnamic acids **4** by a one-pot reaction starting from *trans*-4-chlorosulfonylcinnamic acid **1** in an aqueous medium without separation and purification of the intermediate **2** (Scheme 1).

In recent years, increasing attention has been focused on organic reactions in aqueous media. Water is the most favourable solvent in terms of operating cost and environmental impact. The use of water as a solvent in organic synthesis is often surprisingly effective even for reactions that are traditionally carried out under anhydrous conditions. Generally, sulfides are prepared by the reaction of alkali metal salts of thiols with alkyl halides in organic solvents such as DMF, DMSO, MeCN, *i*-PrOH and EtOH.[20-23] Only one case of the synthesis of an alkyl aryl sulfide in an aqueous medium



Scheme 1 One-pot synthesis of *trans*-4-alkylthio- and 4-arylthio-cinnamic acids.

Table 1 One-pot synthesis of **4** from *trans*-4-chlorosulfonylcinnamic acid **1** and alkyl and activated aryl halides **3**

Entry	R–X (**3**)		Product (**4**)		t/h	T/°C	Yield[a]/%
1	MeI	**3a**		**4a**	2	rt	87
2	*n*-BuBr	**3b**		**4b**	5	70	83
3	$PhCH_2Cl$	**3c**		**4c**	5	90	82
4		**3d**		**4d**	5	90	83
5		**3e**		**4e**	5	90	80

[a]Isolated yield based on acid **1**.

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has been reported.[24] Because of the excellent solubility of compound **2** in dilute aqueous sodium hydroxide, we attempted to develop a novel one-pot synthetic procedure for the preparation of *trans*-4-alkylthio- and 4-arylthio-cinnamic acids from *trans*-4-chlorosulfonylcinnamic acid in an aqueous medium.

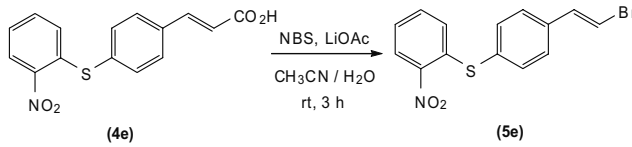
Reduction of *trans*-4-chlorosulfonylcinnamic acid **1** (1.0 equiv.) with stannous chloride dihydrate (5.0 equiv.) followed by alkylation and arylation of the resulting **2** with various kinds of alkyl and activated aryl halides (1.1 equiv.) at room temperature –90 °C in an aqueous medium proceeded in high yields. Results and reaction conditions are shown in Table 1.

To our knowledge, this is the first case of a one-pot procedure for the synthesis of both alkyl aryl sulfides and dialkyl sulfides starting from easily available arylsulfonyl chloride derivatives in an aqueous medium. Applying the one-pot protocol, methyl iodide (**3a**) was reacted at room temperature and the yield of **4a** was considerably improved compared to a two-step method in which compound **2** was separated from the reduction step and **4a** was obtained by the successive alkylation of **2** only in 65% yield. This is mainly due to the instability of **2** which is easily converted into disulfide when exposed to the air and is difficult to purify by crystallisation.[25]

The reactions of *n*-butyl bromide **3b** and benzyl chloride **3c** with **2** proceeded smoothly to give *trans*-4-alkylthiocinnamic acids **4b** and **4c** in good yields at 70 °C and 90 °C, respectively. Experiments were also carried out between the intermediate **2** and activated aryl halides such as 4-chloronitrobenzene **3d** and 2-chloronitrobenzene **3e**. The reactions proceeded at 90 °C and gave the corresponding *trans*-4-arylthiocinnamic acids **4d** and **4e** in high yields.

These synthesised cinnamic acids derivatives could be further applied to the stereoselective synthesis of valuable *trans*-β-arylvinyl bromides,[26,27] which are important building blocks in organic synthesis, especially as intermediates for carbon–carbon and carbon–hetero atom bond formation by transition metal-catalysed coupling reactions. The bromodecarboxylation reaction of **4e** with NBS using a catalytic amount of LiOAc in CH_3CN–H_2O afforded **5e** (Scheme 2).

In summary, *trans*-4-alkylthio- and 4-arylthio-cinnamic acids can be synthesised by a facile one-pot reaction between *trans*-4-chlorosulfonylcinnamic acid and alkyl or activated aryl halides in an aqueous medium. The present method avoids the oxidation of *trans*-4-thiocinnamic acid to form the undesired disulfide, thus enhancing the yields of the products. This method provides several advantages such as high yields, simple work-up procedure and is environmentally friendly.



Scheme 2 Bromodecarboxylation of *trans*-4-(2-nitrophenylthio) cinnamic acid (4e).

Experimental

Melting points were recorded using an A. KRÜSS Optronic GmbH KSPII Melting-Point Meter and were uncorrected. ^{1}H NMR spectra were recorded using a Bruker AM-400 spectrometer in DMSO-d_6 or $CDCl_3$–DMSO-d_6 with $SiMe_4$ as an internal standard. ^{13}C NMR spectra were recorded using a Bruker AM-500 spectrometer in DMSO-d_6 or $CDCl_3$–DMSO-d_6 with $SiMe_4$ as an internal standard. HRMS were measured by the EI method. IR spectra were performed on a Nexus FT-IR spectrophotometer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with HuanghaiGF254 silica gel coated plates. Column chromatography was carried out using 300–400 mesh silica gel at medium pressure.

Typical procedure for the preparation of trans-4-alkylthio- and 4-arylthio-cinnamic acids (**4**)

To a stirred glacial acetic acid (7.4 ml) suspension of *trans*-4-chlorosulfonylcinnamic acid (**1**, 247 mg, 1 mmol), which was prepared from *trans*-cinnamic acid and chlorosulfuric acid according to the procedure of Finn *et al.*,[28] was added stannous chloride dihydrate (1125 mg, 5 mmol) in hydrochloric acid (1.1 ml) at 70 °C and the resulting colourless solution was allowed to reach room temperature for 2 h until a large amount of white solid appeared. To the stirred solution was added 20% aqueous sodium hydroxide (15 ml) to basify the reaction system to a pH of 9 and then halides **3** (1.1 mmol) were added at the reaction temperature specified in Table 1. The reaction mixture was stirred for 2 h at the corresponding reaction temperature, cooled to room temperature, acidified with 6 M aqueous hydrochloric acid (12 ml) and filtered. The solid was washed with 6 M aqueous hydrochloric acid (30 ml), cooled water (3 × 15 ml), and dried under reduced pressure to give the crude products. Purification of the crude products by column chromatography on silica gel (petroleum ether/ethyl acetate/HOAc = 80/40/1) provided the desired products **4**.

Trans-4-methylthiocinnamic acid (**4a**): Following the general procedure at room temperature, *trans*-4-chlorosulfonyl cinnamic acid **1** (247 mg, 1 mmol) was converted into *trans*-4-methylthiocinnamic acid **4a**. This was a white powder (169 mg, 95% yield). M.p. 172–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52 (3H, s), 6.47 (1H, d, J = 15.9 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.54 (1H, d, J = 15.9 Hz), 7.62 (2H, d, J = 8.4 Hz); ^{13}C NMR (500 MHz, DMSO-d6): δ 14.90, 118.36, 126.03, 128.69, 130.76, 141.67, 143.64, 167.93; IR (KBr): 3433, 2961, 1681, 1617, 1591, 1493, 1423, 980, 815, 710 cm^{-1}. HRMS calc. for $C_{10}H_{10}O_2S$ [M]$^+$: 194.0401; found: 194.0402.

Trans-4-(butylthio)cinnamic acid (**4b**): Following the general procedure at 70 °C, *trans*-4-chlorosulfonylcinnamic acid **1** (247 mg, 1 mmol) was converted into *trans*-4-butylthiocinnamic acid **4b**. This was a white powder (195 mg, 83% yield). M.p.139–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (3H, t, J = 7.3 Hz), 1.38–1.52 (2H, m), 1.54–1.59 (2H, m), 2.99 (2H, t, J = 7.3 Hz), 6.47 (1H, d, J = 15.9 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.54 (1H, d, J = 15.9 Hz), 7.60 (2H, d, J = 8.4 Hz); ^{13}C NMR (500 MHz, DMSO-d_6): δ 13.70, 21.84, 30.94, 46.64, 118.32, 127.64, 128.36, 130.67, 135.48, 143.60, 168.24; IR (KBr): 3456, 2958, 2920, 2862, 1681, 1626, 1588, 1493, 1426, 986, 815, 716 cm^{-1}. HRMS calc. for $C_{13}H_{16}O_2S$ [M]$^+$: 236.0872; found: 236.0871.

Trans-4-benzylthiocinnamic acid (**4c**): Following the general procedure at 90 °C, *trans*-4-chlorosulfonyl cinnamic acid **1** (247 mg, 1 mmol) was converted into *trans*-4-benzylthiocinnamic acid **4c**. This was a white powder (223 mg, 83% yield). M.p. 194–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.35 (2H, s), 6.52 (1H, d, J = 15.9 Hz), 7.26–7.29 (1H, m), 7.33–7.39 (2H, m), 7.36 (2H, d, J = 8.2 Hz), 7.39–7.44 (2H, m), 7.56 (1H, d, J = 15.9 Hz), 7.64 (2H, d, J = 8.2 Hz), 12.40 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ 36.87, 118.74, 127.28, 128.06, 128.46, 128.54, 128.89, 131.86, 137.11, 139.56, 143.31, 167.79; IR (KBr): 3429, 2958, 1676, 1618, 1583, 1497, 1419, 978, 816, 715 cm^{-1}. HRMS calc. for $C_{16}H_{14}O_2S$ [M]$^+$: 270.0715; found: 270.0716.

Trans-4-(4-nitrophenylthio)cinnamic acid (**4d**): Following the general procedure at 90 °C, *trans*-4-chlorosulfonylcinnamic acid **1** (247 mg, 1 mmol) was converted into *trans*-4-(4-nitrophenylthio)cinnamic acid **4d**. Ths was a pale yellow powder (250 mg, 83% yield). M.p. 215.5–216.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.62 (1H, d, J = 16.2 Hz), 7.34 (2H, d, J = 8.2 Hz), 7.56 (2H, d, J = 7.9 Hz), 7.63 (1H, d, J = 16.2 Hz), 7.82 (2H, d, J = 7.9 Hz), 8.16 (2H, d, J = 8.2 Hz), 12.53 (1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ 121.08, 124.54, 128.27, 129.84, 132.98, 134.08, 135.60, 142.74, 145.84, 146.63, 167.61; IR (KBr): 3429, 1681, 1624, 1583, 1497, 1419, 1338, 978, 845, 738 cm^{-1}. HRMS calc. for $C_{15}H_{11}NO_4S$ [M]$^+$: 301.0409; found: 301.0410.

Trans-4-(2-nitrophenylthio)cinnamic acid (**4e**): Following the general procedure at 90 °C, *trans*-4-chlorosulfonyl cinnamic acid **1** (247 mg, 1 mmol) was converted into *trans*-4-(2-nitrophenylthio)cinnamic acid **4e**. This was a yellow solid (241 mg, 80% yield). M.p. 261–262 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.64 (1H, d, J = 15.9 Hz), 6.96 (1H, d, J = 8.4 Hz), 7.40–7.44 (1H, m), 7.58–7.60 (1H, m), 7.62 (2H, d, J = 8.4 Hz), 7.64 (1H, d, J = 15.9 Hz), 7.84 (2H, d, J = 8.4 Hz), 8.23–8.25 (1H, m), 12.55(1H, s); ^{13}C NMR (500 MHz, DMSO-d_6): δ 121.27, 125.77, 126.27, 129.08, 129.76, 133.01, 134.16, 135.49, 135.65, 136.11, 137.22,

142.64; IR (KBr): 3438, 1688, 1624, 1557, 1511, 1421, 1334, 978, 854, 822, 781, 724 cm^{-1}. HRMS calc. for $C_{15}H_{11}NO_4S$ $[M]^+$: 301.0409; found: 301.0409.

Preparation of trans-4-arylthio arylvinyl bromides (**5e**): To a stirred solution of lithium acetate (20 mg, 0.2 mmol) in CH_3CN/H_2O (96/4, 20 ml) was added *trans*-4-(2-nitrophenylthio)cinnamic acid **4e** (301 mg, 1 mmol), NBS (214 mg, 1.2 mmol). The reaction mixture was stirred at room temperature for 3 h. The resulting solution was concentrated and the residue was dissolved in ethyl acetate (30 ml). The solution was washed with brine (2 × 30 ml) and water (30 ml), dried over Na_2SO_4 and concentrated to obtain the crude product. Purification of the crude product by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) provided the desired product **5e** as a yellow solid (326 mg, 97% yield). M.p. 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87–6.89 (1H, m), 6.91 (1H, d, J = 14.1 Hz), 7.15 (1H, d, J = 14.1 Hz), 7.24–7.26 (1H, m), 7.33–7.37 (1H, m), 7.40 (2H, d, J = 8.2 Hz), 7.54 (2H, d, J = 8.2 Hz), 8.22–8.24 (1H, m); ^{13}C NMR (500 MHz, $CDCl_3$): δ 108.76, 125.15, 125.73, 127.53, 128.42, 131.15, 133.39, 136.07, 137.43, 138.83, 139.25, 145.33; IR (KBr): 1598, 1560, 1508, 1453, 1334, 980, 932, 845, 779, 729 cm^{-1}. HRMS calc. for $C_{14}H_{10}{}^{79}BrNO_2S$ $[M]^+$: 334.9616; found: 334.9617.

This work was supported by the Natural Science Foundation of Shanghai, China (No. 06ZR14085) and by the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry. We would like to thank the Centre for Instrumental Analysis, Tongji University, China.

Received 20 June 2008; accepted 7 July 2008
Paper 08/5338 *doi: 10.3184/030823408X347576*
Published online: 8 September 2008

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