



## Rapid Ullmann-type synthesis of aryl sulfides using a copper(I) catalyst and ligand under microwave irradiation

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### ABSTRACT

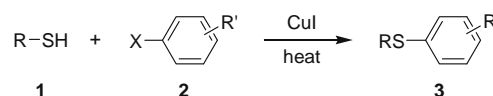
A rapid and efficient method for C–S bond formation under microwave irradiation is reported. The reaction of both electron-rich and electron-poor aryl halides with thiols using copper(I) iodide as a catalyst is facilitated by the addition of 2 equiv of *trans*-cyclohexane-1,2-diol as ligand in the presence of K<sub>2</sub>CO<sub>3</sub> as base in 2-propanol. Microwave irradiation at 120 °C for 3 h gives the corresponding aryl sulfide in a procedure amenable to library production.

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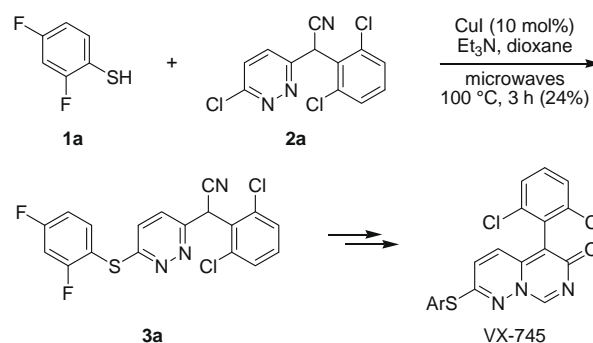
The copper-mediated synthesis of aryl sulfides by the reaction of a thiol and aryl iodide under classical Ullmann conditions has long been established as a valuable yet challenging transformation.<sup>1</sup> Ullmann reactions require harsh conditions (although often less so for C–S bond formation than for the corresponding C–O or C–N bonds), notably in their requirement for very high temperatures and strong bases, and thus often demonstrate poor functional group tolerance. This, in addition to often suffering from low product yields, severely limits the usefulness and application of this classical condensation reaction, in particular on large scale. Recent advances in Ullmann chemistry has seen efforts to overcome these deficiencies with the introduction of new procedures for unactivated substrates, new nucleophiles and increasing functional group tolerance<sup>2–4</sup> as well as the use of soft non-organometallic nucleophiles in Pd-catalysed processes<sup>5</sup> as well as a number of alternative strategies for C–S bond formation.<sup>6</sup> Several groups have found that many of the problems associated with the Ullmann condensation of thiols under copper catalysis (Scheme 1), such as high temperatures, prolonged reaction times, stoichiometric use of copper, toxic solvents and low yields, can be overcome through the use of specific ligands or additives,<sup>7</sup> or more recently by the use of a phase transfer catalyst.<sup>8</sup>

Recently we undertook the synthesis of the p38 $\alpha$  inhibitor VX-745 in order to study its effect on accelerated ageing in Werner syndrome cells.<sup>9</sup> This inhibitor displays potent p38 activity, clinical efficacy and an exquisite selectivity profile, effective at 5.0 nM concentration with 1000-fold selectivity over closely related kinases, including ERK1, JNK1-3 and MK2. Our synthesis of the (arylthio)pyrimido[1,6-*b*]pyridazinone core utilised an Ullmann condensation of thiol **1a** and chloropyridazine **2a** to establish the

C–S linkage of sulfide **3a** and was most effective under copper-catalysed conditions (10 mol % CuI, Et<sub>3</sub>N, dioxane, 90 °C, 16 h, 82%). However, all our efforts to transfer this method to an effective microwave-mediated procedure for rapid C–S bond formation resulted in extremely low yields of the product (e.g., 10 mol % CuI, Et<sub>3</sub>N, dioxane, microwaves, 100 °C, 3 h, 24%) (Scheme 2). Frustrated by the poor efficiency of available procedures for Ullmann C–S bond formation, we set out to address a new method for carrying out this condensation under microwave irradiation that was amenable to automation and library production.



Scheme 1. Cu-catalysed Ullmann condensation of thiols.



Scheme 2. C–S bond formation in the synthesis of VX-745.

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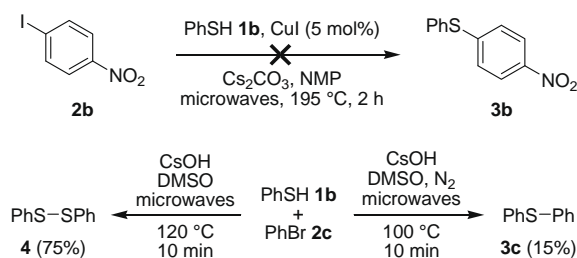
E-mail addresses: bagleymc@cf.ac.uk, bagleymc@cardiff.ac.uk (M.C. Bagley).

Microwave dielectric heating has received increasing attention in recent years as a valuable alternative to the use of conductive heating for accelerating transformations, in both synthetic chemistry and the biosciences.<sup>10</sup> Considering the benefits in evidence for many transition metal-mediated processes using microwave irradiation, it was surprising to find that little effort had been made to carry out Ullmann-type condensation reactions under these conditions. Following the ground-breaking work by Buchwald and Kwong on the copper(I)-catalysed coupling of aryl iodides and thiols using potassium carbonate as base in 2-propanol in the pres-

ence of ethylene glycol,<sup>7a</sup> the copper-catalysed cross-coupling of aryl bromides and iodides has been reported using microwave heating under ligand-free conditions using copper nanoparticles<sup>11</sup> or with copper(I) iodide and caesium carbonate in NMP (195 °C, 2–6 h),<sup>12</sup> but the latter procedure still required high temperatures and prolonged reaction times. Such precedent appeared to be a good starting point for our own investigation.

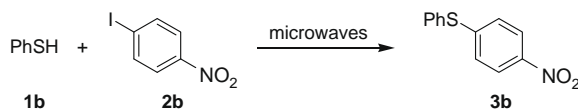
In preliminary studies, 1-iodo-4-nitrobenzene **2b** was irradiated with thiophenol **1b** in the presence of 5 mol % CuI and Cs<sub>2</sub>CO<sub>3</sub> (1 equiv) in NMP, according to the method of Wu and He,<sup>12</sup> but disappointingly, only unreacted **1b** was recovered (Scheme 3). Furthermore, attempts to reproduce catalyst- and ligand-free sealed tube experiments<sup>7e</sup> using thiophenol **1b**, bromobenzene **2c** and CsOH with microwave dielectric heating either gave sulfide **3c** in very low yield (15%) under inert anhydrous conditions or generated disulfide **4** when carried out in the presence of air and moisture, presumably as a consequence of reaction with oxygen.

Clearly an effective general procedure was required and so various ligands were screened (Table 1) in the copper-catalysed reaction of 1-iodo-4-nitrobenzene **2b** and thiophenol **1b**. It was apparent that for this electron-deficient halide, the use of a diol ligand, similar to the Kwong–Buchwald conditions,<sup>7a</sup> with catalytic quantities of CuI gave improved yields of sulfide **3b**. Two diamine



Scheme 3. Preliminary reactions for C–S bond formation.

Table 1  
Screening ligands for the Cu-catalysed synthesis of sulfide **3b** under microwave irradiation



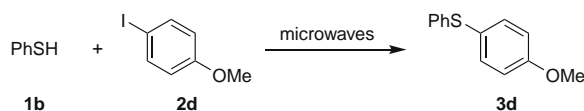
Entry	Catalyst	Ligand <sup>a</sup>	Conditions <sup>b</sup>	Yield <sup>c</sup> of <b>3b</b> (%)
1	CuI (5 mol %)	—	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 × 1 h	63
2	—	—	<i>t</i> -BuONa (1.5 equiv), PhMe, microwaves, 100 °C (150 W), 3 × 1 h	58
3	CuI (10 mol %)	Neocuproine (10 mol %)	<i>t</i> -BuONa (1.5 equiv), PhMe, microwaves, 80 °C (150 W), 3 × 1 h	61
4	CuI (10 mol %)	Neocuproine (10 mol %)	<i>t</i> -BuONa (1.5 equiv), PhMe, microwaves, 100 °C (150 W), 3 × 1 h	60
5	CuI (10 mol %)	Ethylenediamine (4 equiv)	H <sub>2</sub> O, microwaves, 120 °C (150 W), 2 × 1 h	46
6	CuI (10 mol %)	(±)- <i>trans</i> -1,2-Diamino-cyclohexane (4 equiv)	H <sub>2</sub> O, microwaves, 120 °C (150 W), 2 × 1 h	69
7	CuI (5 mol %)	Ethylene glycol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 × 1 h	82

<sup>a</sup> Indicates no additional ligand was added.

<sup>b</sup> Microwaves refer to microwave irradiation in a single-mode CEM Discover<sup>®</sup> microwave synthesiser at the given temperature through moderation of the initial microwave power (150 W).

<sup>c</sup> Isolated yield after purification on silica gel.

Table 2  
Optimising the reaction conditions for the Cu-catalysed synthesis of sulfide **3d** under microwave irradiation



Entry	Catalyst	Ligand <sup>a</sup>	Conditions <sup>b</sup>	Yield <sup>c</sup> of <b>3d</b> (%)
1	CuI (5 mol %)	Ethylene glycol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 1 h	73
2	CuI (5 mol %)	Ethylene glycol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 100 °C (150 W), 2 h	77
3	CuI (5 mol %)	Ethylene glycol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	89
4	CuCl (5 mol %)	Ethylene glycol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	20
5	CuI (5 mol %)	(±)- <i>trans</i> -1,2-Diamino-cyclohexane (8 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 2 h	65
6	CuI (5 mol %)	(±)- <i>trans</i> -Cyclohexane-1,2-diol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	95
7	CuI (5 mol %)	—	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	63
8	—	(±)- <i>trans</i> -Cyclohexane-1,2-diol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	— <sup>d</sup>
9	CuI (5 mol %)	(±)- <i>trans</i> -Cyclohexane-1,2-diol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (1.05 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	88
10	CuI (5 mol %)	(±)- <i>trans</i> -Cyclohexane-1,2-diol (5 mol %)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), 2-propanol, microwaves, 120 °C (150 W), 3 h	70
11	CuI (5 mol %)	(±)- <i>trans</i> -Cyclohexane-1,2-diol (2 equiv)	K <sub>2</sub> CO <sub>3</sub> (2 equiv), H <sub>2</sub> O, microwaves, 120 °C (150 W), 3 h	31

<sup>a</sup> Indicates no additional ligand was added.

<sup>b</sup> Microwaves refer to microwave irradiation in a single-mode CEM Discover<sup>®</sup> microwave synthesiser at the given temperature through moderation of the initial microwave power (150 W).

<sup>c</sup> Isolated yield after purification on silica gel.

<sup>d</sup> Indicates no **3d** was obtained from the reaction and only unreacted thiophenol **1b** was isolated.

ligands also proved effective in aqueous media, with ( $\pm$ )-*trans*-1,2-diaminocyclohexane (4 equiv) giving the highest yield. The use of neocuproine as ligand was also successful but, for this substrate, no appreciable improvements over control reactions were observed. Although the addition of ethylene glycol (entry 7) clearly gave an increase in yield when compared with the ligand-free control (entry 1), electron-deficient iodide **2b** reacted readily in the presence of strong base without the addition of either catalyst or ligand (entry 2) and so a more informative test reaction was sought for optimisation work.

In view of the success of the ligand- and catalyst-free procedures in the reaction of electron-deficient halide **2b**, further studies

were carried out on 4-iodoanisole **2d** (Table 2) for which it was anticipated catalyst and ligand combinations would have a more dramatic effect. It was apparent from the reactions of this electron-rich iodide **2d** with thiophenol **1b**, in equimolar ratios, that: (i) CuI was a much more effective catalyst than CuCl (entry 3 vs entry 4); (ii) a high reaction temperature (120 °C) and longer reaction times gave improved yields (entry 3 vs entry 1); (iii) although ethylene glycol and *trans*-1,2-diaminocyclohexane were effective as ligands, ( $\pm$ )-*trans*-cyclohexane-1,2-diol was superior (entry 6); (iv) 2-propanol was a better solvent than H<sub>2</sub>O (entry 6 vs entry 11); (v) using 2 equiv of both base and ligand gave higher yields of product (entry 3 vs entries 9 and 10). The optimised procedure<sup>13</sup>

**Table 3**

Scope of the microwave-assisted reaction using CuI (5 mol %), ( $\pm$ )-*trans*-cyclohexane-1,2-diol (2 equiv) and K<sub>2</sub>CO<sub>3</sub> (2 equiv) in 2-propanol<sup>a</sup>

Entry	Thiol <b>1</b>	Halide <b>2</b>	Sulfide <b>3</b>	Yield <sup>b</sup> (%)
1				86
2				32
3				— <sup>c</sup>
4				95
5				16
6				91
7				73
8				85
9				78
10				94
11				82
12				50

<sup>a</sup> Reaction was carried out under microwave irradiation at 120 °C in a sealed tube for 3 h using a CEM Discover<sup>®</sup> microwave synthesiser by moderating the initial microwave power (150 W).

<sup>b</sup> Isolated yield after purification on silica gel.

<sup>c</sup> Only unreacted starting materials were recovered from the reaction.

<sup>d</sup> Two equivalents of thiophenol **1b** were used.

(entry 6) employed CuI (5 mol %), ( $\pm$ )-*trans*-cyclohexane-1,2-diol (2 equiv) and  $K_2CO_3$  (2 equiv) in 2-propanol at 120 °C for 3 h and gave sulfide **3d** in excellent yield (95%), as identified by both spectroscopic and spectrometric data. Experiments run under identical conditions in the absence of the ligand gave a much lower yield (entry 7, 63%), and in the absence of the catalyst, did not give any product at all (entry 8), clearly demonstrating the benefit of these new conditions.

In order to explore the scope of the optimised microwave-assisted procedure, a range of both electron-rich and electron-poor aryl halides were reacted in turn with a selection of thiols (Table 3). In general, the reaction gave very good yields and was highly successful for iodides and specific bromides. An alkyl thiol was used as an alternative to aryl thiols, with some reduction in efficiency. Furthermore, the simultaneous formation of two C–S bonds proceeded in excellent yield using dihalobenzene substrates.

In conclusion, microwave irradiation of aryl iodides, or in some cases the analogous bromide, and a thiol in the presence of catalytic CuI, a cyclohexanediol ligand and base in 2-propanol gives the corresponding sulfide rapidly and efficiently under microwave irradiation. This method should be amenable to library synthesis and applicable for the synthesis of a range of sulfur-containing targets.

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- In the optimised experimental procedure, a solution of 4-iodoanisole **2d** (117 mg, 0.5 mmol), PhSH **1b** (55 mg, 0.05 mL, 0.5 mmol), CuI (5 mg, 25  $\mu$ mol), ( $\pm$ )-*trans*-cyclohexane-1,2-diol (116 mg, 1.0 mmol),  $K_2CO_3$  (138 mg, 1.0 mmol) in 2-propanol (2 mL) was irradiated at 120 °C for 3  $\times$  1 h in a pressure-rated glass tube (10 mL) using a CEM Discover<sup>®</sup> microwave synthesiser by moderating the initial power (150 W). After cooling in a flow of compressed air, the reaction mixture was filtered and evaporated in vacuo. Purification by column chromatography on silica gel, eluting with hexane–CH<sub>2</sub>Cl<sub>2</sub> (3:1), gave sulfide **3d** (103 mg, 95%) as a yellow oil (found:  $M^+$ , 216.0607. C<sub>13</sub>H<sub>12</sub>OS [M] requires 216.0609); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.42 (2H, m), 7.30 (2H, m), 7.18 (1H, m), 7.13–7.11 (2H, m), 7.01 (2H, m), 3.78 (3H, s); <sup>13</sup>C NMR (125 MHz; DMSO-*d*<sub>6</sub>) 159.7 (C), 137.8 (C), 135.3 (CH), 129.2 (CH), 127.7 (CH), 126.0 (C), 123.0 (CH), 115.4 (CH), 55.3 (Me); MS (EI)  $m/z$  (rel. intensity) 216 ( $M^+$ , 100%), 201 (55).