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## Ionic liquid-promoted green synthesis of biologically relevant diaryl thioethers

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### ABSTRACT

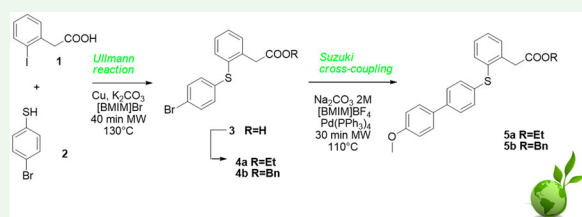
This study reports an ionic liquid (IL) promoted green method to obtain diaryl thioethers useful as key intermediates for the synthesis of matrix metalloproteinase (MMP) inhibitors. The synthetic pathway includes a sequential Ullmann reaction and Suzuki cross-coupling. The Ullmann conditions were optimized as regards the ionic liquid, reaction time, and temperature. Under optimal conditions (1-butyl-3-methylimidazolium bromide ([BMIM]Br) as solvent; catalyst, Cu; base,  $K_2CO_3$ ; reaction time, 22 h; reaction temperature, 150°C) the aryl iodide conversion was 95%. The Suzuki cross-coupling was conducted in 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF<sub>4</sub>) at 110°C, using Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst and Na<sub>2</sub>CO<sub>3</sub> as base. For both reactions, a combination of ILs with microwave (MW) irradiation determined a substantial improvement of reaction time and yields compared to conventional heating. This multi-step process reduces reaction times and removes organic solvents providing a more eco-friendly alternative for the synthesis of important pharmaceutical building blocks.

### ARTICLE HISTORY

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### KEYWORDS

Ionic liquids; diaryl thioethers; Ullmann reaction; Suzuki cross-coupling; microwave irradiation






## Introduction

Nowadays, synthetic procedures for the preparation of biologically active compounds entail multistep pathways which often require high temperatures and long reaction times. Moreover, the subsequent work-up and/or purification processes demand the use of toxic and non-green solvents, which could raise serious concerns. As innovative approaches, several environmentally friendlier reaction media (e.g. supercritical fluids (1), fluorinated solvents (2), alcohols (3), liquid polymers, deep eutectic solvents (DESs) and ionic liquids (ILs) (4)) than common organic solvents (VOCs) were studied both in the academic milieu and at the industrial scale.

Since the beginning of this century, ILs have been considered promising alternatives to conventional VOCs, also being classified as sustainable and green media. ILs are molten organic salts liquid at room temperature or below 100°C endowed with unique

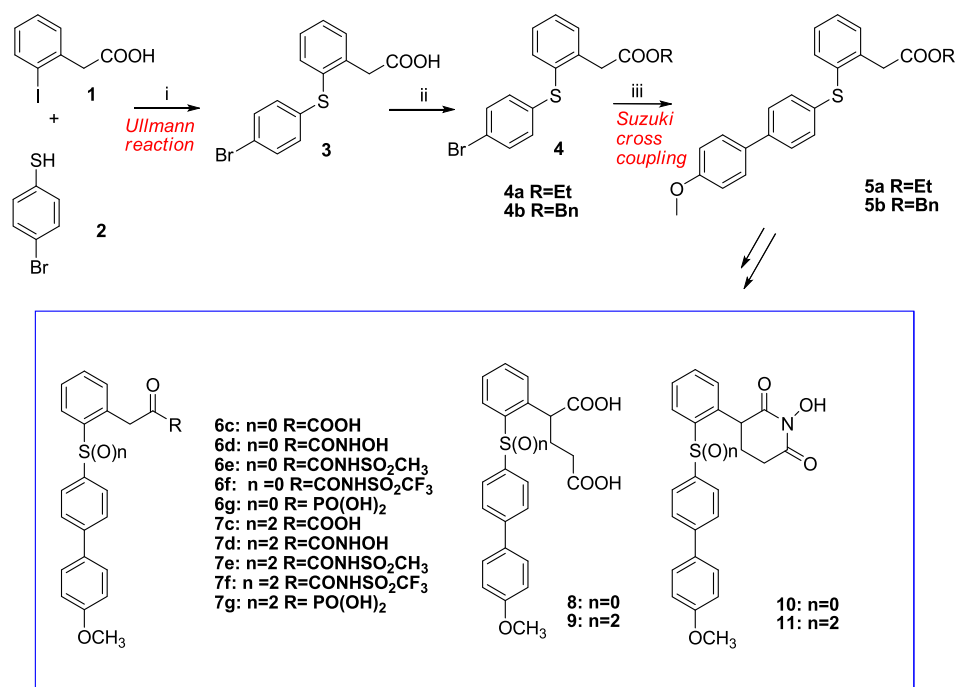
physicochemical properties which include negligible vapor pressure, good thermal and chemical stability, tunable polarity, non-flammability and good solvation potential (5,6). A recent great impact technique is the microwave (MW)-assisted synthesis combined with ILs as solvent, co-solvent, catalyst, and/or template (7). Due to their ionic nature, high polarity and the increase of their complex permittivity ( $\epsilon^*$ ) as a function of the temperature, ILs perfectly support the MW technology, affording often in high yields products which are difficult to obtain by other means. The synergistic combination of MW and ILs can be crucial to convert non-green chemical processes and/or low yield reactions into sustainable high yielding ones (8,9). It is worth mentioning that thanks to the above mentioned null vapor pressure, ILs represent the safest systems for the MW technology, allowing for working at high temperatures with no risks of overpressure.

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\*In beloved memory.

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**Scheme 1.** Reported synthesis of MMP-12 inhibitors **6c–g**, **7c–g** and **8–11** (12).

Diaryl thioethers are fundamental building blocks for the synthesis of biologically active molecules (10,11). We recently reported (12) the development of novel thioaryl-based matrix metalloproteinase-12 (MMP-12) inhibitors (**6c–g**, **7c–g**, **8–11**, Scheme 1) using diaryl thioethers **5a** (12) and **5b** (13) as key intermediates for the entire synthesis.

The synthetic route is based on two consecutive steps: an Ullmann-type reaction and a Suzuki cross-coupling (Scheme 1). The reagents and solvents used are particularly toxic and non-eco-friendly, especially for the Suzuki cross-coupling. Due to the importance of diaryl thioethers **5a** and **5b** for the large scale preparation of MMP-12 inhibitors, the development of a green and efficient synthetic strategy was highly sought.

Among the transition metal-catalyzed cross-coupling reactions, the copper catalyzed Ullmann-type reaction is one of the most straightforward for the synthesis of diaryl ethers, even if the required harsh reaction conditions are often a limitation. Although several C–C, C–O, C–N Ullmann-type coupling reactions were successfully performed in ILs (14,15), only few efforts have been reported for the synthesis of diaryl thioethers (16).

On the contrary, Suzuki coupling in environmentally friendly reaction media has been increasingly reported in recent years (17). In particular, several Pd-based (18,19) catalytic systems were introduced using different ILs as solvents (20). The use of ILs allows for operating at room temperature, for reducing the reaction time, and sometimes for eliminating the use of

the base. Herein, we report the optimization of the green profile of the synthetic pathway to obtain diaryl thioethers **5a** and **5b**, especially focusing on cross coupling reactions. ILs were used as reaction media and the best reaction conditions were combined with MW irradiation to investigate potential synergic effects able to reduce reaction times and improve reaction yields.

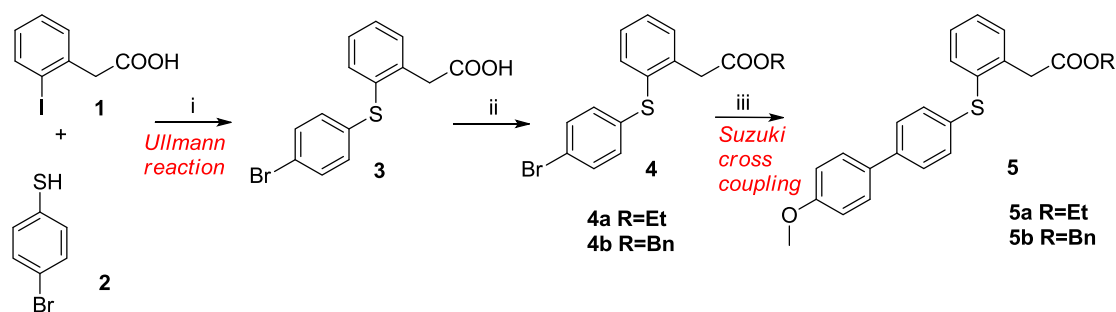
## Results and discussion

The synthetic route followed to optimize the cross-coupling reaction conditions (i and iii) is outlined in Scheme 2.

As a first step, the carboxylic acid **3** was synthesized according to a reported Ullmann reaction protocol (15) using copper at different oxidation states as catalyst and 1-butyl-3-methylimidazolium bromide ([BMIM]Br) as solvent, at different reaction times and temperatures. Then, esters **4a** (12) and **4b** (13) were obtained from the carboxylic acid **3**, following previously reported procedures. Finally, esters **4a,b** were converted into their corresponding biphenyl derivatives **5a,b** by Suzuki cross-coupling using 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF<sub>4</sub>) as reaction medium.

### IL-mediated Ullmann reaction

As previously reported by Luo et al. (15), diaryl ethers can be obtained through Ullmann reaction between a phenol and aryl iodide in ILs such as [BMIM]Br or 1-butyl-3-methylimidazolium chloride ([BMIM]Cl).



**Scheme 2.** Proposed green synthesis of diaryl thioethers **5a** and **5b**. *Reagents and conditions:* (i) Cu, [BMIM]Br, K<sub>2</sub>CO<sub>3</sub>, MW, 130°C, 40 min, 85%; (ii) (a) SOCl<sub>2</sub>, EtOH, 60°C, 85%; (b) BnBr, K<sub>2</sub>CO<sub>3</sub>, dioxane, H<sub>2</sub>O, RT, 72%; (iii) 4-methoxyphenylboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, Na<sub>2</sub>CO<sub>3</sub>, [BMIM]BF<sub>4</sub>, MW, 110°C, 30 min, 56–58%.

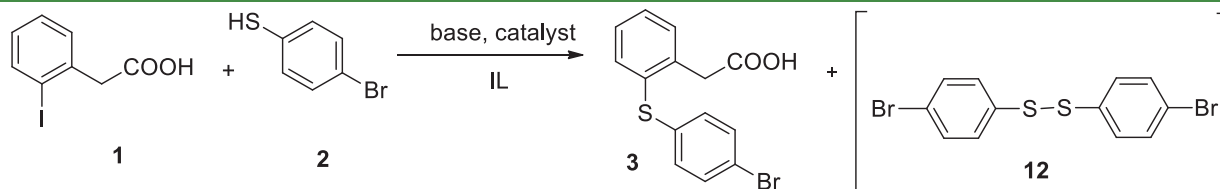
K<sub>2</sub>CO<sub>3</sub> was employed as base and copper halides as catalysts and the reaction was performed at 110°C. Our optimization study was based on this set of starting reaction conditions. All the results have been evaluated through NMR analysis (<sup>1</sup>H) of the reaction crudes (Table 1, entries 1–13) which were constituted exclusively by a mixture of the carboxylic acids **1** and **3**. In particular, the chemical shift of methylene protons (CH<sub>2</sub>CO, δ 3.82 (**1**) and δ 3.84 (**3**)), and of the aromatic AA'XX' system were selected as diagnostic signals. In Figure 1 and Figure 2 the <sup>1</sup>H and <sup>13</sup>C NMR spectra of thiol **2**, carboxylic acid **1**, thioether **3** and the corresponding mixture of **1** and **3** (**1**:**3** = 30:70) obtained in entry R9 (Table 1) are compared.

First, the effect caused by the use of different bases was analyzed (Table 1, entries 1–6). Reaction between

2-iodophenylacetic acid and 4-bromothiophenol was performed at 120°C (conventional heating) using CuI as catalyst and [BMIM]Br as solvent, quenching the reaction at variable reaction times (9–29 h). Regarding the bases, K<sub>2</sub>CO<sub>3</sub> (entries 1–2), tetrabutylammonium hydroxide (TBAOH) (entries 5–6) and choline hydroxide (entries 3–4) were tested, in order to evaluate whether the solubility of the base in the IL medium could affect the reaction outcome. In fact, tetrabutylammonium hydroxide (TBAOH) and choline hydroxide are soluble in ILs while K<sub>2</sub>CO<sub>3</sub> is insoluble in ILs, generating a heterogeneous reaction mixture.

The NMR analysis highlighted conditions of entry 1 as the best performing conditions (70% conversion in 9 h) using K<sub>2</sub>CO<sub>3</sub> as base, a result which is in line with previous findings (21). It is worth mentioning

**Table 1.** Optimization of reaction conditions for the IL-promoted synthesis of **3**.



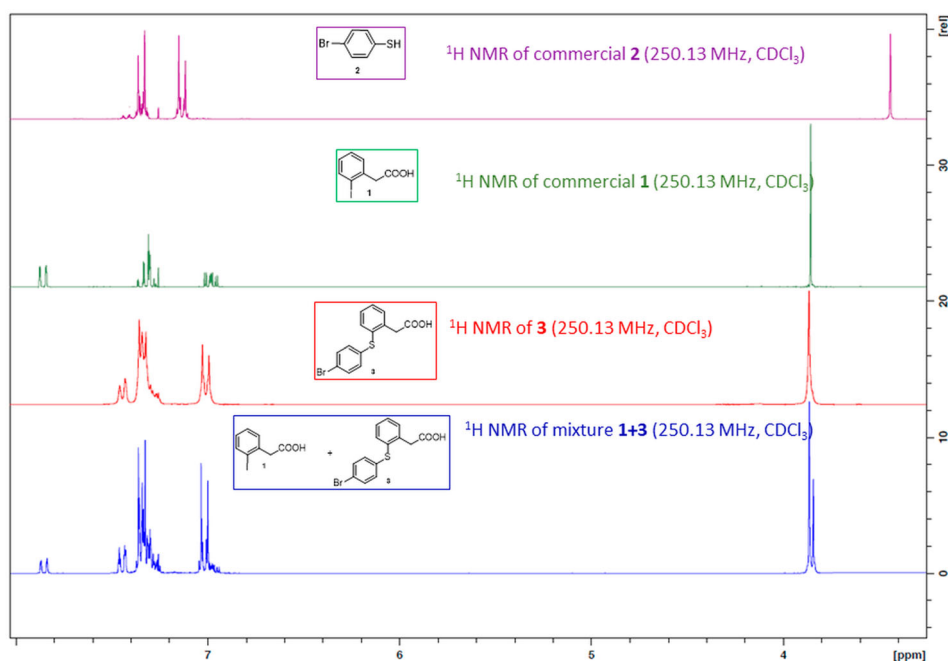
| Entry | IL <sup>a</sup> | Base <sup>a</sup>              | Catalyst <sup>a</sup> | T (°C) | Time (h) | Conversion (%) <sup>b</sup> |
|-------|-----------------|--------------------------------|-----------------------|--------|----------|-----------------------------|
| 1     | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 120    | 9        | 70                          |
| 2     | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 120    | 20       | 65                          |
| 3     | [BMIM]Br        | Choline hydroxide              | CuI                   | 120    | 29       | 56                          |
| 4     | [BMIM]Br        | Choline hydroxide              | CuI                   | 120    | 21       | 35                          |
| 5     | [BMIM]Br        | TBAOH                          | CuI                   | 120    | 21       | Trace <sup>c</sup>          |
| 6     | [BMIM]Br        | TBAOH MeOH                     | CuI                   | 120    | 29       | Trace <sup>c</sup>          |
| 7     | [BMIM]Cl        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 120    | 27       | 66                          |
| 8     | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 100    | 22       | 55                          |
| 9     | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 100    | 27       | 70                          |
| 10    | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 100    | 68       | 70                          |
| 11    | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 120    | 115      | 85                          |
| 12    | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | CuI                   | 150    | 22       | 90 <sup>d</sup>             |
| 13    | [BMIM]Br        | K <sub>2</sub> CO <sub>3</sub> | Cu                    | 150    | 22       | 95 <sup>d</sup>             |

<sup>a</sup>Reaction conditions: 2-iodophenylacetic acid (**1**) (0.6 mmol), 4-bromothiophenol (**2**) (0.7 mmol), base (0.7 mmol), catalyst (0.11 mmol), IL (2.5 mmol)

<sup>b</sup>Yields of compound **3** were determined from <sup>1</sup>H NMR data in the crude reaction mixture

<sup>c</sup>According to TLC and NMR analysis of the reaction mixture.

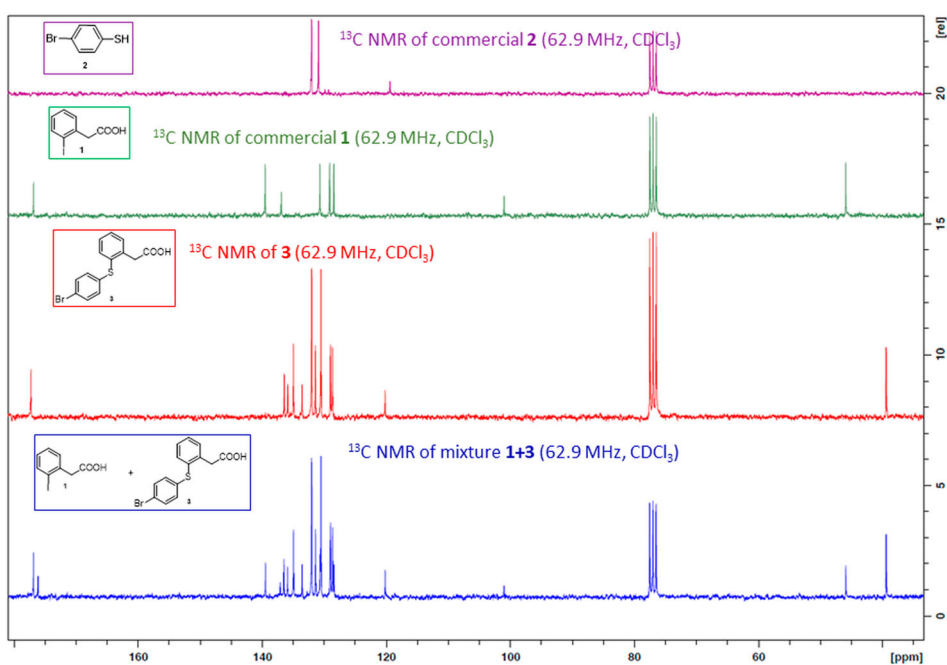
<sup>d</sup>Compound **3**, isolated yields after trituration with Et<sub>2</sub>O/*n*-hexane of crude product: entry 12: 81%; entry 13: 85%



**Figure 1.**  $^1\text{H}$  NMR spectra of mixture of **1** and **3** (blue), compound **3** (red), compound **1** (green), and compound **2** (violet).

that the systems studied in entries 3–6 give rise to mixtures of ILs and therefore a substantially different reaction environment (22). Furthermore, in all these tests a sensible amount of disulfide **12** (Table 1) was found as reaction byproduct, with an obvious (detrimental) effect on the yield of the target cross-coupling compound. Moreover, the concurrent

deactivation of the metal catalyst due to the strong coordinative and adsorptive properties of sulfur, caused a decreased catalytic activity (23). As reported (24), this inconvenient is promoted by non-anhydrous condition and  $\text{O}_2$  presence. In order to overcome this drawback the following tests were performed under inert Ar atmosphere.



**Figure 2.**  $^{13}\text{C}$  NMR spectra of mixture of **1** and **3** (blue), compound **3** (red), compound **1** (green), and compound **2** (violet).

**Table 2.** Optimization of reaction conditions for the IL-promoted synthesis of **3** under MW irradiation.

| Entry | Catalyst <sup>a</sup> | T (°C) | Time (min) | Yield (%) <sup>b</sup> |
|-------|-----------------------|--------|------------|------------------------|
| 14    | Cu                    | 130    | 40         | 85                     |
| 15    | CuI                   | 130    | 25         | 70                     |
| 16    | Cu                    | 100    | 40         | 38                     |

<sup>a</sup>Reaction conditions: 2-iodophenylacetic acid (**1**) (0.56 mmol), 4-bromothiophenol (**2**) (0.7 mmol), K<sub>2</sub>CO<sub>3</sub> (0.7 mmol), catalyst (0.11 mmol), [BMIM]Br (2.5 mmol).

<sup>b</sup>Product **3**, isolated yields.

In entry 7, conversion of **1** into thioether **3** was only 66% after 27 h at 120°C, using CuI, K<sub>2</sub>CO<sub>3</sub> and changing the IL. Therefore, the replacement of [BMIM]Br with [BMIM]Cl gave disappointing results.

In entries 8–12, the reaction temperature was varied. Under anhydrous conditions and using K<sub>2</sub>CO<sub>3</sub> as base, the combination of longer reaction time (22 h) and higher temperature (150°C) gave the best yield, with a 90% conversion (entry 12).

Finally, the effect of different catalysts was investigated (entry 13), keeping unchanged the other parameters (K<sub>2</sub>CO<sub>3</sub> as base, [BMIM]Br as solvent, conventional heating to 150°C for 22 h). A different oxidation state of the copper, Cu<sup>o</sup> was also tested. Comparable results were obtained with both catalysts, reaching up to 90–95% of the target diaryl thioether **3** in the crude mixture. The following purification process through trituration afforded **3** in 85% (Cu, entry 13) and in 81% isolated yields (CuI, entry 12), respectively.

Considering the promising results obtained in entries 12 and 13, a combination of ILs and MW irradiation has been evaluated in comparison with conventional heating (Table 2). Under the best conditions, reaction time was reduced from 22 h (entries 12 and 13) to 25–40 min under MW irradiation, maintaining high yield in the isolation of carboxylic acid **3**. The

results in Table 2 (entry 14) show that a combination of MW irradiation with ILs is the most efficient method to promote the Ullmann reaction to obtain diaryl thioether **3** in high yield (85%) and short time (40 min).

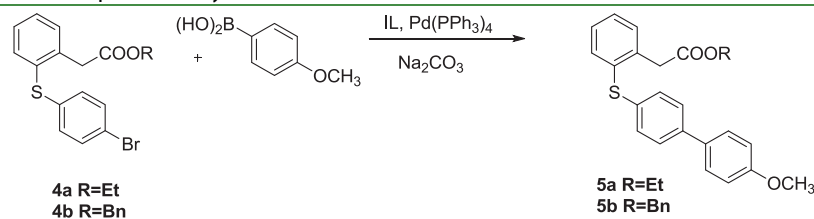
### IL-mediated Suzuki–Miyaura reaction

Suzuki cross-coupling in ILs has been widely reported in the literature (17). Our starting point was the procedure reported by Matthew et al. (25), using 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF<sub>4</sub>) as solvent. Reactions have been conducted on ethyl ester **4a** and benzyl ester **4b** (Table 3, entries 17–20), since better Suzuki cross-coupling results were previously obtained on protected carboxylic acids (12,13).

Initially, reactions were performed by conventional heating to 110°C using Na<sub>2</sub>CO<sub>3</sub> as base, Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst, and [BMIM]BF<sub>4</sub> as solvent, to give the biphenyl derivatives **5a** or **5b** in 15–25% yield after 36–48 h (entries 17 and 19).

With the aim to improve yields and reduce reaction times, the use of the IL was combined with MW irradiation. Aryl bromides **4a** or **4b** and 4-methoxyphenylboronic acid were reacted under MW irradiation (Table 3, entries 18 and 20) affording, after treatment of the mixture (see experimental section), biphenyl derivatives **5a** and **5b** in good yields, without the need of chromatographic purifications.

In particular, ethyl ester **5a** was obtained in a 15% yield with conventional heating (entry 17) and in a 56% yield by MW irradiation (entry 18), with a reduction of reaction time from 48 h to 30 min. Similarly, for benzyl ester **5b** the yield increased from 25% (conventional heating, entry 19) to 58% (MW-assisted reaction, entry

**Table 3.** Comparison between IL-promoted synthesis of **5a** and **5b** under conventional and MW conditions.

| Entry | Substrate <sup>a</sup> | Product | T (°C) | Time   | Method       | Yield (%) <sup>b</sup> |
|-------|------------------------|---------|--------|--------|--------------|------------------------|
| 17    | 4a                     | 5a      | 110    | 48 h   | Conventional | 15                     |
| 18    | 4a                     | 5a      | 110    | 30 min | MW           | 56                     |
| 19    | 4b                     | 5b      | 110    | 36 h   | Conventional | 25                     |
| 20    | 4b                     | 5b      | 110    | 30 min | MW           | 58                     |

<sup>a</sup>Reaction conditions: Aryl bromides (**4a** or **4b**) (0.14 mmol), 4-methoxyphenyl boronic acid (0.16 mmol), Na<sub>2</sub>CO<sub>3</sub> 2M (0.29 mmol), [BMIM]BF<sub>4</sub> (1 mL, 5.35 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.002 mmol).

<sup>b</sup>Isolated yields.

20), with a reduction of the reaction time (from 36 h to 30 min).

MW irradiation determined a substantial improvement of reaction time and yields compared to conventional heating (Table 3, entries 17/18 and 19/20). Therefore, a combination of ILs with MW irradiation provides a valid and ecofriendly alternative to a Suzuki cross-coupling traditionally conducted in toluene or dioxane.

## Conclusion

In conclusion, a convenient and green procedure was developed to obtain diaryl thioethers, **5a** and **5b**, which represent important intermediates for the synthesis of MMP-12 inhibitors. The already reported synthetic route was based on two consecutive steps: an Ullmann-type reaction and a Suzuki cross-coupling. ILs were used as alternative reaction media and the best reaction conditions were combined with MW irradiation, resulting in a synergic effect. After an optimization process, the Ullmann reaction was performed in [BMIM]Br at 130°C to give diaryl thioether **3** in high yield (85%) and short time (40 min, MW). The following Suzuki cross-coupling with 4-methoxyphenyl boronic acid was conducted in [BMIM]BF<sub>4</sub> at 110°C, to afford **5a, b** in good yields and short time (30 min, MW). This multi-step process reduces reaction times and removes organic solvents providing a more eco-friendly and safe alternatives for the synthesis of important pharmaceutical building blocks.

## Experimental section

<sup>1</sup>H NMR spectra were recorded in appropriate solvents with a Bruker Avance II operating at 250.12 MHz or a Bruker Avance III HD 400 spectrometer operating at 400 MHz. <sup>13</sup>C NMR spectra were recorded with the spectrometers operating at 62.9 or 100.57 MHz. The assignments were made, when possible, with the aid of DEPT, COSY, and HSQC experiments. The first order proton chemical shifts are referenced to residual solvents and *J*-values are given in Hz. Where indicated, the elemental compositions of the compounds agreed to within 0.4% of the calculated value. All reactions were followed by TLC on Kieselgel 60 F<sub>254</sub> with detection by UV light and/or with ethanolic 10% phosphomolybdic or sulfuric acid. Kieselgel 60 (Merck, 70–230 and 230–400 mesh, respectively) was used for column and flash chromatography. Some chromatographic separations were performed using the automated system Isolera Four SVTM (Biotage®), equipped with UV detector with variable wavelength (200–400 nm) or using pre-packed ISOLUTE Flash Si II cartridges (Biotage®). Microwave-assisted reactions were run in a microwave

synthesizer (Initiator+, Biotage®) setting a 'very high' absorption level. Unless otherwise noted, solvents, reagents and [BMIM]BF<sub>4</sub> were obtained from commercial suppliers and used without further purification. [BMIM]Br (**26**), [BMIM]Cl (**25**) were prepared according to the reported procedure. All reactions involving air- or moisture-sensitive reagents were performed under an argon atmosphere using anhydrous solvents. MgSO<sub>4</sub> or Na<sub>2</sub>SO<sub>4</sub> were used as the drying agents.

## Ullmann reaction

### IL-assisted reaction in bottom flask (entries 1–6)

A suspension of 2-iodophenylacetic acid (**1**) (150 mg, 0.56 mmol), 4-bromothiophenol (**2**) (130 mg, 0.7 mmol), the proper base (0.7 mmol), and copper iodide (21 mg, 0.11 mmol) in [BMIM]Br (547 mg, 2.5 mmol) was stirred in a bottom flask at 120°C. After 9–29 h the mixture was triturated with Et<sub>2</sub>O (10 × 20 mL) and the crude residue was analyzed by NMR without further purification.

### IL-assisted reaction in bottom flask (entries 7–11)

A suspension of 2-iodophenylacetic acid (**1**) (150 mg, 0.56 mmol), 4-bromothiophenol (**2**) (130 mg, 0.7 mmol), K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.7 mmol), and copper iodide (21 mg, 0.11 mmol) in 2.5 mmol of [BMIM]Cl (entry 7) or [BMIM]Br (entries 8–11) was stirred in a bottom flask at the appropriate temperature (100–150°C). After 27–115 h, the mixture was portioned with Et<sub>2</sub>O (20 mL) and H<sub>2</sub>O (20 mL), the aqueous phase was treated with HCl 1N until pH 4 and extracted with Et<sub>2</sub>O (5 × 2 mL). The organic phase dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated at diminished pressure afforded a crude product that was analyzed by NMR without further purification.

### IL-assisted reaction in bottom flask (entries 12–13)

A suspension of 2-iodophenylacetic acid (**1**) (150 mg, 0.56 mmol), 4-bromothiophenol (**2**) (130 mg, 0.7 mmol), K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.7 mmol), and copper powder or copper iodide (0.11 mmol) in [BMIM]Br (547 mg, 2.5 mmol) was stirred in a bottom flask at 150°C for 22 h. Trituration of mixture with of Et<sub>2</sub>O/*n*-hexane afforded pure the carboxylic acid **3** as a white solid (entry 12: 81%; entry 13: 85%). The <sup>1</sup>H and <sup>13</sup>C NMR data were in accordance with those reported in the literature (**13**). (For NMR spectra see Supporting info).

### MW-assisted reaction (entries 14–16)

A suspension of 2-iodophenylacetic acid (**1**) (150 mg, 0.56 mmol), 4-bromothiophenol (**2**) (130 mg, 0.7 mmol), K<sub>2</sub>CO<sub>3</sub> (97 mg, 0.7 mmol), and copper

powder or copper iodide (0.11 mmol) in [BMIM]Br (547 mg, 2.5 mmol) was stirred in a microwave sealed tube at 100–130°C. After 25–40 min the mixture was portioned with Et<sub>2</sub>O (20 mL) and H<sub>2</sub>O (20 mL), the aqueous phase was treated with HCl 1N until pH 4 and extracted with Et<sub>2</sub>O (5 × 10 mL) and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The crude was purified by a trituration with a mixture of Et<sub>2</sub>O/*n*-hexane to give the carboxylic acid **3** as a white solid (entry 14: 85%; entry 15: 70%, entry 16: 38%). The <sup>1</sup>H and <sup>13</sup>C NMR data were in accordance with those reported in the literature (13). (For NMR spectra see Supporting info).

### Suzuki cross-coupling reaction

#### IL-assisted reaction in bottom flask (entries 17 and 19)

A mixture of the appropriate aryl bromide (**4a** or **4b**, 0.14 mmol), 4-methoxyphenylboronic acid (24 mg, 0.16 mmol), Na<sub>2</sub>CO<sub>3</sub> 2M (0.14 mL, 0.29 mmol), [BMIM]BF<sub>4</sub> (1 mL, 5.35 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1.95 mg, 0.002 mmol) was stirred in a bottom flask at 110°C for 36–48 h. Then, the mixture was portioned with Et<sub>2</sub>O (5.0 mL) and H<sub>2</sub>O (5.0 mL), the aqueous phase was treated with HCl 1N until pH=4 and extracted with Et<sub>2</sub>O (3×5 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The crude was purified by a trituration with *n*-hexane followed by a flash chromatography (for **5a**: 15:1 *n*-hexane–EtOAc; for **5b**: 9:1 *n*-hexane–EtOAc) affording pure esters **5a** (15% yield) or **5b** (25% yield) as white solids. The <sup>1</sup>H and <sup>13</sup>C NMR data were in accordance with those reported in the literature (12,13). (For NMR spectra see Supporting info).

#### MW-assisted reaction (entries 18 and 20)

A mixture of the appropriate aryl bromide (**4a** or **4b**, 0.14 mmol), 4-methoxyphenylboronic acid (24 mg, 0.16 mmol), Na<sub>2</sub>CO<sub>3</sub> 2M (0.14 mL, 0.29 mmol), [BMIM]BF<sub>4</sub> (1 mL, 5.35 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1.95 mg, 0.002 mmol) was stirred in a microwave sealed tube at 110°C for 30 min. Then, the mixture was portioned with Et<sub>2</sub>O (5.0 mL) and H<sub>2</sub>O (5.0 mL), the aqueous phase was treated with HCl 1N until pH=4 and extracted with Et<sub>2</sub>O (3 × 5 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The crude was purified by a trituration with *n*-hexane affording pure esters **5a** (56% yield) or **5b** (58% yield) as white solids. The <sup>1</sup>H and <sup>13</sup>C NMR data were in accordance with those reported in the literature (12,13). (For NMR spectra see Supporting info).

### Disclosure statement

No potential conflict of interest was reported by the author(s).

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### Notes on contributors

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### Supplemental data and research materials

Supplemental data for this article can be accessed at <https://doi.org/10.1080/17518253.2020.1831082>.

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### References

- [1] Jessop, P.G.; Leitner, W. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim, Germany, 2008.



- [2] Gladysz, J.A.; Curran, D.P.; Horváth, I.T. *Handbook of Fluorous Chemistry*, 2nd ed.; Wiley-VCH: Weinheim, 2005.
- [3] Keim, W. *Angew. Chem. Int. Ed.* **2013**, *52*, 12492–12496.
- [4] Clarke, C.J.; Tu, W.C.; Levers, O.; Bröhl, A.; Hallett, J.P. *Chem. Rev.* **2018**, *118*, 747–800.
- [5] Angell, C.A.; Byrne, N.; Belieres, J.P. *Acc. Chem. Res.* **2007**, *40*, 1228–1236.
- [6] Greaves, T.L.; Drummond, C.J. *Chem. Rev.* **2008**, *108*, 206–237.
- [7] Polshettiwar, V.; Varma, R.S. *Acc. Chem. Res.* **2008**, *41*, 629–639.
- [8] Levenque, J.M.; Cravotto, G. *Chimia (Aarau)* **2006**, *60*, 613–620.
- [9] Floris, B.; Sabuzi, F.; Galloni, P.; Conte, V. *Catalysts* **2017**, *7*, 261.
- [10] Liu, L.; Stelmach, J.E.; Natarajan, S.R.; Chen, M.-H.; Singh, S.B.; Schwartz, C.D.; Fitzgerald, C.E.; O’Keefe, S.J.; Zaller, D.M.; Schmatz, D.M.; Doherty, J.B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979–3982.
- [11] De Martino, G.; Edler, M.C.; La Regina, G.; Cosuccia, A.; Barbera, M.C.; Barrow, D.; Nicholson, R.I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947–954.
- [12] Nuti, E.; Cuffaro, D.; Bernardini, E.; Camodeca, C.; Panelli, L.; Chaves, S.; Ciccone, L.; Tepshi, L.; Vera, L.; Orlandini, E.; Nencetti, S.; Stura, E.A.; Santos, M.A.; Dive, V.; Rossello, A. *J. Med. Chem.* **2018**, *61*, 4421–4435.
- [13] Nuti, E.; Panelli, L.; Casalini, F.; Avramova, S.I.; Orlandini, E.; Santamaria, S.; Nencetti, S.; Tuccinardi, T.; Martinelli, A.; Cercignani, G.; D’Amelio, N.; Maiocchi, A.; Uggeri, F.; Rossello, A. *J. Med. Chem.* **2009**, *52*, 6347–6361.
- [14] Sambiagio, C.; Marsden, S.P.; Blacker, A.J.; McGowan, P.C. *Chem. Soc. Rev.* **2014**, *43*, 3525–3550.
- [15] Luo, Y.; Wu, J.X.; Ren, R.X. *Synlett.* **2003**, *11*, 1734–1736.
- [16] Schwab, R.S.; Singh, D.; Alberto, E.E.; Piquini, P.; Rodrigues, O.E.D.; Braga, A.L. *Catal. Sci. Technol.* **2011**, *1*, 569–573.
- [17] Li, J.; Yang, S.; Wu, W.; Jiang, H. *Eur. J. Org. Chem.* **2018**, *2018*, 1284–1306.
- [18] Karthikeyan, P.; Vanitha, A.; Radhika, P.; Suresh, K.; Sugumaran, A. *Tetrahedron Lett.* **2013**, *54*, 7193–7197.
- [19] Boruah, P.R.; Koiri, M.J.; Bora, U.; Sarma, D. *Tetrahedron Lett.* **2014**, *55*, 2423–2425.
- [20] Hooshmand, S.E.; Heidari, B.; Sedghi, R.; Varma, R.S. *Green Chem.* **2019**, *21*, 381–405.
- [21] Deepa, K.D.; Wakharkar, R.D.; Choudhary, V.R. *Synthetic Comm.* **2010**, *41*, 164–169.
- [22] Niedermeyer, H.; Hallett, J.P.; Villar-Garcia, I.J.; Hunt, P.A.; Welton, T. *Chem. Soc. Rev.* **2012**, *41*, 7780–7802.
- [23] Kondo, T.; Mitsudo, T.A. *Chem. Rev.* **2000**, *100*, 3205–3220.
- [24] Mezzetta, A.; Poderelli, L.; D’Andrea, F.; Pomelli, C.S.; Chiappe, C.; Guazzelli, L. *Molecules* **2019**, *24*, 3571.
- [25] Matthews, C.; Smith, P.J.; Welton, T. *Chem. Commun.* **2000**, 1249–1250.
- [26] Chiappe, C.; Mezzetta, A.; Pomelli, C.S.; Puccini, M.; Seggiani, M. *Org. Process Res. Dev.* **2016**, *20*, 2080–2084.