

An efficient microwave-assisted Suzuki cross-coupling reaction of imidazo[1,2-*a*]pyridines in aqueous medium

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Abstract—A new simple, rapid and high yielding synthesis of various 6-aryl-2-arylsulfonylmethyl-3-nitroimidazo[1,2-*a*]pyridines by Suzuki cross-coupling reaction is described using microwave irradiation in aqueous medium without organic co-solvent in the presence of tetrabutylammonium bromide.

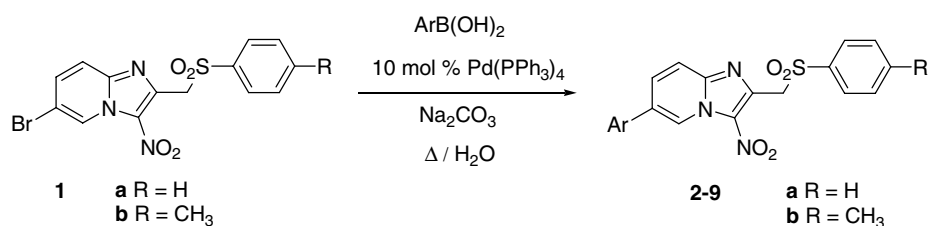
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Over the last 30 years, the use of sulfones in organic chemistry and medicinal chemistry has increased dramatically. Sulfones have been employed in many synthetic methodologies as intermediates enabling the preparation of a great number of functionalized products such as natural products and bioactive substances. The auxiliary sulfonyl group enables the deprotonation of a neighbouring carbon atom and the resulting carbanions can be involved in various transformations after which the sulfonyl group can be removed directly or by different methods including reductive, oxidative and alkylative desulfonylation.¹

Furthermore, the Suzuki reaction has proved extremely versatile and has found extensive use in natural products and heterocyclic synthesis.² Some examples of Suzuki-type cross-coupling reactions in 3- and 6-haloimidazo[1,2-*a*]pyridine series were described.³ Recently,

Gueiffier and co-workers have defined the best conditions of Suzuki reaction on 8-haloimidazo[1,2-*a*]pyridines,^{3f} but the compatibility of a nitro group in imidazo[1,2-*a*]pyridine series with the Suzuki reaction remains unknown. In addition to that, various substituted arylsulfonylmethyl derivatives bearing an electron-withdrawing group have been employed as substrates in different reactions, although these compounds have rarely been exploited in Suzuki or related palladium-catalyzed coupling reactions.⁴

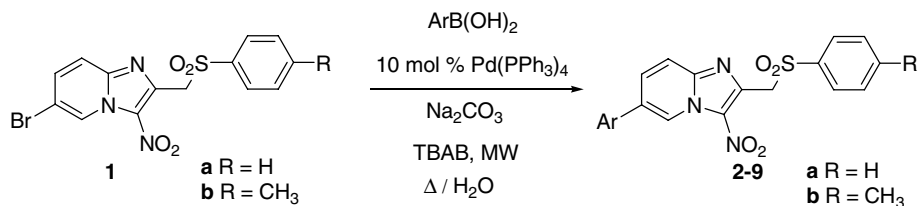
We have recently reported an efficient synthetic route to new imidazo[1,2-*a*]pyridines by Suzuki cross-coupling reactions in aqueous medium.⁵ The coupling reactions of two sulfonyl compounds (**1a,b**) with bromine atom in 6 position were tested with arylboronic acids according to Suzuki reaction in water. The method, which was tested to carry out cross-coupling reaction, used as



Scheme 1.

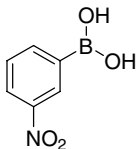
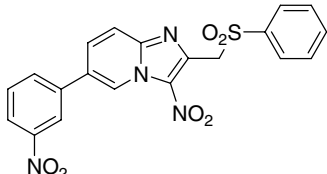
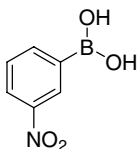
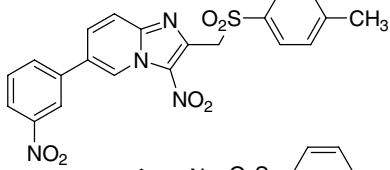
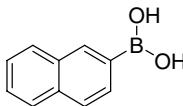
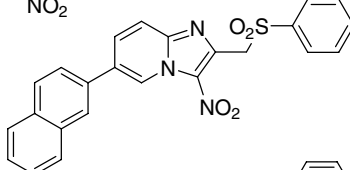
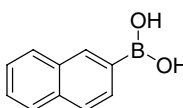
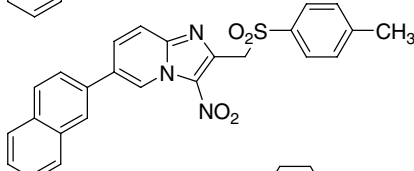
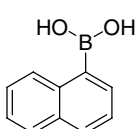
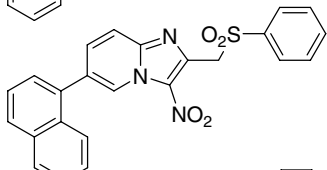
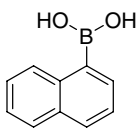
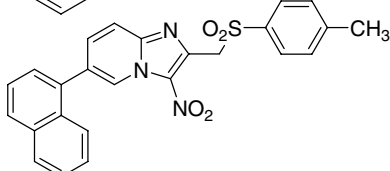
Keywords: Imidazo[1,2-*a*]pyridines; Microwave irradiation; Aqueous medium; Suzuki.

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Table 1. Microwave-mediated Suzuki coupling reaction of 2-(arylsulfonylmethyl)-6-bromo-3-nitroimidazo[1,2-*a*]pyridines and arylboronic acids in water using Pd(PPh₃)₄^a

Entry	Arylboronic acid	Product	Compound number	<i>t</i> (h)	Yield (%)
1			2a	0.33 [20 ^b]	85 [60 ^b]
2			2b	0.66 [2 ^b]	60 [60 ^b]
3			3a	0.66 [2 ^b]	67 [60 ^b]
4			3b	0.66 [24 ^b]	60 [72 ^b]
5			4a	0.33 [1.75 ^b]	69 [60 ^b]
6			4b	0.66 [2 ^b]	94 [97 ^b]
7			5a	0.33 [4.5 ^b]	77 [77 ^b]
8			5b	0.66 [3 ^b]	85 [60 ^b]
9			6a	0.33 [1.5 ^b]	69 [76 ^b]
10			6b	0.66 [1.5 ^b]	86 [55 ^b]

Table 1 (continued)

Entry	Arylboronic acid	Product	Compound number	<i>t</i> (h)	Yield (%)
11			7a	1 ^c [5 ^b]	65 ^c [50 ^b]
12			7b	0.66 [2 ^b]	86 [90 ^b]
13			8a	1 [1 ^b]	78 [63 ^b]
14			8b	0.66 [20 ^b] 1 ^d	90 [20 ^b] 33 ^d
15			9a	1 [4.5 ^b]	85 [63 ^b]
16			9b	0.66 [3 ^b]	78 [55 ^b]

^a Conditions: catalyst Pd(PPh₃)₄ 10 mol %, 2-(arylsulfonylmethyl)-6-bromo-3-nitroimidazo[1,2-*a*]pyridine (**1a,b**) (1 equiv), arylboronic acid (1.3 equiv), Na₂CO₃ (5 equiv), TBAB (1 equiv), H₂O. An initial microwave irradiation of 300 W was used, the temperature being ramped from rt to 105 °C where it was then held for a *t* time.

^b Time reaction and yields in square brackets correspond to reactions performed using oil-bath heating (100 °C).

^c Microwave irradiation (500 W, 105 °C).

^d Catalyst Pd(PPh₃)₄ 5 mol %.

catalyst 10 mol % of Pd(PPh₃)₄, as base 5 equiv of Na₂CO₃, 1.3 equiv of arylboronic derivatives and an oil-bath heating (Scheme 1). Because of facile formation of the anion (**1a**) and (**1b**), a large amount of base was employed. The formation of the sulfonyl anion in basic medium could allow a better solubility of the reagent in water, what would allow the cross-coupling reaction to proceed in aqueous medium. However reaction conditions for the synthesis of sulfonyl derivatives (**2a,b–9a,b**) had to be optimized (shorter reaction time, higher yields, catalyst loading).

Based on a number of reports regarding the Suzuki–Miyaura reaction in aqueous media and in order to optimize the cross-coupling reactivity, we decided to use Na₂CO₃ as base (5 equiv) and Pd(PPh₃)₄ as catalyst. It has been suggested that in the Suzuki reaction, the boro-

nic acid is oxidized by the Pd(II) salt leading to formation of the Pd(0) complex and the generation of a biaryl formed by concomitant homocoupling of the boronic acid.⁶ In light of this, we only investigated the use of Pd(PPh₃)₄ catalyst. Furthermore, the development of water-compatible transition-metal reagents for use in aqueous solvent system has been proved to simplify catalyst–product separation and to increase catalyst activity.⁷ Our alternative method was to use phase transfer agent (TBAB) in order to increase solvation of organic substrates.⁶ We focused our research around the use of water as a solvent in conjunction with microwave heating. Water offers practical advantages over organic solvents. It is cheap, readily available, non toxic, nonflammable and proves to be an excellent solvent for microwave-promoted synthesis.⁸ As well as being energy efficient, microwaves can also enhance the rate of

reactions and in many cases improve product yield. The interest in this area is evidenced by the large number of papers and reviews appearing in the literature during the past few years.⁹

We present here the results from our investigations into the tetrakis(triphenylphosphine) palladium catalysis of the Suzuki reaction in pure water using a modification of the methodology previously described including 1 equiv of tetrabutylammonium bromide (TBAB) and microwave heating.¹⁰

The mixture of 2-arylsulfonylmethyl-6-bromo-3-nitroimidazo[1,2-*a*]pyridine (**1**), arylboronic acid, Pd(PPh₃)₄, Na₂CO₃, TBAB and water was carried out under microwave irradiation (300 W) from 20 min to 1 h (Table 1).¹¹ The disappearance of starting materials was monitored by TLC.

No organic solvent or co-solvent was used or investigated.

As expected it proved more convenient to carry out the Suzuki reaction in a microwave reactor. In order to reduce the aggregation observed when reactions were performed using oil-bath heating, we investigated the use of tetraalkylammonium salts. In fact, the role of ammonium salts is thought to be twofold. First, they facilitate solvation of the organic substrates in the solvent medium and second, they are thought to enhance the rate of the coupling reaction by activating the boronic acid by formation of a boronate complex [ArB(OH)₃]⁻[R₄N]⁺.¹² Contrary to the classical heating methodology, we did not observe any aggregation and thus we simplified the workup.⁵

Moreover, the reaction rates were accelerated up to 30 times yet giving equivalent or higher yields. Furthermore, our attempt to use a lower catalyst loading (5 mol % Pd(PPh₃)₄) led to a dramatic decrease of the yield (i.e., nearly one-third; entry 14) despite a longer reaction time.

In summary, we have shown that by using microwave promotion, TBAB and water as solvent, it is possible to couple a range of arylboronic acids with 2-arylsulfonyl-methyl-6-bromo-3-nitroimidazo[1,2-*a*]pyridines more efficiently and more rapidly with an easier purification of coupled compounds than classical heating methodology. The extension of this rapid and safe method to other nitroheterocyclic sulfones is in progress in our laboratories. In addition to that the use of water-compatible transition-metal catalysts will also be investigated.

Acknowledgements

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- Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006, and references cited herein.
- Multimode reactor: ETHOS Synth Lab station (Ethos start, Milestone Inc)*. The multimode microwave has a twin magnetron (2 × 800 W, 2.45 GHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. During the course of the experiments, time, temperature and power were

measured with the 'easy WAVE' software package. The temperature was measured throughout the reaction and evaluated by an infrared detector, which indicated the surface temperature.

11. *Typical procedure for the coupling of 2-benzenesulfonylmethyl-6-bromo-3-nitro-imidazo[1,2-a]pyridine with phenylboronic acid:* In a 250 mL round-bottom flask were placed 2-benzenesulfonylmethyl-6-bromo-3-nitro-imidazo[1,2-a]pyridine (250 mg, 0.63 mmol), phenylboronic acid (100 mg, 0.82 mmol), Na₂CO₃ (335 mg, 3.16 mmol), TBAB (203 mg, 0.63 mmol), Pd(PPh₃)₄ (73 mg, 0.06 mmol) and water (20 mL). The vessel was then placed into the microwave cavity (Ethos start). Initial microwave irradiation of 300 W was used, the temperature being ramped from rt to the desired temperature of 105 °C. Once

this was reached the reaction mixture was held at this temperature for 20 min. The reaction mixture was stirred continuously during the reaction. After allowing the mixture to cool to room temperature, the solid was collected by filtration, washed with propan-2-ol and dried in the air. The required product was then isolated and characterized by comparison of NMR data with that in the literature.

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