An efficient aqueous microwave-assisted Suzuki–Miyaura cross-coupling reaction in the thiazole series†

Anita Cohen, Maxime D. Crozet, Pascal Rathelot and Patrice Vanelle*

Received 25th May 2009, Accepted 10th August 2009
First published as an Advance Article on the web 3rd September 2009
DOI: 10.1039/b916123f

A new simple, rapid and high yielding synthesis of various 5-substituted thiazoles by Suzuki–Miyaura cross-coupling reaction is described using microwave irradiation in aqueous medium without organic co-solvent in the presence of tetrabutylammonium bromide.

Introduction

Nowadays, the development of the field of green chemistry through organic reactions conducted in water has become one of the most exciting research endeavours for organic chemists in order to prepare new biologically active molecules.[1] Therefore, within the last years, many faster, cleaner and eco-friendlier chemical processes have been developed.[2,3,4]

Two substantial areas of current green research are the use of water as a solvent for organic synthesis in addition to microwave irradiation for efficient heating of reaction mixtures.[5] Actually, water is an attractive alternative to traditional organic solvents because it is inexpensive, non-flammable, non-toxic, and environmentally sustainable by alleviating the problem of pollution by organic solvents. Furthermore, water is an attractive solvent for metal-catalyzed reactions, such as Suzuki–Miyaura couplings.[6] The Suzuki reaction has gained prominence in recent years[7] because of the availability of functionally substituted boronic acids which are environmentally safer than most other organometallics and the importance of biaryl or aryl-heteroaryl pharmacophores in a variety of biologically active molecules (losartan[8] or many other compounds described as potential antiemetics[9] or antimalarials[10] for example).

Nevertheless, only a few examples of Suzuki–Miyaura cross-coupling reactions using water in conjunction with microwave irradiation are reported in the literature.[2,11,12]

In view of our general interest in microwave-assisted organic reactions[12,13] and cleaner chemical processes in order to synthesize new potentially bioactive compounds,[14] we examined the Suzuki–Miyaura reaction in the thiazole series. Indeed, this coupling reaction has found extensive use in heterocyclic synthesis[15] but surprisingly very few investigations were conducted in the thiazole series.

The thiazole nucleus is commonly found in the chemical structure of natural compounds, such as the coenzyme derived from vitamin B_1 (thiamin), and various synthetic compounds exhibiting a wide variety of biological activity,[16] as gastric anti-secretory agents (famotidin, nizatidin) or anti-infectious agents (ritonavir, nitazoxanide, tenonitrozole, aminitrozole, *etc.*), while others have found applications as liquid crystals[17] and cosmetic sunscreens.[18]

The classical method for the synthesis of thiazoles is the Hantzsch process.[19] This method gives excellent yields for simple thiazoles; however, for some substituted examples low yields have been reported.[18,20] In order to synthesize aryl-substituted thiazoles, only few examples are described, particularly using standard conditions of heating in pure organic solvent (toluene,[21,22] DME,[9,23,24] xylene,[24] dioxane,[25] THF[6]), or blended with an hydrophilic co-solvent (DME/water,[26,27] benzene/methanol[6,28]). These processes afforded the synthesis of thiazoles especially 2-aryl-substituted with various yields (from 17% to 92% according to the different reported examples). Indeed, thanks to the most electron-deficient 2-position, studies report regiocontrolled Suzuki–Miyaura reaction and thus show that the C-2 position is the most reactive one.[6,21,24,26–29] Nevertheless, cross-coupling in the C-5 position is also possible under standard Suzuki–Miyaura conditions but with prolonged reaction times and an excess of arylboronic acid.[21]

Thus, we report herein a practical, inexpensive, rapid and green microwave-promoted method for the preparation of 4-arylsulfonyl-5-aryl-2-methylthiazole and 4-arylsulfonyl-5-styryl-2-methylthiazole derivatives in water.

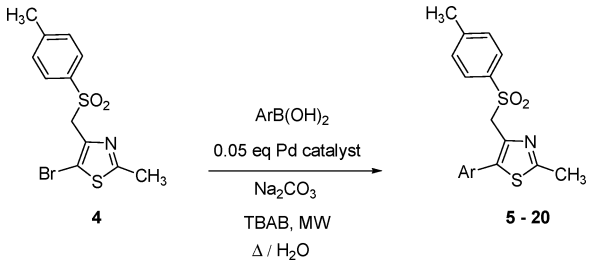
Results and discussion

We present here the results from our investigations concerning the Suzuki–Miyaura reaction in neat water, catalyzed by 0.05 equivalent (eq) of palladium catalyst, in presence of 1 eq of tetrabutylammonium bromide (TBAB) used as phase transfer agent, 5 eq of Na_2CO_3 used as base and microwave heating, in thiazole series substituted in the C-2 and C-4 positions (Scheme 1).

The required starting material for the Suzuki cross-coupling reaction is the 5-bromo-2-methyl-4-(tosylmethyl)thiazole **4** which was prepared in 59% overall yield by sequential condensation between 1,3-dichloroacetone with thioacetamide,[30] cyclization using $ZnCl_2$ in methanol,[31] bromination with *N*-bromosuccinimide (NBS) in CH_3CN as proposed by Gueiffier

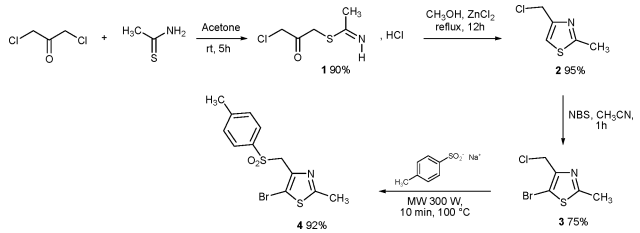
Laboratoire de Pharmaco-Chimie Radicalaire, LPCR, Faculté de Pharmacie, Universités d'Aix-Marseille I, II, III-CNRS 6264: Laboratoire Chimie Provence, 27 Boulevard Jean Moulin, 13385, Marseille Cedex 05, France.
E-mail: patrice.vanelle@pharmacie.univ-mrs.fr;
Fax: +33-4-91-79-46-77; Tel: +33-4-91-83-55-80

† Electronic supplementary information (ESI) available: Experimental and characterisation details and crystallographic data. CCDC reference numbers 727244. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b916123f



Scheme 1

in imidazo[1,2-*a*]-pyridine series[32] and *p*-toluenesulfinic acid sodium salt in water under microwave irradiation (Scheme 2).



Scheme 2

The last reaction which furnished compound **4** (with 92% yield) was adapted to microwave experimental conditions in water in order to avoid using DMSO as solvent, generally used to synthesize arylsulfonyl derivatives[33] through $S_{RN}1$ experimental conditions. The 4-tosylmethyl group was chosen because sulfones are well-known to be employed in many synthetic methodologies[34] and it can be used further for the preparation of various 4-substituted heterocycles.[35]

Owing to the fact that the bromoheterocyclic sulfone **4** is a strongly C–H acidic sulfone, its expected solubility in the basic medium of the Suzuki–Miyaura experimental conditions offers the opportunity to develop Suzuki–Miyaura reactions in aqueous water.

Furthermore, based on the first reports regarding the Suzuki–Miyaura reactions using microwave promotion, we decided to use $Pd(PPh_3)_4$ (method A) as catalyst.[36]

Because of the easy formation of the anion **4**, a large amount of base was employed. The formation of sulfonyl anion in basic medium could allow a better solubility of the reagent in water, which would allow the cross-coupling reaction to proceed in aqueous medium. Moreover, in order to facilitate solvation of the organic reagents, a tetraalkylammonium salt was added as phase transfer agent. As the Suzuki reaction involves many ionic intermediates, tetrabutylammonium bromide is appropriate. According to Leadbeater and co-workers, the ammonium ion also plays a catalytic role activating the boronic acid by the formation of a boronate complex $[ArB(OH)_3]^-[Bu_4N]^+$.[11c,37,38]

The first method which was tested to carry out cross-coupling reaction, used 10 mol% of $Pd(PPh_3)_4$ as catalyst, 5 equivalents of Na_2CO_3 as base, 1 equivalent of tetrabutylammonium bromide (TBAB) as phase transfer agent and 1.3 equivalent of arylboronic acid under microwave irradiation (300 W) for 1 h at 100 °C. The disappearance of starting materials was monitored by TLC. No organic solvent or co-solvent were used or investigated.

Unfortunately, with 1.3 equivalent of arylboronic acid we did not observe complete conversion of compound **4**. As the starting sulfone **4** is a relatively strong C–H acid, we decided to confirm the position of the aryl group by X-ray crystallography for compound **7** (Fig. 1) which gave clean crystals, in order to verify the reactivity of the bromine atom in C-5 position and to eliminate the possible formation of arylated sulfones as proposed by Beletskaya.[39] The other structures were assigned by analogy and spectral comparison.

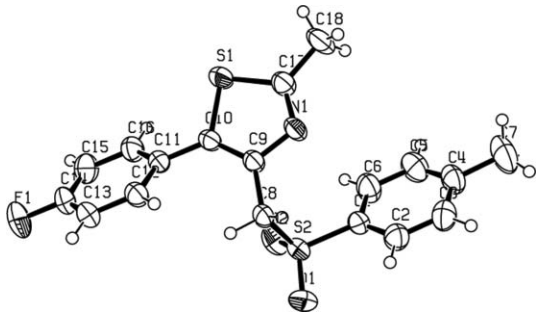


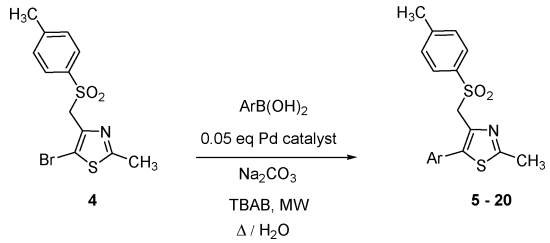
Fig. 1 X-Ray structure of the compound **7**.

After confirmation of the desired reactivity, our research was directed by the appropriate arylboronic amount needed to lead the reaction to completion.

Finally, the optimum quantity of arylboronic acid was found to be 3.5 equivalents for complete consumption of starting materials without any prolonged reaction times. The excess of arylboronic acid is then recovered after column chromatography. As recommended by Stefaniak *et al.* for a green work-up procedure, we used ethyl acetate for extraction as "preferred" solvent and ethyl acetate/cyclohexane (5/5) for column chromatography eluent as "usable" mixture.[40] In order to optimize the method already developed in our laboratories for imidazo[1,2-*a*] pyridine series,[12] we tried using a lower catalyst loading. Thus, we succeeded in reducing the loading from 10 mol% to 5 mol% without any reduction of yield (Method A: Table 1, entries 1–8 and 11–13). However, when no reaction was observed or poor yields were obtained, we decided to use 5 mol% of $Pd(OAc)_2$ as catalyst (Method B: Table 1, entries 9–10 and 15–16). Indeed, Badone and co-workers reported that, when using water, addition of $Pd(OAc)_2$ and 1 equivalent TBAB to the reaction mixture greatly accelerates the Suzuki reaction.[37]

Unfortunately, diphenylboronic acid reacted poorly under these last conditions. Thus, we finally investigated the use of $[PPh_3]_2PdCl_2$ (Method C: Table 1, entry 14) which is known to give good results under microwave irradiation conditions with aryl chlorides in DMF.[41] Consequently, after a 10 h reaction time, no starting material remained by TLC, affording, after flash chromatography, the thiazole derivative **18** in 96% yield. Finally, in order to estimate the usefulness of the microwave heating, we performed, as representative examples, the synthesis of compounds **5**, **18** and **19** under conventional heating. The desired products were obtained with lower or similar yields but with longer reaction times (compound **5**: 2.5 h with 80%, compound **18**: 18 h with 82%, compound **19**: 23 h with 85%).

Table 1 Microwave-mediated Suzuki coupling reaction of 5-bromo-2-methyl-4-(tosylmethyl)thiazole and arylboronic acids in water



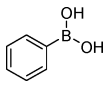
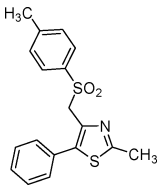
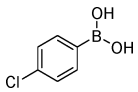
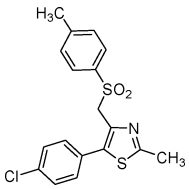
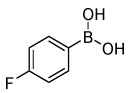
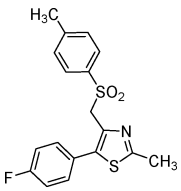
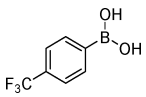
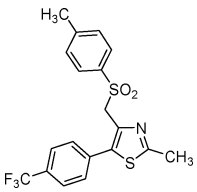
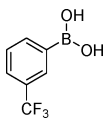
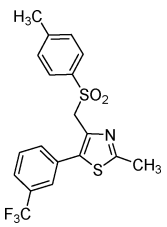
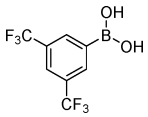
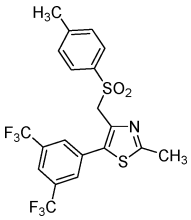
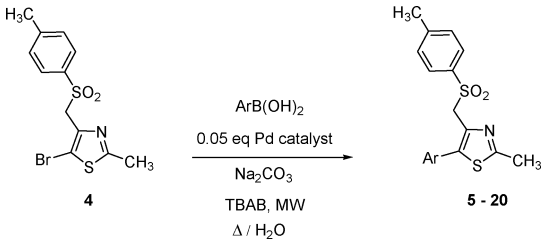
Entry	Arylboronic acid	Product	Compound number	Experimental conditions: Time [method]	Yield%
1			**5**	1.5 h [A[a]]	97
2			**6**	1 h [A[a]]	95
3			**7**	1 h [A[a]]	89
4			**8**	1 h [A[a]]	96
5			**9**	1.5 h [A[a]]	81
6			**10**	2 h [A[a]]	91

Table 1 *(Contd.)*



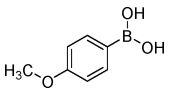
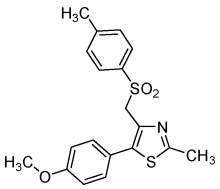
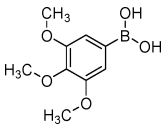
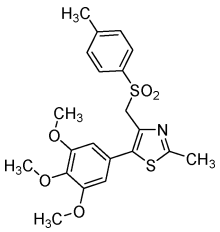
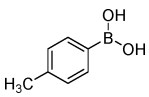
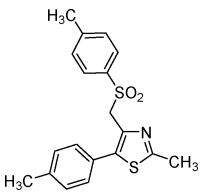
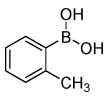
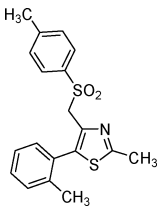
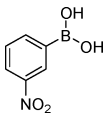
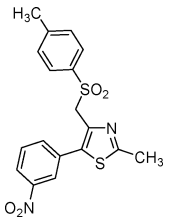
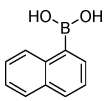
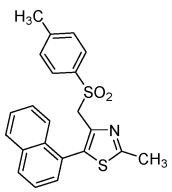
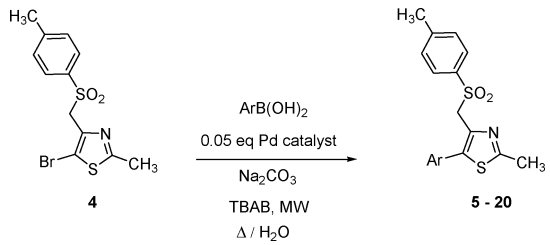
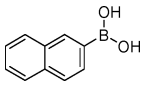
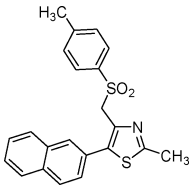
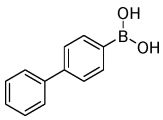
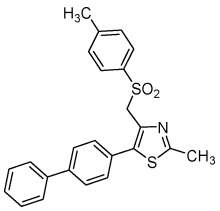
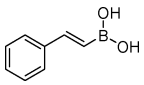
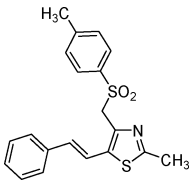
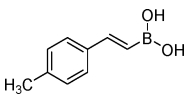
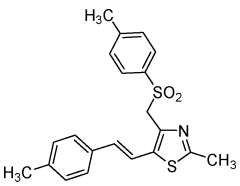
Entry	Arylboronic acid	Product	Compound number	Experimental conditions: Time [method]	Yield%
7			**11**	1 h [A[a]]	92
8			**12**	1.5 h [A[a]]	98
9			**13**	1 h [B[b]]	84
10			**14**	2 h [B[b]]	74
11			**15**	2.5 h [A[a]]	74
12			**16**	2 h [A[a]]	73

Table 1 *(Contd.)*



Entry	Arylboronic acid	Product	Compound number	Experimental conditions: Time [method]	Yield%
13			**17**	2 h [A[a]]	88
14			**18**	10 h [C[c]]	96
15			**19**	4.5 h [B[b]]	87
16			**20**	6 h [B[b]]	93

[a] Method A: 5-bromo-2-methyl-4-(tosylmethyl)thiazole (**1**) (1 eq), arylboronic acid (3.5 eq), $Pd(PPh_3)_4$ (0.05 eq), Na_2CO_3 (5 eq), TBAB (1 eq.), H_2O. An initial microwave irradiation of 300 W was used, the temperature being ramped from room temperature (rt) to 100 °C where it was then held for a time *t*. [b] Method B: 5-bromo-2-methyl-4-(tosylmethyl)thiazole (**1**) (1 eq), arylboronic acid (3.5 eq), $Pd(OAc)_2$ (0.05 eq), Na_2CO_3 (5 eq), TBAB (1 eq.), H_2O. An initial microwave irradiation of 500 W was used, the temperature being ramped from rt to 100 °C where it was then held for a time *t*. [c] Method C: 5-bromo-2-methyl-4-(tosylmethyl)thiazole (**1**) (1 eq), arylboronic acid (3.5 eq), $[(C_6H_5)_3P]_2PdCl_2$ (0.05 eq), Na_2CO_3 (5 eq), TBAB (1 eq.), H_2O. An initial microwave irradiation of 500 W was used, the temperature being ramped from rt to 100 °C where it was then held for a time *t*.

Conclusion

In summary, we have shown that by using microwave irradiation and water as a solvent, it was possible to realize Suzuki–Miyaura cross-couplings and synthesize a series of 5-substituted thiazoles more efficiently, more rapidly and more ecologically than was described in the literature under standard conditions. Furthermore, the presence of a tosylmethyl group at the 4-position makes the 5-position less electron-deficient, and thus leads to a poor theoretical reactivity of this last position. The synthetic utility of this developed method could now be exploited by a variety of substituents at the 4-position allowing access to a large series of substituted thiazoles. Moreover, these experimental conditions allowed the synthesis by reaction with (*E*)-styrylboronic acid and (*E*)-4-methylstyrylboronic acid compounds **19** and **20** with excellent yields, which constitutes an interesting alternative to the Heck reaction, which is well-known to be idiosyncratic in 5-bromothiazole series.[24] The extension of this green approach to other heterocycles and palladium-catalyzed coupling reactions involving bioactive compounds is in progress in our laboratory.

Experimental

General procedure

In a 100 mL round-bottom flask were placed 5-bromo-2-methyl-4-(tosylmethyl)thiazole (300 mg, 0.87 mmol), arylboronic or styrylboronic acid (3.5 eq, 3.05 mmol). palladium catalyst (0.05 eq, 4.35 μmol), tetrabutylammonium bromide (1 eq, 0.87 mmol), sodium carbonate (5 eq, 4.33 mmol) and water (20 mL). The vessel was then placed into the synthesis multimode microwave oven cavity (ETHOS Synth Lab station) and carried out under microwave irradiation at 100 °C for appropriate time at the appropriate power. The reaction mixture was stirred continuously during the reaction. The disappearance of starting materials was monitored by TLC. After being cooled down, the mixture was then extracted with EtOAc (8 × 15 mL). The organic layers were dried over anhydrous sodium sulfate and removed under vacuum. Purification by chromatographic column, eluting with EtOAc/cyclohexane (5/5), and recrystallization from propan-2-ol gave the corresponding required product.

For example: 2-methyl-5-phenyl-4-(tosylmethyl)thiazole **5** (290 mg, 97%)

Yellow needles; mp 166 °C (from propan-2-ol); (Found: C, 62.9; H, 5.0; N, 4.05. $C_{18}H_{17}NO_2S_2$ requires C, 62.9; H, 5.0; N, 4.1%). δ_H(200 MHz; $CDCl_3$) 2.43 (3 H, s, CH_3), 2.67 (3 H, s, CH_3), 4.51 (2 H, s, CH_2), 7.22-7.36 (7 H, m, H ar), 7.62 (2 H, d, *J* 8.2, H ar); δ_C(50 MHz, $CDCl_3$) 18.7, 21.7, 56.0, 128.6, 128.9, 129.1, 129.5, 129.6, 136.0, 136.6, 139.4, 144.8, 165.3.

Acknowledgements

This work was supported by the CNRS and the Universities of Aix-Marseille. The authors thank V. Remusat for ^{1}H and ^{13}C spectra recording, M. Giorgi for the X-ray diffraction and structure analysis. A. Cohen thanks the Assistance Publique-Hôpitaux de Marseille for hospital appointment.

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