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Efficient synthesis of functionalized 6-substituted-thiosalicylates via microwave-promoted Suzuki cross-coupling reaction

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ABSTRACT

Functionalized 6-substituted-thiosalicylates are key intermediates for the synthesis of pyrimidinyl(thio) salicylic acids, a group of important herbicides targeting plant acetohydroxyacid synthase. Therefore, it is of great interest to develop an efficient method for the syntheses of 6-substituted-thiosalicylates. Herein, we have developed a direct and efficient method for the synthesis of functionalized 6-substituted-thiosalicylates (**4**) from aryl iodide (**1**) by using an improved microwave-assisted Suzuki cross-coupling reaction. Almost all the reactions proceeded smoothly and afforded moderate to excellent yields of products. Moreover, this protocol is obviously superior to the traditional available methods and could be utilized to synthesize pyrimidinyl(thio)salicylic acid and its derivatives.

1. Introduction

The pyrimidinyl(thio)salicylic acids are an important class of commercial herbicides targeting acetohydroxyacid synthase.[1] As shown in Fig. 1, functionalized 6-substituted-thiosalicylates[2] are commonly found as a privileged structure in almost all the herbicidal pyrimidinyl(thio)salicylic acids.

Traditionally, these compounds have been prepared by three practical approaches. As shown in Fig. 2, the first pathway has relied on transition-metal-catalyzed[3] and metal-free C–S coupling reactions;[4] The second method involved formal [3+3]-cyclization of 3-aryloxythio-1-trimethylsilyloxybuta-1,3-dienes with 3-alkoxy-2-en-1-ones;[5] The third synthetic methodology is based on the carbanion-induced ring transformation of 2*H*-pyran-2-ones.[2i,6] Although these methods have provided useful access to the substituted 6-substituted-thiosalicylates, there are still noticeable drawbacks, such as relatively harsh reaction conditions, inaccessible substrates, and low yields. Therefore, the development of general and direct strategies for the preparation of functionalized 6-substituted-thiosalicylates would be highly interesting.

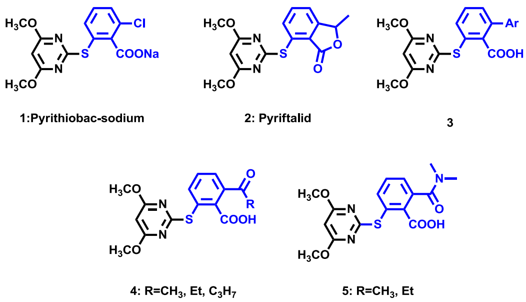
1:Pyrithiobac-sodium
2: Pyriftalid
3
4: R=CH$_3$, Et, C$_3$H$_7$
5: R=CH$_3$, Et

Fig. 1. Chemical structures of pyrimidinyl(thio)salicylic herbicides.

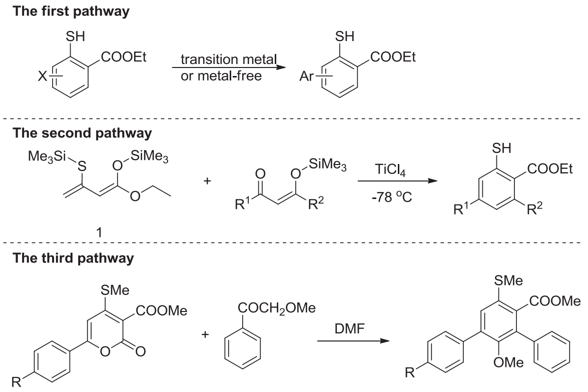

Fig. 2. Three practical approaches for the synthesis of the thiosalicylates.

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Not long ago, our laboratory successfully employed microwave irradiation[7] to synthesize 6-arylsalicylates.[8] However, application of this strategy to prepare 6-substituted-thiosalicylates has been surprisingly unsuccessful. As shown in Fig. 3, although the optimal conditions have been used on the synthesis of **3a′** with excellent yield, this methodology did not give similar results for the synthesis of**3a**.

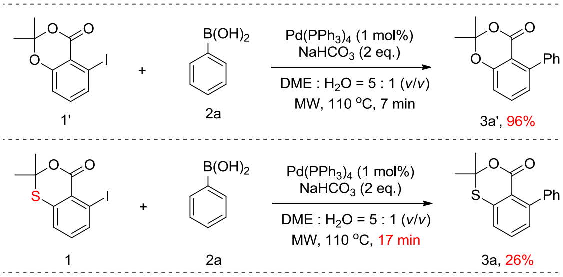


Fig. 3. Synthesis of 2,2-dimethyl-5-phenyl-4*H*-benzo[*d*][1,3]oxathiin-4-one and 2,2-dimethyl-5-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one.

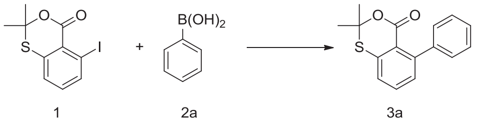
Herein, as a continuation of our research on the synthesis of structurally diverse heterocyclic compounds, we report the synthesis of functionalized 6-substituted-thiosalicylates via an improved Suzuki cross-coupling reaction under microwave irradiation.

2. Result and discussion

The aryl iodide (**1**) was prepared by using a previously reported synthetic strategy.[8,9] To optimize the conditions for the palladium-catalyzed Suzuki cross-coupling reaction, we selected the reaction between aryl iodide (**1**) and phenylboronic acids (**2a**) as a model. We initially studied the reaction with the optimal conditions previously established for the synthesis of functionalized 6-arylsalicylates.[8] As shown in Table 1, the reaction was carried out at 110 °C, with 1% of Pd(PPh$_3$)$_4$, 2 equiv of NaHCO$_3$, in a solution of DME (3 mL), and H$_2$O (0.6 mL). However, the transformation was incomplete and the yield was only 26% (Table 1, entry 1). During optimization, the stoichiometric ratio of the catalyst and the temperature proved to be important parameters for this reaction (Table 1, entries 2–4). The yield was notably increased to 84% when the reaction was carried out at 120 °C, with 2 mol % of Pd(PPh$_3$)$_4$ (Table 1, entry 4). A survey of solvents revealed that toluene/H$_2$O=5:1 (v/v) was optimal (Table 1, entries 4–8). Most surprisingly, we observed no conversion of aryl halide into product **3s** when the phenylboronic acid was changed to furan-2-ylboronic acid (Table 1, entry 9), indicating that this condition is not generally applicable for different substrates. Therefore, the reaction conditions were further adjusted. As shown in Table 1 (entries 10–12), when we added a small amount of tetrabutyl ammonium bromide (TBAB) into the reaction mixture, the yields of the product were improved markedly. Maybe it is due to that TBAB can facilitate the migration of a reactant from one phase into another phase where reaction occurs. Furthermore, as compared with conventional heating methods, microwave irradiation dramatically accelerated these reactions and increased the reaction yields (Table 1, entry 13).

With the optimized conditions defined, we investigated the scope of substrates by employing a variety of arylboronic acids substituted with electron-donating and electron-withdrawing groups. As shown in Table 2, significant structural variations in the arylboronic acid components were well tolerated and afforded the corresponding functionalized 6-substituted-thiosalicylates (**3**) in moderate to good yields. Both electron-rich and electron-poor arylboronic acids could be successfully utilized in this transformation; methyl, methoxy, *tert*-butyl, nitro, trifluoromethyl, and acetyl derivatives showed no significant effects on the transformation and afforded good yields of products (Table 2, **3g**–**l**). Even the potentially problematic bromo-substituted arylboronic acid resulted in product **3e** with acceptable yields. It should be noted that incorporation of halogen-substituents at the *ortho*, *meta* or *para* positions in arylboronic acids did not retard the reaction, demonstrating that steric modification can be accomplished without compromising the efficiency of the process (Table 2, **3b**–**d**).

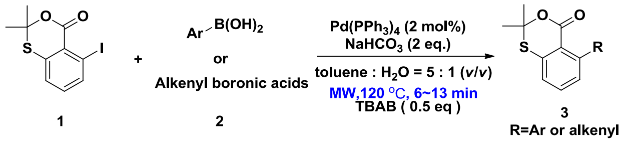
Table 1
Optimization of the reaction conditions[a]

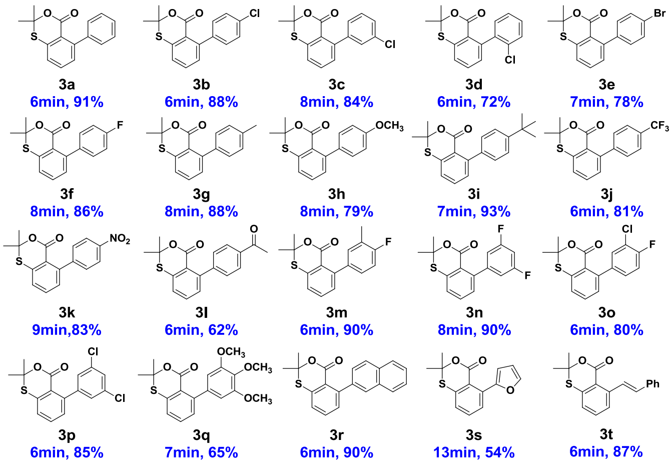


No	Temp (°C)	Solvent (v/v)	Pd(PPh$_3$)$_4$	TBAB[b]	Time (min)	Yield[c]
1	MW:110[d]	DME/H$_2$O=5:1	1 mol %	0	17	26%
2	MW:110	DME/H$_2$O=5:1	2 mol %	0	6	70%
3	MW:110	DME/H$_2$O=5:1	5 mol %	0	6	62%
4	MW:120	DME/H$_2$O=5:1	2 mol %	0	3	84%
5	MW:120	DMF/H$_2$O=5:1	2 mol %	0	4	35%
6	MW:120	THF/H$_2$O=1:1	2 mol %	0	4	84%
7	MW:120	1,4-Dioxane/H$_2$O=5:1	2 mol %	0	6	37%
8	MW:120	Toluene/H$_2$O=5:1	2 mol %	0	6	89%
9[e]	MW:120	Toluene/H$_2$O=5:1	2 mol %	0	6	0%
10	MW:120	Toluene/H$_2$O=5:1	2 mol %	0.3 equiv	6	90%
11	MW:120	Toluene/H$_2$O=5:1	2 mol %	0.5 equiv	6	91%
12[e]	MW:120	Toluene/H$_2$O=5:1	2 mol %	0.5 equiv	13	54%
13	120[f]	Toluene/H$_2$O=5:1	2 mol %	0.5 equiv	480	75%

[a] Unless otherwise noted, all the reactions were carried out at 0.5 mmol scale in a solution of toluene (3 mL) and H$_2$O (0.6 mL) with 2 mol % of Pd(PPh$_3$)$_4$, 2 equiv of NaHCO$_3$, 0.5 equiv TBAB, protected by N$_2$.
[b] TBAB=tetrabutyl ammonium bromide.
[c] Isolated yields.
[d] Microwave irradiation.
[e] The reaction between aryl iodide (**1**) and furan-2-ylboronic acid (**2s**).
[f] Conventional heating method.

Table 2
The reaction with aryl iodide (**1**) and various arylboronic acids or alkenyl boronic acids[a]





3a 6min, 91%	**3b** 6min, 88%	**3c** 8min, 84%	**3d** 6min, 72%	**3e** 7min, 78%
3f 8min, 86%	**3g** 8min, 88%	**3h** 8min, 79%	**3i** 7min, 93%	**3j** 6min, 81%
3k 9min,83%	**3l** 6min, 62%	**3m** 6min, 90%	**3n** 8min, 90%	**3o** 6min, 80%
3p 6min, 85%	**3q** 7min, 65%	**3r** 6min, 90%	**3s** 13min, 54%	**3t** 6min, 87%

[a] Unless otherwise noted, all the reactions were carried out at 0.5 mmol scale