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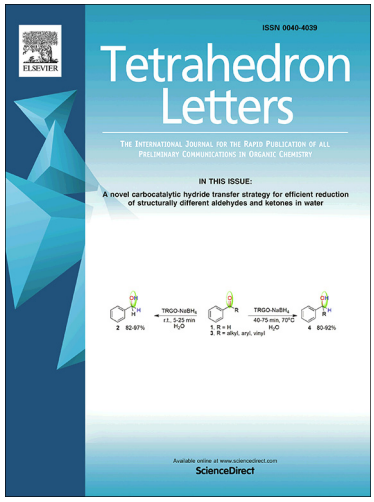


# A microwave-assisted approach to *N*-(2-nitrophenyl)benzenesulfonamides that enhanced peroxidase activity in response to excess cadmium

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## Graphical Abstract

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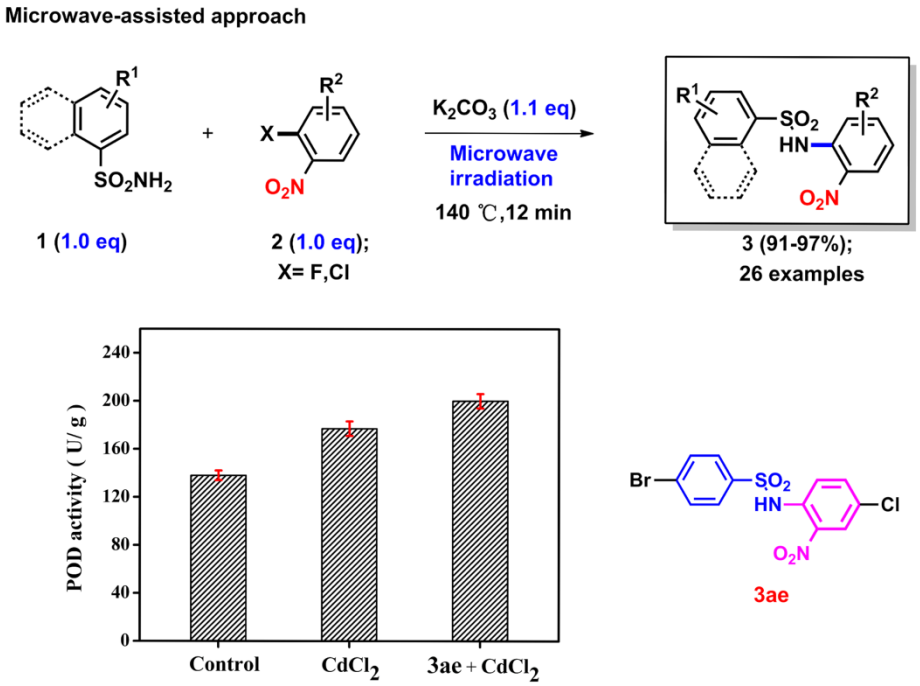

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# A microwave-assisted approach to *N*-(2-nitrophenyl)benzenesulfonamides that enhanced peroxidase activity in response to excess cadmium

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ABSTRACT

A facile and efficient approach to *N*-(2-nitrophenyl)benzenesulfonamides was developed under microwave irradiation. A series of pyrabactin analogues containing nitrophenyl scaffold was obtained in excellent yields. In addition, the method was pretty suitable to prepare flusulfamide. Significantly, the **3ae** could enhance POD activity in response to heavy metal stress.



The core fragment benzenesulfonamide is popular in the agrochemical(oryzalin, penoxsulam, sulam)[1] and pharmaceutical industries(sulfameter, sulfisoxazole)[2]. In particular, the derivative pyrabactin(Py) activates the receptor of abscisic acid which help plant overcome abiotic stresses such as heavy metal stress, soil salinity and drought.[3] However, the Py is a weak agonist which motivates more efforts to identify novel agonists. On the base of Py, we have gotten many biphenyl analogues.[4] Now, we intend to replace the 2-methylpyridine with the nitrophenyl scaffold (**Figure 1**) which is crucial synthetic blocks[5] and agrochemicals[6].

Until now, the most common approaches to *N*-(2-nitrophenyl) benzenesulfonamides are electrophilic substitution using the mixture of nitric acid and strong brønsted acid. However, these methodologies give many by-products and cost much acid. So, many alternative methods have been developed. [7-9] The base promoted *N*-benzenesulfonation of 2-nitroaniline(**Scheme 1**, **a**) which cost a large amount of base and time[7]. Also, the yields of *ortho*-nitration were undesirable when the *tert*-butyl nitrite was used for electron-withdrawing substrates (**Scheme 1**, **b**)[8a]. Especially, the yield of **3ck** was mere 20%. Additionally, the oxone/$NaNO_2$ was not suitable for **3ce-3cj** which provided incompletely conversion and was failed to give the **3ck**.[8b] What's more, the NaH-based nucleophilic aromatic substitution($S_NAr$) wasted 1 equivalent of NaH and benzenesulfonamide, cost

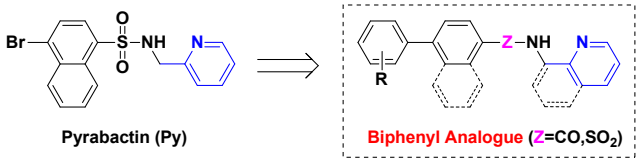
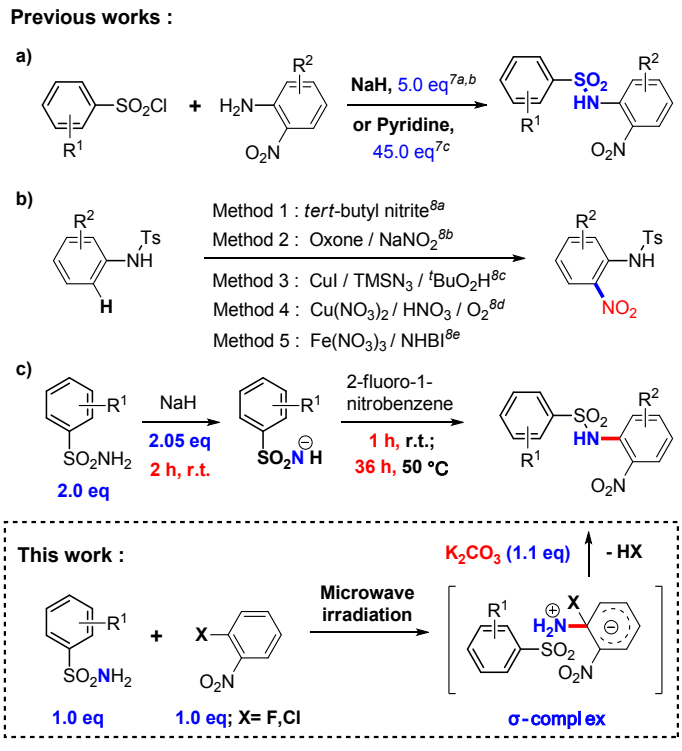
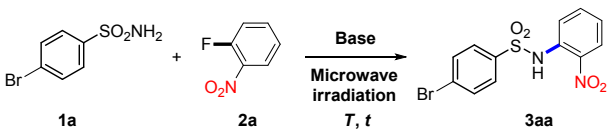



**Figure 1** Our previous work about the biphenyl analogues




**Scheme 1** Selected methods to synthesize *N*-(2-nitrophenyl)benzene-sulfonamides

**Table 1** The optimization microwave-assisted $S_NAr$ reaction[a]




1a 2a 3aa

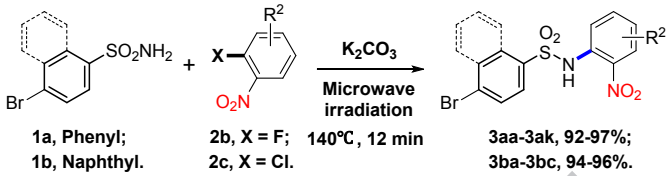
| Entry | Solvent | Base | T (°C) | t (min) | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 | DMF | $K_2CO_3$ | 80 | 10 | 43 |
| 2 | DMF | $K_2CO_3$ | 100 | 10 | 74 |
| 3 | DMF | $K_2CO_3$ | 120 | 10 | 89 |
| 4 | DMF | $K_2CO_3$ | 130 | 10 | 94 |
| 5 | DMF | $K_2CO_3$ | 140 | 10 | 96 |
| **6** | **DMF** | **$K_2CO_3$** | **140** | **12** | **97** |
| 7 | DMF | $K_2CO_3$ | 140 | 15 | 97 |
| 8 | DMF | $Na_2CO_3$ | 140 | 12 | 93 |
| 9 | DMF | $Cs_2CO_3$ | 140 | 12 | 94 |
| 10 | DMF | NaOH | 140 | 12 | 91 |
| 11 | Dioxane | $K_2CO_3$ | 140 | 12 | 94 |
| 12 | DMSO | $K_2CO_3$ | 140 | 12 | 95 |
| 13[c] | DMF | $K_2CO_3$ | 140 | 900 | 83 |

[a] Reactions conditons : **1a** 1.0 mmol, **2a** 1.0 mmol, **Base** 1.1 mmol, solvent 5.0 mL. [b] Isolated yield. [c] Conventional heating method.

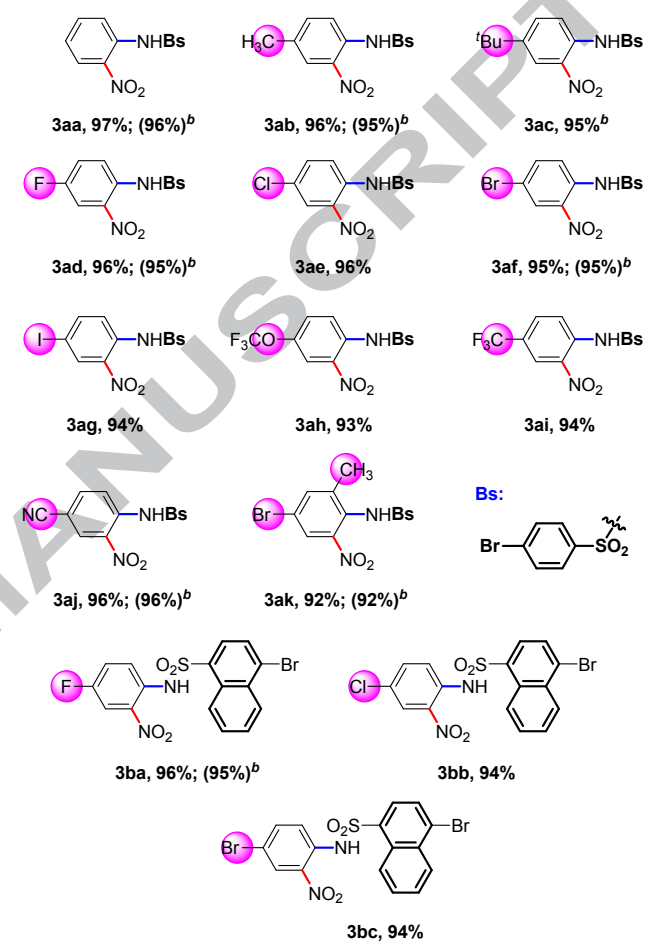
more than 39 hours and gave less than 70% yield(**Scheme 1**, **c**).[9] Thus, it is strongly desirable to develop low-cost, efficient and high yield protocol for the synthesis of *N*-(2-nitrophenyl) benzenesulfonamides. More importantly, the extensive utilization of microwave irradiation can lower the reaction activation energy, accelerate chemical reaction and increase yield notably.[10] Hence, the application of microwave irradiation has drawn much attention of chemists.[11] Of note, we have obtained a large number of bioactivity molecules through the application of microwave irradiation.[4,12] Herein, we report a facilely and efficiently microwave-assisted approach to prepare *N*-(2-nitrophenyl) benzenesulfonamides with excellent yields and broad substrate scope. Significantly, the product could enhance peroxidase activity in response to excess cadmium. In addition, the method gives 91% yield of flusulfamide.

Although the conventional reaction of fluoride nitrobenzene and nucleophilic agent ($R^1OH$, $R^1R^2NH$, and so on) is known, it is still great challenge to find the optimum conditions to perform microwave-assisted strategy. For our initial researches, the reaction of 4-bromophenylsulfonamide(**1a**) and 1-fluoro-2-nitrobenzene(**2a**) in the presence of $K_2CO_3$ under microwave irradiation was chosen as a benchmark reaction(**Table 1**). To our surprise, 43% of **3aa** was obtained with a temperature of 80 °C in 10 minutes(**Table 1**, **entry 1**). The result of TLC exhibited that major of the starting materials were remained. Therefore, in order to improve the yield, the reaction temperature was enhanced. So, the yield of **3aa** was increased with an increase of temperature (**entry 2-5**). Furthermore, the **3aa** was obtained in the highest yield of 97 % in 12 and 15 minutes(**entry 6, 7**). Subsequently, the effect of bases on the reaction was explored, and among these bases, $K_2CO_3$ was identified as the best one(**entry 6, 8-10**). Finally, the different solvents were screened, among these solvents(dioxane, DMF and DMSO), DMF was the most suitable (**entry 6, 11, 12**). Compared with conventional heating method(**entry 13**), microwave irradiation could significantly

**Table 2** Scope of microwave-assisted approach[a]




1a, Phenyl; 1b, Naphthyl. 2b, X = F; 2c, X = Cl. 140℃, 12 min 3aa-3ak, 92-97%; 3ba-3bc, 94-96%.

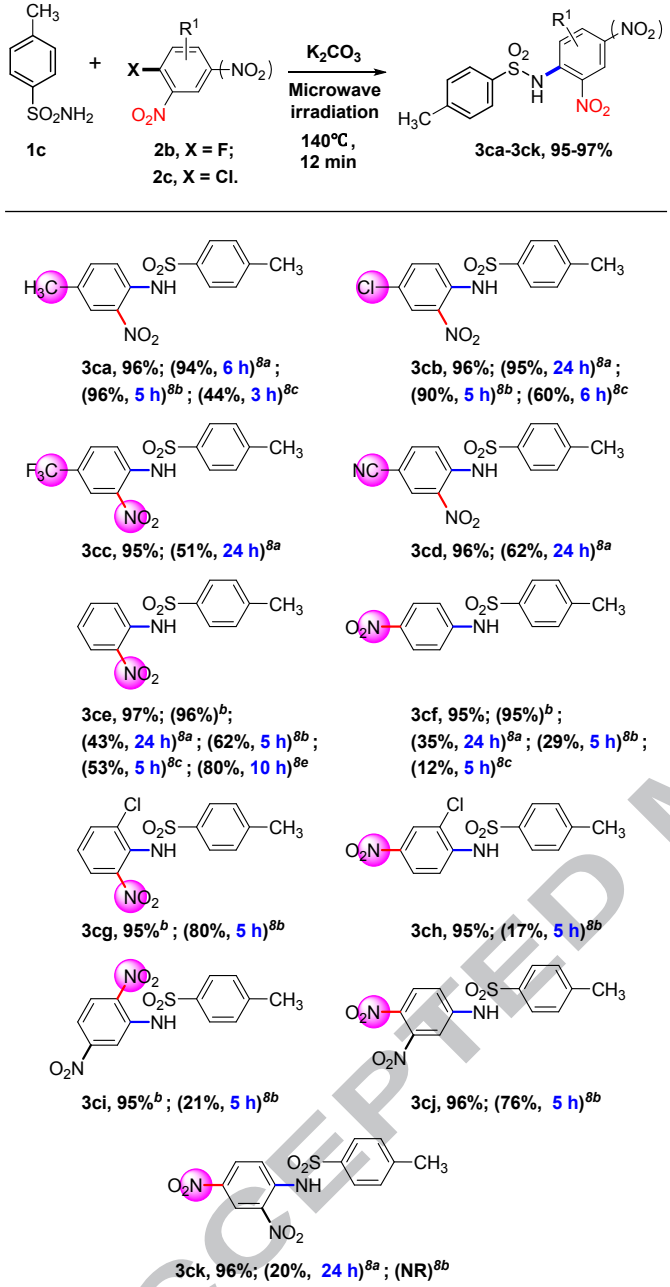



[a] Reactions conditons : **1a-1b** 1.0 mmol, **2** 1.0 mmol, **$K_2CO_3$** 1.1 mmol, solvent 5.0 mL; Isolated yield; **2b**, **X = F**. [b] **2c**, **X = Cl**.

accelerate the reaction and notably improve the yield of the product. As a result, the combination of 1.0 equivalent of **1a**, 1.0 equivalent **2a** and 1.1 equivalents $K_2CO_3$ in DMF with a temperature of 140 °C in 12 minutes was fixed, as optimal conditions.

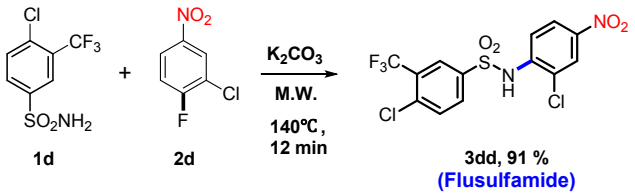
Once the optimized reaction conditions were identified, the limitations and scope of the microwave-assisted approach were examined. Various halogenated nitrobenzene were explored, the results were shown in **Table 2**. The reaction between **1a** and **2b** always went smoothly. Both electron-donating and electron-withdrawing groups, such as 4-methyl(**3ab**), 4-halogen(**3ad-3ag**), 4-trifluoromethoxy(**3ah**) and 4-trifluoromethyl(**3ai**), 4-cyano(**3aj**) afforded the desired products in excellent yields. In addition, 5-bromo-2-fluoro-1-methyl-3-nitrobenzene were also investigated and afforded the desired product(**3ak**). To increase the scope of SNAr reaction, 4-bromonaphthalene-1-sulfonamide(**1b**) and **2b** was tested. The yields of **3ba-3bc** were 90%. Of note, chloride nitrobenzenes(**2c**) and **1a-1b** could be successfully converted to the products(**3aa-3ad**, **3af**, **3aj-3ak**, **3ba**). Not only electron-rich but also electron-deficient substrates

**Table 3** Scope of halogenated nitrobenzene(**2**) and 4-methylbenzene-sulfonamide(**1c**)[a]




[a] Reactions conditons : **1c** 1.0 mmol, **2** 1.0 mmol, $K_2CO_3$ 1.1 mmol, solvent 5.0 mL; Isolated yield; **2b**, **X = F**. [b] **2c**, **X = Cl**.

with 4-methyl(**3ab**), 4-*tert*-butyl(**3ac**), 4-bromo(**3af**) and 4-cyano(**3aj**) groups, were found to be suitable for the method. Furthermore, the reaction of 1-chloro-4-fluoro-2-nitro-benzene and **1b** gave excellent yield of **3ba**.




**Scheme 2** The microwave-assisted approach to flusulfamide (**3dd**)

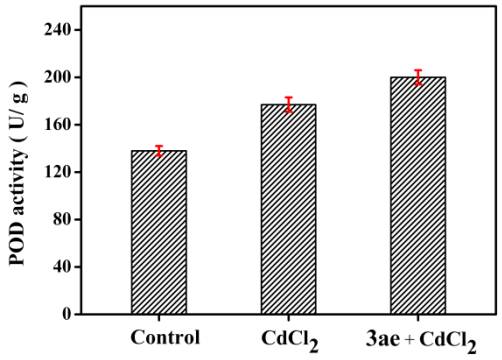



**Figure 2 3ae** treatments enhanced the POD activity in response to excess cadmium(**3ae**, 50μM; $CdCl_2$, 30 mg/L)

Notably, the 4-methylbenzenesulfonamide(**1c**) was suitable for microwave-assisted approach. The reaction of chloride or fluoride nitrobenzenes(**2**) and **1c** produced the desired compounds in excellent yields(**Table 3**). It was obvious that the approach could give a higher yield of *para*- and *ortho*-nitro group products( **3cc-3cf**, **3ch**, **3ci** and **3ck**) than the reference reported.[8]

To fully demonstrate the applicability of this methodology, the **1d** and **2d** were examined(**Scheme 2**). The yield was higher than 90%. It indicates that the novel approach could be synthetically useful and suitable to prepare flusulfamide.[6]

Finally, the peroxidase(POD) activity was determined in soybean seed in response to cadmium which was one of the utmost toxic heavy metals. The POD activity of **3ae+$CdCl_2$** and **$CdCl_2$** group were 200 ± 6 U/g and 177 ± 6 U/g, while that of control was only 138 ± 4 U/g. Thus, the activity of POD was 13.0 % higher in **3ae+$CdCl_2$** group relative to the **$CdCl_2$** group(**Figure 2**). The result was similar to **ABA** treatments in walnut in cadmium stress.[13]

In summary, we have reported a facile and efficient approach to *N*-(2-nitrophenyl)benzenesulfonamides via a microwave-assisted reaction. A series of pyrabactin analogues containing nitrophenyl scaffold was obtained in excellent yields. In addition, the method was very suitable to prepare flusulfamide. Importantly, the **3ae** was similar to ABA which could enhance POD activity in response to heavy metal stress. Further efforts to examine the bioactivity of these compounds are underway and will be reported in due course.

## Acknowledgments

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## Notes

The authors declare no competing financial interest.

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**Supplementary material**

Supplementary material available: Experimental procedures, characterization data, $^{1}$H-NMR and $^{13}$C-NMR spectra for the compounds, POD activity.

## Hightlight

1. Microwave-assisted approach to nitrophenyl pyrabactin analogues;

2. Excellent yields (91%-97%) and broad substrate scope;

3. Very suitable to prepare **flusulfamide(**fungicide**)**;

4. Enhancing POD activity in response to heavy metal stress.