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Synthesis and fungicidal activity of novel 2-aryl-3-(1,3,4-thiadiazolyl)-6(8)-methyl-1,3-benzoxazines

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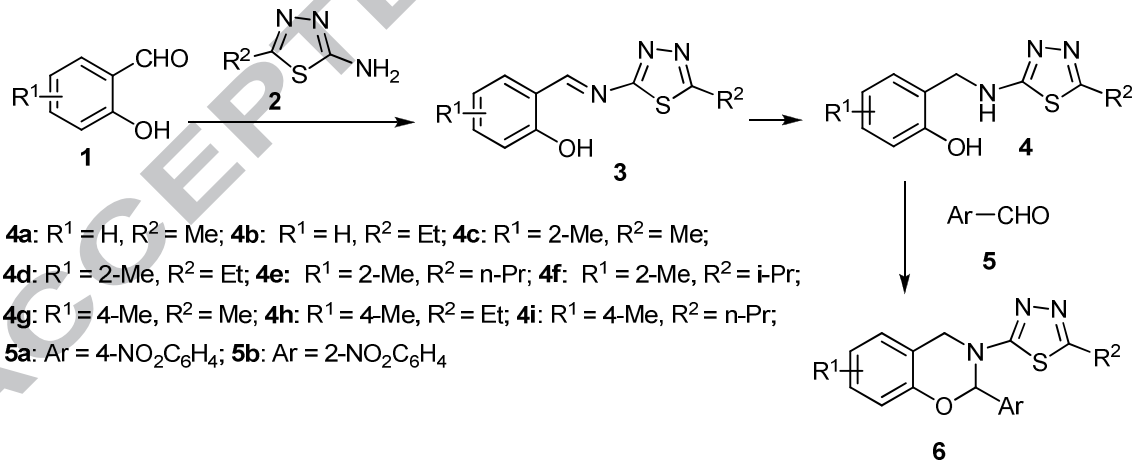
Abstract : A class of novel 2-aryl-3-(1,3,4-thiadiazolyl)-6(8)-methyl-1,3-benzoxazines was prepared by reactions of 2-methyl-6-((1,3,4-thiadiazolylamino)methyl)phenols or 4-methyl-2-((1,3,4-thiadiazolylamino)methyl)phenols and 2- or 4-nitrobenzaldehyde in the presence of TMSCl in refluxing toluene. The electron-donating methyl group on the benzene ring played an essential role on the reactivity of the substituted phenols, which was proved by DFT calculation. The fungicidal activity of the resultant products were also preliminarily evaluated, most of which displayed moderate to good fungicidal activity. Especially, compound **6f** showed 98.0% activity against *Sclerotonia sclerotiorum* and *Botrytis cinerea* at concentration of 25 μg/mL.

Keywords: (1,3,4-thiadiazolyl)-1,3-benzoxazines; synthesis; TMSCl; fungicidal activity

The importance of 1,3-benzoxazine derivatives in biological systems has received much attention because of their broad biological activities, such as analgesic[1], anticancer[2-4], antitumour[5], antiplatelet[6], antibacterial and fungicidal[7-9], antituberculosis[10], antihypertensive[11], and antithromobotic activities[12]. Particularly, some 1,3-benzoxazines are potential and orally bioavailable CCR2 and CCR5 dual antagonist[13], epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors[4], anticancer agents[14] and HCV NS5a inhibitor[15]. In addition, 2-unsubstituted 1,3-benzoxazine derivatives are important materials to prepare phenol-formaldehyde resins[16-18]. Consequently, the synthesis of new 1,3-benzoxazine derivatives with special character attracts great interests from organic chemists. Therefore,

many reports have been disclosed to access these chemicals in the past few decades[19-26]. Previously, we reported the synthesis of substituted 1,3-benoxazines by reactions of 2-aminomethylphenols and aromatic aldehydes with $SnCl_4$, $(CH_3)_3SiCl$ (TMSCl) as catalysts[8,27-29], and most of which showed good fungicidal activity. As a part of our continuous project aimed at searching for new effective fungicides, we planed to prepare a series of new 2-aryl-3-(1,3,4-thiadiazolyl)-1,3-benzoxazines. However, under the same conditions, the reactions of 2-(1,3,4-thiadiazolylaminomethyl)phenols **4a** or **4b** and aromatic aldehydes to prepare the target compounds failed. Presumably, the reactivity of 2-((1,3,4-thiadiazolylamino)methyl)phenol might be so low because of the electron-withdrawing effect of 1,3,4-thiadiazolyl group. Alternatively, we prepared a new class of 3-(1,3,4-thiadiazolyl)-1,3-benzoxazines by phase transfer catalyzed reactions of 2-((1,3,4-thiadiazolylamino)methyl)phenols and CH_2Cl_2[30]. Interestingly, we found that 2-methyl-6-((1,3,4-thiadiazolylamino)methyl)phenol formed by introducing a methyl group on the benzene ring can smoothly react with aromatic aldehydes under the aforementioned conditions, affording the desired 2-aryl-3-(1,3,4-thiadiazolyl)-6(8)-methyl-1,3-benzoxazines (Scheme 1). Thus, we present herein the results on the synthesis and fungicidal activity investigation of these compounds.



Scheme 1 Synthesis of 2-aryl-3-(1,3,4-thiadiazolyl)-6(8)-methyl-1,3-benzoxazines

According to the synthetic route as shown in Scheme 1, reactions of 2-amino-5-alkyl/aryl-1,3,4-thiadiazloes **2** with salicylaldehyde or substituted salicylaldehydes with TsOH as catalyst in refluxing anhydrous ethanol smoothly gave out the corresponding

Schiff bases **3**, which was reduced by $NaBH_4$ to 2-((1,3,4-thiadiazolylamino)methyl)phenols **4a**-**4i**[30,31]. We then tried the reaction of **4a** (R^1 = H, R^2 = Me) with 4-nitrobenzaldehyde **5a** in toluene or THF or chloroform/cyclohexane (v:v= 1: 4) with $SnCl_4$ as catalyst[27], the reaction did not occur at all (No. 1-3, Table 1), neither did the reaction with TMSCl as catalyst in toluene (No. 4)[28, 29]. It was also observed that the reaction of **4b** (R^1 = H, R^2 = Et) with **5a** in the presence of TMSCl or $(CH_3)_3SiI$ (TMSI) in toluene or chloroform/cyclohexane (v : v= 1 : 4) failed to yield the desired product (No. 5-7). Likewise, the reaction of **4a** with formaldehyde using TMSCl as catalyst in toluene did not generate the desired product (entry 8). The main reason for these failure is possibly the low reactivity of compound **4a** and **4b** caused by the electron-withdrawing nature of 1,3,4-thiadiazolyl group. Of course, the relatively low solubility of **4a** and **4b** in the mentioned solvent might also lead to the failure of the reaction. Considering the relatively higher solubility of **4a** in DMF, we then carried out the reaction of **4a** with **5a** in DMF with $SnCl_4$ as catalyst. However, this reaction still did not work (entry 9). By comparison, we considered that the solubility of compound **4a** or **4b** in solvent did not play an important role in the failure of the reaction. So, we tried to introduce an electron-donating group on the benzene ring to increase the nucleophilicity of the phenol substrate. As expected, compound **4c** with a methyl group at 2-position of the benzene ring reacted with 4-nitrobenzaldehyde **5a** in toluene in the presence of $SnCl_4$ (20 mol%) delivering the desired product **6d** in 38 % yield (No. 10), but the reaction yield decreased to 22% in 1,4-dioxane (No. 11), and even only trace of the product was obtained in mixed solvent of chloroform and cyclohexane (v : v= 1 : 4) (No 12). Therefore, we concluded that toluene was a suitable solvent for the reaction. To our exciting, the reaction yield increased to 57% with TMSCl as catalyst (No 13). But in contrast, the yield decreased to 30% and 35% with $BF_3.OEt_2$ and Sc(OTf) as catalyst, respectively (No 16, 17). Moreover, the reaction did not work at all when TsOH was employed as the catalyst (No 15). In addition, the yield decreased to 37% when the reaction time was shortened to 5 h (No 14). Clearly, the methyl group on the benzene ring played an essential role on the reaction due to its electron-donating nature, which increases the nucleophilicity of compound **4c**. At the meantime, the

introduction of methyl group also improves the solubility of compound **4c**.

Table 1 Results of the preparation of compound **6a-6n**

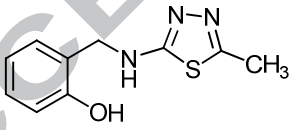
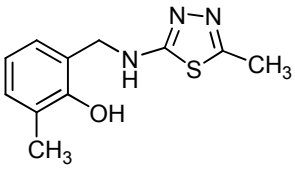
No	Conditions[a]	Product	R^1	R^2	Ar	Yield/%
1	$SnCl_4$, toluene, 110°C, 13 h	**6a**	H	Me	4'-$NO_2C_6H_4$	0
2	$SnCl_4$, THF, reflux, 13 h	**6a**	H	Me	4'-$NO_2C_6H_4$	0
3[b]	$SnCl_4$, $CHCl_3/C_6H_{12}$, 85°C, 13 h	**6a**	H	Me	4'-$NO_2C_6H_4$	0
4	TMSCl, toluene, 110°C, 13 h	**6a**	H	Me	4'-$NO_2C_6H_4$	0
5	TMSCl, toluene, 110°C, 13 h	**6b**	H	Et	4'-$NO_2C_6H_4$	0
6[b]	TMSCl, $CHCl_3/C_6H_{12}$, 85°C, 13 h	**6b**	H	Et	4'-$NO_2C_6H_4$	0
7[b]	TMSI, $CHCl_3/C_6H_{12}$, 85°C, 13 h	**6b**	H	Et	4'-$NO_2C_6H_4$	0
8[c]	TMSCl, toluene, 110°C, 13 h	**6c**	H	Me	/	0
9	$SnCl_4$, DMF, 110°C, 13 h	**6a**	H	Me	4'-$NO_2C_6H_4$	0
10	$SnCl_4$, toluene, 110°C, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	38
11	$SnCl_4$, 1,4-dioxane, reflux, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	22
12[b]	$SnCl_4$, $CHCl_3/C_6H_{12}$, 85°C, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	trace
13	TMSCl, toluene, 110°C, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	57
14	TMSCl, toluene, 110°C, 5 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	37
15	TsOH, toluene, 110°C, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	0
16	$BF_3.OEt_2$, toluene, 110°C, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	30%
17	$Sc(OTf)_3$, toluene, 110°C, 13 h	**6d**	8-Me	Me	4'-$NO_2C_6H_4$	35%
18	TMSCl, toluene, 110°C, 13 h	**6e**	8-Me	Me	2'-$NO_2C_6H_4$	54
19	TMSCl, toluene, 110°C, 13 h	**6f**	8-Me	Et	2'-$NO_2C_6H_4$	60
20	TMSCl, toluene, 110°C, 13 h	**6g**	8-Me	Et	4'-$NO_2C_6H_4$	62
21	TMSCl, toluene, 110°C, 13 h	**6h**	8-Me	*n*-Pr	2'-$NO_2C_6H_4$	59
22	TMSCl, toluene, 110°C, 13 h	**6i**	8-Me	*n*-Pr	4'-$NO_2C_6H_4$	64
23	TMSCl, toluene, 110°C, 13 h	**6j**	8-Me	*i*-Pr	2'-$NO_2C_6H_4$	58
24	TMSCl, toluene, 110°C, 13 h	**6k**	8-Me	*i*-Pr	4'-$NO_2C_6H_4$	58
25	TMSCl, toluene, 110°C, 13 h	**6l**	6-Me	Me	2'-$NO_2C_6H_4$	55

26	TMSCl, toluene, 110°C, 13 h	**6m**	6-Me	Et	4'-$NO_2C_6H_4$	57
27	TMSCl, toluene, 110°C, 13 h	**6n**	6-Me	*n*-Pr	4'-$NO_2C_6H_4$	52

[a] n (**4**): n (**5**) = 1 : 1.3. The amount of catalyst is 20 mol% based on substituted phenols **4** for all reactions. All the reactions were performed with a Dean Stark trap. [b] C_6H_{12}: cyclohexane, $CHCl_3/C_6H_{12}$ = 1:4 (v:v). [c] Formaldehyde used.

In order to explore the contribution of the methyl group on the benzene ring, we carried out DFT calculations about the Mulliken charge of some atoms (O, N (NH), S) of compounds **4a** and **4c** (with a methyl group on the benzene ring) using B3LYP method with the triple-zata basis set 6-311++G(d, p) in Gaussian03 suite of programs[32]. The results are summarized in Table 2. It is clear that the biggest change in Mulliken charge is N (NH) of compound **4c**, which is two times more than that of compound **4a**. Second, the Mulliken charge of S atom is almost two fold than that of compound **4a**. But, there is no change for O atom. So, it is true that the introduction of a methyl group increases the nucleophilicity of the NH group and in turn increases the reactivity of compound **4c**, but it does not impact effect on the O atom. In fact, the experiment results showed that introduction of a methyl group at 4-position of the benzene ring also can enhance the nucleophilicity of the NH group.

Table 2 The Mulliken charge of O, N (NH) and S atoms of compounds **4a** and **4c**

Compound	Mulliken charge /au		
	O	**N(NH)**	**S**
 **4a**	-0.263	0.010	0.019
 **4c**	-0.263	0.024	0.037

In addition, from the mechanistic point of view, it can also be understood that the yield of the reaction catalyzed by TMSCl is higher than those of the reactions catalyzed by $SnCl_4$

or by TsOH. Although TsOH can activate the carbonyl group of the aromatic aldehyde, it also lowers the nucleophilicity of the nitrogen atom by protonating the nitrogen atom of the aminomethylphenol. Hence, the reaction did not work[27]. In contrast, because of their oxophilicity TMSCl and $SnCl_4$ are more liable to coordinate with the oxygen atom of the carbonyl group of the aromatic aldehyde compared to the nitrogen atom, and increase the reactivity of aldehydes and lead to higher yield. Moreover, due to its relatively higher oxophilicity than $SnCl_4$, TMSCl is easier to coordinate with the oxygen atom of the carbonyl group and finally lead to much higher yield.

Under the above optimized conditions, compounds **6e**-**6n** were also prepared in 52-64% yields (see Table 1). Generally, the yields mainly depended on the position of the nitro group on the benzene ring connected with the nitrogen atom within the benzoxazine ring in the order of *para* > *ortho* (No 13 *vs* 15, No 17 *vs* 16, No 19 *vs* 18) possibly because of the bigger steric hindrance present in the latter case. Secondly, the position of the methyl group on the benzene ring impacted influence on the yield in the order of 8-position > 6-position (No 17 *vs* 23, No 19 *vs* 24). When the methyl group is at 8-position, the nitro group at the 4′-position, alkyl groups on the 1,3,4-thiadiazole ring affected the yields abiding the following order of *n*-Pr > Et > Me (No 19 *vs* 17 *vs* 13), which corresponds to their electron-donating ability[33].

The structures of all the target products were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. All compounds exhibit characteristic signals appropriately (see experimental section). This can be illustrated with compound **6e**. In the IR spectra, an absorption at 3024 cm^{-1} relates to the stretching vibration of C–H bond of the benzene ring, and 1621 cm^{-1} for ν C=N bond, 1609 cm^{-1} for ν C=C bond, signal at 1366 cm^{-1} indicates the presence of the NO_2 group. In ^{1}H NMR, two singlets at 2.39 and 2.29 ppm correspond to two CH_3 protons. The proton's chemical shift of OCHN moiety of the benzoxazine ring occurs at 7.05 ppm. The downfield shift of this proton is due to the strong electronegativity of the nitrogen and oxygen atoms. Particularly, the NCH_2 proton absorbs at 4.99 and 4.15 ppm as two doublets instead of a singlet. This fact strongly suggests the formation of the benzoxazine ring, otherwise the NCH_2 proton should appear as singlet. In ^{13}C NMR, the carbons of $2CH_3$

group show signals at 15.76 and 15.57 ppm, signal at 45.70 for CH_2N and signal at 85.54 for OCHN.

According to SOP procedure developed by Hunan Branch of National Pesticide R&D South Center of China[34], fungicidal activity of the prepared compounds **6d–6n** against *Sclerotonia sclerotiorum, Gibberella zeae*, *Phytophythora capsici*, *Alternaria alternate*, *Botrytis cinerea* and *Rhizoctorzia solani* were evaluated using the mycelium growth rate test at concentration of 25 μg/mL. The fungicidal activity was expressed as inhibition rate (%) and summarized in Table 3. In general, most of the compounds displayed moderate to good activity. Compound **6f** showed 98.0% activity against *Sclerotonia sclerotiorum* and *Botrytis cinerea*, and 61.8% activity against *Gibberella zeae*. This meant that compound **6f** had broad fungicidal activity. Compound **6g** exhibited 70.0% activity against *Alternaria alternate*. When methyl group locates at 8-position and NO_2 group at 2′-position, the alkyl group on 1,3,4-thiadiazole ring affects the activity against *Sclerotonia sclerotiorum* and *Botrytis cinerea* following the order of Et > Me > *i*-Pr > *n*-Pr. There was no other apparent structure-activity relationship.

Table 3 Fungicidal activity (inhibitory rate /%) of products **6d-6n***

No	Prod.	*S. sclerotiorum*	*G. zeae*	*P. capsici*	*A. alternata*	*B. cinerea*	*R. solani*
1	**6d**	52.0	20.6	18.6	26.0	43.8	0
2	**6e**	52.0	20.6	18.6	26.0	58.4	0
3	**6f**	98.0	61.8	56.0	26.0	98.0	0
4	**6g**	0	0	0	70.0	46.0	0
5	**6h**	0	20.6	0	26.0	0	0
6	**6i**	26.0	0	18.6	26.0	29.2	0
7	**6j**	23.1	0	25.9	0	8.8	31.0
8	**6k**	21.9	17.3	0	12.3	13.6	0
9	**6l**	0	18.7	0	12.7	18.3	0
10	**6m**	34.6	0	48.1	0	14.7	38.1
11	**6n**	21.9	9.9	0	0	13.6	0

*: Activity grade: A, inhibitory rate ≥ 90%; B, 70% ≤ inhibitory rate ＜ 90%; C, 50% ≤ inhibitory rate ＜ 70%; D, ＜ 70%.

In summary, we have designed a kind of relatively high nucleophilicity 2-methyl-6-((1,3,4-thiadiazolylamino)methyl)phenols and 4-methyl-2-((1,3,4-thiadiazolylamino)-methyl)phenols compared with 2-((1,3,4-thiadiazolylamino)methyl)phenols by introducing electron-donating methyl group on the benzene ring, and thereby a series of novel 2-aryl-3-(1,3,4-thiadiazolyl)-6(8)-methyl-1,3-benzoxazines were prepared by reactions of the above mentioned methyl substituted (1,3,4-thiadiazolylamino)methylphenols with 2- or 4-nitrobenzaldehyde in the presence of TMSCl. Theory calculations showed that the methyl group on the benzene ring played an important role on the increasing reactivity of the substituted phenols. The fungicidal activity assay showed that most of the tested compounds displayed moderate to good fungicidal activity**.** Especially, compound **6f** showed 98.0% activity against *Sclerotonia sclerotiorum* and *Botrytis cinerea* at concentration of 25 μg/mL.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://.....

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Graphic abstract:

Synthesis and fungicidal activity of novel 2-aryl-3-(1,3,4-thiadiazolyl)-6(8)-methyl-1,3-benzoxazines

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