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Synthesis of 1,2,4-Triazine Compounds via Two Distinct One-Pot Domino Protocols

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1,2,4-Triazine compounds were synthesized via two coupled domino strategies employing simple and readily available arylacetaldehydes/arylethyl alcohols as starting materials. The reactions proceed smoothly in one pot with the advantages of high functional groups tolerance, being transition metal-free, and employing environmentally friendly oxidants such as I_2 and IBX, providing access to the desired 1,2,4-triazine products in excellent yields.

Keywords triazines, aldehydes, alcohols, *N*-aminobenzamidines, domino

Introduction

The synthesis of 1,2,4-triazines has garnered significant attention due to the potential applications of 1,2,4-triazines in organic materials and medicinal chemistry. The 1,2,4-triazine motif is frequently found in natural products and bioactive molecules exhibiting antihypertensive,[1] analgesic,[2] anti-inflammatory,[3] antimalarial,[4] anticancer,[5] anticonvulsant[6] and antiepileptic properties.[7] Some common methods for assembling 1,2,4-triazines include direct condensation of *N*-aminobenzamidines and 1,2-dicarbonyl compounds to offer 3,5-disubstituted-1,2,4-triazines,[8] or replacing *N*-aminobenzamidines with ammonium acetate and benzhydrazide to construct 3,5,6-trisubstituted-1,2,4-triazine.[9] However, these current approaches require an excess amount of acid or base, toxic oxidants, and complex synthetic precursors. Consequently, developing efficient protocols involving simple substrates and mild conditions to obtain 1,2,4-triazine derivatives remains a synthetic challenge.

Recently, domino reactions have gained increasing interest in synthetic organic chemistry due to the high efficiency and low consumption.[10] Previously, our group demonstrated the power and potential of domino-based strategy to construct triazoles, imidazoles, *etc*.[11] Inspired by the above strategy, we have designed two simple, metal-free, domino pathways to construct 1,2,4-triazine compounds using simple and readily available aryl acetaldehydes and aryl ethyl alcohols.

Experimental

Typical procedure for the reaction between hyacinthins/2-phenylethanols and *N*-aminobenzamidines: synthesis of 3,5-diphenyl-1,2,4-triazine (3aa)[12]

Procedure A The reaction was performed in a round-bottom sidearm flask (10 mL). Compound **2** (0.2 mmol), I_2 (0.24 mmol) and DMSO (2 mL) were added to the 10 mL-flask containing a magnetic stirring bar under air. After stirring for 2 h at 100 ℃, **1** (0.2 mmol) was introduced into the catalyst system and the reaction was stirred for an additional hour. After cooling to room temperature, the mixture was washed with 20 mL water and extracted with ethyl acetate (10 mL×3). The organic-layers were combined and concentrated under reduced pressure to obtain the crude product, which was further purified by silica gel chromatography [*V*(petroleum)/*V*(ethyl acetate)=5/1 as eluent] to obtain product **3**.

Procedure B The reaction was performed in a round-bottom sidearm flask (10 mL). Compound **4** (0.24 mmol), IBX (0.26 mmol), and DMSO (2 mL) were added to the flask containing a magnetic stirring bar under air. After stirring for 2 h at 100 ℃, **1** (0.2 mmol) was added into the catalyst system and the reation was stirred for an additional hour. The following processing method was referred to procedure A.

Results and Discussion

To develop an iodine-mediated domino strategy for construction of 3,5-disubstituted-1,2,4-triazine, we first began optimizing the reaction employing *N*-aminobenzamidine and 2-phenylacetaldehyde. I_2 and CuO af-

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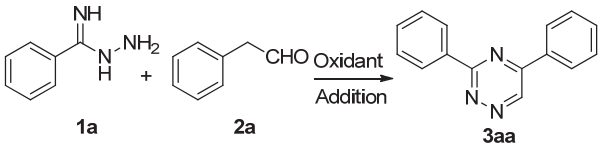
forded the desired product in a low yield at 100 ℃ in DMSO (Table 1, entry 1). To improve the reactivity, other additives such as TBHP, KI, NIS and IBX, were screened, and NIS furnished superior yields (Table 1, entries 2—5). Surprisingly, during the control experiments, using 1.2 equiv. I_2 alone afforded the desired product in a good yield of 86% in the absence of additives (Table 1, entry 6). Replacing I_2 with other oxidants, such as NIS, CuI, H_2O_2, failed to improve reaction yields (Table 1, entries 7—9). Further optimization also showed that altering key operating parameters, such as increasing the amount of iodine, or adjusting the temperature, had a negligible effect on the yields (Table 1, entries 10—13). Notably, the production of **3aa** did not decrease under nitrogen atmosphere, which indicated that oxygen did not participate in the reaction (Table 1, entry 14). Next, different types of solvents such as toluene and DMF were also investigated, and DMSO was the most efficient media for the domino reaction (Table 1, entries 15—16). A complete optimization identified 1.2 equiv. of I_2 at 100 ℃ in DMSO as the optimal reaction conditions (Table 1, entry 6).

Table 1 Reaction optimization for the domino reaction between hyacinthin and benzimidohydrazide



1a **2a** **3aa**

Entry	Oxidant/equiv.	Additive/equiv.	Solvent	Yield/%
1	I_2 (0.1)	CuO (1.0)	DMSO	34
2	I_2 (0.1)	KI (1.0)	DMSO	72
3	I_2 (0.1)	NIS (1.0)	DMSO	82
4	I_2 (0.1)	IBX (1.0)	DMSO	74
5	I_2 (0.1)	TBHP (1.0)	DMSO	67
6	I_2 (1.2)	—	DMSO	86
7	CuI (1.2)	—	DMSO	30
8	IBX (1.2)	—	DMSO	84
9	NIS (1.2)	—	DMSO	83
10[b]	I_2 (1.2)	—	DMSO	81
11[c]	I_2 (1.2)	—	DMSO	85
12	I_2 (1.3)	—	DMSO	81
13	I_2 (1.1)	—	DMSO	81
14[d]	I_2 (1.2)	—	DMSO	86
15	I_2 (1.2)	—	DMF	30
16	I_2 (1.2)	—	toluene	trace

[a] Reaction conditions: **2a** (0.24 mmol), oxidant (0.24 mmol), and additive were heated at 100 ℃ for 2 h, then **1a** (0.2 mmol) was added in DMSO for another 1 h. [b] Reaction conditions: temperature was 90 ℃. [c] Reaction conditions: temperature was 110 ℃. [d] Reaction conditions: under nitrogen atmosphere.

Using the optimized conditions, we explored the scope of the reaction employing a diversity of both aryl acetaldehydes and *N*-aminoarylamidines. First, the substrate scope with respect to *N*-aminoarylamidines with various aryl substituents was examined (Scheme 1). *N*-Aminoarylamidines bearing electron-donating groups were well-tolerated, affording the desired products in satisfactory yields (**3ab**—**3ad**). Electrophilic functional groups, such as bromine, chlorine and fluorine, were also compatible in the reaction to furnish the corresponding halogenated products in 55%—90% yields (**3ae** — **3ag**). Notably, *N*-aminoarylamidines bearing electron-donating moieties showed superior reactivity and produced higher yields than *N*-aminoarylamidines bearing electron-withdrawing substituents.

The reaction scope was also evaluated with respect to coupling partner **2** (Scheme 1). The electronic and steric properties of the aryl acetaldehydes exhibited a pronounced effect on the reactions. For example, electron-rich derivatives containing methyl, ethyl and methoxy functional groups, afforded the corresponding products in good yields (**3ba**—**3bg**); however, electron-deficient substrates, such as **3bh** and **3bi**, were less reactive in the reactions. *N*-Aminobenzamidine with substituents in the *para*-position provided the higher yields than *ortho*-substituted reactants (**3ba** and **3bc**, **3bd** and **3bg**), which was a result of steric interactions possibly. These results revealed that the steric hindrance from the *ortho*-position of phenylacetaldehydes showed an adverse effect in the domino reaction.

We subsequently explored the feasibility of the reaction using *N*-aminobenzamidine **1a** and phenethyl alcohol **4a** as model substrates. The desired product **3aa** was isolated in a 40% yield by the use of above-mentioned I_2 as the catalyst in DMSO at 100 ℃ (Table 2, entry 1). To improve the yield, various oxidants were screened including MnO_2, CuO, SeO_2, $KMnO_4$, NIS and IBX (Table 2, entries 2—7). To our surprise, a 76% yield of product was obtained using 1.2 equiv. of IBX as an oxidant. We then investigated the effect of IBX loading on reactivity. For example, the yield of **3aa** was improved by increasing the amount of IBX. Using 1.3 equiv. of IBX, 84% yield of the desired product was observed; however, higher loading failed to further improve yields (Table 2, entries 8—9). Furthermore, the effect of temperature was examined, and it was found that lower temperature produced lower yields for **3aa** and that no yield change was observed for higher temperature such as 110 ℃ (Table 2, entries 10—11). Subsequently, only 30% of **3aa** was detected in the presence of nitrogen, which indicated oxygen was crucial to the reaction (Table 2, entry 12). Finally, we explored other polar and non-polar solvents, such as DMF, toluene and dioxane; however, no improvement in yields was observed (Table 2, entries 13—15).

Considering the easier availability of alcohols compared to the corresponding aldehydes, the reaction of phenyl ethyl alcohols with benzimidohydrazides was investigated using optimized reaction conditions and the

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Scheme 1 Reactions scopes for the domino reaction between substituted benzimidohydrazides and various benzaldehydes

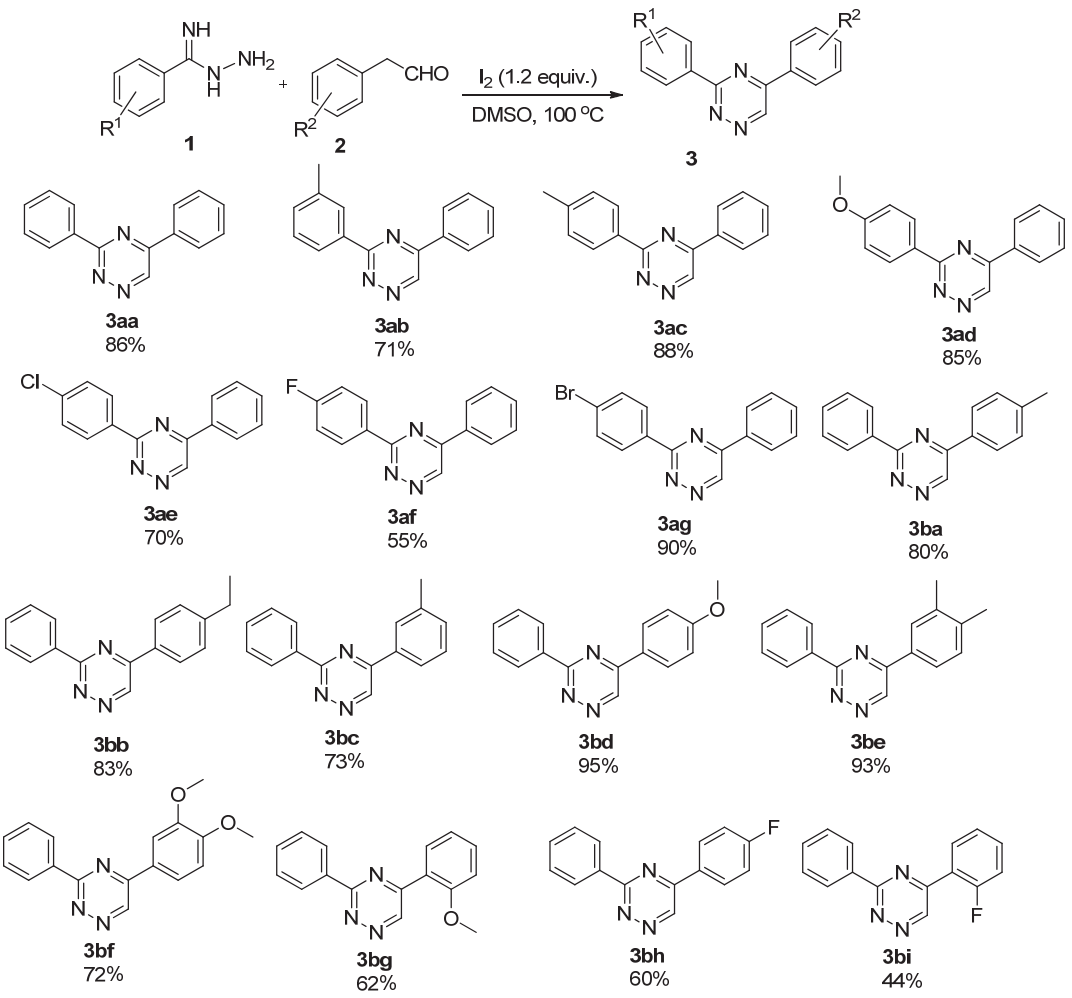
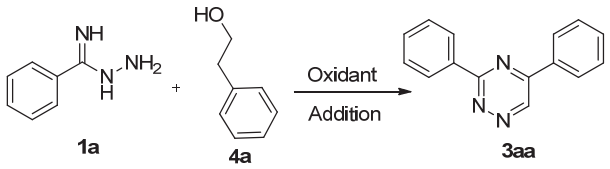


Table 2 Optimization of reaction conditions of phenethyl alcohol and benzimidohydrazide



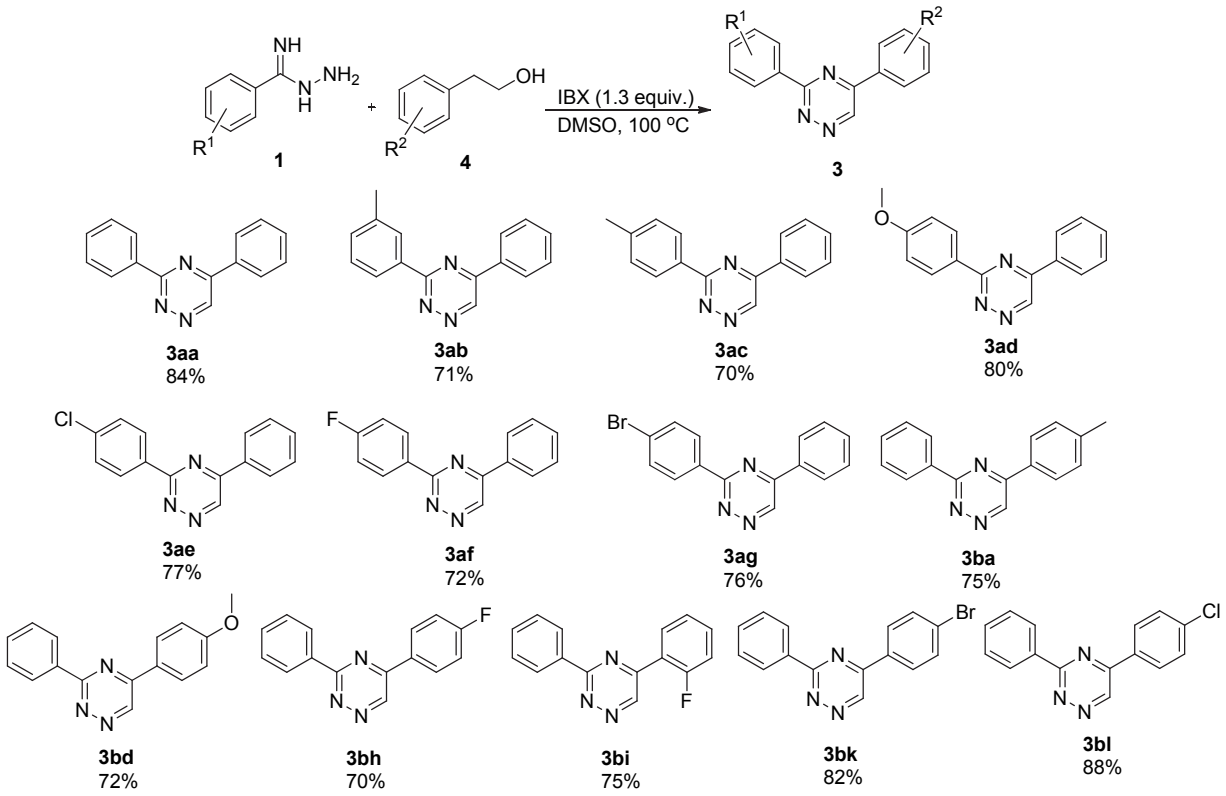
Entry	Oxidant/equiv.	Solvent	Yield/%
1	I_2 (1.2)	DMSO	40
2	MnO_2 (1.2)	DMSO	trace
3	CuO (1.2)	DMSO	trace
4	SeO_2 (1.2)	DMSO	40
5	$KMnO_4$ (1.2)	DMSO	trace
6	NIS (1.2)	DMSO	40
7	IBX (1.2)	DMSO	76
8	IBX (1.3)	DMSO	84
9	IBX (1.4)	DMSO	81
10[b]	IBX (1.3)	DMSO	70
11[c]	IBX (1.3)	DMSO	84
12[d]	IBX (1.3)	DMSO	30
13	IBX (1.3)	DMF	17
14	IBX (1.3)	toluene	trance
15	IBX (1.3)	dioxane	19

[a] Reaction conditions: **4a** (0.24 mmol) and oxidant (0.26 mmol) were heated at 100 ℃ in solvent (2 mL) for 2 h, then **1a** (0.2 mmol) was added for another 1 h. [b] Reaction conditions: temperature was 90 ℃. [c] Reaction conditions: temperature was 110 ℃. [d] Reaction conditions: under nitrogen atmosphere.

results are presented in Scheme 2. Much to our delight, a wide range of functional groups for benzimidohydrazide partner furnished the desired products in moderate to good yields, which include methyl-, methoxyl-, chloro-, fluoro-, bromo- groups, *etc.* (Scheme 2, **3aa**—**3ag**). Similarly, higher yields were obtained for 4-substitued triazines such as **3ad** containing electron-rich groups (Scheme 2, **3ad**) compared to electron-deficient substrates (Scheme 2, **3ae**—**3ag**).

To further explore the generality and scope of this protocol, a variety of the substitution patterns on the

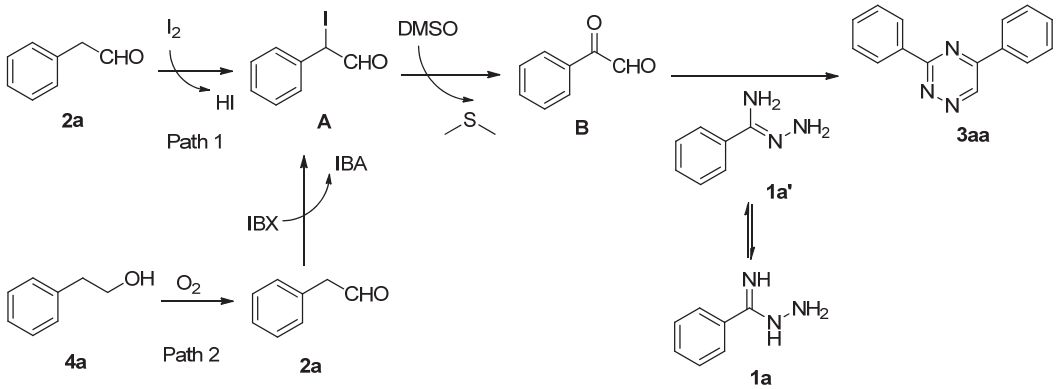
Scheme 2 Reactions of substituted benzimidohydrazides with various phenyl ethanol



aryl ethyl alcohols were also investigated. As summarized in Scheme 2, various aryl ethyl alcohols bearing both electron-donating and electron-withdrawing groups smoothly underwent the cyclization reaction with **1**, delivering a series of triazines in moderate to good yields. Electron-donating substituents provided desired products in the yields of 72%—75% (Scheme 2, **3ba**, **3bd**), which were lower than those of electron-withdrawing substitution (Scheme 2, **3bh**—**3bl**). Steric hindrance from the 2-position of phenyl ethyl alcohols produced a slightly lower yield.

Inspired by the previous similar reactions,[13] a possible reaction mechanism for this domino reaction is proposed in Scheme 3. Initially, 2-phenylacetaldehyde (**2a**) is iodinated to 2-iodo-2-phenylacetaldehyde **A** in the presence of I_2[14] (path 1). Correspondingly, phenethyl alcohol **4a** is first oxidized to hyacinthin by oxygen[15] and then is converted into **A** in the presence of IBX[16] (path 2). Subsequently, **A** is further converted into 2-oxo-2-phenylacetaldehyde **B** through a Komblum oxidation in DMSO.[17] To the best of our knowledge, *N*-aminobenzamidine **1a** and (*Z*)-*N*'-aminobenzamidine **1a'** can be converted into each other. Then, **B** is reacted with **1a'** via a condensation reaction affording the desired products 3,5-diphenyl-1,2,4-triazine (**3aa**).[18]

Scheme 3 Proposed mechanism



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Conclusions

In conclusion, we have developed a novel method for the synthesis of 3,5-diaryl-1,2,4-triazines using simple and readily available 2-arylacetaldehyde and 2-arylethanols with *N*-aminobenzamidine in the presence of iodine sources. Notably, for both the I_2 and IBX systems, no transition-metals are required, the reaction is environmentally friendly and excellent yields were obtained. In addition, the protocols eliminate the need to prepare 1,2-dicarbonyl precursors. Further studies on the application of this strategy will be reported in due course.

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