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Synthesis of 1,2,4-Triazine Derivatives via [4+2] Domino Annulations Reactions in Onepot

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The simple and efficient [4+2] domino annulation reactions have developed for the synthesis 1,2,4-triazine derivatives. The strategies exhibit high performance with moderate to high yields by using easily available materials including ketones, aldehydes, alkynes, secondary alcohols and alkenes, and represent a powerful tool for the formation of potentially biological active derivatives.

Introduction

The 1,2,4-triazine moiety represents an important class of heterocycles, and the 1,2,4-triazine derivatives have been reported to possess a broad spectrum of biological activities including anti-convulsant,[1a] anti-cancer,[1b] anti-cytokine,[1c] anti-tumor,[1d] anti-viral,[1e] anti-hypertensive[1f] and anti-malarial.[1g] In addition, some important metal coordinating ligands contain 1,2,4-triazine skeleton.[2] These classes of compounds are significant and useful, however, the systemic, operable and versatile strategies are shortage to construct 1,2,4-triazine skeleton for meeting the demand of synthetic chemistry. Among the known methods for 1,2,4-triazines, the reactions of amidrazones and 1,2-diketone compounds are the most available protocols to form 3,5-disubstituted or 3,5,6-trisubstituted 1,2,4-trizaines.[3] Otherwise, the multi-component reactions (MCR) of hydrazides, dicarbonyl compounds and ammonium acetate also a pathway to synthesize 3,5-disubstituted 1,2,4-trizaines.[4] Nevertheless, it is remained considerable scope for improvement, such as availability of the starting materials, tedious process and poor tolerance.

In past years, our group had reported to obtain imidazole skeleton by employing amidines and ketone / nitroolefin.[5] To the best of our knowledge, the units of ketone, acetaldehyde, alkyne and alkene are useful building blocks providing two carbon atoms to construct five or six member rings.[6] Based on our previous works, we shifted our attention to develop six member nitrogen heterocyclic with simple operation, high utilization of atoms and good yields. Herein, we report the SeO_2 or iodine sources catalyzed [4+2] domino annulation reactions for making 1,2,4-triazine derivatives without the addition of transition metal catalyst, and the works systematically study the reactions of ketones / alkynes and amidrazones[7] to synthesize 1,2,4-triazine derivatives. These strategies may be an highly efficient alternative to the synthesis of 1,2,4-triazine compounds in pharmaceutical chemistry and other fields.

Results and discussion

Initially, we examined the reaction of acetophenone **1a** and benzimidohydrazide **2a** as a model reaction, as shown in Table 1. A mixture of **1a** (0.2 mmol), **2a** (0.2 mmol), CuO (0.24mmol) and I_2 (0.24mmol) were carried out in DMSO under air at 110 ^oC for 2 h, and the desired product (**3aa**) was isolated in 14% yield (Table 1, entry 1), the structure was identified by X-ray (Figure 1). Encouraged by this result, we continued to explore other iodine sources, but only inferior results were obtained (Table 1, entries 2-4). Noteworthily, when the reaction was completed, we found that the byproduct of 1,2,4-triazole was formed by TLC, and this side reaction had been documented in previous reports.[8] In order to avoid the loss of **2a**, we, then, introduced **2a** into the reaction system after the acetophenone reacted for 2 hours in presence of I_2. To our delight, a 60% yield of **3aa** was obtained (Table 1, entry 5). Other oxidants, such as MnO_2, CuO and SeO_2, were also evaluated, and the SeO_2 showed a better catalytic activity (Table 1, entries 6-8). When the reaction time was prolonged to 4 hours before **2a** added, the yield was improved to 80% (Table 1, entry 9). In the screening of solvents including DMF, toluene, dioxane and H_2O, and no better results were obtained (Table 1, entries 10-13).

Table 1 The reaction conditions optimization of **acetophenone** and **benzimidohydrazide** [a]

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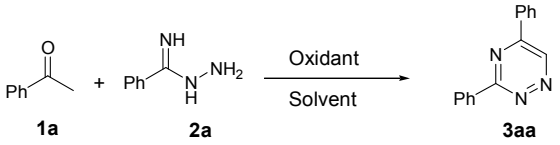


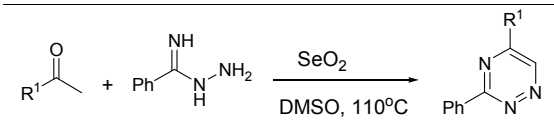
1a 2a 3aa

Entry	Oxidant	Solvent	Yield [b]
1	CuO /I_2	DMSO	14
2	I_2	DMSO	27
3	I_2/TBHP [c]	DMSO	24
4	TBAI/TBHP [c]	DMSO	12
5	I_2 [d]	DMSO	60
6	MnO_2 [d]	DMSO	0
7	CuO [d]	DMSO	0
8	SeO_2 [d]	DMSO	71
9	SeO_2 [e]	DMSO	80
10	SeO_2 [e]	DMF	trace
11	SeO_2 [e]	Tolene	12
12	SeO_2 [e]	Dioxane	0
13	SeO_2 [e]	H_2O	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), oxidant (1.2 equiv.), solvent (2 mL), 110 °C, under air. [b] Isolated yield based on **1a**. [c] Iodine source (0.1 equiv.), TBHP (6 equiv.). [d] **2a** was added after reaction initiated for 2 hours. [e] **2a** was added after reaction initiated for 4 hours.

With the optimized conditions in hand, the scope of this domino annulation reaction was expanded. A variety of different substituted ketones **1** were examined under optimal conditions, and the results were summarized in Table 2. The reaction tolerated well with both electron-withdrawing and electron-donating groups on the aromatic ring, and the expected products were obtained in moderate to high yields. Generally, the substrates with electron rich groups provided better yields than the ones with electron deficient groups (Table 2, entries 1-10). Furthermore, the steric effect had no remarkable influence on the yields (Table 2, entries 1-6), and the substrates with steric bulk groups on the ketones, such as 1-(naphthalen-1-yl)ethanone (**1m**) and 1-([1,1'-biphenyl]-4-yl)ethanone (**1n**), and with heterocycle, such as 1-(furan-2-yl)ethanone (**1o**), were well tolerated, affording good yields in 75-78% (Table 2, entries 12-14). Somewhat disappointingly, when the aliphatic ketones and the substrates with amino were performed in the catalyst system, the desired products were not found (Table 2, entries 11 and 15).

Table 2 The scope investigation of arylketones with **2a** [a]



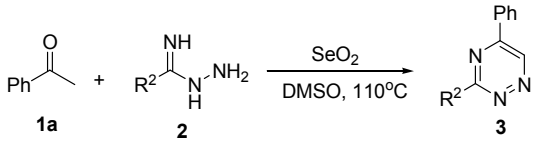
1a 2a 3aa

Entry	R^1	Product	Yield [b]
1	4-MeO-C_6H_4, **1b**	**3ab**	80
2	3-MeO-C_6H_4, **1c**	**3ac**	77
3	2-MeO-C_6H_4, **1d**	**3ad**	89
4	4-Me-C_6H_4, **1e**	**3ae**	77
5	3-Me-C_6H_4, **1f**	**3af**	85
6	2-Me-C_6H_4, **1g**	**3ag**	73
7	3,4-MeO-C_6H_4, **1h**	**3ah**	75
8	4-F-C_6H_4, **1i**	**3ai**	76
9	4-Cl-C_6H_4, **1j**	**3aj**	72
10	3,4-Cl-C_6H_4, **1k**	**3ak**	69
11	4-NH_2-C_6H_4, **1l**	**3al**	0
12	1-Nap, **1m**	**3am**	75
13	4- C_6H_5-C_6H_4, **1n**	**3an**	76
14	2-furan, **1o**	**3ao**	78
15	Propyl, **1p**	**3ap**	0

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), SeO_2 (0.24 mmol), DMSO (2 mL), 110 °C , **2a** was added after reaction initiated for 4 hours. [b] Isolated yield based on **1**.

To further investigate the reaction scope, various amidrazones (**2b**-**h**) were employed to react with acetophenone (**1a**), as shown in Table 3. Those transformations displayed good functional groups tolerance including methyl, methoxyl, fluoro, chloro and bromo, and the amidrazones with electron-donating or electron-withdrawing groups had no remarkable difference on yields and gave the corresponding 1,2,4-triazines in good yields (Table 3, entries 1–7). Notably, picolinimidohydrazide (**2h**) was also proceeded smoothly and produced yield in 58% (Table 3, entry 7).

Table 3 The scope investigation of amidrazones with **1a** [a]



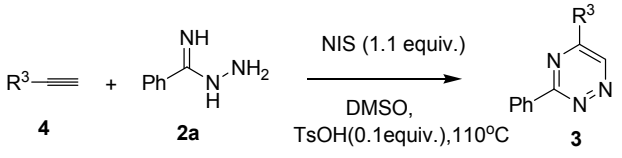
1a 2 3

Entry	R^2	Product	Yield [b]
1	4-Me- C_6H_4, **2b**	**3ba**	85
2	3-Me- C_6H_4, **2c**	**3bb**	79
3	4-MeO- C_6H_4, **2d**	**3bc**	88
4	4-F- C_6H_4, **2e**	**3bd**	75
5	4-Cl- C_6H_4, **2f**	**3be**	74
6	4-Br- C_6H_4, **2g**	**3bf**	82
7	2-Py, **2h**	**3bg**	58

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), SeO_2 (0.24 mmol), DMSO (2 mL), 110 °C, **2** was added after reaction initiated for 4 hours. [b] Isolated yield based on **1a**.

Inspired by the above results, we shifted our attention to explore the reaction feasibility of alkynes and amidrazones. The reaction conditions were also investigated (For details see supporting information), and it was found that the reactions of **4a** (0.4 mmol) and **2a** (0.2 mmol) in presence of N-iodosuccinimide (NIS) (0.24 mmol) and p-toluenesulfonic acid (TsOH, 0.02 mmol) in DMSO (2 mL) furnished desired product yield in 62% at 110 °C. Then, the substrate scopes were investigated in details. Aryl-alkynes with different functional groups, such as methoxyl, methyl, fluoro, chloro, bromo and phenyl, all could provide the corresponding products in good yields ranging from 51 to 82% (Table 4, entries 1-9). Notably, the substrates with electron-donating groups tended to obtain better yields, and the steric effect was not critical for those transformations (Table 4, entries 7 and 9).

Table 4 The scope investigation of arylalkynes with **2a** [a]



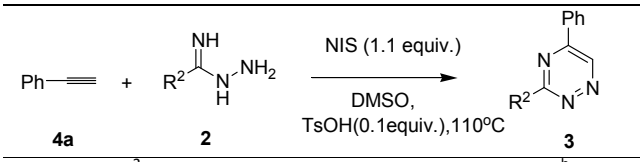
4 **2a** **3**

Entry	R^3	Product	Yield [b]
1	4-MeO-C_6H_4, **4b**	**3ab**	82
2	3-MeO-C_6H_4, **4c**	**3ac**	77
3	4-Me-C_6H_4, **4e**	**3ae**	59
4	3-Me-C_6H_4, **4f**	**3af**	67
5	4-F-C_6H_4, **4i**	**3ai**	66
6	4-Br-C_6H_4, **4r**	**3ar**	57
7	4-Cl-C_6H_4, **4j**	**3aj**	60
8	3-F-C_6H_4, **4s**	**3as**	51
9	2-Cl-C_6H_4, **4t**	**3at**	58
10	4-C_6H_5-C_6H_4, **4n**	**3an**	79

[a] Reaction conditions: **4** (0.4 mmol), **2a** (0.2 mmol), NIS (0.24 mmol), TsOH (0.02 mmol), DMSO (2 mL), 110 °C, **2a** was added after reaction initiated for 4 hours. [b] Isolated yield based on **2a**.

With regards to the scope and generality of amidrazones, different amidrazones were employed to react with ethynylbenzene (**4a**). As expected, the reactions of amidrazone substrates **2a**-**h** and **4a** proceeded smoothly to give the corresponding coupling products **3ba**–**3bg** in moderate to good yields (Table 5, entries 1-7, 65–79%). Regardless of the electronic nature, the functional groups had no remarkable impact on the yields. It was noteworthy that the picolinimidohydrazide (**2h**) was also afforded the desired products in 64 % (Table 5, entry 7).

Table 5 The scope investigation of amidrazones with **4a** [a]



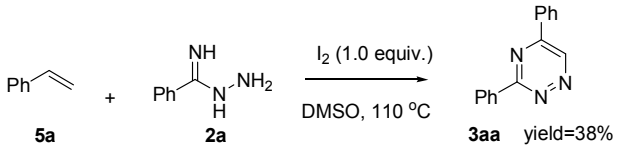
4a **2** **3**

Entry	R^2	Product	Yield [b]
1	4-Me- C_6H_4, **2b**	**3ba**	78
2	3-Me- C_6H_4, **2c**	**3bb**	77
3	4-MeO-ph, **2d**	**3bc**	71
4	4-F- C_6H_4, **2e**	**3bd**	65
5	4-Cl- C_6H_4, **2f**	**3be**	79
6	4-Br- C_6H_4, **2g**	**3bf**	77
7	2-Py, **2h**	**3bg**	64

[a] Reaction conditions: **4a** (0.4 mmol), **2** (0.2 mmol), NIS (0.24 mmol), TsOH (0.02 mmol), DMSO (2 mL), 110 °C, **2** was added after reaction initiated for 4 hours. [b] Isolated yield based on **2**.

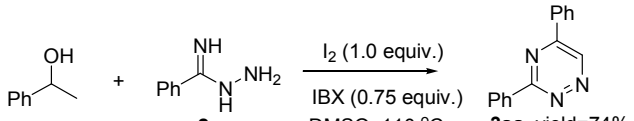
To get more insight into the diversity synthetic strategies for 1,2,4-triazine derivatives, the building blocks including styrene (**5a**), 1-phenylethanol (**6a**), 1,2-diphenylethyne (**7a**) and 2-phenylacetaldehyde (**8a**) were introduced into this class of reactions. The styrene (**5a**) and **2a** were carried out in the presence of iodine (1 equiv.) and DMSO (2ml) at 110 °C, and the desired product **3aa** was isolated in 38% (Scheme 1a). Moreover, 1-phenylethanol (**6a**) and 1,2-diphenylethyne (**7a**) were reacted with **2a** in presence of iodine (1 equiv.), 2-iodoxybenzoic acid (IBX) (0.75 equiv.) and DMSO (2 ml) at 110 °C, and we were pleased to obtain the corresponding products **3aa** and **8aa** in 74% and 51% yields, respectively. To our surprise, 2-phenylacetaldehyde (**8a**) was also compatible to the reaction to the desired product **3aa** in 53%. These reactions are attractive, making a range of interesting 1,2,4-triazine scaffolds through the useful, efficient, simple procedure by using easily available starting materials.

a) The reaction property of styrene.



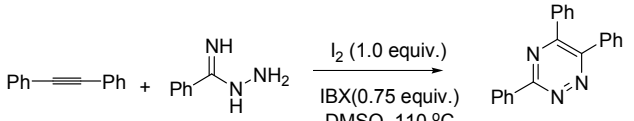
5a **2a** **3aa** yield=38%

b) The reaction property of 1-phenylethanol.



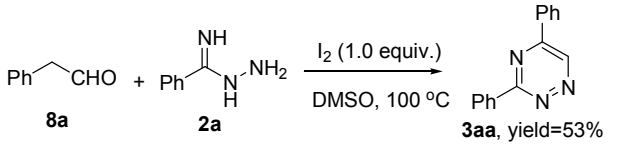
6a **2a** **3aa** yield=74%

c) The reaction property of 1,2-diphenylethyne.



7a **2a** **8aa** yield=51%

d) The reaction property of phenylacetaldehyde.



8a **2a** **3aa**, yield=53%

Scheme 1 The alternative transformations to construct 1,2,4-triazine derivatives.

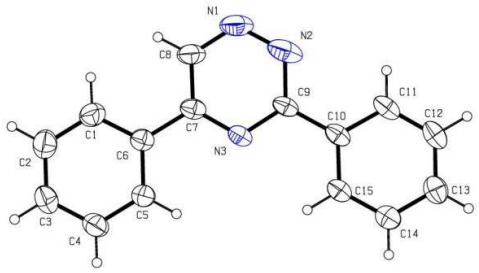
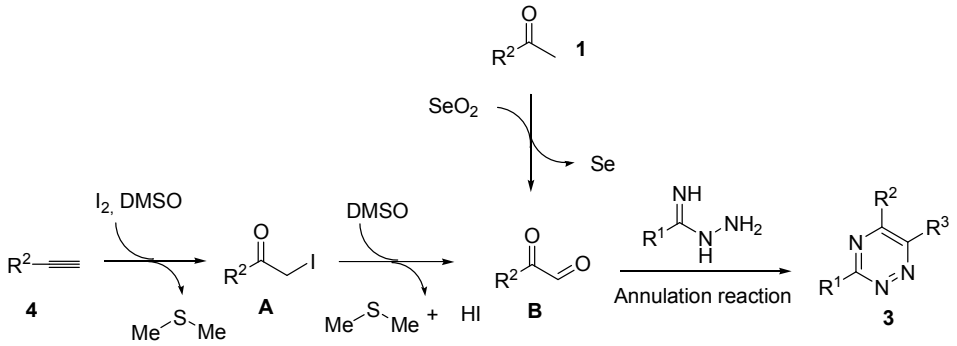


Figure 1 The X-ray crystal structure of **3aa**.

For the probable mechanism of those kinds of reactions, some works had reported that the starting materials, such as arylketones[9] and arynes,[10] converted into corresponding diketones **B**. Similarly, the arylacetaldehydes, 1-Arylethanol[11] and alkenes[12] might follow a parallel procedure. Subsequently, the diketones combined with amidrazones via [4+2] annulation reaction to obtain the final 1,2,4-triazines products **3** (Scheme 2). [13]



Scheme 2 Plausible reaction pathway.

Conclusions

In conclusion, we have reported effective and simple strategies to synthesize 1,2,4-triazine derivatives through [4+2] domino annulations in onepot. These transformations employ SeO_2 or iodine sources as oxidant without using transition metal catalyst and show good tolerance with moderate to high yield. Moreover, the reactions can access important 1,2,4-triazine skeleton which can be potentially applied to afford a series of biological activity derivatives.

Experimental

Typical procedure for the preparation of 1,2,4-triazine derivatives **3.**

Procedure **A**: The reaction was carried out in a round-bottom sidearm flask (10 mL), **1** (0.2 mmol), SeO_2 (0.24 mmol) and DMSO (2 mL) were added to the flask with a magnetic stirring bar at 110 ^{o}C under air. After 4 h stirring at this temperature, **2** (0.2 mmol) was introduced into the catalyst system. 2 hours later, the flask was, then, took out and cooled to room temperature. The mixture was washed with 20 ml water and extracted with ethyl acetate (3 × 50mL). The oil layer was combined and concentrated under reduced pressure to distill ethyl acetate, which was further purified by silica gel chromatography (petroleum/ethyl acetate = 5/1 as eluent) to obtain product **3**.

Procedure **B**: The reaction was carried out in a round-bottom sidearm flask (10 mL), **4** (0.4 mmol), NIS (0.24 mmol), TsOH (0.02 mmol) and DMSO (2 mL) were added to the flask with a magnetic stirring bar at 110 ^{o}C under air. After 4 h stirring at this temperature, **2** (0.2 mmol) was introduced into the catalyst system. The following processing method was referred to the procedure **A**.

^{1}H NMR and ^{13}C NMR spectra were determined on 300 MHz and 75 MHz in $CDCl_3$. unknown products were further characterized by HRMS (TOF-ESI), the melting points of solid products were determined on a microscopic apparatus.

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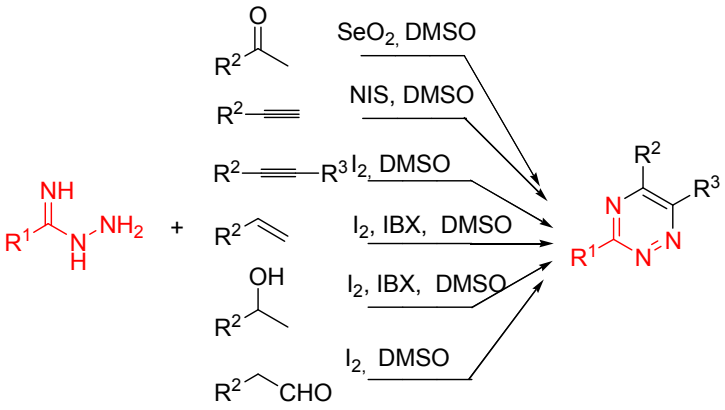

The simple and efficient [4+2] domino annulation reactions have developed for the synthesis 1,2,4-triazine derivatives. The strategies exhibit high performance with moderate to high yields by using easily available materials including ketones, aldehydes, alkynes, secondary alcohols and alkenes, and represent a powerful tool for the formation of potentially biological active derivatives.