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Scalable Synthetic Strategy for Unsymmetrical Trisubstituted *s*-Triazines

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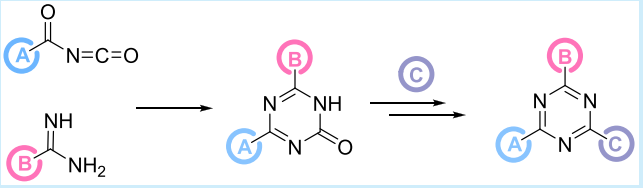
ABSTRACT: A scalable synthetic strategy to produce a large variety of unsymmetrical trisubstituted 1,3,5-triazines was developed. This protocol applied in situ formed acyl isocyanate from amide to react with amidine, introducing two substituents to the 1,3,5-triazinone ring with a low production cost and a simple workup procedure. The scalability of this method was demonstrated by translating a small-scale procedure to a multi-kilogram-scale synthesis. Chlorination and a further coupling reaction with various nucleophiles could provide unsymmetrical trisubstituted 1,3,5-triazines bearing diverse functional groups.



1,3,5-Triazines and their derivatives based on nitrogen-containing heterocycles are key structural features with wide-ranging biological activities in drug discovery programs, including antimicrobial, anticancer, antiviral, and antituberculosis activities.[1] The distinctive structure of *s*-triazines makes them a remarkable synthon in material science,[2] supramolecular chemistry,[3] and coordination chemistry.[4] Since the year 2000, the strong electron acceptability and excellent structural modifiability of the triazine moiety have made it an exciting target, allowing an exponential increase in the usage of its derivatives as electron transporters and hole-blocking materials. A simple search of these compounds would provide hundreds of articles and patents. Via modifying the substituents on the triazine core to easily tune the mobility and the LUMO energy for adjusted injection, *s*-triazine derivatives were developed for fluorescence sensors,[5] luminescent liquid crystals,[6] photovoltaic devices,[7] and phosphorescent organic light-emitting diodes (OLEDs).[8]

Given the important and extensive applications of 1,3,5-triazines, many efforts have been made to introduce different substitutions on the triazine core unit and increase the diversity of the compound libraries. A representative strategy to achieve unsymmetrical trisubstituted *s*-triazines is via the multistep sequential Pd-catalyzed coupling of cyanuric chloride with various nucleophiles due to the different reactivities of C−Cl bonds (Figure 1, top);[9] however, multiple reaction steps and the purification of each step led to tedious work and a low yield of final product. Reaction condition screening also takes laborious work to find the right combination of catalyst and ligand. Concerning the introduction of different substituents into a triazine core, the satisfactory synthesis of unsymmetrical trisubstituted 1,3,5-triazines from readily available reagents is still rare.[10] To circumvent this limitation, we aimed to design a ring construction strategy that is easily and efficiently achieved

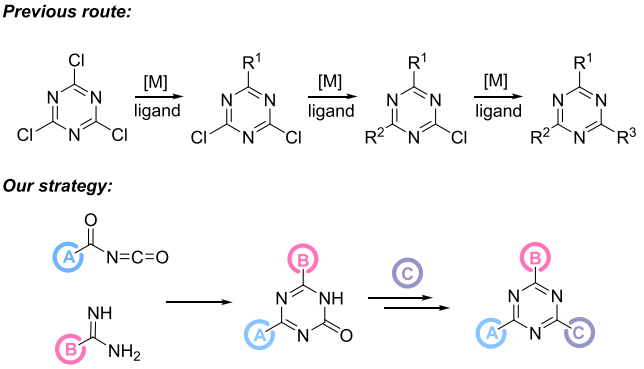


Figure 1. Synthetic strategies for unsymmetrical trisubstituted *s*-triazines.

from cheap and commercially available starting materials in a straightforward manner.

Owing to the complex system of double bonds, acyl isocyanate as a synthon was used to undergo cycloaddition reactions with unsaturated bonds to synthesize a wide range of heterocycles.[11] We hypothesized that we could utilize the high reactivity of acyl isocyanate to develop a convenient and versatile method for the distinct construction of 1,3,5-triazin-2(1*H*)-one, which is a precursor to 1,3,5-triazines (Figure 1, bottom). Compared with the state of the art, such a strategy for the unsymmetrical trisubstituted 1,3,5-triazine synthesis

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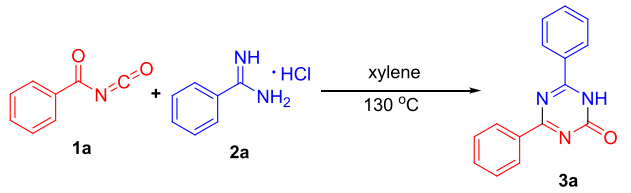
could offer a few superior features: (1) a wide choice of functional groups on the triazine ring according to need, (2) a feasible separation and purification procedure due to the avoidance of coupling byproducts resulting from multiple reactive sites, (3) shortened reaction steps by introducing two functional groups via a single step, and (4) a low production cost by utilizing cheap starting materials. The disubstituted 1,3,5-triazinones could be efficiently converted into the desired unsymmetrical trisubstituted 1,3,5-triazines via facile chlorination and coupling reactions. Herein we report the realization of an unsymmetrical trisubstituted 1,3,5-triazine precursor via the one-pot cyclization of acyl isocyanate with amidine. Our ring-construction strategy offers good functional group compatibility and operational simplicity. A large variety of 1,3,5-triazinones could be obtained by precipitation in water, and the NMR spectrum showed good purity without any column chromatography. We envision that this strategy could be the key to opening new synthetic possibilities for the manufacturing of OLED materials at more affordable price points.

As a model reaction for the initial investigations, benzoyl isocyanate **1a** was formed in situ by treating amide with oxalyl chloride $(COCl)_2$ followed by the addition of amidine **2a** to accomplish the one-pot cyclization and give 1,3,5-triazin-2(1*H*)-one **3a** as a desired product. In terms of solvents, xylene was identified as optimal (Table 1, entries 1−3). Lowering the

Table 1. Reaction Condition Screening[a,b]



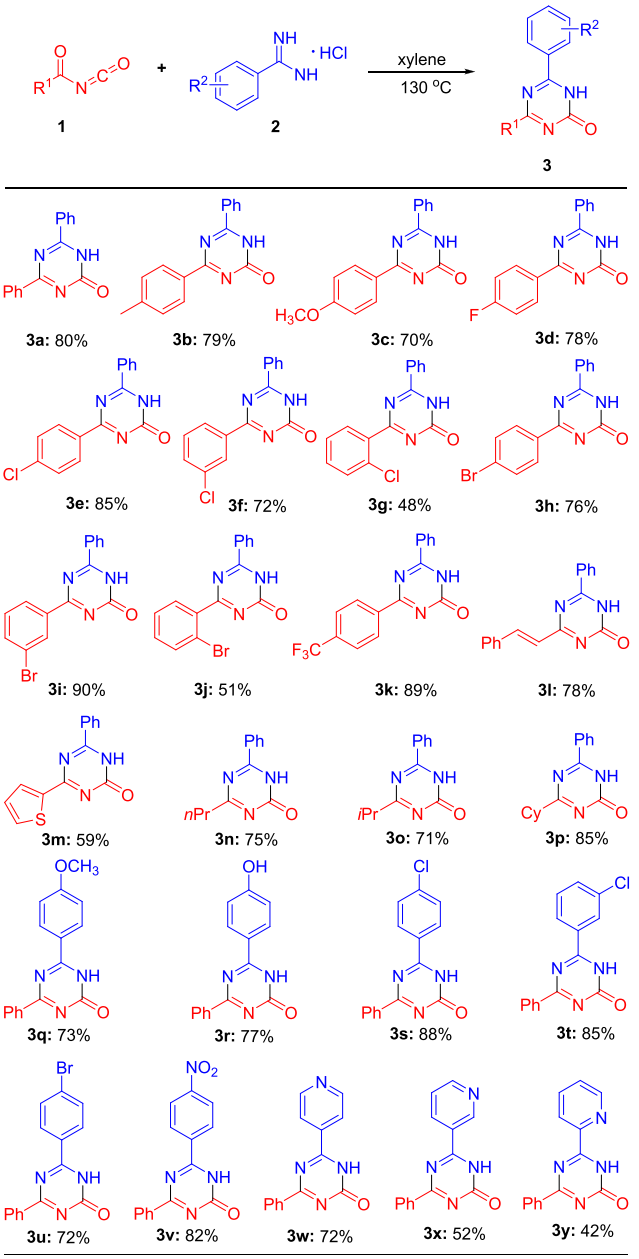
entry	**1a** (equiv)	solvent	*T* (°C)	time (h)	yield (%)
1	1.5	xylene	130	12	80
2	1.5	DMF	130	12	25
3	1.5	DMSO	130	12	35
4	1.1	xylene	130	12	65
5	1.5	xylene	130	8	70
6	1.5	xylene	100	12	65

[a]Benzamide and oxalyl chloride reacted in solvent (3 mL) at 60 °C for 2 h to form **1a** (*x* equiv); then, **2a** (0.6 mmol) was added to react with the in situ formed **1a** at *x* °C for *y* h. [b]Isolated yields.

equivalent of **1a** to 1.1 equiv led to a diminished product yield (entry 4). Either less reaction time or a lower temperature resulted in decreased yields as well (entries 5, 6). Finally, the optimal reaction condition was determined without the usage of any catalyst or additives.

With the optimal reaction conditions in hand, we continued to explore the substrate scope of **1** with aryl amidines to synthesize disubstituted 1,3,5-triazin-2(1*H*)-one (Table 2). A large variety of aryl and alkyl isocyanates formed in situ from amides underwent the reaction with amidines to furnish moderate to excellent yields. Aryl amides bearing electron-donating groups, such as methyl and methoxyl, and electron-withdrawing groups, such as fluoro, chloro, bromo, and trifluoromethyl, on the phenyl rings were transformed into the respective isocyanates, which successfully reacted with phenyl amidine to form disubstituted 1,3,5-triazin-2(1*H*)-ones (**3a**−**k**). In terms of the chloro group on the phenyl ring of

Table 2. Substrate Scope of 1 with Aryl Amidines to Synthesize Disubstituted 1,3,5-Triazin-2(1*H*)-ones[a,b]



[a]Amide and oxalyl chloride reacted in xylene (3 mL) at 60 °C for 2 h to form **1** (0.9 mmol); then, **2** (0.6 mmol) was added to react with the in situ formed **1** at 130 °C for 12 h. [b]Isolated yields.

amide, the *para*-site (**3e**) was more favorable compared with meta and ortho sites (**3f**, **3g**). In the case of the bromo group, the *meta*-site was converted into the respective product **3i** in the highest yield. The steric effect of ortho substituents might be the cause of lower yields, as seen in the case of **3g** and **3j**. Note that these halogen groups offer a versatile functional handle for further functionaliaztion, which is essential for drug discoveries and material development. This protocol is also applicable for amides bearing an extended π-framework (**3l**) and *S*-heteroaryl group (**3m**). Aliphatic amides bearing primary (**3n**) and secondary (**3o**, **3p**) α-carbon atoms were transferred into the desired product in good yields. Under the optimal reaction conditions, we also screened various aryl amidines

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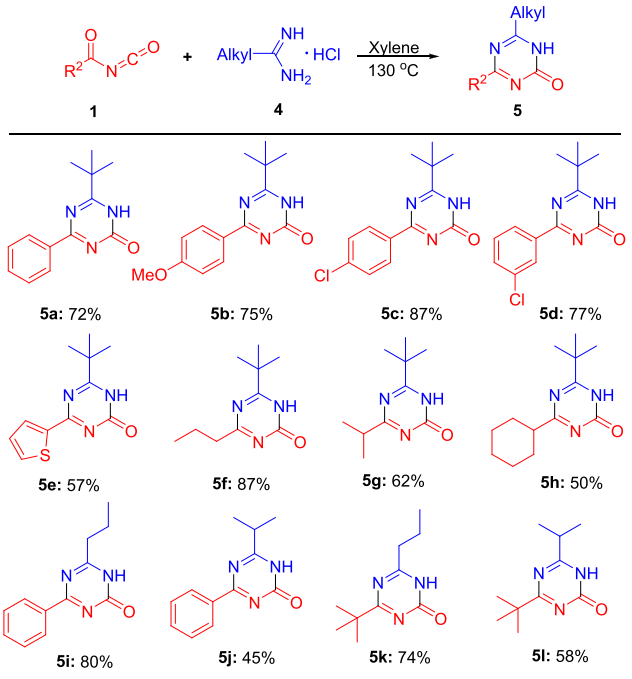
with phenylamide. The in situ formed benzoyl isocyanate **1a** from phenylamide could react with aryl amidines containing an electron-efficient group, such as methoxyl (**3q**) and hydroxyl (**3r**), and electron-deficient groups, such as chloro (**3s**, **3t**), bromo (**3u**), and nitro (**3v**), to furnish the target 1,3,5-triazin-2(1*H*)-ones in good yields. Chloro groups on para or meta sites of the phenyl ring did not show much effect on the reaction. In addition, disubstituted 1,3,5-triazin-2(1*H*)-ones deduced from pyridine amidines are accessible in moderate to good yields (**3w**–**y**). The results indicated that the electronic properties of pyridine ring were essential for the reaction.

We continued to explore the synthesis of dialkyl- and alkylaryl-functionalized 1,3,5-triazin-2(1*H*)-ones by utilizing alkyl amidines as substrates (Table 3). By using *t*-

Table 3. Substrate Scope to Synthesize Dialkyl- and Alkylaryl-Substituted 1,3,5-Triazin-2(1*H*)-ones[a,b]



[a]Amide and oxalyl chloride reacted in xylene (3 mL) at 60 °C for 2 h to form **1** (0.9 mmol); then, **4** (0.6 mmol) was added to react with the in situ formed **1** at 130 °C for 12 h. [b]Isolated yields.

butylcarbamidine as a reaction partner, phenylamide (**5a**) and other aryl amides bearing an electron-rich group, such as methoxyl (**5b**), and an electron-poor group, such as chloro (**5c**, **5d**), on the phenyl ring led to alkylaryl-substituted 1,3,5-triazin-2(1*H*)-ones in good yields. Amide with an *S*-heteroaryl group, in this case, thiophene, could be converted into the corresponding product **5e**. Alkyl amides with primary and secondary α-carbon atoms formed products **5f**–**h** in moderate yields. Propyl and isopropyl amidines could successfully react with phenylamide and*t*-butylamide to form dialkyl- and alkylaryl-substituted 1,3,5-triazin-2(1*H*)-ones (**5i**–**l**), respectively.

The absolute configurations of the obtained 1,3,5-triazinones **3y** and **5b** were determined by X-ray crystallographic analysis (Figure 2). According to the bond lengths and angles observed in the analysis, the N–H bond on the triazinone ring was identified to originate from the corresponding amidine.

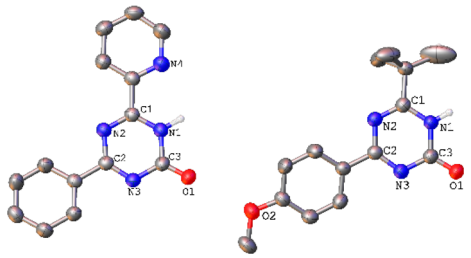
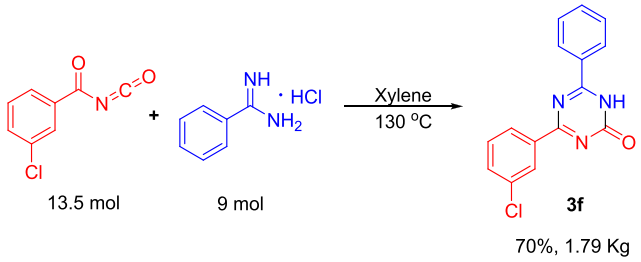


Figure 2. Crystal structures of compound **3y** (left, displacement ellipsoids are drawn at the 50% probability level) and **5b** (right, displacement ellipsoids are drawn at the 50% probability level).

This protocol requires no catalyst or any other additive. Once the reaction was completed, the reaction mixture was concentrated under vacuum, then redissolved in a small amount of DMF. The above DMF solution was dropped into hot water, and the desired product would precipitate due to the low solubility. After simple filtration, clean product could be obtained as a solid. NMR showed that the purity of the product was quite acceptable. Gratifyingly, this protocol was successfully translated to a multi-kilogram-scale experiment. Taking the reaction between 3-chlorobenzamide and phenylamidine as an example (Scheme 1), compound **3f** was

Scheme 1. Multi-Kilogram-Scale Synthesis of 3f



synthesized in 70% yield (1.79 kg). It is worth noting that this product yield is quite close to that of the small-scale trial (Table 2, 72%).The scalability of this technology to synthesize unsymmetrical disubstituted 1,3,5-triazin-2(1*H*)-ones is solid evidence that our strategy might have great potential in industrial manufacturing.

The ability to procure an ample amount of 1,3,5-triazin-2(1*H*)-ones and introduce two different substituents in a single step affords a unique opportunity to explore the synthesis of unsymmetrical trisubstituted 1,3,5-triazines, as we expected. The chlorination of 1,3,5-triazin-2(1*H*)-ones could be accomplished by the treatment with $POCl_3$. As shown in Table 4, diaryl-, heteroaryl-, arylalkyl-, and dialkyl-substituted 1,3,5-triazin-2(1*H*)-ones were successfully transferred into the corresponding 2-chloro-1,3,5-triazines. With regard to these compounds, previous methods involved the Pd-catalyzed Suzuki coupling reaction, Grignard reagents, or expensive starting materials.[12]

The palladium-catalyzed cross-coupling reaction to forge carbon–carbon bonds and carbon–heteroatom bonds is a prominent synthetic tool to introduce the third functional group onto the triazine core (Scheme 2). The 2-chloro-1,3,5-triazine derivative **6a** was taken as an example. The Pd-catalyzed Suzuki coupling reaction of **6a** with arylboronic esters was realized to afford the desired product in excellent yields (reactions 1 and 2). In addition, the amination reaction

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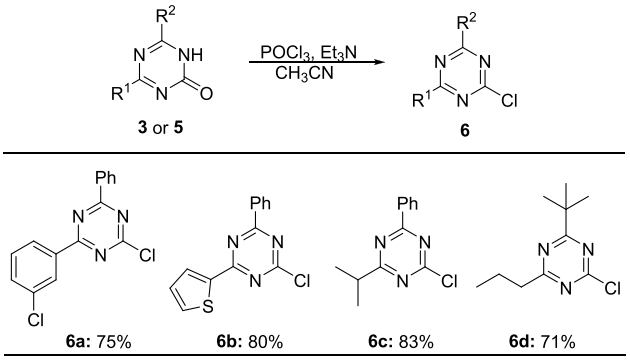
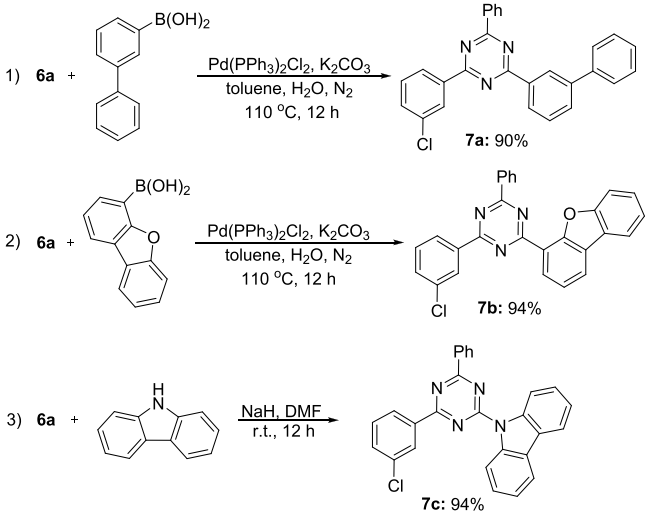
Table 4. Chlorination of 1,3,5-Triazin-2(1*H*)-ones[a]



[a]Triazinone (0.2 mmol), $POCl_3$ (3 equiv), Et_3N (3 equiv), CH_3CN (2 mL), 90 °C, 12 h.

Scheme 2. Functionalization of 2-Chloro-1,3,5-triazines to Synthesize Unsymmetrical Trisubstituted 1,3,5-Triazines



of **6a** with carbazole formed the corresponding unsymmetrical trisubstituted 1,3,5-triazine in 94% yield (reaction 3). The chloro group on the benzene serves as a synthetic handle for further functionalization. These compounds have been synthesized via a multiple-step coupling reaction and used as intermediates in an organic material layer of an organic electroluminescent device in patents.[13]

In summary, we have developed a novel synthetic strategy to achieve unsymmetrical trisubstituted *s*-triazines. The unique reactivity of the in situ formed isocyanate from amide allows for cyclization with amidine and the successful transformation into 1,3,5-triazin-2(1*H*)-ones while introducing two functional groups (aryl or alkyl) to the core unit in a single step. The disubstituted 1,3,5-triazin-2(1*H*)-ones could be purified via simple precipitation in water and filtration, avoiding a multiple-step coupling reaction and a tedious workup procedure. Chlorization and the Pd-catalyzed coupling reaction with various nucleophiles enable the synthesis of the desired unsymmetrical trisubstituted 1,3,5-triazines with a wide range of functional groups. Much to our delight, the 1,3,5-triazin-2(1*H*)-ones could be produced on a multi-kilogram-scale, ensuring the application of this protocol in chemical manufacturing. Considering the rapid development of OLED technology and the growing demand for low-cost materials, our method could greatly lower the production cost and provide a new perspective to overcome challenges in the industrial manufacturing of triazine-based organic luminescent materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01970.

Materials and methods, experimental procedures, useful information, ^{1}H NMR spectra, ^{13}C NMR spectra, MS data, crystal data, and structure refinement for **3y** and **5b** (PDF)

Accession Codes

CCDC 2080869−2080870 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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