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Construction of Bicyclic 1,2,3-Triazine *N*-Oxides from Aminocyanides

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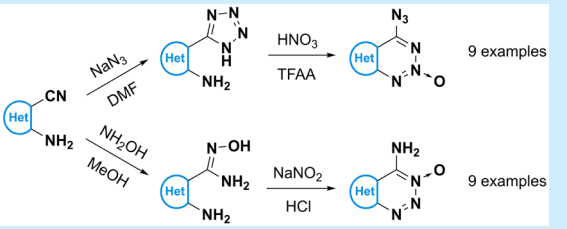
ABSTRACT: Using a facile and cost-effective method, nine bicyclic 1,2,3-triazine 2-oxides were synthesized from *o*-aminocyanide substrates through an unusual nitration cyclization. The reaction mechanism was studied experimentally and theoretically. Moreover, nine 1,2,3-triazine 3-oxides were also obtained in good yields.



Triazines are a special class of heterocyclic compounds which are extensively studied for potential applications in agrochemicals,[1,2] pharmaceuticals,[3−5] energetic materials,[6,7] and synthetic intermediates.[8,9] Among the three possible isomers of triazine, 1,2,3-triazine is more favored than the 1,2,4- and 1,3,5-triazine isomers, largely due to their potent efficacy and less side effects as pharmaceuticals,[10] as well as higher energy content as energetic materials (Figure 1a).[11]

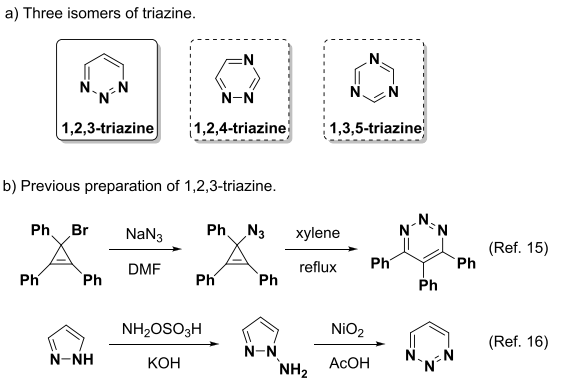


Figure 1. Structures and synthetic methods of 1,2,3-triazine.

However, 1,2,3-triazine is also the least studied due to synthetic difficulties in constructing such a catenated nitrogen chain in an aromatic ring. It was first prepared by Pinnow et al. in 1896 via reaction of 2-amino-*N*′-hydroxybenzimidamide with nitrous acid.[12] In 1910, Chandross et al. reported another approach via a pyrolytic rearrangement of 1,2,3-triphenylcyclopropyl azide.[13] Over the next 60 years, there were no significant advances in its synthesis until Igeta et al. reported the preparation of neat 1,2,3-triazine with an oxidative rearrangement from 1-aminopyrazole (Figure 1b).[14−16] Even now, it is still a great challenge to develop new facile and universal methods to prepare 1,2,3-triazine derivatives.

Although several monocyclic 1,2,3-triazine compounds have been reported over the past decades, 1,2,3-triazine *N*-oxides have attracted little attention. It was reported that the *N*-oxide functionality on aromatic heterocycles can enhance their pharmacological and energetic properties.[17−19] Few reports on preparation of 1,2,3-triazine *N*-oxides include a direct oxidation to 1,2,3-triazine 1-, 2-, and 3-oxides with *m*-chloroperoxybenzoic acid (*m*-CPBA)[20−23] and amino diazotization to a diazonium salt followed by reactions with a neighboring oxime to afford 1,2,3-triazine 1- or 3-oxide.[24,25] However, the majority of these reactions suffer from low tolerance of functional groups, multiple byproducts, and low selectivity of *N*-oxide positions. Thus, universal methods for the synthesis of 1,2,3-triazine *N*-oxide do not exist. Additionally, very little is known about the construction of bicyclic 1,2,3-triazine *N*-oxides. In recent efforts to develop new energetic compounds, two bicyclic compounds based on 1,2,3-triazine 2-oxide and 1,2,3-triazine 3-oxide skeletons were synthesized by us and Shreeve.[26,27] They showed promising detonation performances as primary explosives and fluorescent energetic materials. However, the reaction scope and mechanism of these methods for constructing other bicyclic 1,2,3-triazine *N*-oxides remain unclear.

In this work, we are interested in preparing a variety of bicyclic 1,2,3-triazine *N*-oxides from different *o*-aminocyanide substrates based on five- or six-membered aromatic rings. In method (I), *o*-aminocyanide is reacted with NaN_3 to give *o*-tetrazolylamine derivatives, followed by a one-step ring-closure reaction to yield the target products of bicyclic 1,2,3-triazine 2-oxides. In the first step reaction, 12 six- or five-membered

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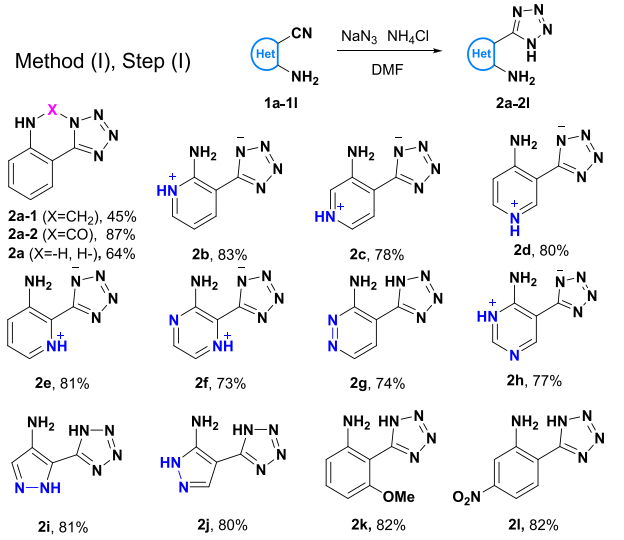
aromatic heterocycle precursors were prepared, including pyridine, pyrazine, pyrimidine, pyridazine, and pyrazole (Scheme 1). Most substrates gave high yields from 73% to

Scheme 1. Reaction of *o*-Aminocyanides 1a−1l with NaN_3

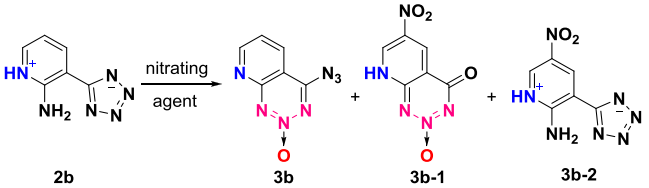


82%. The reaction of pyridines **1b−1e** to form **2b−2e** gave slightly higher yields than the diazine-based analogues **1f−1h** possibly because the higher nitrogen content of a six-membered ring depressed the efficiency of this transformation. Five membered azoles **2i−2j** all were formed in high yields of 80% to 82%. The reaction between 2-aminobenzonitrile (**1a**) and NaN_3 is noteworthy. When catalyzed by $NHMe_2$·HCl, an unexpected tricyclic compound 5,6-dihydrotetrazolo[1,5-*c*]-quinazoline (**2a-1**) was separated. With NH_4Cl, another tricyclic compound tetrazolo[1,5-*c*]quinazolin-5-one (**2a-2**) was formed. It is likely that the methylene or carbonyl moiety came from the solvent DMF. When the solvent was replaced with DMA, the desired product **2a** was finally obtained in a yield of 64%.

The second step in method I is a tandem nitration−cyclization which forms 1,2,3-triazine 2-oxides. Here, **2b** is used as the substrate, and several commonly used nitrating agents are selected for this reaction. The results are shown in Table 1. It should be noted that the HNO_3/TFAA nitrating system gives a modest yield of 63% at −5 °C because some byproducts, detected on TLC, were detrimental to the recovery of the product. However, when the reaction was repeated at −15 °C, a pure product with an isolated yield up to 83% was obtained. Therefore, a mixture of HNO_3/TFAA was chosen to be the optimal nitrating system. From entries 5−8, it was found that temperature has a major impact on the reaction yield. The highest isolated yield was found at −15 °C. As the temperature was increased, more byproducts began to form and the isolated yield dropped significantly. At 50 °C, only a *C*-nitrated 1,2,3-triazine compound, 6-nitro-4-oxo-4,8-dihydropyrido[2,3-*d*][1,2,3]triazine 2-oxide (**3b-1**), was separated as the only product. Also, a trace amount of 5-nitro-3-tetrazolylpyridin-2-amine (**3b-2**) was separated from the nitration mixture with column chromatography. Its structure was confirmed with single-crystal XRD.

After the condition optimization of the second step reaction in method I, the substrate scope was expanded to other six- or five-membered aromatic heterocycles (Scheme 2). Most of the

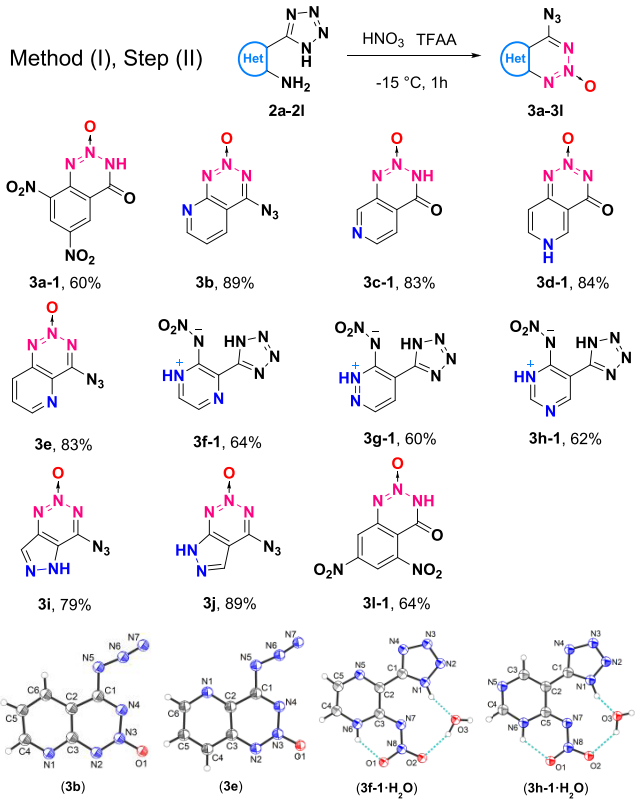
Table 1. Optimization for Nitrating Conditions for 2b



entry	nitrating agent	temp (°C)	yield[a] (%)
1	HNO_3/H_2SO_4	−5	65
2	HNO_3/Ac_2O	−5	72
3	HNO_3/TFAA	−5	63 (5)
4	NO_2BF_4/MeCN	−5	70
5	HNO_3/TFAA	−15	83
6	HNO_3/TFAA	5	43 (12)
7	HNO_3/TFAA	rt	15 (42)
8	HNO_3/TFAA	50	0 (64)

[a]Yields in parentheses are separated yields for **3b-1**.

Scheme 2. Nitration of *o*-tetrazolylamines, 2a−2l to 1,2,3-Triazine 2-Oxide[a]



[a]Thermal ellipsoid plots were drawn at 50% probability level.

new *o*-tetrazolylamines **2a−2l** prepared in step I, were readily transformed to 1,2,3-triazine 2-oxides **3a−3l**, with yields from 60% to 89%. It is interesting that some of the 1,2,3-triazine 2-oxides (**3b**, **3e**, **3i**, **3j**) bear an azide on the 4-position, while others hold a carbonyl at the same position. The mechanism for the formation of carbonyl products was proposed by Zhou et al.,[28,29] while the mechanism for azide products will be discussed later. For phenyl compounds **2a** and **2l**, nitro moieties were inevitably introduced to the ring even at −15 °C, giving dinitro products **3a-1** and **3l-1**, with a yield of 60% and 64%, respectively. For heterocycles, nitro-free products

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could be prepared by carefully controlling the temperature to no more than −10 °C. It was also found that the reactions of the diazines **3f**−**3h** did not fully proceed to 1,2,3-triazine 2-oxides and only nitramine products were separated. The structures of **3b**, **3d-1**, **3e**, **3f-1**, and **3h-1** were confirmed by single-crystal XRD.

To gain more insight into the nitration mechanism, quantum calculations were carried out to study the reaction intermediates and transition states for the nitration of **2b**. A plausible mechanism is proposed in Figure 2. Its energy profile

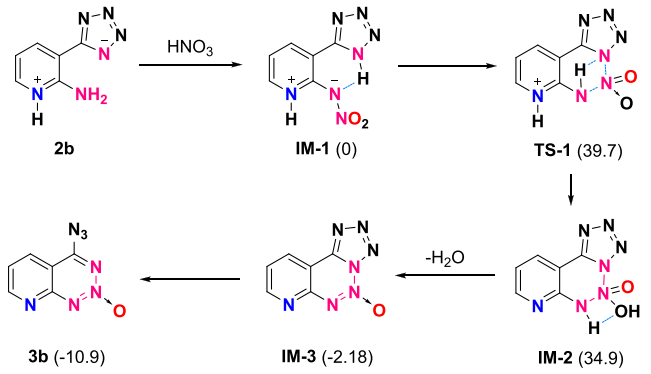


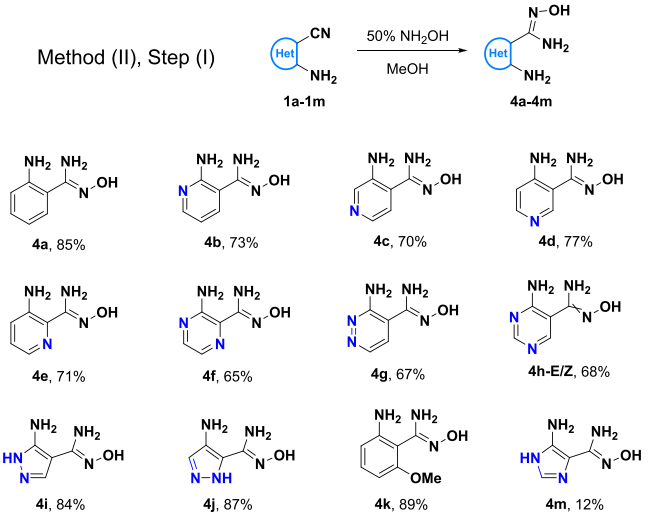
Figure 2. Calculated reaction mechanism. Numbers in parentheses are calculated energy barriers (in kcal/mol).

is also shown (more calculation details could be found in the Supporting Information). The reaction from **IM-1** to **TS-1** has a relatively high energy barrier of 39.7 kcal/mol and is considered as the key step of the whole reaction process. The intermediate **IM-2** already bears a 1,2,3-triazine skeleton and is dehydrated to **IM-3**, with a huge energy release of 37.1 kcal/mol. A final tetrazole−azide transformation yields the product **3b** with another energy drop of 8.7 kcal/mol. Calculated results reveal that initially a nitramine intermediate IM-1 was formed. It was further dehydrated via a complicated process to generate the product **3b**. According to this mechanism, the nitrogen atom of the *N*-oxide comes from nitric acid. To verify this mechanism experimentally, a ^{15}N-labeled KNO_3 with 10% abundance was used in place of nitric acid in the nitrating reaction. The ^{15}N NMR spectrum of ^{15}N-labeled **3b** shows a single peak with chemical shift at 334.14 ppm (liquid NH_3 as external standard), which is assigned to the nitrogen atom of the *N*-oxide. This is in good agreement with the calculated mechanism.

After the successful syntheses of the bicyclic 1,2,3-triazine 2-oxides, the syntheses of bicyclic 1,2,3-triazine 3-oxide were explored. In this synthetic method, *o*-aminocyanide reacts readily with hydroxylamine to give *o*-aminoamidoxime. This is followed by diazotization and cyclization to the product 4-amino-1,2,3-triazine 3-oxide. Twelve different six- and five-membered precursors were prepared (Scheme 3). Reactions for most substrates achieved medium-to-high yields up to 92%. The reaction for compound **4l** showed the highest yield, which could be attributed to the electron-donating methoxy group on the ring. Imidazole, **1k**, has a low reactivity with aqueous NH_2OH, giving rise to a low conversion yield even after a couple of days. Pyrimidine derivative **1h**, upon reacting with NH_2OH, gave a pair of *E*/*Z* isomers of **4h-E**/**Z**.[30,31]

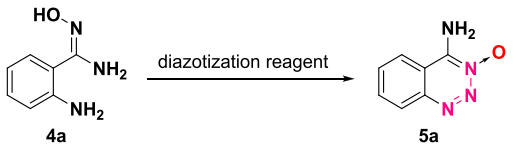
The second step is a diazotization reaction followed by a cyclization to 1,2,3-triazine 3-oxide. 2-Amino-*N*′-hydroxybenzimidamide (**4a**) was selected as the substrate to optimize the

Scheme 3. Reactions of *o*-Aminocyanides 1a−1m with Hydroxylamine



reaction conditions. The results are listed in Table 2. From entries 1−3, temperature has a crucial influence on the yield.

Table 2. Optimization of Diazotization Reactions for 4a



entry	diazotization agent	temp (°C)	yield (%)
1	$NaNO_2$/HCl	−5	72
2	$NaNO_2$/HCl	10	46
3	$NaNO_2$/HCl	rt	0
4	$NaNO_2$/H_2SO_4	−5	23
5	$NaNO_2$/AcOH	−5	64
6	^{i}AmONO/HBF_4	−5	23
7	^{t}BuONO/AcOH	−5	45
8	$NOBF_4$/MeCN	−5	0

The highest yield of 72% was achieved at −5 °C. Increasing the temperature to 10 °C resulted in a lower yield of 46%. At room temperature, no 1,2,3-triazine 3-oxide was detected on TLC from the reaction. Different diazotization agents had varied reactivities in the diazotization reaction. A mixture of $NaNO_2$/HCl led to the highest yield of 72%. Replacing the acid with H_2SO_4 significantly reduced the yield to 23%. Using AcOH as the acid resulted in a modest yield of 64%. Other diazotization agents such as isoamyl nitrite or *tert*-butyl nitrite gave relatively lower yields up to 45%.

After the determination of the best optimized conditions, the reaction scope was expanded to other oxime compounds prepared in Scheme 3. Among these new compounds, phenyl and pyridine derivatives **4a**−**4e**, **4k** gave smooth reactions with medium-to-high yields from 65% to 79% (Scheme 4). The structure of 1,2,3-triazine 3-oxide was further confirmed with single-crystal XRD for **5a**. However, the diazine compounds **4f**−**4h** showed very different reactivity. They all gave chloroxime products **5f-1**, **5g-1**, and **5h-1** instead of the expected 1,2,3-triazine 3-oxides. It could be inferred that the formation of a 1,2,3-triazine 3-oxide or a chloroxime are competing reactions. The reaction pathway depends on the

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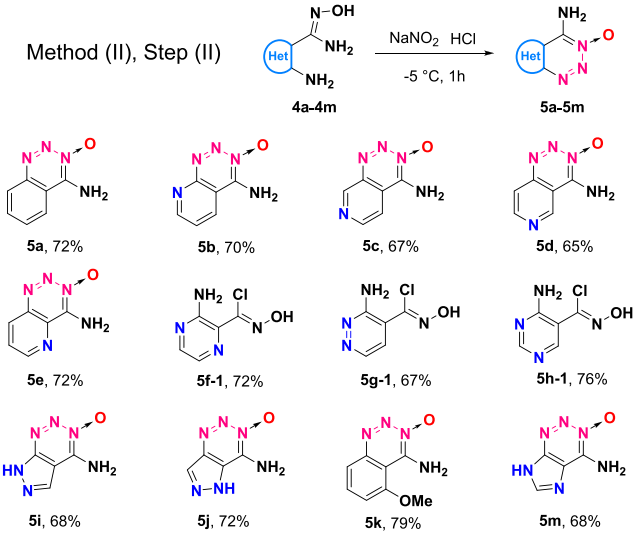
Scheme 4. Diazotization of *o*-Aminoamidoxime 4a−4m to 1,2,3-Triazine 3-Oxide



relative reactivities of the two amino groups. The amino group with a higher reactivity forms diazonium salt and proceeds through the final product.

In conclusion, a series of bicyclic 1,2,3-triazine 2-oxides and 1,2,3-triazine 3-oxides were synthesized from *o*-aminocyanides in good yields using two simple methods. The ring-closing reaction mechanism of bicyclic 1,2,3-triazine 2-oxide was investigated with the aid of quantum calculations and isotope-labeled experiments, respectively. These reactions provide efficient approaches to the construction of bicyclic 1,2,3-triazine *N*-oxides from a variety of *o*-aminocyanide substrates, which are also applicable to the synthesis of 1,2,3-triazine heterocycles with high nitrogen content under mild conditions. This work provides useful insights for developing new fused-ring 1,2,3-triazine derivatives that usually require lengthy or multistep synthetic routes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03952.

Experimental procedures, characterization data, calculation details, and crystallographic data (PDF)

Accession Codes

CCDC 2035798−2035800, 2035802−2035807, and 2047071 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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