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One-Pot Acid-Catalyzed Ring-Opening/Cyclization/Oxidation of Aziridines with *N*-Tosylhydrazones: Access to 1,2,4-Triazines

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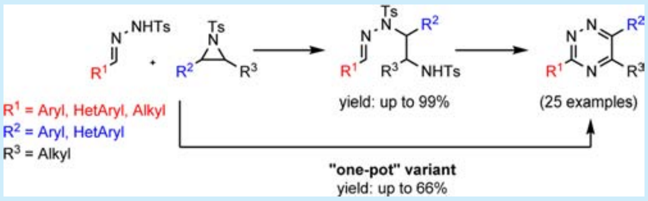
Supporting Information

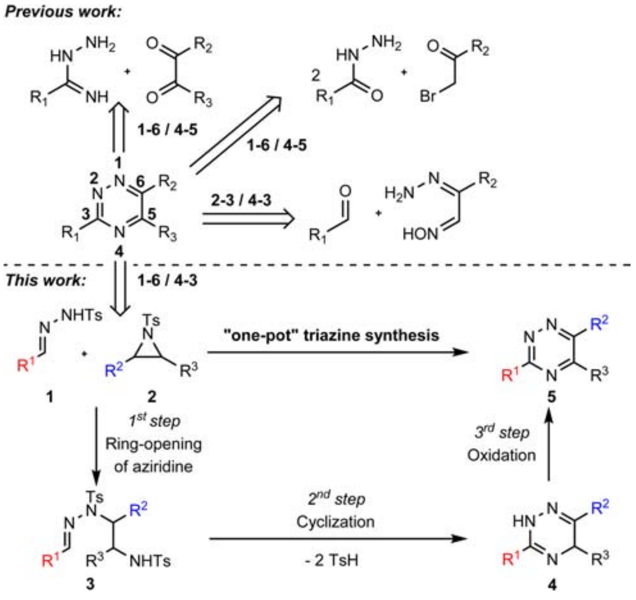
ABSTRACT: A new, three-step, telescoped reaction sequence for the regioselective conversion of *N*-tosyl hydrazones and aziridines to 3,6-disubstituted and 3,5,6-trisubstituted 1,2,4-triazines is described. The process involves an efficient nucleophilic ring opening of the aziridine, giving access to a wide range of aminohydrazones, isolated with excellent yields. A "one-pot" procedure, combining the ring opening with a cyclization and an oxidation step, allows the preparation of diversified triazines in good yields.



1,2,4-Triazine derivatives represent an important class of nitrogen heterocycles: they possess a wide range of applications from ligands for transition-metal complexes[1] to agrochemistry[2] and medicine. They have been shown to exhibit a broad spectrum of biological activities with anti-inflammatory,[3] antitumor,[4] antibacterial,[5] anticonvulsant,[6] and antiviral[7] properties being reported. They are also widely used as key synthetic building blocks for the preparation of heterocyclic systems via hetero-Diels−Alder cycloadditions.[8]

To date, the main methods for the preparation of 1,2,4-triazines include two types of bond formation: the construction of the N^1-C^6/N^4-C^5 bonds between 1,2-diketones and amidrazones leads to 3,5-disubstituted or 3,5,6-trisubstituted 1,2,4-triazines[9] while the reaction between 2 equiv of acid hydrazides and *β*-halogeno ketones forms 3,6-disubstituted triazines.[10] These disubstituted compounds are also accessible via the formation of the N^2-C^3/N^4-C^3 bonds from the addition of an oxime hydrazone and an aldehyde.[11] More recently, other methods have emerged using diazo compounds or domino annulation reactions.[12] Despite the formation of triazines being well studied in recent decades, new and versatile strategies to construct the 1,2,4-triazine core are still of high interest for both fragment-based drug discovery and synthetic chemistry programs. The synthesis of trisubstituted triazines bearing different substituents on the C5- and C6-positions still remains problematic with the current use of unsymmetrical diketones often producing a mixture of regioisomers.[9d,g] Moreover, an analysis of internally synthesized compounds in the Pfizer file showed that only 17% of triazines made have different substituents on the C5- and C6-positions, reinforcing the challenge in accessing this substitution pattern.

Scheme 1. Pathways for the Preparation of 1,2,4-Triazines



In light of the above comments, we report a conceptually new pathway using a double disconnection N^1-C^6/N^4-C^3 for the preparation of 1,2,4-triazines. It was envisaged that this approach would allow the formation of 3,6-disubstituted and 3,5,6-trisubstituted triazines via a three-step, "one-pot" procedure, starting with a Lewis acid catalyzed *N*-alkylation of *N*-tosyl hydrazones **1** with aziridines **2**. The cyclization of the intermediate **3** followed by a double elimination of the tosyl groups would afford the dihydrotriazine **4**, which upon oxidation would form the corresponding 1,2,4-triazine **5** (Scheme 1).

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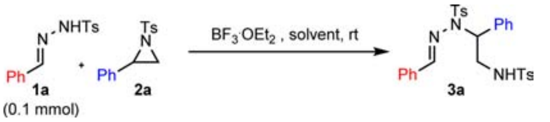
Although an aminohydrazone close to **3** has been observed once as an intermediate in an aerobic copper-catalyzed tandem reaction involving tosyl hydrazones and aziridines by the Wang group,[13] to the best of our knowledge, acid-catalyzed *N*-alkylation of *N*-tosyl hydrazones with aziridines has never been reported previously.[14] This observation encouraged us to explore the ring opening of aziridines more closely to find suitable conditions to prepare aminohydrazones **3**, a class of novel molecules whose chemistry remains mostly unknown. The optimization process was attempted with two readily accessible compounds: the phenyl tosyl hydrazone **1a** and the phenyl tosylaziridine **2a** (Table 1). Mixing of the two reactants in CH_2Cl_2 resulted in clean recovery of starting materials only (Table 1, entry 1). A screen of Lewis acids revealed that BF_3·OEt_2 was the most suitable, and in the presence of a stoichiometric amount, the reaction led to 37% of the intermediate **3a** after 24 h, with a significant amount of decomposition in the crude being observed (Table 1, entry 2). By lowering the reaction time to 1 h and using a catalytic amount of BF_3·OEt_2, a significant increase in yield to 90% was noted (Table 1, entry 3). A solvent screen showed that CH_2Cl_2 was the solvent of choice as the reaction proceeded with incomplete conversion in both toluene and Et_2O (Table 1, entries 5 and 6), while THF afforded polymerization (Table 1, entry 4). Finally, it was found that reducing the amount of aziridine to 1.2 equiv resulted in a 91% yield of the desired product **3a** (Table 1, entry 7).

Table 1. Optimization of the Ring Opening of Aziridine 1a with *N*-Tosylhydrazone 2a

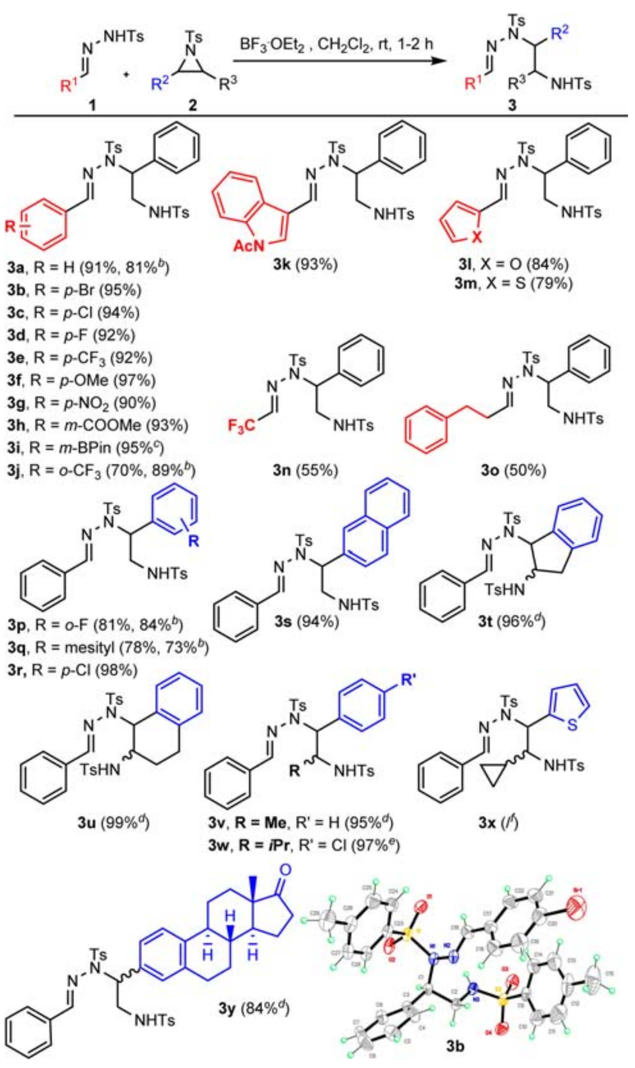


entry	aziridine (equiv)	BF_3·OEt_2 (equiv)	solvent	reaction time (h)	yield[a] (%)
1	1.5		CH_2Cl_2	24	0[b]
2	1.5	1.5	CH_2Cl_2	24	37
3	1.5	0.2	CH_2Cl_2	1	90
4	1.5	0.2	THF	1	[c]
5	1.5	0.2	toluene	1	70[d]
6	1.5	0.2	Et_2O	1	40[d]
7	**1.2**	**0.2**	**CH_2Cl_2**	**1**	**91**

[a] Isolated yields reported unless stated otherwise. [b] No reaction. [c] Polymerization was observed. [d] Percent conversion of starting material.

Under the optimized conditions, we next investigated the scope of the reaction (Scheme 2). A wide range of tosyl hydrazones **1** reacted with phenylaziridine and led to the amino hydrazones **3** in excellent yields. Hydrazones bearing both electron-donating and electron-withdrawing aryl substituents (**3a–i**) were tolerated, and steric hindrance at the *ortho*-position led to only a small decrease in yield (**3j**). Electron-rich heteroaryls such as thiophene or furan were also suitable substrates (**3l,m**). The only limitation found was the incompatibility of the Lewis acid with electron-rich amines: *N*-methylindole or pyridine hydrazones were unreactive toward the reaction conditions. This restriction could be partially overturned by the use of an electron-withdrawing functionality on the nitrogen atom: acetylindole hydrazone gave **3k** in excellent yield. Alkyl hydrazones also reacted under the standard conditions with moderate yields (**3n,o**). Replacement of BF_3·OEt_2 with the safer reagent BF_3·THF was also possible, resulting in similar yields.[15] Further investigations using various *N*-tosylaziridines **2** were then carried out: monosubstituted aziridines proceeded very smoothly (**3p–s**), while disubstituted aziridines led to a mixture of diastereoisomers, isolated in excellent combined yields, with a single regioisomer being observed (**3t–w**). Moreover, the aziridine presenting a complex steroid structure was found to be a suitable partner, leading to **3y** in 84% yield. The regioselectivity of the ring-opening of the aziridine was confirmed by X-ray crystallography for product **3b** (see the SI).[16]

Scheme 2. Scope of the Ring-Opening Reaction[a]

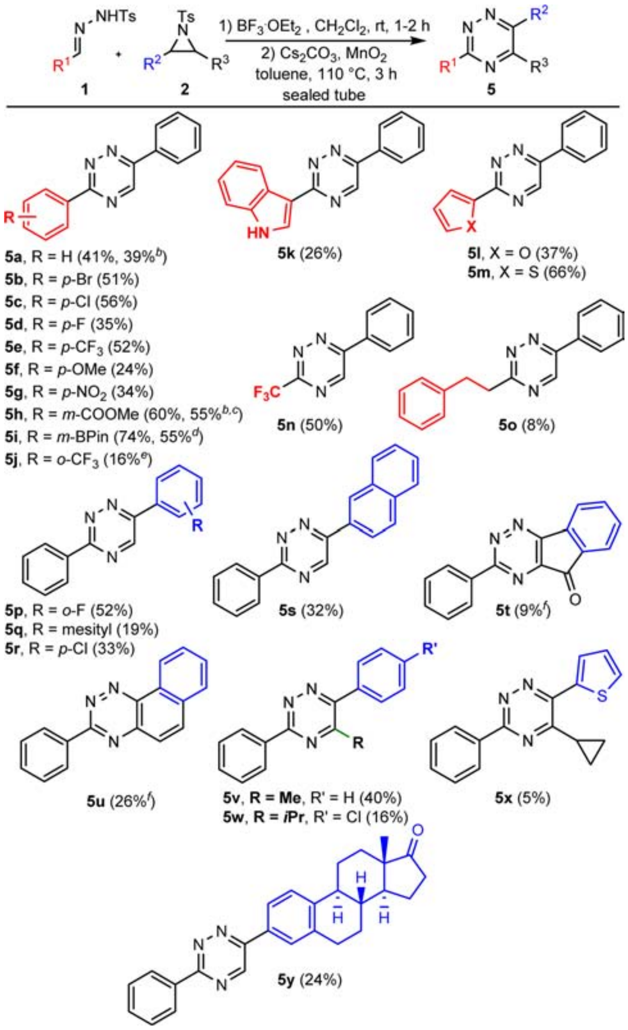


[a] Conditions: **1** (0.2 mmol), **2** (1.2 equiv), BF_3·OEt_2 (0.2 equiv), CH_2Cl_2 (0.2 M), rt, 1–2 h. [b] Reaction performed with BF_3·THF instead of BF_3·OEt_2. [c] Product unstable to column chromatography, yield from the crude. [d] dr = 50:50. [e] dr = 78:22. [f] Product **3x** observed by mass, unstable to purification or any other analysis.

With these excellent initial results in hand, a three step, "one-pot" procedure was attempted. The second step consisted of the cyclization of the aminohydrazones **3** and the elimination of both tosyl groups, requiring an excess of a base. This step was found to be very dependent on both solvent and the nature of the base, with the reaction occurring only in toluene at 110 °C in the presence of cesium carbonate.

With the objective of avoiding the isolation of the dihydrotriazines **4**, activated manganese dioxide was chosen as the oxidant for its compatibility with the cyclization conditions step and was used together with cesium carbonate to afford directly the 1,2,4-triazines **5** after 3 h at 110 °C in toluene in a sealed tube (see the SI for the full discussion of the optimization).

Scheme 3. Scope for the Preparation of Triazines 5[a]

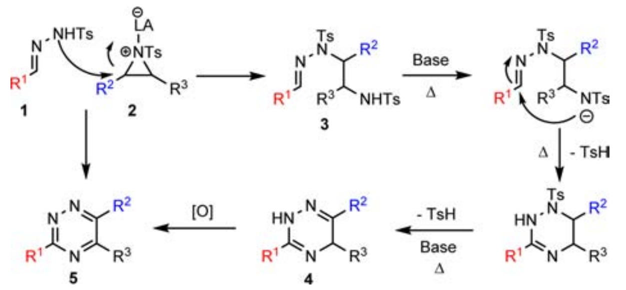


[a] Conditions: 1) **1** (0.5 mmol), **2** (1.2 equiv), BF$_3$·OEt$_2$ (0.2 equiv), CH$_2$Cl$_2$ (0.2 M), rt, 1−2 h. 2) Cs$_2$CO$_3$ (3.5 equiv), MnO$_2$ (12 equiv), toluene (0.1 M), 110 °C, 3 h, sealed tube. [b] Reaction carried out under reflux in toluene instead of a sealed tube. [c] 5 mmol scale. [d] The BPin-substituted triazine was oxidized to the corresponding alcohol before isolation. [e] Cs$_2$CO$_3$ (5 equiv), MnO$_2$ (16 equiv). [f] Overoxidation in situ by MnO$_2$.

With the optimized conditions established, a wide range of 3,6-disubstituted and 3,5,6-trisubstituted 1,2,4-triazines were prepared with moderate to good yields (up to 66%) for the telescoped process (Scheme 3). The reaction could be easily scaled (5 mmol) with no significant change in the yield (**5h**). Electron-withdrawing, halogeno-substituted aryls and CF$_3$ hydrazones led to the desired triazines in yields between 34% and 60%. Substrates with electron-donating substituted aryls or sterically hindered hydrazones tended to react in a lower yield (**5f,j**) while the unactivated hydrazone **1o** formed the product **5o** in only 8% yield. We were delighted that the useful Bpin functionality was tolerated under the reaction conditions (**5i**), allowing further elaboration of the product through cross-coupling reactions.[17] Heteroaryl hydrazones gave the triazines in good yields, and in the case of the indole, the acetyl nitrogen was deprotected *in situ* due to the basic conditions of the reaction (**5k−m**). Monosubstituted aziridines were also suitable partners to afford 1,2,4-triazines **5p−s**. In particular, the sterically hindered mesityl susbtituent was tolerated (**5q**). Moreover, the natural product-derived triazine **5y** was formed efficiently. Two fused triazines could also be prepared (**5t,u**) and isolated in their oxidized form. One of the benefits of the “one-pot” procedure was the opportunity to synthesize triazines such as **5x** whose corresponding intermediate **3x** was too unstable to be isolated. Finally, although the formation of the trisubstituted triazines is currently limited to alkyl groups on the C5-position (**5v−x**) in low to moderate yields, this methodology offers access to complex trisubstituted triazines as single regioisomers. Therefore, our approach compares favorably with the methods using 1,2-diketones which lead to regioisomeric mixtures. The 3,5,6-trisubstituted triazine scaffold can also be easily accessed via a nucleophilic addition/oxidation process on the synthesized 3,6-disubstituted triazines.[18]

Mechanistically, we believe that the aziridine is activated by the Lewis acid and the hydrazone acts as a nucleophile to effect the ring opening. This ring opening is known to occur selectively via a C−N bond cleavage, and the nucleophile only attacks at the benzylic position, leading to the single observed regioisomer **3**.[19] Next, compound **3** is deprotonated, and thermal activation allows the closure the 6-membered ring, followed by the successive elimination of the two tosyl groups to form the dihydrotriazine **4**, for which the structure is confirmed spectroscopically (see the SI). The intermediate from the monoelimination of the tosyl group can also be observed when the reaction is performed at 80 °C, where no second elimination occurs. To end the sequence, oxidation of the dihydrotriazine with MnO$_2$ affords the desired 1,2,4-triazines (Scheme 4).

Scheme 4. Plausible Mechanism for the Synthesis of Triazines



In conclusion, we have reported a new method to access the 1,2,4-triazine scaffold via a three-step, telescoped reaction sequence using *N*-tosyl hydrazones and aziridines. This approach represents a complementary alternative to well-known procedures and affords the 3,6-disubstituted and 3,5,6-trisubstituted 1,2,4-triazines in a regioselective manner. The diverse library of triazines synthesized by this route generates 15 previously unknown structures as potentially useful compounds for both medicinal and agrochemical applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00101.

Crystallographic data for **3b** (CIF)

Experimental procedures, compound characterization data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

Additional data related to this publication is available at the University of Cambridge Institutional Data Repository (https://doi.org/10.17863/CAM.7001).

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(16) CCDC 1526630 contains supplementary crystallographic data for compound **3b**.

(17) The trivalent boronate product formed from the *m*-Bpin-phenyl hydrazone was oxidized before isolation, these compounds being prone to decomposition via hydrolysis and/or protodeboronation during column chromatography. For the oxidation procedure, see: Yamashita, Y.; Tellis, J. C.; Molander, G. A. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 12026.

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