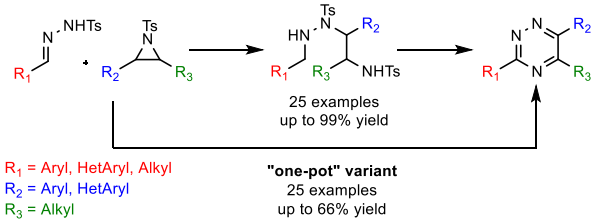
One-Pot Acid-Catalyzed Ring-Opening/Intramolecular Cyclization/Oxidation of Aziridines with *N*-Tosylhydrazones: a New Access to 1,2,4-Triazines

Lorène Crespin,[†] Lorenzo Biancalana,[†] Tobias Morack,[†] David C. Blakemore,[‡] Steven V. Ley*[,†]

[†]University of Cambridge, Department of Chemistry, Lensfield Road, Cambridge, CB2 1EW, UK

[‡]Medicine Design, Pfizer Inc, Eastern Point Road, Groton, CT 06340, USA

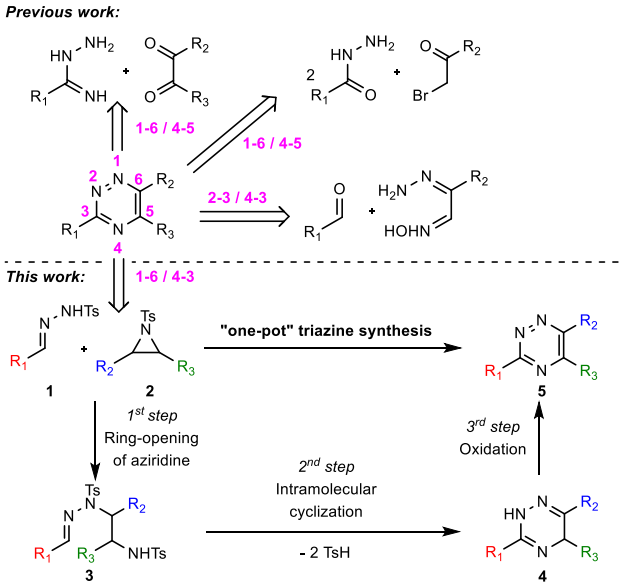


ABSTRACT: A new three-step telescoped reaction sequence for the regioselective conversion of *N*-tosylhydrazones and aziridines to 3,6-disubstituted and 3,5,6-trisubstituted 1,2,4-triazines is described. The process involves an efficient nucleophilic ring-opening of the aziridine, giving access to a 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-triazines 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]

Up to now, the main methods for the preparation of 1,2,4-triazines include two types of bond formation: the N^1-C^6/N^4-C^5 bonds construction 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 two equivalents of acid hydrazides and β-halogeno ketones forms 3,6-disubstituted triazines.[10] These disubstituted compounds are also accessible from the formation of the N^2-C^3/N^4-C^3 bonds via 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-triazines 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 5- and 6-positions still remains problematic with the current use of unsymmetrical diketones often producing a mixture of regioisomers.[9d,9g] Moreover, an analysis of internally synthetized compounds in the Pfizer file showed that only 17% of triazines made have different substituents on the 5- and 6-positions, reinforcing the challenge in accessing this substitution pattern.

Scheme 1. Pathways for the preparation of 1,2,4-triazines

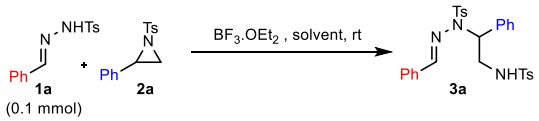


In the light of above the comments, we wish to report a conceptually new pathway using a double disconnection N^1-C^6/N^4-C^3 for the preparation of 1,2,4-triazines. It was envisaged that this approach would allow the formation of 3,6-disubstituted and 3,5,6-trisubstituted triazines via a three-step/"one-pot" procedure, starting with a Lewis-acid catalyzed *N*-alkylation of *N*-tosylhydrazones **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).

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

Table 1. Optimisation of the ring opening of aziridine 1a with *N*-tosylhydrazone 2a



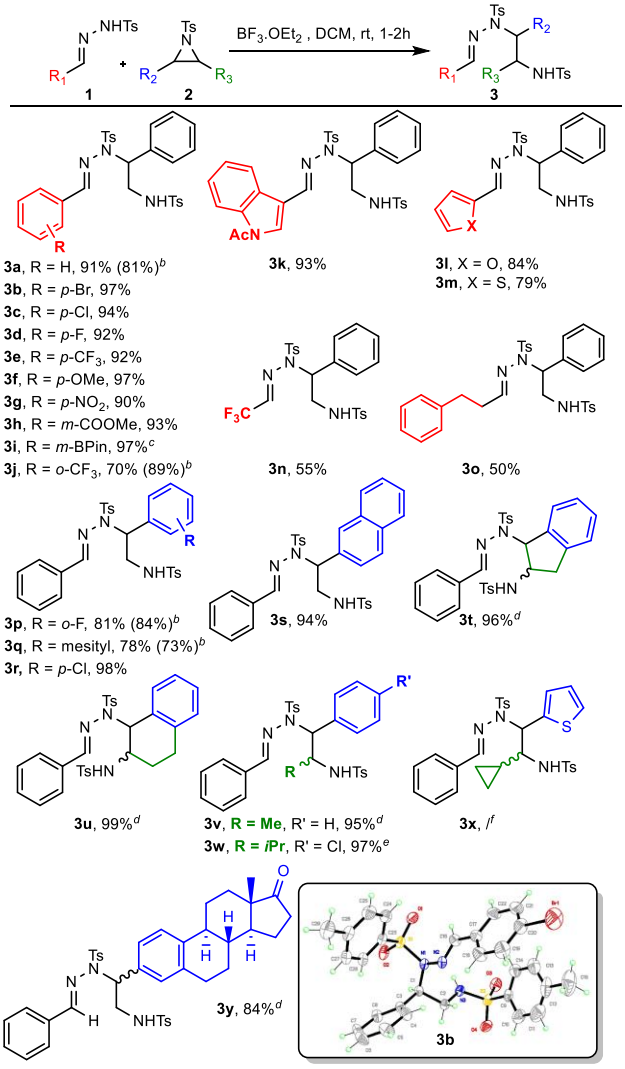
1a (0.1 mmol) **2a** **3a**

Entry	Aziridine (equiv)	$BF_3.OEt_2$ (equiv)	Solvent	Reaction time (h)	Yield[a] (%)
1	1.5	-	DCM	24	/[b]
2	1.5	1.5	DCM	24	37
3	1.5	0.2	DCM	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	DCM	1	91

[a]Isolated yields reported unless stated otherwise. [b]No reaction. [c]Polymerization was observed. [d]Conversion observed in the crude mixture.

Under the optimized conditions, we next investigated the scope of the reaction (Scheme 2). A wide range of hydrazones **1** could react with phenylaziridine and led to the aminohydrazones **3** in excellent yields. The reaction tolerated hydrazones bearing both electron-donating and electron-withdrawing aryl substituents (**3a**-**3i**), 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**-**3m**). The only limitation found was the incompatibility of the Lewis acid with basic amines: *N*-methylindole or pyridine hydrazones were unreactive towards 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**-**3o**). Replacement of $BF_3.OEt_2$ by 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 reacted very well, even in the presence of hindered substituents (**3p**-**3s**) or in the presence of a complex steroid scaffold (**3y**). In the case of the disubstituted aziridines, a mixture of cis/trans diastereoisomers was observed, isolated in excellent combined yields, with a single regioisomer being observed (**3t**-**3w**). The regioselectivity of the ring-opening of the aziridine was confirmed by X-ray crystallography for product **3b** (see SI).

Scheme 2. Scope of the ring-opening reaction[a]

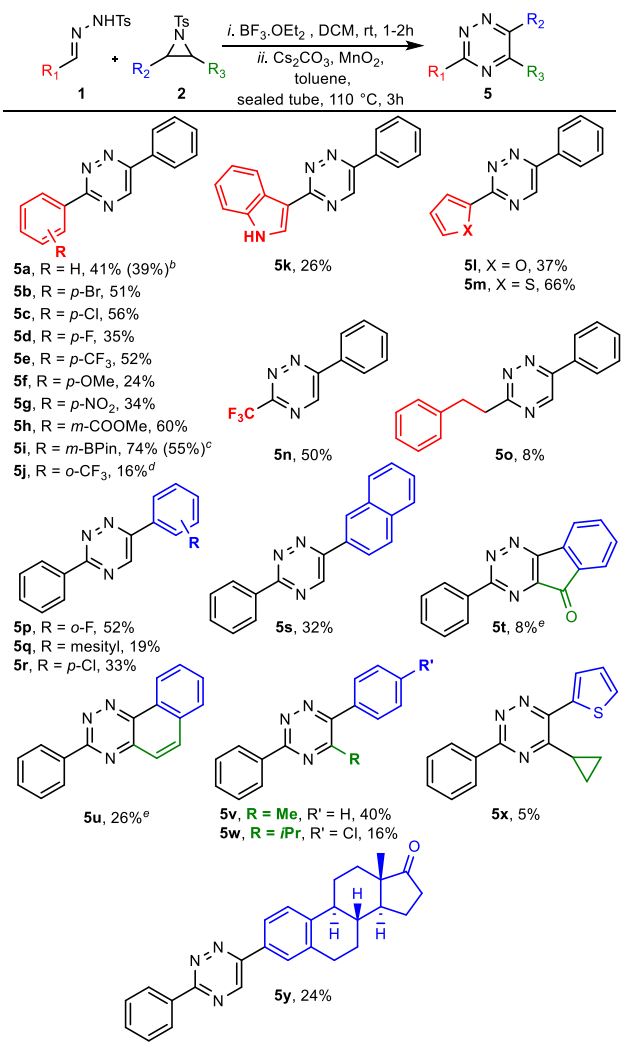


[a]Conditions: **1** (0.2 mmol), **2** (1.2 equiv), $BF_3.OEt_2$ (0.2 equiv), DCM (0.2 M), rt, 1-2h. [b]Reaction performed with $BF_3.THF$ instead of $BF_3.OEt_2$. [c]product unstable to column chromatography,

yield from the crude. [d]dr 50:50. [e]dr 78:22. [f]Product **3x** observed by mass, instable 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 dependant on both solvent and the nature of the base, the reaction occuring only in toluene at 110 °C in the presence of cesium carbonate. With the objective of avoiding the isolation of the dihydrotriazines **4**, activated mangenese dioxide was chosen as the oxidant for its compatibility with the cyclization conditions step[16] 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 SI for the complete optimisation).

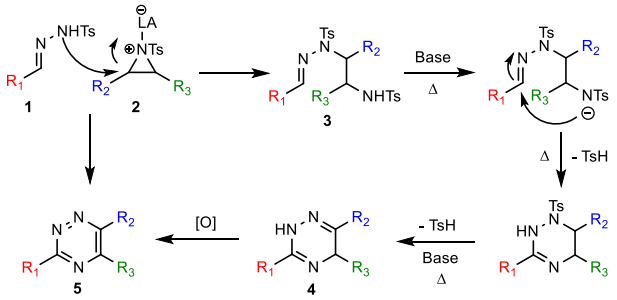
Scheme 3. Scope for the preparation of triazines 5[a]



[a]Conditions: *i*. **1** (0.5 mmol), **2** (1.2 equiv), $BF_3.OEt_2$ (0.2 equiv), DCM (0.2 M), rt, 1-2 h, then concentration. *ii*. Cs_2CO_3 (3.5 equiv), MnO_2 (12 equiv), toluene (0.1 M), sealed tube, 110°C, 3 h. [b]Reaction carried out under reflux of toluene with a condenser instead of a sealed tube. [c]The BPin-substituted triazine was oxidized in alcohol before isolation. [d]Cs_2CO_3 (5 equiv), MnO_2 (16 equiv). [e]Over-oxidation 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 was prepared with moderate to good yields (up to 66%) for the consecutive process (Scheme 3). 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**, **5j**) while the unactivated hydrazone **1o** formed the product **5o** in only 8% yield**.** We were delighted that these conditions also tolerate the useful Bpin functionality (**5i**), allowing further elaboration of the product through cross-coupling reactions.[17] Heteroaryl hydrazones gave the triazine in good yield and, in the case of the indole, the acetyl-nitrogen was deprotected in situ due to the basic conditions of the reaction (**5k**-**5m**). Mono-substituted aziridines were also suitable partners to afford 1,2,4-triazines (**5p**-**5s**). In particular, the sterically hindered mesityl susbtitutent was tolerated (**5q**). Moreover, the natural product-derived triazine **5y** was formed efficiently (**5y**). Two fused-triazines could also be prepared (**5t, 5u**) - isolated in their oxidised form due to benzylic oxidation of the cyclized intermediates. One of the benefits of the "one-pot" procedure is the opportunity to synthezise triazines whose the intermediate **3** would be too unstable to be isolated: despite the aminohydrazone **3x** was highly unstable, the trisubstituted triazine **5x** could be isolated. To finish, even if the formation of the trisubstitued triazines is, for now, limited to alkyl group on the 5-position (**5v**-**5x**) in low to moderate yields, this methodology still offers an access to complex trisusbtituted triazines as single regioisomers. Therefore, our approach compares favorably with the methods using 1,2-diketones which head to regioisomeric mixtures. The 3,5,6-trisubstituted triazines scaffold can also be accessed via a nucleophilic addition/oxidation process on the synthetized 3,6-disubstituted triazines.[18]

Scheme 4. Plausible mechanism for the synthesis of triazines



Mechanistically, 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. The intermediate from the mono-elimination of the tosyl could also be observed during the optimisation using a lower temperature (80 °C) where no second elimination occured. To end the sequence, oxidation of the dihydrotriazine with MnO_2 affords the desired 1,2,4-triazines (Scheme 4).

In conclusion, we have reported a new method to access to the 1,2,4-triazine scaffold via a three-step telescoped reaction sequence using *N*-tosylhydrazones and aziridines. This approach represents a complementary alternative to well-known procedures and affords the 3,6-disusbtituted and 3,5,6-trisusbtituted 1,2,4-triazines in a regioselective manner. The diverse library of triazines synthetized 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.

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

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

AUTHOR INFORMATION

Corresponding Author

* E-mail: svl1000@cam.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by a postdoctoral fellowship from Pfizer (L.C.) and the EPSRC grants EP/K009494/1 and EP/M004120/1 (S.V.L.).

REFERENCES

(1) For recent examples, see: (a) Hudson, M. J.; Boucher, C. E.; Braekers, D.; Desreux, J. F.; Drew, M. G. B.; Foreman, M. R. St J.; Harwood, L. M.; Hill, C.; Madic, C.; Marken, F.; Youngs, T. G. A. *New J. Chem*. **2006**, *30*, 1171. (b) Wolińska, E. *Tetrahedron* **2013**, *69*, 7269. (c) Marandi, F.; Jangholi, M.; Hakimi, M.; Rudbari, H. A.; Bruno, G. *J. Mol. Struct*. **2013**, *1036*, 71. (d) Guillet, G. L.; Hyatt, I. F. D.; Hillesheim, P. C.; Abboud, K. A.; Scott, M. J. *New J. Chem*. **2013**, *37*, 119. (e) Coogan, N. T.; Chimes, M. A.; Raftery, J.; Mocilac, P.; Denecke, M. A. *J. Org. Chem*. **2015**, *80*, 8684. (f) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Geist, A.; Kozhevnikov, V. N.; Distler, P.; John, J. *Chem. Sci.* **2015**, *6*, 4812.

(2) Braun, R.; Waldraff, C.; Dietrich, H.; Gatzweiler, E.; Rosinger, C. H.; Schmutzler, D. *PCT Int. Appl.* **2014**, WO 2014053473 A1 20140410.

(3) Khosneviszadeh, M.; Ghahremani, M. H.; Foroumadi, A.; Miri, R.; Firuzi, O.; Madadkar-Sobhani, A.; Edraki, N.; Parsa, M.; Shafiee, A. *Bioorg. Med. Chem*. **2013**, *21*, 6708.

(4) (a) Yurttaş, L.; Demirayak, S.; Ilgın, S.; Atlı, O. *Bioorg. Med. Chem.* **2014**, *22*, 6313. (b) Karczmarzyk, Z.; Wysocki, W.; Urbańczyk-Lipkowska, Z.; Kalicki, P.; Bielawska, A.; Bielawski, K.; Ławecka, J. *Chem. Pharm. Bull*. **2015**, *63*, 531.

(5) For example, naturally occuring antibiotics fervenulin and toxoflavin contains 1,2,4-triazine moiety. See also: (a) Sztanke, K.; Pasternak, K.; Rajtar, B.; Sztanke, M.; Majek, M.; Polz-Dacewicz, M. *Bioorg. Med. Chem*. **2007**, *15*, 5480. (b) Culakova, H.; Dzugasova, V.; Gbelska, Y.; Subik, J. *Microbiol. Res.* **2013**, *168*, 147.

(6) For example, 1,2,4-triazine core can be found in Lamictal®, an anti-epileptic medication produced by GlaxoSmithKline. See also: Mallikarjuna, B. P.; Suresh Kumar, G. V.; Sastry, B. S.; Nagaraj, Manohara, K. P. *J. Zhejiang Univ. Sc. B*. **2007**, *8*, 526.

(7) Rusinov, V. L.; Egorov, I. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Serova, O. A. *Pharm. Chem. J*. **2012**, *45*, 655.

(8) For selected examples on the hetero Diels Alder cycloadditions with 1,2,4-triazines, see: (a) Boger, D. L. *Chem. Rev*. **1986**, *86*, 781. (b) Raw, S. A.; Taylor, R. J. K. *J. Am. Chem. Soc.* **2004**, *126*, 12260. (c) Sainz, Y. F.; Raw, S. A.; Taylor, R. J. K. *J. Org. Chem.* **2005**, *70*, 10086. (d) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343. (e) Shi, B.; Lewis, W.; Campbell, I. B.; Moody, C. J. *Org. Lett.* **2009**, *11*, 3686. (f) Lorion, M.; Guillaumet, G.; Brière, J-F.; Suzenet, F. *Org. Lett*. **2015**, *17*, 3154.

(9) (a) Rätz, R.; Schroeder, H. *J. Org. Chem*. **1958**, *23*, 1931. (b) Paudler, W. W.; Barton, J. M. *J. Org. Chem*. **1966**, *31*, 1720. (c) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. Eds. Pergamon: Oxford, **1996**, *6*, 50. For recent application of the method, see (d) Zhao, Z.; Leister, W. H.; Strauss, K. A.; Wisnoski, D. D.; Lindsley, C. W. *Tetrahedron Lett.* **2003**, *44*, 1123. (e) Ernd, M.; Heuschmann, M.; Zipse, H. *Helvetica Chimica Acta*, **2005**, *88*, 1491. (f) Laphookhieo, S.; Jones, S.; Raw, S. A.; Fernández Sainz, Y.; Taylor, R. J. K. *Tetrahedron Lett.* **2006**, *47*, 3865. (g) Phucho, T.; Nogpiur, A.; Tumtin, S.; Nongrum, R.; Myrboh, B.; Nongkhlaw, R. L. *Arkivoc*, **2008**, *xv*, 79. (h) Ghorbani-Vaghei, R.; Shahriari, A.; Salimi, Z.; Hajinazari, S. *RSC Adv*. **2015**, *5*, 3665.

(10) (a) Saraswathi, T. V.; Srinivasan, V. R. *Tetrahedron Lett*., **1971**, *25*, 2315. For recent examples, see: (b) see ref. 9e. (c) Kidwai, M.; Sapra, P., Bushan, K. R.; Misra, P. *Synth. Commun.* **2001**, *31*, 1639. (d) Kopchuk, D. S.; Khasanov, A. F.; Kosalev, I. S.; Zyryanov, G. V.; Rusinov, V. L.; Chupakhin, O. N. *Medeleev Commun.* **2013**, *23*, 209.

(11) (a) see ref. 9c, 9d and 10d. (b) Kopchuk, D. S.; Chepchugov, N. V.; Kim, G. A.; Zyryanov, G. V.; Kovalev, I. S.; Rusinov, V. L.; Chupakhin, O. N. *Tetrahedron Lett.* **2016**, *57*, 296.

(12) Other methods for the synthesis of 1,2,4-triazines: (a) see ref. 8e. (b) Lukin, A.; Vedekhina, T.; Tovpeko, D.; Zhurilo, N.; Krasavin, M. *RSC Adv*. **2016**, *6*, 57956. (c) Tang, D.; Wang, J.; Wu, P.; Guo, X.; Li, J-H.; Yang, S.; Chen, B-H. *RSC Adv*. **2016**, *6*, 12514.

(13) Hong, D.; Lin, X.; Zhu, Y.; Lei, M.; Wang, Y. *Org. Lett.* **2009**, *11*, 5678.

(14) The acid-catalyzed *N*-alkylation of hydrazones has only been reported in two publications in the presence of alcohol substrates: (a) Reddy, C. R.; Jithender, E. *Tetrahedron Lett.* **2009**, *50*, 5633. (b) Theerthagiri, P.; Lalitha, A. *J. Iran. Chem. Soc.* **2013**, *10*, 717.

(15) From a safety issue point of view, more particularly during larger scale reactions for industry, replacement of $BF_3.OEt_2$ by $BF_3.THF$ was possible, with no significant drop of the yield.

(16) DDQ also worked but the resulting phenolate was co-eluting with the formed triazines. $KMnO_4$ was also a suitable oxidant but MnO_2 was chosen for its midler activity towards functional groups.

(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. USA* **2015**, *112*, 12026.

(18) (a) Konno, S.; Sagi, M.; Yuki, Y.; Yamanaka, H. *Heterocycles* **1985**, *23*, 2807. (b) Khasanoc, A.; Kopchuk, D. S.; Kovalev, I. S.; Taniya, O. S.; Zyryanov, G. V.; Rusinov, V. L.; Chupakhin, O. N. *Medeleev Commun.* **2015**, *25*, 332. (c) Utepova, I. A.; Trestsova, M. A.; Chupakhin, O. N.; Charushin, V. N.; Rempel, A. A. *Green Chem*. **2015**, *17*, 4401.

(19) For reviews on the nucleophilic ring-opening of aziridines and its regioselectivity, see: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701. (b) Padwa, A.; Murphree, S. S. *Arkivoc* **2006**, *iii*,6.