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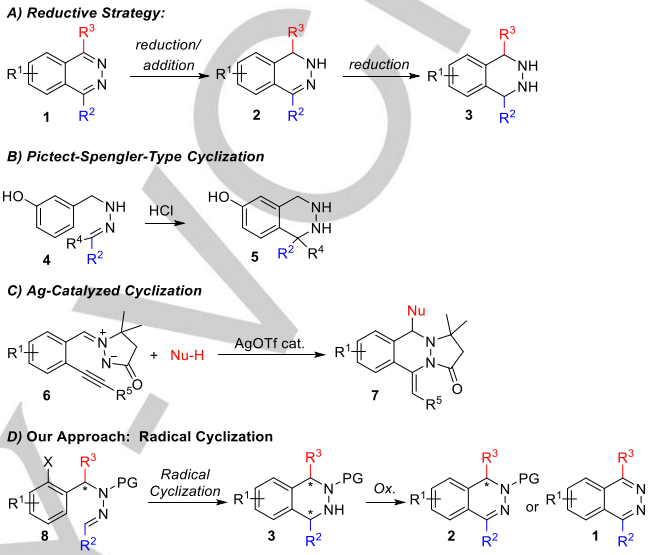
Regiocontrolled and Stereoselective Syntheses of Tetrahydrophthalazine Derivatives using Radical Cyclizations

Wei Zhang, Jia Yi Mo, Weiying He, Pierre Kennepohl, and Glenn M. Sammis*

Abstract: *Tetrahydrophthalazine derivatives have found important applications in pharmaceutical research, but existing synthetic methods are unable to access them regio- and stereoselectively. Herein, we present a new approach that addresses these challenges by utilizing a 6-endo-trig radical cyclization in the key step. The desired tetrahydrophthalazines can be accessed in high yields (55-98%) and high diastereoselectivities for the trans-product (>95:5) starting either from readily accessible hydrazones, or from the corresponding aldehydes and substituted Boc-hydrazides in a one-pot process. The synthetic versatility of the tetrahydrophthalazine core was demonstrated by its straightforward conversion to dihydro-phthalazines, phthalazines, or pyrazolo dione derivatives. Furthermore, the N-N bond can readily be reduced to afford a new route to 1,4-diamines.*

Nitrogen heterocycles are prevalent in bioactive molecules and represent 59% of the U.S. FDA approved small-molecule drugs.[1,2] The pharmaceutical importance of these heterocycles has led to substantial research into the development of new synthetic technologies for their preparation.[3] Considering the vast diversity and variability of nitrogen-containing rings,[1,4] there are still many pharmaceutically interesting substituted heterocycles that cannot be regio- and stereoselectively accessed using existing synthetic technology. Two such examples are di- (Scheme 1A, **2**) and tetrahydrophthalazines (**3**), which have been found to have important medicinal activities.[5] These heterocycles are commonly accessed by first synthesizing the requisite high-oxidation state phthalazine (**1**), followed by sequential additions or reductions to afford the desired reduced analogs (**2** or **3**)[5,6] This approach has two limitations: it can be challenging to regioselectively synthesize the starting phthalazine (**1**, if $R^1 \neq H$) efficiently,[5e,6a-b,7] and there is no demonstrated stereocontrol in the subsequent addition/reduction steps.[5a,5e,6c-d] A more direct approach would be a cyclization to form the diazene ring. There are only a few examples of ionic cyclizations, including a Pictet-Spengler-type cyclization (Scheme 1B)[8] and a silver-catalyzed cyclization (Scheme 1C),[9] and they are limited to electron-rich arenes (R^1=electron donating groups), have a narrow substituent scope at R^2, or can only access specific substitution patterns (**7**). As a result of all of these challenges, there are currently no efficient and stereoselective routes to many substituted di- and tetrahydrophthalazine analogs. Most notably, there are no literature examples of stereoselective routes to 1,4-disubstituted tetrahydrophthalazines (**3**).



Scheme 1. Strategies for the syntheses of phthalazine derivatives.

We hypothesized that we could directly access tetrahydrophthalazine derivatives from a *6-endo-trig* radical cyclization of a suitably-substituted hydrazone (Scheme 1D, **8**). Unlike previous synthetic methods of phthalazine, this radical cyclization method allows for complete control of substituents at R^1, R^2, and R^3, which provides a direct route to unsymmetric phthalazine derivatives (**1**, **2**, and **3**). Furthermore, the stereocenter in the starting material (**8**) may influence the diastereoselectivity of the cyclization, allowing for a diastereoselective route to 1,4-disubstituted tetrahydrophthalazines (**3**).

This radical cyclization is not only an unprecedented approach for the syntheses of phthalazine derivatives, but also involves an underexplored *6-endo* cyclization onto a C=N bond. While many synthetic studies have examined radical cyclizations onto C=N-R containing functional groups, such as oximes,[10] imines,[11] and hydrazones,[12] most of them have focused on the *exo*-cyclizations.[13] There are no examples of *6-endo* cyclizations onto oximes, and the only *6-endo* hydrazone cyclization was demonstrated by our group in a method that featured cyclization of a vinyl radical with a hydrazone to afford a transient tetrahydropyradazine radical.[12w] Unfortunately, this method was unsuccessful with aryl hydrazones, which are essential to access biologically active aryl-substituted phthalazine derivatives. We, therefore, sought to develop a new, general method for the efficient *6-endo-trig* cyclization of Boc-hydrazone **8**.

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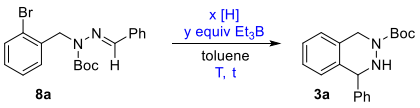
To ensure optimized conditions would work for aryl substitution at R^2, we began our investigations into the radical cyclization of benzaldehyde-derived hydrazone **8a** (Table 1).[14] When triethylborane was used as a radical initiator with slow addition of tributyltin hydride, tetrahydrophthalazine **3a** was formed in poor conversion (entry 1). However, quantitative conversion was achieved when the tin reagent was added in one portion (entry 2). We next examined the less toxic[15] reagent *tris*(trimethylsilyl)silane (TTMSS)[16] and found that it could also effectively promote the cyclization with comparable conversion (entry 3), although the reaction was considerably slower. The long reaction time could be significantly decreased by using an elevated reaction temperature (entry 4).

Table 1. Optimization of the radical cyclization of hydrazone **8a**.

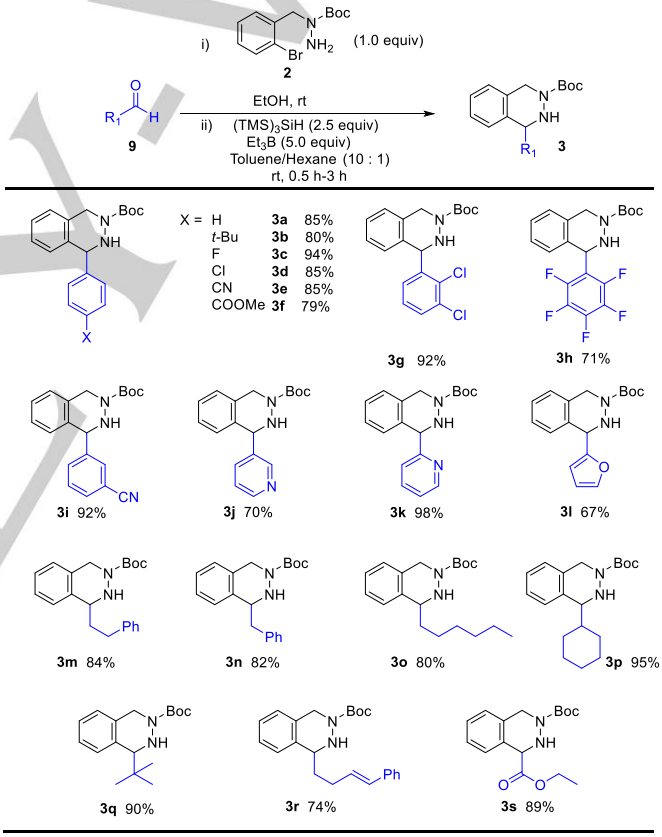


Entry	x [H]	y (Et_3B)	T (°C)	t (h)	Conversion (%)[d]
1[a][b]	1.5 equiv Bu_3SnH	10	-78→rt	6	28
2[a]	1.5 equiv Bu_3SnH	10	-78→rt	6	>95
3[a]	3.0 equiv $(TMS)_3SiH$	10	-78→rt	52	91
4[a]	3.0 equiv $(TMS)_3SiH$	10	50	6	>95
5[c]	3.0 equiv $(TMS)_3SiH$	10	50	6	>95
6[c]	2.5 equiv $(TMS)_3SiH$	10	50	6	>95
7[c]	2.0 equiv $(TMS)_3SiH$	10	50	6	85
8[c]	2.5 equiv $(TMS)_3SiH$	5	50	6	>95
9[c]	2.5 equiv $(TMS)_3SiH$	2.5	50	6	54
10[c]	**2.5 equiv $(TMS)_3SiH$**	**5**	**rt**	**1.5**	**>95 (87)[e]**

All optimization reactions were run on 0.10 mmol scale and Et_3B was purchased as a 1.0 M solution in hexanes in inert atmosphere. Boc = *tert*-butoxycarbonyl, rt = room temperature. [a] Reactions were run under N_2 atmosphere with anhydrous toluene as the solvent. [b] [H] reagent was added slowly as a 0.2 M solution in anhydrous toluene over 4 h. [c] Reactions were run under air atmosphere with toluene that was not specially dried. [d] Conversions to **3a** were determined via ^1H NMR spectroscopy of the crude reaction mixture. [e] Isolated yield on 1.5 mmol scale.

Further trials revealed that the reaction was sufficiently robust to allow for comparable conversions using open-flask conditions with toluene that had not been specially dried (entry 5). Optimization of the equivalents of TTMSS (entries 6-7), triethyl borane (entries 8-9), and temperature (entry 10) resulted in conditions that could effect near-quantitative cyclization in only 1.5 hours at room temperature (entry 10). To improve the efficiency of this cyclization process, we next investigated the possibility of achieving more direct access to the tetrahydrophthalazine directly from the aldehyde. After optimization, we were able to achieve a one-pot process, with a solvent switch, to afford the final product without any degradation in yield (Scheme 2, **3a**) compared to the two-step protocol (Table 1, entry 10).

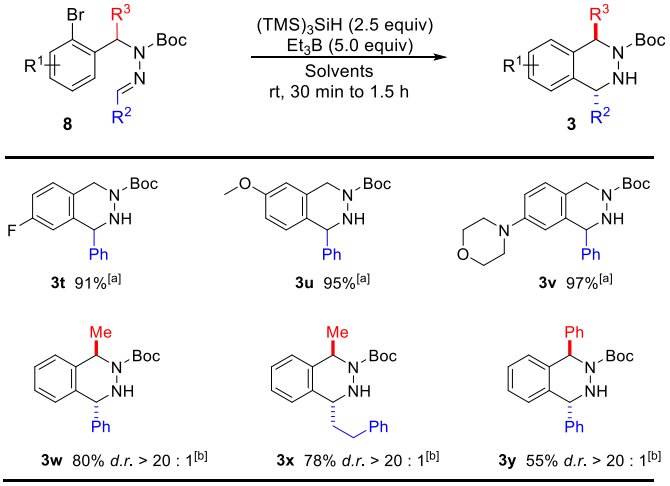
With optimized conditions established, we next explored the scope of this new cyclization methodology (Scheme 2). The reaction afforded high isolated yields of the desired tetrahydrophthalazine (**3**), regardless of whether the R^2 arene contained electron donating (**3b**) or electron withdrawing groups (**3c**-**3i**).[17] The cyclization was also effective for heterocycles, such as pyridine (**3j**-**3k**) and furan derivatives (**3l**), affording the tetrahydrophthalazine products in 57-96% yield. Aliphatic aldehydes were shown to be compatible in the reactions to form alkyl tetrahydrophthalazine products (**3m**-**3r**) in good to excellent yields regardless of steric hindrance. A substituted alkene could also be tolerated in the sidechain (**3r**).[18] Glyoxylate-derived **3s** was also efficiently synthesized in 89% yield.



Scheme 2. Syntheses of 1-substituted tetrahydrophthalazines from aldehydes **9** and hydrazide **2**. Reactions were carried out on a 0.20 to 0.40 mmol scale for 0.5 h to 3 h and Et_3B was purchased as a 1.0 M solution in hexanes in inert atmosphere. Boc = *tert*-butoxycarbonyl, rt = room temperature.

With the fundamental cyclization reactivity established, we next examined the syntheses of unsymmetrical and 1,4-disubstitutued tetrahydrophthalazine derivatives (Scheme 3). The cyclization proceeded efficiently with either electron withdrawing (**3t**) or electron donating groups (**3u, 3v**) on the hydrazide arene. We then investigated the cyclization diastereoselectivity starting with hydrazide derivatives with

substitution at R^3 (**3w**-**3y**). Under our standard reaction conditions, we observed only a moderate yield of cyclized product along with a significant amount of uncyclized, dehalogenated product. After a brief optimization, we were able to effect the desired cyclization to achieve cyclized product **3w** in high yield exclusively as the 1,4-*trans*-diastereomer.[19] Similarly good to high yields could be achieved with alkyl or aryl groups at R^2 and R^3 (entries **3x**, **3y**) in very high diastereoselectivities.



Scheme 3. Syntheses of multi-substituted tetrahydrophthalazines from hydrazone **8**. Reactions were carried out on 0.14 to 0.30 mmol scale for 30 min to 1.5 h. [a] Toluene/hexanes (10:1) were solvents. [b] MeOH/hexanes (10:1) were solvents. Boc = *tert*-butoxycarbonyl, rt = room temperature.

To explain the observed diastereoselectivities, we conducted computational studies on two cyclization pathways for substrate **8w** leading to the *trans* and *cis* products. Calculations indicated that the lowest energy transition states (TS) have boat-like conformations with methyl at the pseudo-axial position to avoid 1,3-strain from Boc group (Figure 1). In the optimized transition state (TS2) leading to the *cis* product, there is a significant steric interaction between the phenyl group on the hydrazone and the methyl group. This interaction is absent in the transition state (TS1) leading to the *trans* product, which decreases the $\Delta\Delta G^{\ddagger}$ by approximatedly 5 kcal/mol.[20]

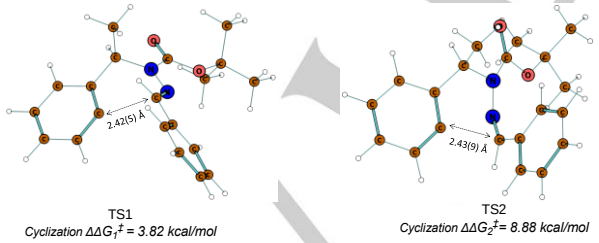
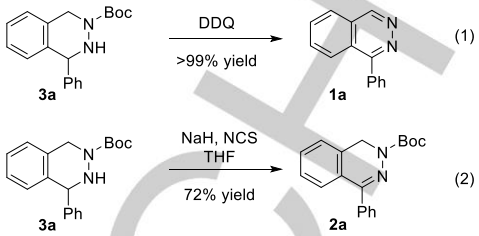


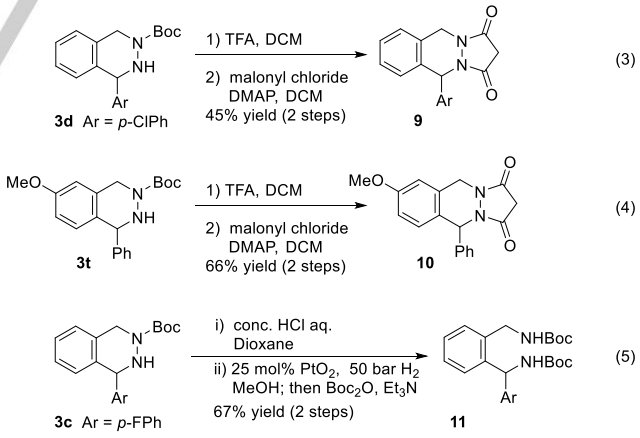
Figure 1. The calculated transition states and corresponding energy barriers of two pathways.

The oxidation state of the tetrahydrophthalazine rings can be readily modified to access substituted phthalazines (eq. 1) and dihydrophthalazines (eq. 2). Oxidation of the tetrahydrophthalazine (**3a**) with DDQ affords desired phthalazine **1a** in quantitative conversion and 99% yield.[21] Similarly, the starting tetrahydrophthalazine can be selectively oxidized to the corresponding dihydrophthalazine (**2a**) by treatment with NaH and NCS, to afford the product in 72% yield.



To test the synthetic versatility of this new cyclization methodology, we next investigated whether the tetrahydrophthalazine core could be converted into pyrazolo dione **9**, a key intermediate towards the synthesis of an active central nervous system depressant (eq. 3).[5a] Gratifyingly, a simple two-step sequence involving Boc deprotection followed by treatment with malonyl chloride[22] afforded **9** in 45% yield. Compared to existing synthetic routes, our new methodology has the advantage of being able to selectively access derivatives of **9** with substitution on the tetrahydrophthalzidine arene. For example, methoxy-substituted product **10** can readily be prepared in only 2 steps from cyclized product **3t** (eq. 4) in 66% yield.

Another advantage of directly accessing the tetrahydrophahalazine is that it provides a versatile and rapid route to 1,4-diamine derivatives through N-N bond reduction (eq. 5). As a representative example, tetrahydrophahalazine **3c**, can be converted to the corresponding diamine (**11**) in high yield using a one-pot process involving deprotection, followed by reduction of the N-N bond,[23] and Boc protection.



Overall, we have developed a novel one-pot process for the syntheses of tetrahydrophthalazines from aldehydes and hydrazides utilizing a key *6-endo-trig* radical cyclization onto a hydrazone. Not only does this approach represent a new class of radical cyclization onto hydrazones, but also it proved to be an efficient, robust, and high yielding method to access tetrahydrophthalazines regardless of the electronics of the starting aldehydes. This new cyclization also provides the first method for the highly stereoselective syntheses of *trans*-1,4-

disubstituted tetrahydrophthalazines. Further synthetic manipulation demonstrated versatility of the heterocycle products as precursors to oxidized phthalazine analogs, such as dihydro- and aromatic phthalazines, or to pyrazolo diones. The synthetic versatility of the tetrahydrophthalazines was also highlighted in a new route to 1,4-diamines. It's anticipated that our new methodology will provide access to a greater diversity of these heterocycles and diamines for further pharmaceutical and synthetic development.

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Keywords: nitrogen heterocycle • tetrahydrophthalazine • radical cyclization • hydrazone • synthetic methods

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[13] Compared to hydazones, exo radical cyclizations for imines differ by approximately 2 orders of magnitude (ref 12t). For representative reports on *6-endo-trig* cyclization to imines see Ref. 11a, 11b, 11d, and 11f-n. The imine cyclization conditions developed in ref 11d were unsuccessful when applied to hydrazones.

[14] Hydrazone **8a** can be readily synthesized via two routes: alkylation of the hydrazide followed by hydrazone formation, or hydrazone formation first, followed by alkylation. See the Supporting Information for more information.

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[17] Dehalogenated products were observed in less than 5% yields in reactions using aldehydes **9a** and **9h**.

[18] No products resulting from radical cyclization with the alkene on the sidechain were observed.

[19] The relative configuration of the 1,4-stereocenters was determined by nOe NMR experiments. See the Supporting Information for details.

[20] See the Supporting Information for details of the computational studies.

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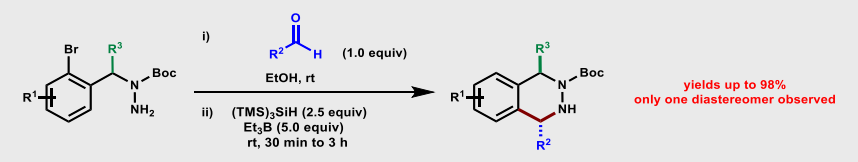

*Wei Zhang, Jia Yi Mo, Weiying He, Pierre Kennepohl, and Glenn M. Sammis**

Page No. – Page No.

Regiocontrolled and Stereoselective Syntheses of Tetrahydrophthalazine Derivatives using Radical Cyclizations