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A Straightforward Approach toward Multifunctionalized Pyridazines via Imination/Electrocyclization

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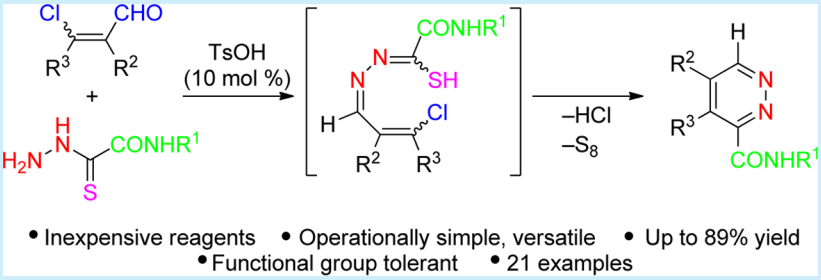
Supporting Information



ABSTRACT: A facile synthesis of functionalized 3-carbamide pyridazines starting from readily available chlorovinyl aldehydes and oxamic acid thiohydrazides via cascade imination/electrocyclization is reported. In the presence of *p*-toluenesulfuric acid, various ketones have been efficiently incorporated into the pyridazine derivatives through a two-step sequence involving a Vilsmeier–Haack reaction and imination. The synthetic value of this method has been demonstrated by efficient synthesis of steroidal pyridazines.

Pyridazines are an important structural subunit found in a variety of biologically active agents, including a number of natural products (e.g., Pyridazomycin[1] and Azamerone[2]) and major drugs (e.g., antihypertensive - hydralazine, dihydralzine, endralazine;[3] antidepressants - pipofezine, minaprine).[4] The prevalence of the pyridazine motif in medicinally relevant compounds,[5] dyes,[6] ligands for metal catalysts,[7] and crystal engineering[8] has inspired the development of many novel methods for their preparation.[9] However, there are only limited protocols for assembling 3-carbonyl substituted pyridazine derivatives, important intermediates in organic synthesis.[10] Traditional methods include diaza-Wittig reactions of 1,3-diketones,[11] addition of diazo compounds to Morita–Baylis–Hillman carbonates,[12] [4 + 2] cycloaddition of substituted 1,2,3-triazines,[13] cascade reactions of pyridiniumylides,[14] and cycloaddition of 1,2,4,5-tetrazine with alkynes.[15] Despite the impressive progress made in this area, it is still a great challenge to synthesize functionalized pyridazines from readily available and easily varied starting materials using a simple procedure. Known methods suffer from the requirements of a stringent anaerobic procedure, harsh conditions, and limited substrate scope.

On the other hand, electrocyclic processes are valued for their mild reaction conditions, excellent functional group tolerance, and ability to produce six-membered aromatic rings. There have been a number of reports over the past decade demonstrating the utility of azahexatrienes for synthesis of pyridines,[16] 1,2-dihydropyridines,[17] and pyrimidines.[18] In particular, transformations of 1-ethoxy-4-azahexatrines **1** into pyridines **2**[16b] and cyclization of 1-dimethyamine-2,4-azahexatrienes **3** to give pyrimidines **4**[18] should be mentioned. To the best of our knowledge, diazahexatrienes in the synthesis of pyridazines are unknown to date.

Reasonably, we proposed a 2,3-diazahexatrienyl system bearing a carbonyl group along with a good leaving group can be effective for 3-carboxy pyridazine construction (Scheme 1). Initial sourcing of 2,3-azahexatrienyl synthons possessing a carboxy moiety clued us to hydrazones of oxamic acid thiohydrazides.[19] Distinctive thione–thiol tautomerism together with the SH good leaving group character made them highly promising substrates for transformations. The presence of a chlorine atom in their structure could favor the aromatization step, whereby we intensely examined *β*-chlorohydrazones **5** as precursors for pyridazines **6**. Note that hydrazones **5** are readily available from ketones by the Vilsmeier–Haack reaction and subsequent imination with oxamic acid thiohydrazides.

We initiated our investigation on the model reaction of chlorovinyl aldehyde **8a** derived from 2-hexanone (**7a**) with hydrazide **9a** in the presence of TsOH (10 mol %) to optimize various reaction parameters. Full data concerning the optimization of temperature (rt → 120 °C), solvent (toluene, $CHCl_3$, CH_3CN, EtOH, 2-methoxyethanol), and amounts of the reagents are presented in the Supporting Information. It was found the principal result was the formation of pyridazines **10a** as the major product in all cases (Scheme 2).

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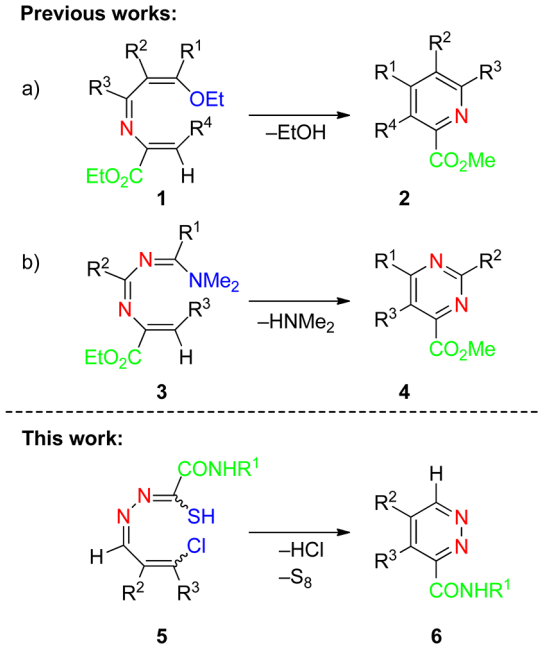
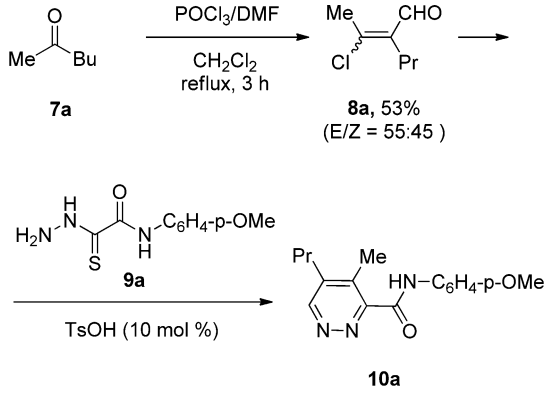
Scheme 1. Azahexatrienes in the Synthesis of Carboxy Substituted Azaheterocycles



Scheme 2. Initial Probe Experiment

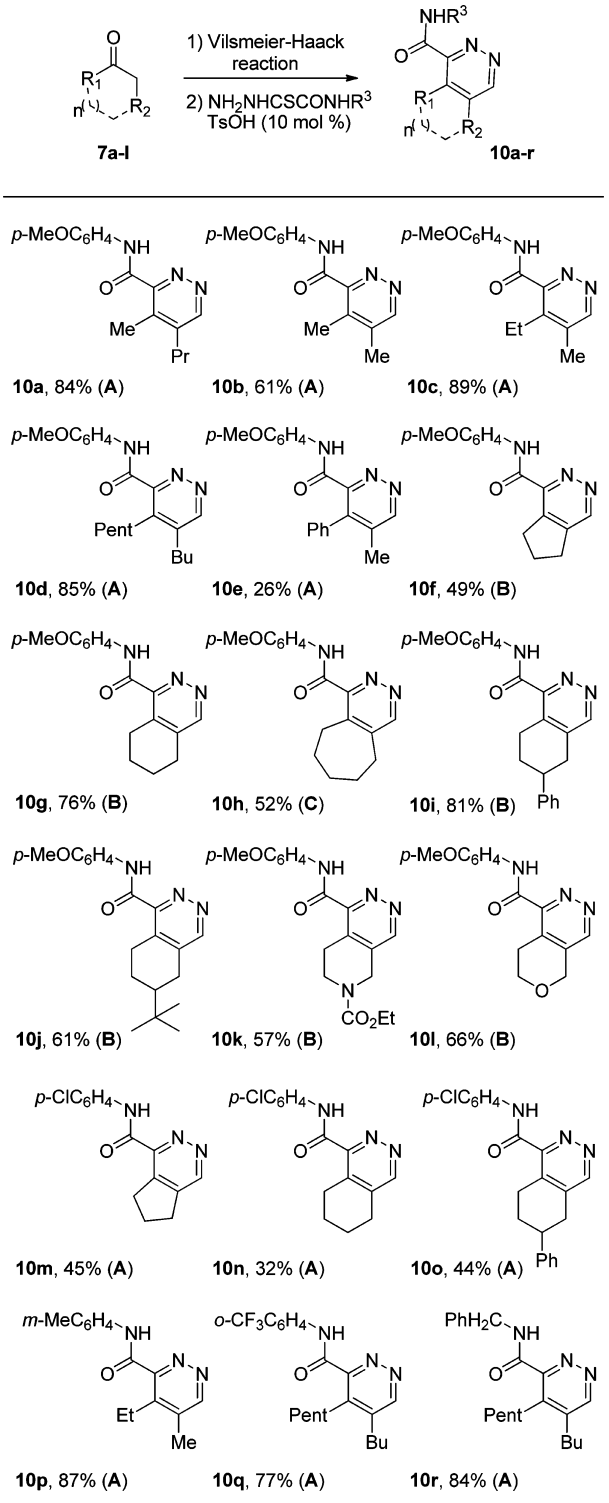


Heterocyclization proceeded smoothly even at room temperature, and complete conversion of the starting material was achieved within 18 h with a good yield of pyridazine **10a**. Solvent effect was not observed; reactions in toluene and 2-methoxyethanol gave comparable yields of product **10a** (80% and 83%, respectively). The best result was obtained by performing the reaction in refluxing 2-methoxyethanol for 5 min to afford compound **10a** in 84% yield (Scheme 3).

With optimal reaction conditions in hand, we studied the use of various ketones **7b–l** as well as different hydrazides **9b–d** to synthesize a variety of 3-carbomide-4,5-disubstituted pyridazines derivatives (Scheme 3). Three general procedures differing in temperature (**A**, 120 °C; **B**, 80 °C; **C**, rt) and solvent were applied in accordance with the intermediate chlorovinyl aldehyde thermal stability.

It was found that this method is quite general since both symmetrical and asymmetrical linear aliphatic ketones reacted smoothly providing diverse pyridazines **10a–d** in excellent yields. Cyclic aliphatic ketones, such as cycloheptanone, -hexanone, and -pentanone, produced the corresponding pyridazines **10f–j** in slightly lower yields (49–81%) that can

Scheme 3. Substrate Scope of Cyclization[a–c]



[a]Reaction conditions: (**A**) aldehyde **8** (0.22 mmol), hydrazide **9** (0.22 mmol), and TsOH (10 mol %) in 2-methoxyethanol (2.5 mL) at 120 °C for 5–10 min; (**B**): aldehyde **8** (0.22 mmol), hydrazide **9** (0.22 mmol), and TsOH (10 mol %) in ethanol (2.5 mL) at refux for 5 min–2 h; (**C**) aldehyde **8** (0.22 mmol), hydrazide **9** (0.22 mmol), and TsOH (10 mol %) in ethanol (2.5 mL) at rt overnight. [b]Isolated yield. [c]Yield calculated with respect to intermediate chlorovinyl aldehyde purity.

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be attributed to decomposition side processes and low solubility of products.

In addition, a 4-tetrahydropyranone **7k**, as well as a 4-piperidone **7l**, was tolerated under these reaction conditions. Substituted 7,8-dihydro-5*H*-pyrano[3,4-*d*]pyridazine **10k** and 5,6,7,8-tetrahydropyrido[3,4-*d*]pyridazine **10l** were obtained in 57% and 66% yields. The reaction could also be performed with aromatic ketones, namely, propiophenone **7e**, producing the corresponding product **10e** in reasonable yield.

Diverse hydrazydes **9a−d** bearing MeO, Me, CF_3, Cl groups in *ortho*-, *meta*-, and *para*-positions were well tolerated under the reaction conditions to give the corresponding pyridazines **10m,n,p−q** in moderate to good yields. In addition to arylamides, benzyl derivative can also be employed to form the corresponding **10r** in 84% yield.

The structures of pyridazines **10** were confirmed by single crystal X-ray analysis of the representative compound **10b** (Figure 1). The structures of **10j,k,m−o** were supported by 2D NMR ($^{13}C-^{1}H$ HMBC and HSQC) techniques.

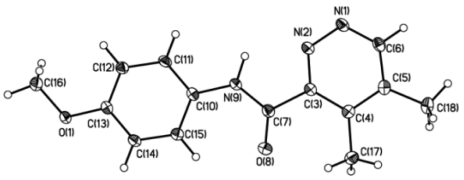


Figure 1. General view of X in representation of atoms by thermal ellipsoids (p = 50%) for compound **10b**.

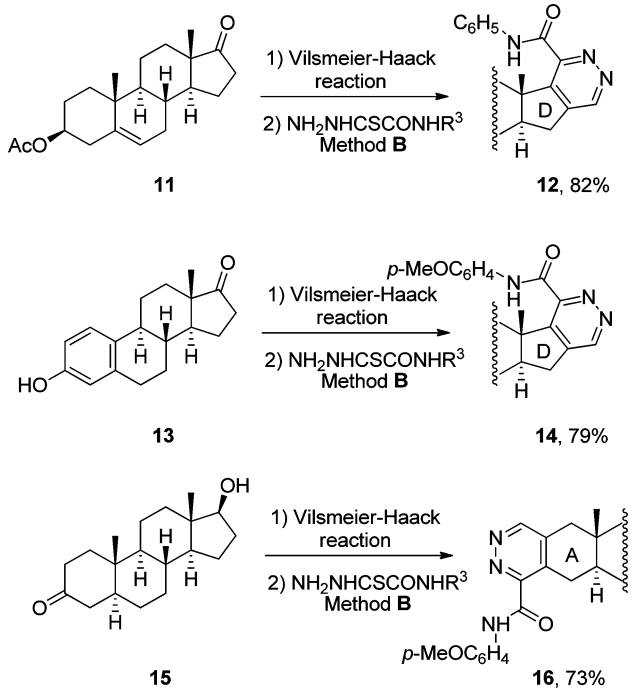
Having established a framework of the method with relatively simple molecules, we extended this method to complex natural products. In this respect, we turned to steroids, one of the largest and most diverse class of natural products.[20] Heterosteroids bearing annulated azaheterocycles are known to exhibit a wide range of biological activities, e.g., antiinflammatory,[21] antimicrobial,[22] antiproliferation,[23] and antitumor properties.[24] We first examined 3β-hydroxyandrost-5-en-17-one **11** and estrone **13** under standard conditions (Scheme 4).

It was found that both compounds **11** and **13** were readily transformed into the corresponding D-ring annulated steroidal pyridazines **12** and **14** (82% and 79%, respectively) upon subsequent treatment with Vilsmeier−Haack reagent and oxamic acid thiohydrazides **9a,e** in the presence of catalytic amounts of TsOH (Scheme 4). A-Ring annulated steroidal pyridazine **16** was obtained similarly from dihydrotestosterone **15** in 73% yield.

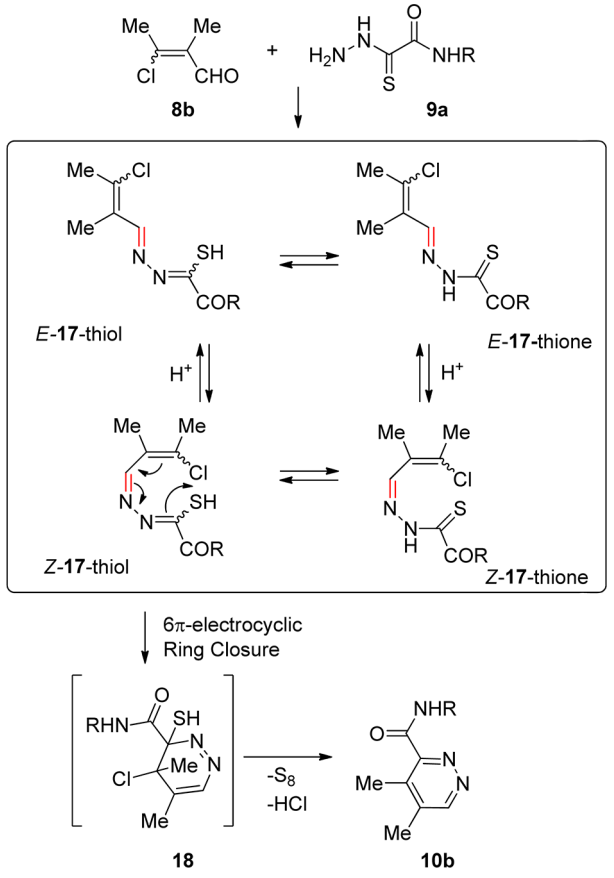
The possible mechanism for the formation of pyridazines **10** by the reaction of chlorovinyl aldehyde **8** with oxamic acid thiohydrazides **9** is shown in Scheme 5 illustrating an example of product **10b**. Imination of the aldehyde **8b** with **9a** under acid catalysis produces 2,3-azahexatirene intermediate **17**. The *E*/*Z*-geometric isomers and thiol−thione tautomers equilibrate under the reaction conditions, and the *Z*-**17**-thiol isomer undergoes 6π-electrocyclization to afford an intermediate dihydropyridine **18**. Rapid hydrochloric acid and molecular sulfur elimination deliver the observed pyridazine product **10b**. The last step was confirmed experimentally since sulfur was isolated in equimolar amounts in all reactions.

The mechanistic rationalization of the observed cyclization remains, at least in part, speculative. The simultaneous presence of a nucleophilic SH-center and electrophilic chlorovinyl

Scheme 4. Synthesis of Steroidal Pyridazines



Scheme 5. Proposed Mechanistic Pathway



moiety in hydrazone **17b** makes possible nucleophilic cyclizations to occur. However, computational studies on activation barriers and heat of the presented disrotatory electrocyclization reaction were found to be without a rival

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low ΔH_r = 6−12 kcal/mol, $E_A^{\ddagger}$ = 2.4−8 kcal/mol [B3LYP/6-311+G(d,p) and semiempirical PM6].[25]

In summary, a novel effective approach to the synthesis of pyridazines by the two-stage procedure from ketones was described. The approach employs simple reactions comprising (1) Vilsmeier−Haack reaction of enolizable ketone leading to chlorovinyl aldehydes and (2) imination of the former with oxamic acid thiohydrazides and cascade electrocyclization/aromatization of the resulting 2,3-diazatriene affording highly substituted pyridazines in moderate to excellent isolated yields (32−89%). Starting materials are readily available, and functional group tolerance is quite good. The ease of 2,3-diazahexatriene system construction and the broad availability of reagents imply that an extensive range of substituents can be selectively incorporated in the pyridazine ring. The full potential of this methodology and an exploration of a greater variety of substituents must await additional studies.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all products, and the X-ray data for **10b** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01718.

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Notes

The authors declare no competing financial interest.

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