SHORT COMMUNICATION

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Efficient Synthesis of Dihydropyrazoles by Halocyclization of β,γ-Unsaturated Hydrazones

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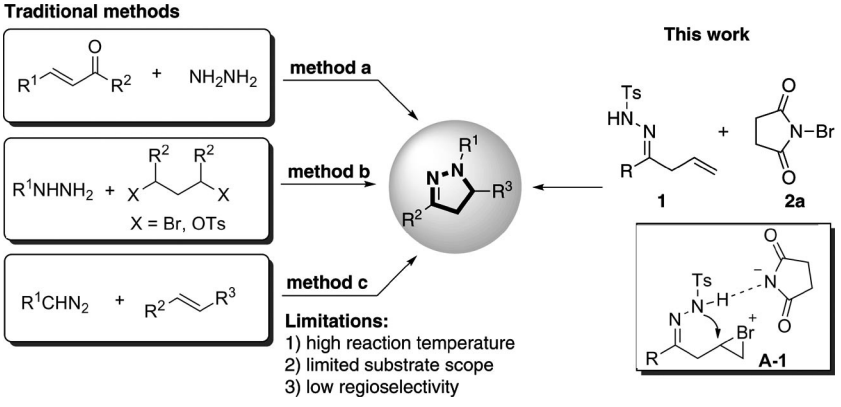
An efficient halocyclization of β,γ-unsaturated hydrazones with *N*-bromosuccinimide was developed without the addition of any additives under mild reaction conditions to provide facile access to biologically important 4,5-dihydropyrazoles. Under the optimized conditions, a variety of highly substituted 4,5-dihydropyrazole derivatives were obtained in generally good yields. Moreover, this reaction can be further applied to the synthesis of pyrazoles in a one-pot fashion.

Introduction

Five-membered nitrogen heterocycles are an important class of compounds, and this structural motif exists widely in many nature products, biologically active molecules, and pharmaceuticals.[1] These heterocycles have also been identified as valuable synthetic building blocks and chiral ligands in asymmetric catalysis.[2] In this context, "privileged" dihydropyrazoles and their derivatives exhibit a broad spectrum of biological activities, including anticancer, antiviral, anti-inflammatory, hypotensive, and antidiabetic activities.[3] Not surprisingly, extensive efforts have been directed toward the synthesis of these scaffolds over the last decades. Typically, the dihydropyrazole architecture can be constructed through the following three ways: cycloaddition reactions of hydrazines with α,β-unsaturated aldehydes or ketones (Scheme 1, method a),[4] microwave-assisted cyclocondensation reactions between alkyl dihalides and hydrazines (Scheme 1, method b),[5] and 1,3-dipolar cycloaddition of diazoalkanes or nitrilimines with alkenes



Scheme 1. Reaction design: intramolecular annulation of β,γ-unsaturated hydrazones with NBS; Ts = *p*-tolylsulfonyl.

(Scheme 1, method c).[6] However, the relatively high reaction temperature and the limited substrate scope of methods a and b, to some extent, limit their broad application in synthetic chemistry, whereas method c sometimes leads to mixture of regioisomers owing to the poor regioselectivity of the cycloaddition process in some cases. Therefore, the development of new and more efficient methods for the construction of diversely substituted dihydropyrazoles is still desirable.

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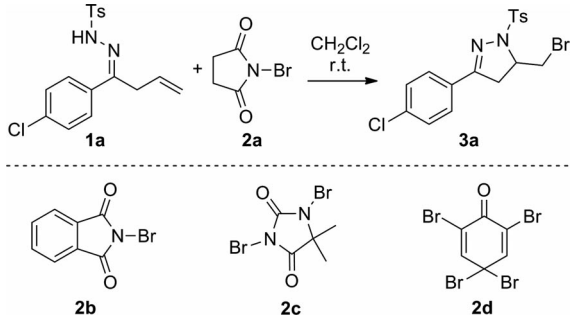
Recently, hydrazones have emerged as versatile reagents as a result of their unique properties and high reactivity.[7,8] Despite advances, β,γ-unsaturated hydrazones remain largely unexploited. In 2013, Loh's group developed a radical-mediated annulation of azodicarboxylates with arylhydrazines to afford highly substituted and functionalized *trans*-diamines.[9] At almost the same time, Han and coworkers independently reported an interesting (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO-) or diisopropyl azodicarboxylate (DIAD)-initiated intramolecular cycloaddition of hydrazone radicals with C=C bonds at high temperature to give the corresponding pyrazolines and tetrahydropyridazines in high yields.[10] As part of our ongoing program on the chemistry of hydrazones[11] and the construction of synthetically useful and biologically important carbo- and heterocycles,[12] we recently reported the first example of the [4+3] cycloaddition of diazadienes generated in situ from α-halo hydrazones with C,N-cyclic azomethine imines to produce various 1,2,4,5-tetrazepine derivatives.[11a] Subsequently, we also developed an enantioselective inverse-electron-demand hetero-Diels–Alder reaction between diazadienes and enol ethers by using a copper/bisoxazoline complex as the catalyst to give enantioenriched pyridazine derivatives in good yields with good enantioselectivities.[11b] Inspired by these works, we envisage the possibility of the intramolecular annulation of β,γ-unsaturated hydrazones **1** with *N*-bromosuccinimide (NBS, **2a**; Scheme 1). In the design, the C=C bond of the β,γ-unsaturated hydrazone might be first activated by NBS to form bromonium ion intermediate **A-1**, which then undergoes intramolecular addition by the nitrogen atom (Scheme 1).[13,14] Importantly, the reaction would provide facile access to 4,5-dihydropyrazole derivatives. In this communication, we wish to disclose our preliminary results.

Results and Discussion

Initially, we selected β,γ-unsaturated hydrazone **1a** and NBS (**2a**) as the model substrates to examine the feasibility of the intramolecular annulation reaction. To our delight, the reaction worked smoothly without the addition of any additive in CH_2Cl_2 at room temperature, and corresponding dihydropyrazole **3a** was obtained in 96% yield within 10 min (Table 1, entry 1). To further improve the reaction efficiency, some other commonly used bromine sources were then investigated. Commercially available bromine sources such as **2b**, **2c**, and **2d** were also tolerated in this transformation, although decreased yields were observed (Table 1, entry 1 vs. entries 2–4). With the optimal bromine source established, that is **2a**, we briefly screened the reaction media. It was found that halogenated solvents such as CH_2Cl_2, $CHCl_3$, and $Cl(CH_2)_2Cl$ gave comparable yields (Table 1, entries 1, 5, 6), whereas the use of PhMe or EtOAc as the solvent decreased the reaction efficiency (Table 1, entries 7 and 8). The use of THF led to only a moderate yield as a result of a complex reaction mixture (Table 1, entry 9). Accordingly, CH_2Cl_2 was chosen as the best solvent for further study.

Table 1. Optimization for the synthesis of dihydropyrazole **3a**.[a]



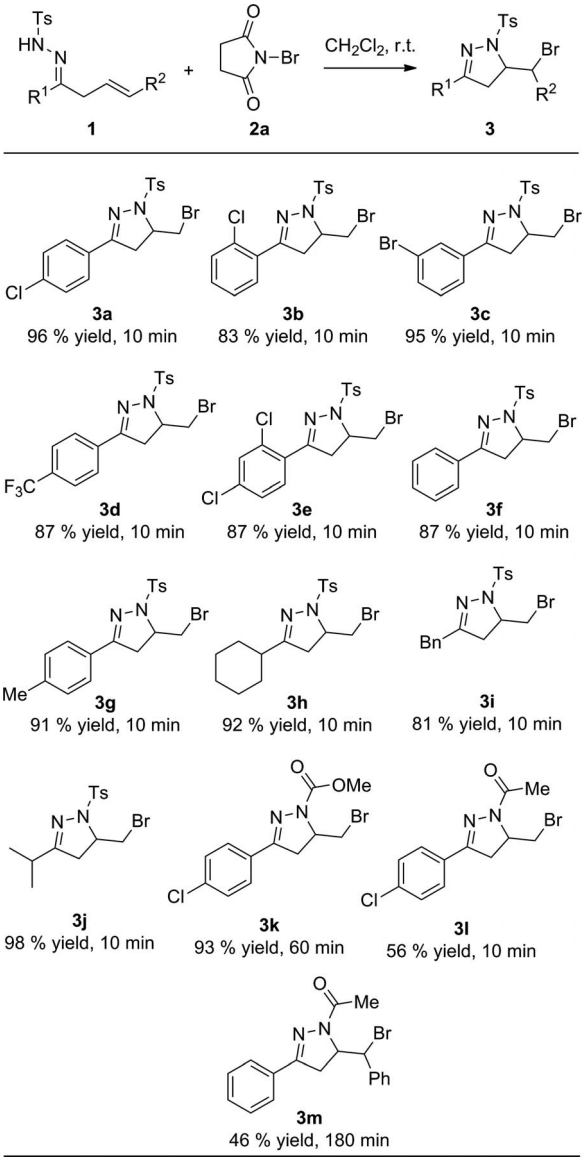
Entry	"Br" source	Solvent	*t* [min]	Yield[b] [%]
1	**2a**	CH_2Cl_2	10	96
2	**2b**	CH_2Cl_2	10	86
3	**2c**	CH_2Cl_2	10	75
4	**2d**	CH_2Cl_2	60	34
5	**2a**	$CHCl_3$	10	87
6	**2a**	$Cl(CH_2)_2Cl$	10	92
7	**2a**	PhMe	60	80
8	**2a**	EtOAc	30	80
9	**2a**	THF	10	30

[a] Reaction conditions: **1a** (0.30 mmol), **2** (0.36 mmol), in solvent (3.0 mL) at room temperature. [b] Yield of isolated product after chromatography.

The generality of this intramolecular annulation reaction was next investigated. As illustrated in Table 2, a wide range of β,γ-unsaturated hydrazones bearing electron-neutral, electron-donating, and electron-withdrawing groups at the 2-, 3-, or 4-position of benzene were well tolerated in this transformation, and corresponding products **3b**–**g** were delivered in high yields (Table 2, 83–95%). Notably, aliphatic hydrazones such as those bearing cyclohexyl, benzyl, and isopropyl groups also reacted with **2a** smoothly to give desired products **3h**–**j** in good yields (Table 2, 81–98%). It was previously found that protecting groups on the nitrogen atom of hydrazones have a substantial influence on the reactivity and reaction modes of the hydrazones.[9] Therefore, the effects of N-protecting groups on the reaction were also investigated. For example, a hydrazone substituted with an ester group also proved to be suitable for this transformation under the standard reaction conditions, and dihydropyrazole **3k** was afforded in 93% yield. In addition, an acetyl-substituted hydrazone also participated in this reaction to give desired product **3l** in moderate yield owing to the formation of some unidentified side products (Table 2, 56%), and the structure was unambiguously confirmed by X-ray analysis (Figure 1).[15] Furthermore, the substrate scope was successfully extended to a bulkier substrate bearing a phenyl group at the terminal double bond to furnish desired **3m** in 46% yield in 3 h.

In addition to NBS, *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS) were also utilized to react with hydrazone **1a** under the standard reaction conditions (Scheme 2). Surprisingly, the reaction with NCS gave rise to a very complex mixture and no desired product was de-

Table 2. Halocyclization of β,γ-unsaturated hydrazones for the synthesis of dihydropyrazole derivatives.[a]



[a] The reaction was performed with **1** (0.30 mmol) and **2a** (0.36 mmol) in CH_2Cl_2 (3.0 mL) at room temperature.

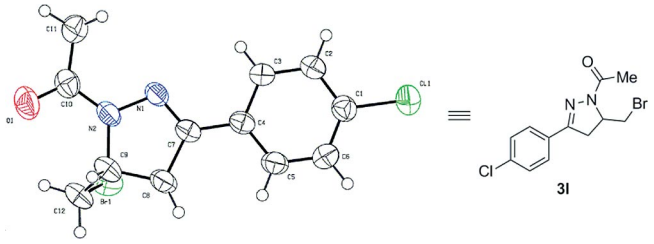
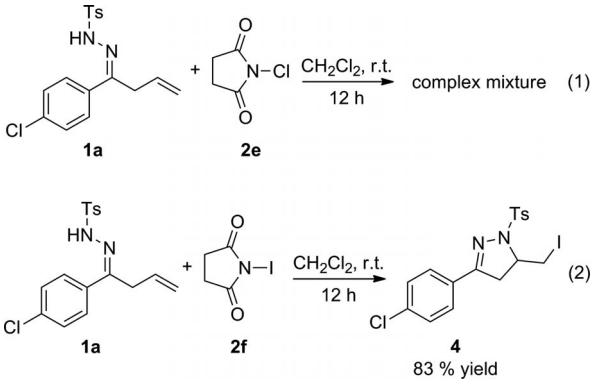


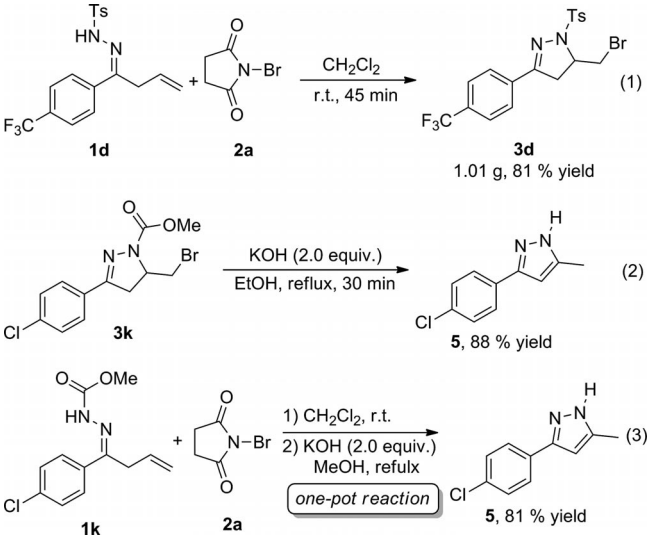
Figure 1. X-ray crystal structure of **3l** (thermal ellipsoids are set at 30% probability).

tected [Scheme 2, Equation (1)]. In contrast, NIS underwent the desired halocyclization reaction smoothly to afford product **4** in 83% yield [Scheme 2, Equation (2)].



Scheme 2. Halocyclization of β,γ-unsaturated hydrazone **1a** with NCS and NIS.

To further explore the synthetic potential of this methodology, a gram-scale reaction was performed with 2.7 mmol of **1d** under the standard reaction conditions [Scheme 3, Equation (1)]. The reaction proceeded very well, and desired product **3d** was obtained in 81% yield. More importantly, these dihydropyrazole products were easily converted into pyrazoles through a simple operation. For example, by using KOH as the base, *N*-free pyrazole **5** was obtained from **3k** in 88% yield within 30 min [Scheme 3, Equation (2)].[16] Furthermore, the one-pot reaction with hydrazone **1k** also worked well to give pyrazole **5** in 81% overall yield [Scheme 3, Equation (3)]. Thus, this one-pot reaction provides a complementary, simple, and practical way to synthesize pyrazole derivatives. Notably, all of the products containing halogen atoms (I, Br) are amenable to further synthetic elaborations, such as nucleophilic substitutions and coupling reactions.



Scheme 3. Gram-scale reaction and synthetic applications.

Conclusions

In conclusion, we developed an efficient halocyclization of β,γ-unsaturated hydrazones with NBS, and a range of dihydropyrazole derivatives were obtained in good to excellent yields (46–98%) without any additives under mild reaction conditions. Significantly, this methodology can be further employed for the synthesis of pharmaceutically important pyrazoles in a one-pot fashion. Further studies toward an asymmetric version of this halocyclization reaction are currently under active investigation in our laboratory.

Experimental Section

Typical Procedure: β,γ-Unsaturated hydrazone **1a** (104.6 mg, 0.30 mmol) and *N*-bromosuccinimide (**2a**; 64.0 mg, 0.36 mmol) were dissolved in CH_2Cl_2 (3 mL) at room temperature until the reaction was complete, as monitored by TLC. The crude reaction mixture was then directly purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1 to 5:1) to give **3a** as a white solid in 96% yield.

Supporting Information (see footnote on the first page of this article): General experimental methods and characterization data.

Acknowledgments

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[15] The structure of **3l** was determined by X-ray analysis. CCDC-981688 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] See the Supporting Information for details.

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