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# Regioselective Synthesis of Highly Functionalized Pyrazoles from *N*-Tosylhydrazones

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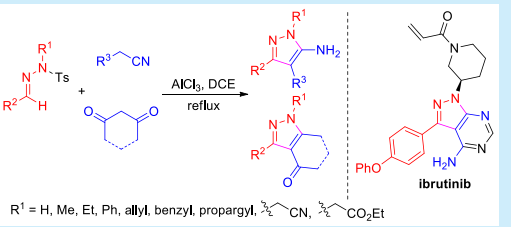
Supporting Information

**ABSTRACT:** A regioselective synthesis of highly functionalized pyrazoles from *N*-tosylhydrazones was developed. The reaction was general for a wide range of substrates and demonstrated excellent tolerance to a variety of substituents, and the method has been successfully applied to the formal synthesis of ibrutinib.






Pyrazoles and their derivatives constitute an important class of compounds that are extensively used in the agrochemical, material, and pharmaceutical industry.[1] Synthesis of pyrazoles has received considerable attention from organic chemists.[2]

Reactivity of aminopyrazoles as a functional motif is frequently applied to the preparation of pharmacologically active agents, such as ibrutinib and sildenafil (Figure 1).[3] The

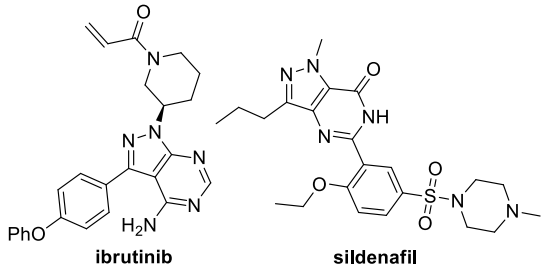
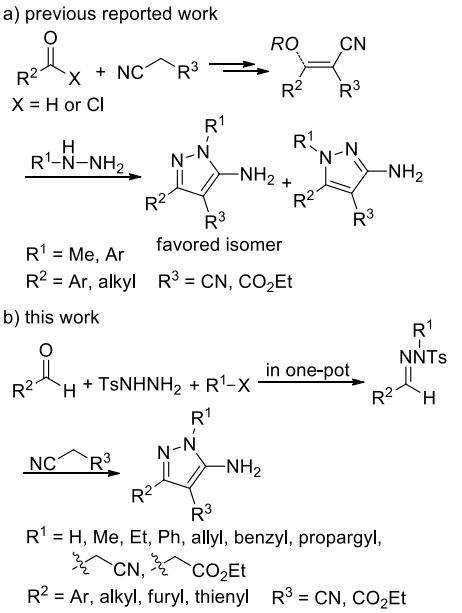



**Figure 1.** Structure of ibrutinib and sildenafil.

addition and cyclization between monosubstituted hydrazines and alkoxyacrylonitriles or acrylonitriles has been a classical reaction toward aminopyrazoles (Scheme 1, a).[3,4] However, the lack of commercially available monosubstituted hydrazines and somewhat limited substrate scope greatly reduces the attractiveness of this method. Commonly, $R^1$ is limited to methyl and phenyl. Furthermore, the initial nucleophilic attack of the more nucleophilic substituted nitrogen of alkyl hydrazines or the unsubstituted nitrogen of aryl hydrazines to either the nitrile or activated olefin results in two isomers, 3-aminopyrazole and 5-aminopyrazole, respectively. In general, the 5-aminopyrazole isomer is favored. To control the site selectivity, Fandrick et al. have developed a Michael equilibration model in the condensation reactions in 2015.[4b]

In continuation of our ongoing interest in the synthesis of pyrazoles,[5] herein, we present a new approach for the regioselective synthesis of highly functionalized pyrazoles

**Scheme 1. Approaches toward aminopyrazoles**




from *N*-tosylhydrazones[6] via a tandem process of nucleophilic addition and intramolecular cyclization (Scheme 1, b). *N*-Alkylation tosylhydrazones could be prepared according to our reported procedure in a one-pot reaction easily.[5b,7]

We initiated the investigation for a reaction of *N*-methyl tosylhydrazone (**1a**) with malononitrile, and the results are summarized in Table 1. The reaction was initially conducted in the presence of $AlBr_3$ in DCE at room temperature, after 24 h, pyrazole **2a** was obtained in 33% yield (entry 1). In order to accelerate the reaction rate and improve the yield, the reaction was performed at reflux temperature, and the yield was

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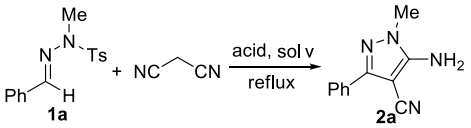
**Table 1. Screening the Reaction Conditions**[a]




| entry | acid | solv | time (h) | yield[b] (%) |
|---|---|---|---|---|
| 1[c] | $AlBr_3$ | DCE | 24 | 33 |
| 2 | $AlBr_3$ | DCE | 1 | 80 |
| 3 | $AlCl_3$ | DCE | 0.5 | 83 |
| 4[d] | $AlCl_3$ | DCE | 1 | 61 |
| 5 | $SnCl_4$ | DCE | 3.5 | 61 |
| 6 | $BF_3{\cdot}OEt_2$ | DCE | 5 | 19 |
| 7 | $TiCl_4$ | DCE | 5 | 25 |
| 8 | $Sc(OTf)_3$ | DCE | 5 | 19 |
| 9 | $FeCl_3$ | DCE | 5 | trace |
| 10 | HCl | DCE | 5 | trace |
| 11 | $AlCl_3$ | $CHCl_3$ | 5 | 63 |
| 12 | $AlCl_3$ | $CH_2Cl_2$ | 5 | 62 |
| 13 | $AlCl_3$ | toluene | 0.5 | 40 |
| 14 | $AlCl_3$ | THF | 5 | NR |
| 15[e] | $AlCl_3$ | DCE | 6 | 72 |

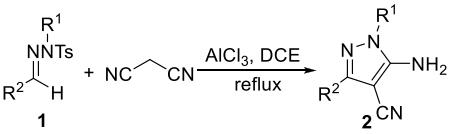
[a]Reactions were performed with **1a** (0.30 mmol), malononitrile (0.75 mmol), and acid (0.75 mmol) in 4 mL of solvent at reflux temperature. [b]Isolated yields. [c]The reaction was performed at room temperature. [d]0.5 mmol of $AlCl_3$ was used. [e]The reaction was performed with **1a** (3.0 mmol), malononitrile (7.5 mmol), and $AlCl_3$ (7.5 mmol) in 20 mL of DCE at reflux temperature.

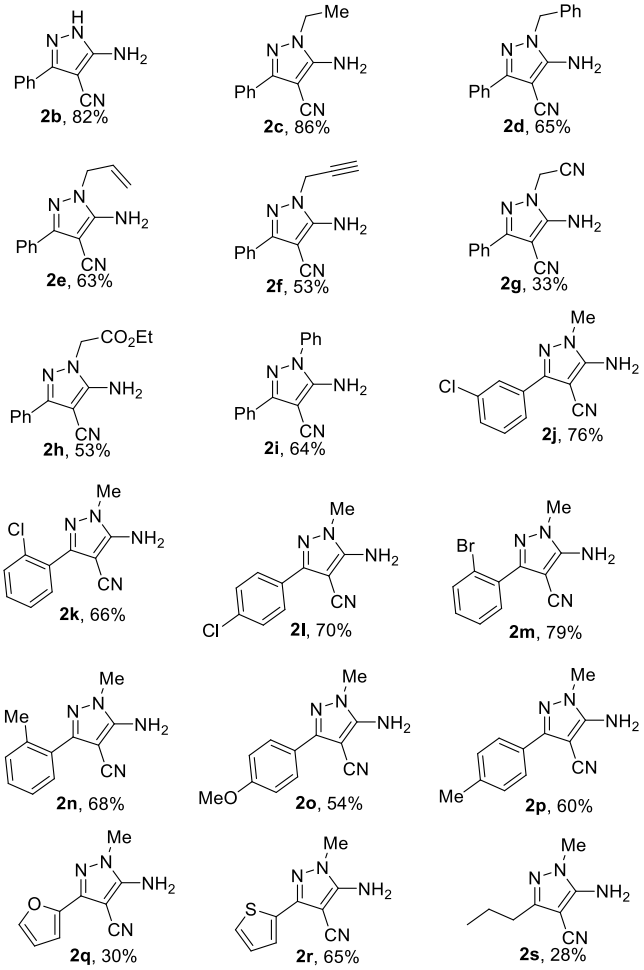
improved to 80% within 1 h (entry 2). Encouraged by the results, we screened other reaction conditions. First, a variety of different acids were tested in the reaction. The use of $AlCl_3$ resulted in 83% yield, and the reaction could reach completion within 0.5 h (entry 3). Decreasing the amount of $AlCl_3$ resulted in lower yield (entry 4). $SnCl_4$ gave 61% yield (entry 5), and other acids led to lower yields (entries 6−10). Of the solvents screened, $CHCl_3$, $CH_2Cl_2$, and toluene could give moderate yields (entries 11−14). To investigate the reaction's practical utility, we also performed the reaction with 3 mmol of **1a**, and the yield was not affected (entry 15).

With our optimized conditions in hand, several *N*-tosylhydrazones **1** were applied to the reaction to test the generality and scope of the method. Different $R^1$ substituents were first evaluated in the reaction. As shown in Table 2, hydrogen (**2b**), ethyl (**2c**), benzyl (**2d**), allyl (**2e**), propargyl (**2f**), carbonitrile (**2g**), ester (**2h**), and phenyl[8] (**2i**) were all applicable and gave the corresponding 5-aminopyrazole derivatives in good to high yields. Additionally, the electronic effect on the aromatic ring of $R^2$ had little influence on the reaction,and *N*-tosylhydrazones derived from benzaldehyde featuring *ortho*-, *meta*-, and *para*-substituents as well as electron-withdrawing (**2j**, **2k**, **2l**, **2m**) or electron-donating (**2n**, **2o**, **2p**) substituents worked well to furnish the corresponding pyrazole derivatives. Furthermore, *N*-tosylhydrazones derived from 2-furaldehyde, 2-thienaldehyde, and aliphatic aldehyde were also appropriate on the reaction, and products **2q**, **2r**, and **2s** were prepared in moderate yields. In some cases, the yields were lower, but no byproducts could be confirmed in the current state.

And then, we investigated any other active methylene compounds to expand the scope of the reaction under similar conditions. First, 1,3-diketones were evaluated. To our delight, the reaction was general for cyclohexane-1,3-dione and

**Table 2. Synthesis of 5-Aminopyrazoles.**[a]




[a]Reactions were performed with **1** (0.30 mmol), malononitrile (0.75 mmol), and $AlCl_3$ (0.75 mmol) in DCE (4 mL) at reflux temperature.

pentane-2,4-dione, and the corresponding products 6,7-dihydro-1*H*-indazol-4(5*H*)-ones (**2t**, **2u**, and **2v**) and 1*H*-pyrazole-4-one (**2w**) were obtained in moderate yields (Scheme 2). No self-condensation products of 1,3-diketones were detected. In addition, 6,7-dihydro-1*H*-indazol-4(5*H*)-ones have been reported in connection with the preparation of antitumor agents.[9] Ethyl 2-cyanoacetate was also suitable for the reaction, and 5-amino-4-ester-pyrazoles (**2x**, **2y**, and **2z**) were obtained in good yields (Scheme 3).[10]

Compared to the previously reported reactions toward aminopyrazoles from monosubstituted hydrazines, our reaction conditions showed good compatibility with different substituents. The reaction was effective for a wide scope of substrates, and a series of highly functionalized pyrazole derivatives were synthesized in good yields. More importantly, the use of monosubstituted hydrazines was unnecessary, and $R^1$ was no longer limited to methyl and phenyl. Hydrogen, alkyl, benzyl, allyl, propargyl, carbonitrile, ester, and phenyl were all applicable, malononitrile, cyclohexane-1,3-dione, pentane-2,4-dione, and ethyl 2-cyanoacetate were all suitable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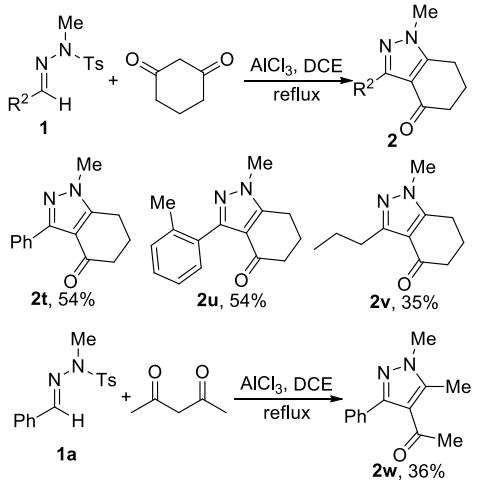
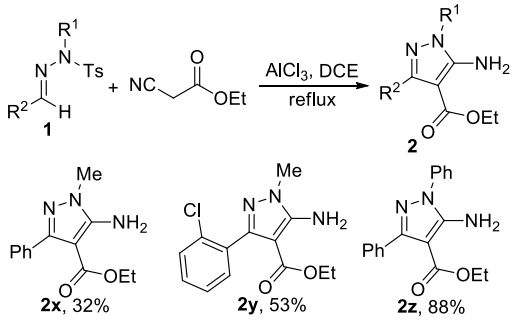
**Scheme 2. Synthesis of 6,7-Dihydro-1*H*-indazol-4(5*H*)-one and 1*H*-Pyrazole-4-one**



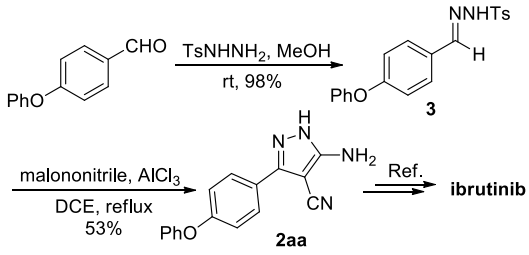

**Scheme 3. Synthesis of 5-Amino-4-ester-pyrazoles**




for the reaction, and the reaction proceeded with complete regioselectivity.

The potential utility of this reaction was exhibited by a synthesis of the key intermediate of ibrutinib (Scheme 4).

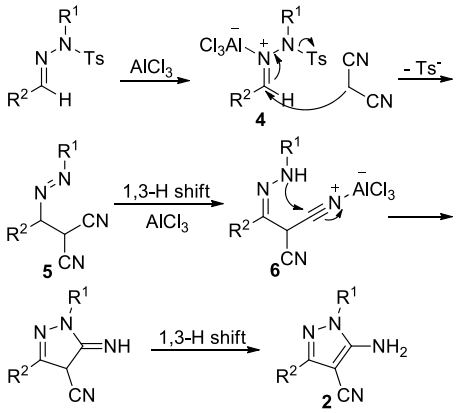
**Scheme 4. Formal Synthesis of Ibrutinib**




Ibrutinib is a first-in-class Bruton tyrosine kinase (BTK) inhibitor. Since its approval for relapsed chronic lymphocytic leukemia (CLL) by the FDA in 2013, ibrutinib has generally been found to have a favorable safety and efficacy profile in all categories of patients with CLL and has been approved for four different cancers and chronic graft-versus-host disease.[11] The *N*-tosylhydrazone **3** was synthesized from 4-phenoxybenzaldehyde and $TsNHNH_2$ in almost quantitative yield and applied in the newly developed cyclization reaction with malononitrile to give the known intermediate **2aa**[12] in 53% yield, completing the formal synthesis of ibrutinib.

A simple mechanism was proposed as shown in Scheme 5. The reaction was initiated by the nucleophilic addition of

**Scheme 5. Proposed Pathway for Aminopyrazole Formation**




malononitrile to *N*-tosylhydrazone iminium salt **4** resulting in **5** by the loss of a *p*-toluenesulfinic acid anion and then a 1,3-H shift producing intermediate **6**, which subsequently went through an intramolecular cyclization and 1,3-H shift to form pyrazoles **2**.

In summary, we have established a simple and efficient procedure for the regioselective preparation of highly functionalized pyrazole derivatives. This strategy proceeded smoothly with complete regioselectivity, and the protocol was applied to a wide range of substrates and demonstrated excellent tolerance to a variety of functional groups. $R^1$ was no longer limited to methyl and phenyl, and the reaction should facilitate the exploration of new pyrazole-related pharmaceuticals. The method has been successfully applied to the formal synthesis of ibrutinib.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00561.

Experimental procedures, characterization data, and copies of NMR spectra for all products (PDF)

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### Author Contributions

All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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