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Reagent-assisted regio-divergent cyclization synthesis of pyrazole†

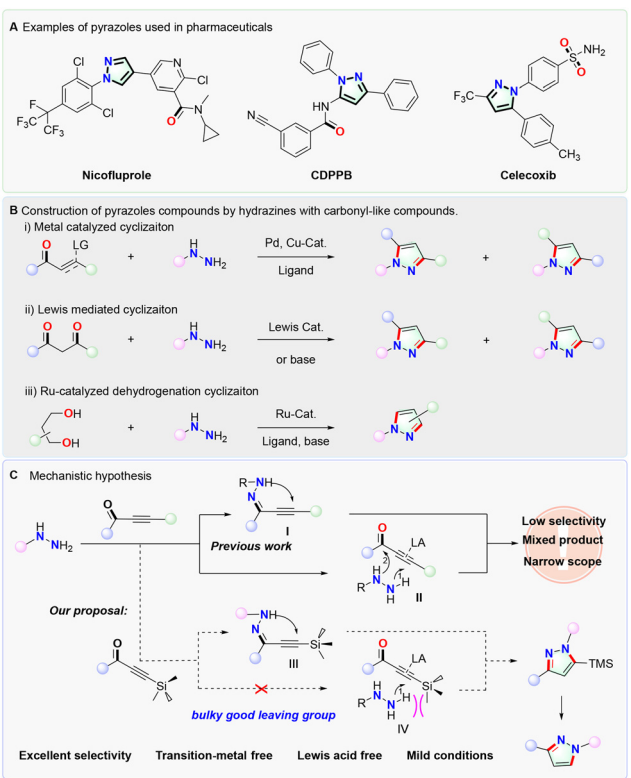
Mengdi Pang,[a,b] Ali Ramazani,[c] Zhengguo Zhang*[a,d] and Guoying Zhang*[b]

The present study reveals a practical one-pot base-promoted regio-divergent cyclization of hydrazines with alkynyl silane under mild conditions, facilitating the synthesis of diverse silicone-substituted pyrazoles and functionalized pyrazoles in great yields with exceptional selectivity. This protocol is expected to afford a streamlined one-pot approach for the synthesis of multiple compounds in water.

Introduction

Pyrazoles are highly regarded structural patterns that are commonly found in a wide range of biologically active, medically important, and functionally significant compounds.[1–6] Moreover, pyrazoles are widely acknowledged as crucial frameworks in numerous reactions for the production of complex and multifunctional compounds (Scheme 1, A).[7–9] There are two primary methods for constructing the pyrazole framework: (1) combining hydrazines with unsaturated carbonyl compounds and then annulation,[10] and (2) utilizing metal-catalyzed coupling transformations of pyrazoles with halides or similar substances to synthesize the desired target frameworks (Scheme 1, B).[11–19] These transformations, however, are often limited by the lack of readily available starting precursors with suitable substitutions and typically require harsh reaction conditions involving complicated catalysts combined with multiple steps. As a result, this inevitably leads to a decrease in atom efficiency due to the generation of unwanted waste byproducts and an increasingly intricate operational process.[20] Therefore, it is crucial to develop efficient and practical methodologies for constructing the structural framework of pyrazoles in organic synthesis.

Mechanistically, the syntheses of functionalized pyrazoles from hydrazines with corresponding carbonyl-like compounds primarily encompass two different categories of reactions: (a) a highly intricate sequential condensation followed by intramolecular annulation in the presence of a metal catalyst;[21,22] (b) a sophisticated intermolecular nucleophilic substitution



Scheme 1 State of the art and the reaction described here.

[a]*School of Chemistry and Chemical Engineering, North University of China, Taiyuan 030051, P. R. China*
[b]*State Key Laboratory of Coal Conversion, Institute of Coal Chemistry, Chinese Academy of Sciences, Taiyuan 030001, P. R. China. E-mail: zhanggy@sxicc.ac.cn*
[c]*The Organic Chemistry Research Laboratory (OCRL), Department of Chemistry, Faculty of Science, University of Zanjan, Zanjan 45371-38791, Iran*
[d]*Department of Materials Science and Engineering, Shanxi Institute of Technology, Yangquan 045000, P. R. China*
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reaction succeeded by intramolecular annulation guided by refined Lewis's acid catalysis.[23] Due to the involvement of these exceptional metal or Lewis acid catalysts, it is frequently observed that these reactions produce products with less-than-optimal chem- and regio-selectivity or unsatisfactory yields.[24,25] In recent studies, numerous significant changes have been documented in the process of producing complex compounds through base manipulation (Scheme 1, C).[26–30]

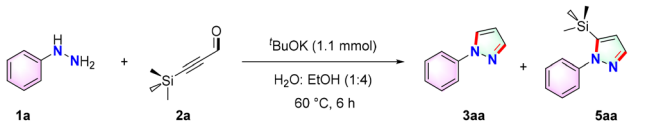
Results and discussion

These discoveries, along with our advancements in utilizing hydrazines as nucleophiles in coupling reactions facilitated by bases,[31–34] have led us to propose that incorporating a bulky leaving group species[35–39] could overcome the inherent substrate inhibition (selectivity) observed during base-mediated annulation reactions involving hydrazines. Based on the assumption of this mechanism, we have observed the formation of an intermediate **I** through the condensation reaction between hydrazine and alkynyl silane. Subsequently, a cyclization process occurs *via* an intramolecular nucleophilic substitution, resulting in the production of the desired product. However, due to hindrance caused by bulky groups, intermolecular nucleophilic substitution reactions for intermediate **III** are hindered, not to mention being followed by intramolecular annulation. In this study, we introduce a practical procedure for the successful synthesis of various pyrazoles by combining different hydrazines with alkynyl silane under base-promoted regio-divergent condensation annulation. This innovative approach allows for the efficient formation of silicone-substituted pyrazoles and functionalized pyrazoles with high yields and excellent selectivity, using H_2O as the co-solvent in a one-pot fashion under mild reaction conditions.

We explored the validity of our hypothesis by investigating the potential for reagent-assisted regio-divergent cyclization transformation of hydrazines with alkynyl silane, resulting in an outstanding yield and high regioselectivity of 1-phenyl-1*H*-pyrazole (**3aa**) (Table 1).

This remarkable outcome was achieved through the utilization of ^{t}BuOK at 60 °C for a duration of 6 hours (entry 1). In the absence of ^{t}BuOK, the desired 1-phenyl-5-(trimethylsilyl)-1*H*-pyrazole (**5aa**) was obtained with exceptional yield and remarkable regioselectivity (entry 2). However, when base was substituted by KOH, K_2CO_3 or $KHCO_3$, this transformation was hindered leading to substantial recovery of the starting materials (entries 3–5). We hypothesize that the weak base modifies the system's pH, thus disrupting the reaction process. It is noteworthy that the successful integration of the trimethylsilyl moiety into the desired product substantiates the feasibility of our strategy. The utilization of alternative organic bases, proved to be unsuitable for this conversion (entry 6). Among the various solvent ratios investigated, a mixture of H_2O/ethanol in a ratio of 1/4 exhibited superior effectiveness, yielding **3aa** with comparable efficiency also observed at a ratio of 1/2 (entry 10). The desired reactions

Table 1 Optimization of the cyclization reaction conditions[a]



1a 2a 3aa 5aa

Entry	Variations from optimal conditions	**3aa** (%)	**5aa** (%)
1	None	>95	<5
2	No base	<5	>95
3	KOH as base	86	<5
4	K_2CO_3 as base	<5	12
5	$KHCO_3$ as base	0	<5
6	Et_3N or DBU as base	0	0
7	H_2O as solvent	21	0
8	EtOH as solvent	48	8
9	TFA as solvent	0	0
10	H_2O : EtOH (1 : 2) as solvent	78	<5
11	40 °C	59	0 (62)[b]
12	O_2 atmosphere	0	0

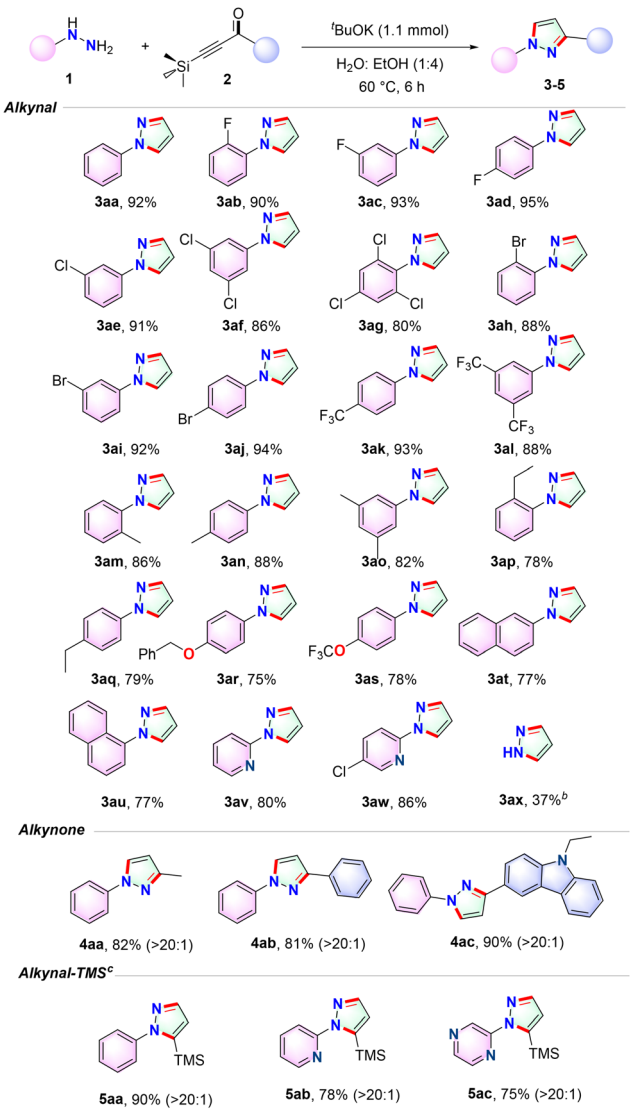
[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.5 mmol), ^{t}BuOK (1.1 mmol), H_2O : EtOH (1 : 4, v/v, 2.0 mL), 60 °C, 6 h. Yields and ratio were determined *via* GC with n-dodecane as the internal standard. [b] No base.

yielded pyrazoles at a lower reaction temperature with relatively acceptable yields, showcasing their remarkable formation even under milder conditions (entry 11). Under an O_2 atmosphere, no desired adducts were observed, and the presence of abundant acid in the reaction mixture was confirmed by GC-MS analysis, showing the absence of cyclization between **2a** and **1a** (entry 12). Furthermore, through meticulous optimization of various reaction parameters including additives, base type and amount, solvent type, substrate ratio, reaction temperature, and time, we achieved the highest yield of **3aa** and **5aa** as demonstrated in our ESI.†[40]

Under optimized reaction conditions, a diverse range of hydrazines were employed in conjunction with **2a** to investigate the extent of reagent-assisted regio-divergent cyclization facilitated by base acceleration. The results are presented in Table 2, where various aromatic hydrazines bearing electron-withdrawing or electron-donating substituents on the aromatic ring afforded their respective substituted pyrazoles with excellent high yields.

The yields obtained with aromatic hydrazines containing electron-withdrawing groups (**3ab–3al**) generally surpass those achieved with aryl hydrazines containing electron-donating groups (**3am–3as**). Furthermore, in comparison to the results obtained with *para*- and *meta*-substituted substrates, no steric hindrance is observed upon substitution at the *ortho* position of hydrazines (**3ab–3ad**, **3am–3aq**). The halide groups, specifically, display remarkable stability, thereby facilitating the formation of desired **3ab–3aj** with exceptional yields. These products can be further employed for synthesizing complicated molecules. It is worth noting that the CF_3 and CF_3O groups exhibit extraordinary resilience throughout the standard procedure, resulting in the generation of **3ak**, **3al** and **3as** respectively.

Table 2 Substrate scope of the cyclization reaction[a]



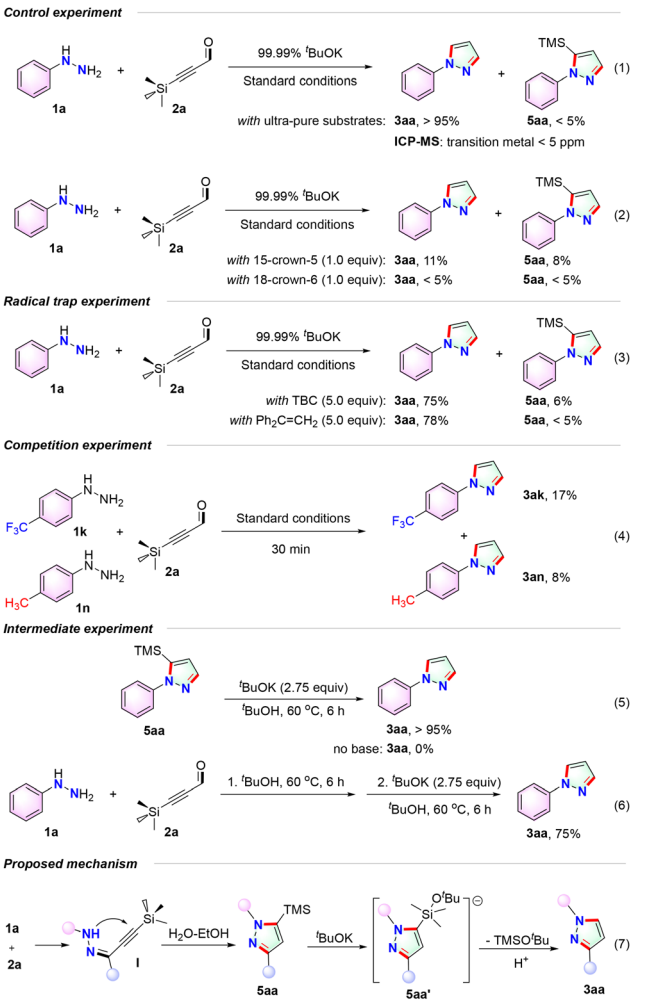
[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.5 mmol), ^{t}BuOK (1.1 mmol), H_2O : EtOH (1 : 4, v/v, 2.0 mL), 60 °C, 6 h. Isolated yield. [b] Yield of **3ax** was determined *via* GC. [c] No base.

The successful synthesis of the annulation products **3at–3au** was achieved with satisfactory yields by utilizing either 1- or 2-naphthalenyl hydrazine, respectively, showcasing impressive efficiency. Additionally, the effortless incorporation of diverse heterocyclic moieties such as pyridyl and substituted pyridyl into **3aw–3ax** was effortlessly accomplished through the use of their corresponding hydrazines. Despite the utilization of more complex mono-hydrazine as reactants, we were able to successfully obtain **3ax** with satisfactory yield. In order to further explore the synthetic potential of this reaction, we investigated a serious of hydrazines while incorporating the more challenging acetylenone silane aliphatic moiety.

The alkyl acetylenone silane also demonstrated remarkable effectiveness as a coupling component, resulting in abundant formation of **4aa** with exceptional selectivity towards specific regions. Furthermore, the aromatic acetylenone silane exhibited divergent cyclization, leading to highly efficient production of **4ab**. Moreover, by employing an aromatic acetylenone silane containing a carbazolyl group as the coupling partner, the transformation persisted and yielded **4ac** with outstanding efficiency and notable selectivity towards specific regions. Additionally, a wide range of pyrazoles that have been modified with silicone exhibited excellent reactivity and successfully produced **5aa–5ac** even without the presence of a base. Notably, the trimethylsilyl group remained intact in the resulting compounds.

The comprehension of the mechanism behind the regiodivergent cyclization process assisted by a reagent was further improved through a series of carefully conducted control experiments (Scheme 2). Initially, various reaction conditions were thoroughly investigated using an innovative reaction tube and highly purified substrates (purity >99.99%), resulting in no noticeable impact on the yields of **3aa** or **5aa**.

Based on ICP-MS analysis, it was determined that the concentration of transition-metal species in the reaction mixture



Scheme 2 Control experiments and mechanistic investigations.

is undetectable, indicating that this transformation does not rely on catalysis facilitated by transition metals (eqn (1)). The inclusion of a complexing agent such as 18-crown-6 led to decreased yields of both products, namely **3aa** and **5aa**, due to its strong affinity for potassium ions or disruption of the alkali-promoted reaction system. Comparable results were obtained with the incorporation of additives like 15-crown-5 (eqn (2)). The presence of TBC or ethene-1,1-diyldibenzene as radical scavengers led to successful yields of **3aa**, suggesting that the reaction may not follow a free radical mechanism (eqn (3)). These findings highlight the crucial role played by ^{t}BuOK in facilitating the process rather than relying on the metal catalyst or any impurities it may contain. Moreover, the electron-withdrawing aromatic hydrazines containing groups (**3ak**) exhibit superior yields compared to aryl hydrazines with electron-donating groups (**3an**) within a 30-minute timeframe (eqn (4)). The experiment on intermolecular competition vividly demonstrates that the reaction proceeds through condensation cyclization rather than affinity attack, with valuable assistance from Lewis's acid. This certainly confirms the remarkable feasibility of our innovative strategy. Moreover, **5aa** can be easily transformed into **3aa** in an exceptional yield. However, without base, obtaining **3aa** remains challenging while **5aa** can be abundantly recovered (eqn (5)).

In addition, the efficient synthesis of **3aa** was achieved through a sequential reaction, demonstrating the feasibility of a continuous cascade process involving annulation, cyclization, and desilicification (eqn (6)). These results support the potential involvement of **5aa** as an intermediate in this consecutive transformation, while the incorporation of base accelerators effectively speeds up both the annulation and desilicification steps. Based on the obtained results and relevant prior researches,[41,42] a preliminary mechanism for this annulation process was proposed. Initially, intermediate **I** is formed through the condensation of **1a** with **2a**. Subsequently, an intramolecular nucleophilic substitution cyclization takes place leading to the formation of compound **5aa**. Eventually, under base-promoted conditions, desilicification from **5aa′** occurs resulting in the desired product being generated.

To further showcase the robustness of cascade annulation and desilicification transformation, we successfully conducted a gram-scale reaction resulting in an impressive yield of **3aa** with 12.2 grams, as elegantly depicted in Fig. 1. Pyrazoles possess exceptional appeal as reactive building blocks that can be effortlessly harnessed for the synthesis of intricate functional compounds. A diverse array of halide-substituted pyrazoles (**B1–B3**) can be efficiently synthesized through halogenation reactions utilizing NXS compounds, which are widely employed in the realm of organic synthesis. Similarly, a series of reactions between pyrazoles and their respective reagents yield an extensive assortment of functionalized pyrazoles on the phenyl moiety. A comparable outcome was observed in a wide range of reactions between pyrazoles and corresponding reagents, resulting in the formation of a diverse array of exquisitely functionalized pyrazoles on the phenyl ring (**B4–B5**). Similarly impressive results were obtained in a series of reactions between pyrazoles and corresponding reagents, leading to the formation of an extensive range of functionally modified pyrazoles on the pyrazole ring (**B6–B7**).

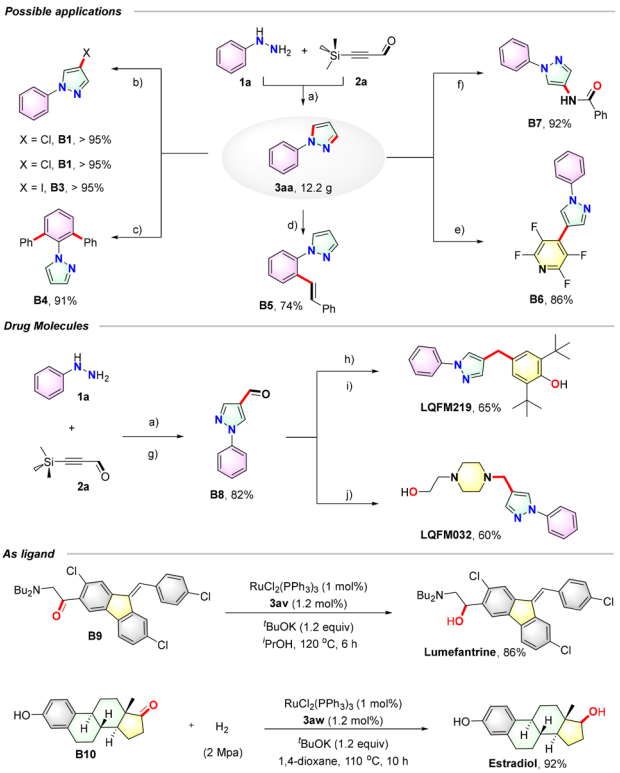


Fig. 1 Possible reactions based on pyrazoles synthesis. [a] Standard conditions. [b] NCS or NBS or NIS, 2,4,6-trimethylaniline, DCM, −40 °C. [c] KOPiv, K_2CO_3, H_2O, 100 °C, 2 h. [d] Cp*Co(CO)I_2, $AgSbF_6$, PivOH, DCE, 60 °C, 5 h. [e] DMSAuCl, AgOAc, PIDA, 1,4-dioxane, 100 °C. [f] [Cp*$RhCl_2$]$_2$, $AgSbF_6$, $B(OH)_3$, $KHCO_3$, DCM, 90 °C, 24 h. [g] HMTA, CF_3CO_2H, 90 °C, 12 h. [h] $NaBH_4$, MeOH, 2 h, r.t. [i] HCO_2H, CH_3Cl, 65 °C, 8 h. [j] $ZnCl_2$, Na(CN)BH_3, MeOH, 1 h.

Additionally, through the utilization of the newly developed base-mediated annulation procedure, **LQFM032** was synthesized with exceptional efficiency *via* formylation and subsequent conversions of **3aa**. This compound exhibits promising potential as a muscarinic receptor agent for specific sympathoinhibitory, hypotensive, and antihypertensive effects.[43] Moreover, **3aa** can be employed for further transformations to construct the remarkable **LQFM219** compound with notable antinociceptive and anti-inflammatory activity (Fig. 1, middle).[44] Furthermore, the newly developed base-mediated products facilitate the synthesis of **3av** and **3aw**, showcasing their exceptional catalytic activity as diazo ligands in hydrogenation applications (Fig. 1, bottom). The incorporation of bidentate **3av** as an auxiliary ligand in the presence of $RuCl_2(PPh_3)_2$ led to the remarkable yield of **Lumefantrine** through transfer hydrogenation.[45,46]

Additionally, utilizing bidentate **3aw** as a ligand under a dihydrogen atmosphere in the presence of Ru-catalyst allowed for the excellent production yield of **Estradiol**.[47] **Lumefantrine**, as our first antimalarial drug, can be used to prevent or treat

potentially multi-drug resistant malaria. **Estradiol** is currently the main estrogen that not only monitors women's health, but also shows a strong relationship with inflammation and anti-inflammatory activity.

Conclusions

In summary, we have devised a practical method for the regio-divergent cyclization of substituted pyrazoles with hydrazines and alkynyl silanes under mild conditions. This innovative approach effectively overcomes the hindrance caused by alkynyl silane in a one-pot manner, demonstrating its impressive efficiency. The procedure offers an efficient and direct route to access a wide range of silicone-substituted pyrazoles and functionalized pyrazoles, thereby expanding synthetic possibilities. Moreover, it can be easily scaled up to larger grams quantities, showcasing its versatility on a larger scale. Our carefully designed strategy significantly broadens the scope of base-promoted annulation for synthesizing pyrazole molecules without relying on metal or Lewis's acid catalysts, while cleverly utilizing water as a co-solvent. Currently, our esteemed research group is actively involved in conducting comprehensive studies aimed at gaining a detailed mechanistic understanding of this regio-divergent cyclization and exploring its potential applications in other transformative reactions.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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