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Brønsted acid-promoted hydroamination of unsaturated hydrazones: access to biologically important 5-arylpyrazolines†

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A novel and efficient Brønsted acid-promoted hydroamination of hydrazone-tethered olefins has been developed. A variety of pyrazolines have been easily obtained in good to excellent yields with high chemo- and regioselectivity under simple and mild conditions. This method represents a straightforward, facile, and practical approach toward biologically important 5-arylpyrazolines, which are difficult to access by previously reported radical hydroamination of β,γ-unsaturated hydrazones.

Introduction

The functionalization of olefins is one of the most efficient and powerful strategies to rapidly construct structurally diverse and valuable molecules.[1–3] In this context, the hydroamination of olefins has drawn considerable attention from chemists. Great progress has been made in the transition-metal-catalyzed,[4,5] acid-promoted,[6,7] and miscellaneous[8] hydroaminations of olefins.

Pyrazolines are an important class of five-membered nitrogen-containing heterocycles that present in many pharmaceuticals and bioactive molecules.[9,10] In this context, 5-arylpyrazolines often exhibit diverse and significant biological properties such as anti-cancer, anti-depressant, anti-infective, and anti-convulsant activities, *etc.* (Fig. 1).[11] Recently, the elegant synthesis of pyrazolines from β,γ-unsaturated hydrazones has been accomplished *via* a novel C–N bond-forming cyclization strategy by the groups of Loh, Xiao, Han, and others.[12–16] Despite recent impressive advances, the examples of the hydroamination of β,γ-unsaturated hydrazones for the construction of pyrazolines are rare.[16] In 2014, Xiao and Chen *et al.* disclosed a novel visible-light-driven photocatalytic hydroamination of β,γ-unsaturated hydrazones, in which the generation of N-centered hydrazonyl radicals has been achieved for the first time by a visible-light photocatalytic oxidation strategy (Scheme 1a, method A).[16a] Shortly afterwards, the same group developed a mild and efficient radical hydroamination of β,γ-unsaturated hydrazones for the synthesis of pyrazolines with stoichiometric amounts of $PhI(OAc)_2$ as the oxidant and DABCO as the base (Scheme 1a, method B).[16b] In 2019, the group of Song reported the facile and metal-free access to pyrazolines from β,γ-unsaturated hydrazones *via* a radical pathway with the use of the oxidant TBHP in n-Bu_2O at 80 °C under N_2 atmosphere (Scheme 1a, method C).[16c] The previously reported hydroaminations[14] of unsaturated hydrazones represent the rapid, facile, and straightforward approaches to pyrazolines. However, the substrates employed in such hydroamination reactions are only β-unsubstituted unsaturated hydrazones, thus providing the corresponding 5-methylpyrazolines through a radical 5-*exo*-trig cyclization (Scheme 1a). In 2016, Chen *et al.*

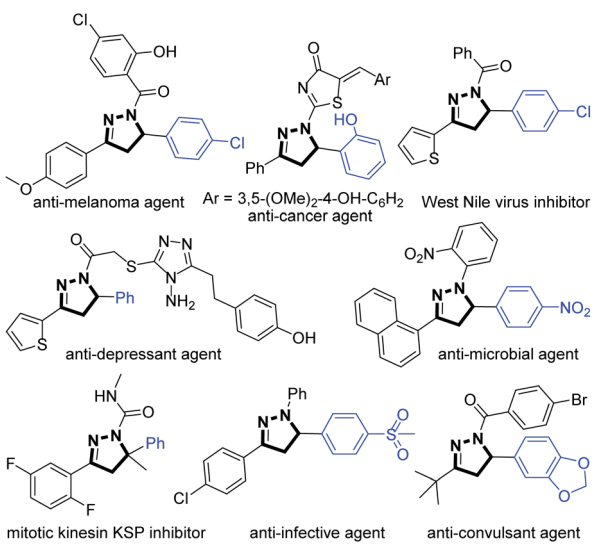

Fig. 1 5-Arylpyrazoline-containing bioactive molecules.

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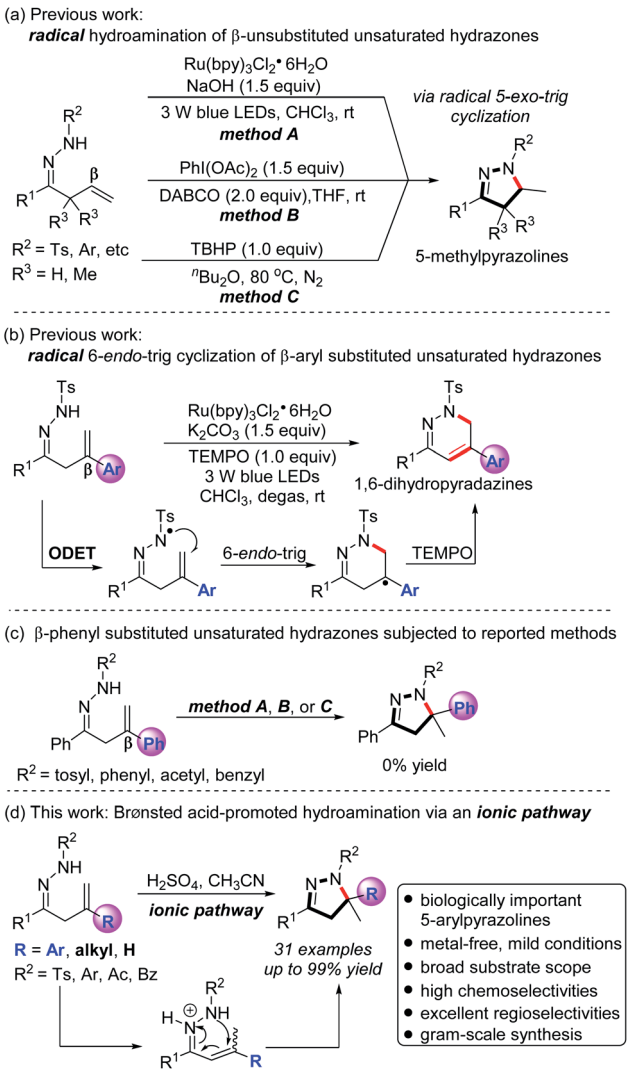


Scheme 1 Previous work and this work.

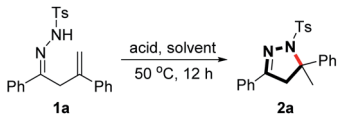
reported an impressive and elegant protocol for the preparation of 1,6-dihydropyradazines from β-aryl substituted β,γ-unsaturated hydrazones, in which a novel visible-light photocatalytic oxidative deprotonation electron transfer (ODET)/6-*endo*-trig cyclization/TEMPO-mediation strategy was developed (Scheme 1b).[17]

Given the fact that 5-arylpyrazolines display a broad spectrum of important biological activities, it is highly demanded to develop mild, efficient, practical, and selective methods for the construction of such type of pyrazolines. To test whether 5-arylpyrazolines could be obtained from β-aryl substituted unsaturated hydrazones, we synthesized β-phenyl substituted unsaturated hydrazones (R^2 = Ts, Ph, Ac, Bz) and subjected them to the previously reported radical hydroamination methods.[16] Surprisingly, no desired 5-phenylpyrazoline products were observed (Scheme 1c). Based on these observations and considering the biological significance of 5-arylpyrazolines, we decided to explore new synthetic methods for the construction of the scaffolds. Inspired by the above breakthrough[12–18] and following our continuous interest in the synthesis of *N*-heterocycles,[15f,g] we herein report a novel Brønsted acid-promoted hydroamination of β,γ-unsaturated hydrazones to afford a wide range of pyrazolines in generally excellent yields and with high chemo- and regioselectivities through an ionic pathway (Scheme 1d). It is noteworthy that the present method provides a facile, mild, efficient, and practical access to biologically significant 5-arylpyrazolines.

Results and discussion

Our studies commenced with β-phenyl substituted β,γ-unsaturated hydrazone **1a** as model substrate to optimize the reaction conditions. To our delight, the desired product 5-arylpyrazoline **2a** was obtained in 71% yield by the treatment of **1a** with TsOH (1.0 equiv.) in CH_3CN at 50 °C for 12 h (Table 1, entry 1). Other Brønsted acids, including TsOH, TfOH, CH_3SO_3H, CF_3COOH, CH_3COOH, H_3PO_4, HCl, HBr, HI, and H_2SO_4 were also tested (Table 1, entries 2–10). Among the above acids examined, H_2SO_4 was found to be the best for this transformation, giving product **2a** in 94% yield (Table 1, entry 10). The screening of solvents showed that CH_3CN was superior to other solvents, such as CH_2Cl_2, EtOH, DMF, and THF (Table 1, entries 10–14). Decreasing the amount of H_2SO_4 resulted in the lower yields of

Table 1 Optimization of reaction conditions[a]



Entry	Acid (equiv.)	Solvent	Yield[b] (%)
1	TsOH (1.0)	CH_3CN	71
2	TfOH (1.0)	CH_3CN	82
3	CH_3SO_3H (1.0)	CH_3CN	62
4	CF_3COOH (1.0)	CH_3CN	Trace
5	CH_3COOH (1.0)	CH_3CN	0
6[c]	H_3PO_4 (1.0)	CH_3CN	0
7[d]	HCl (1.0)	CH_3CN	0
8[e]	HBr (1.0)	CH_3CN	62
9[f]	HI (1.0)	CH_3CN	81
10[g]	H_2SO_4 (1.0)	CH_3CN	94
11	H_2SO_4 (1.0)	CH_2Cl_2	58
12	H_2SO_4 (1.0)	C_2H_5OH	0
13	H_2SO_4 (1.0)	DMF	0
14	H_2SO_4 (1.0)	THF	18
15	H_2SO_4 (0.2)	CH_3CN	29
16	H_2SO_4 (0.5)	CH_3CN	65
17[h]	H_2SO_4 (1.0)	CH_3CN	14
18	—	CH_3CN	0

[a] All reactions were performed with **1a** (0.20 mmol) and acid (0.20 mmol) in solvent (2 mL) at 50 °C for 12 h unless otherwise noted. [b] Isolated yields. [c] H_3PO_4 (85 wt% in water). [d] HCl (36 wt% in water). [e] HBr (40 wt% in water). [f] HI (55 wt% in water). [g] H_2SO_4 (98 wt% in water). [h] At 25 °C. Ts = *p*-toluenesulfonyl, Tf = trifluoromethanesulfonyl, DMF = *N*,*N*-dimethyl formamide, THF = tetrahydrofuran.

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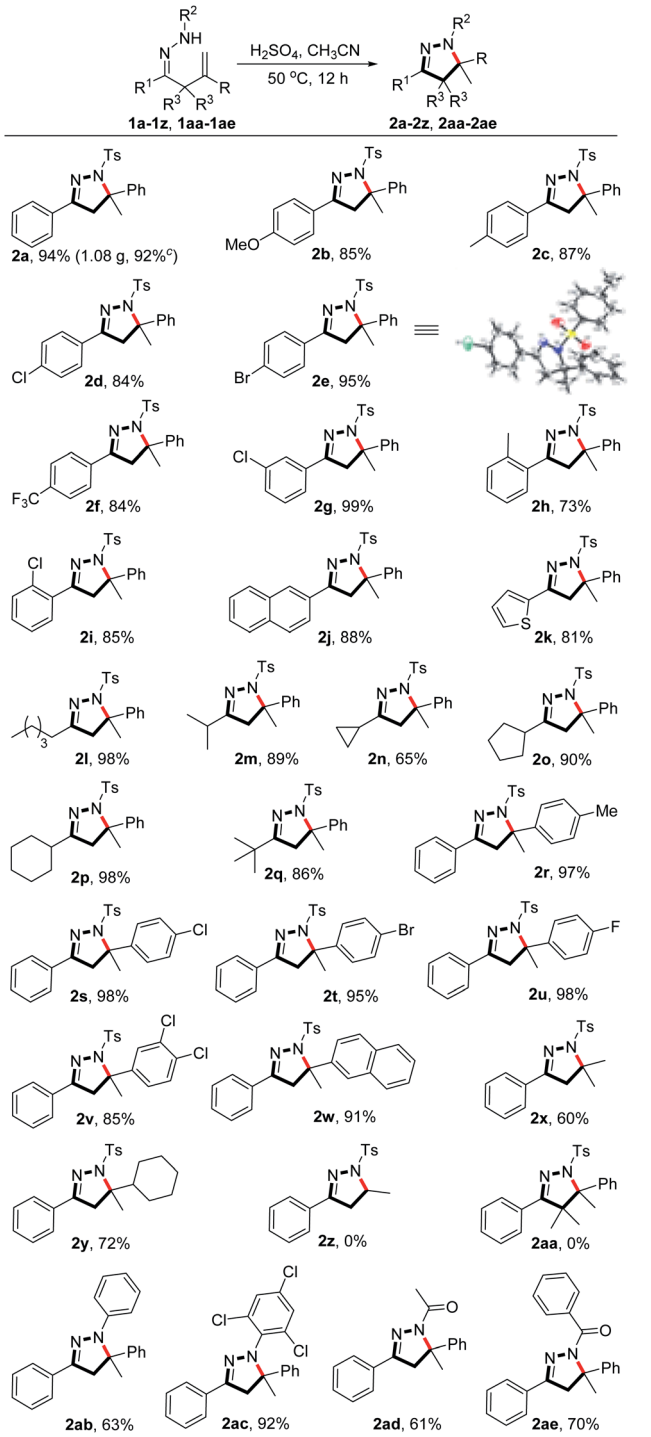
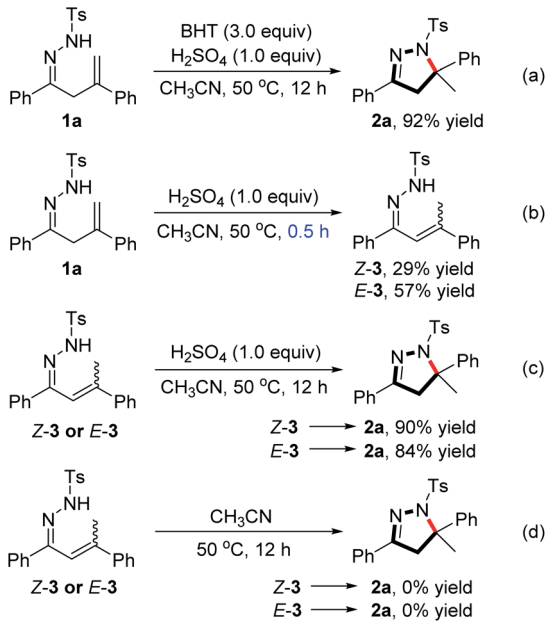
2a (Table 1, entries 15 and 16). Additionally, the significantly decreased yield of **2a** was obtained when the reaction was conducted at a lower temperature (Table 1, entry 17). No reaction occurred in the absence of a Brønsted acid, suggesting that the acid plays a crucial role in the transformation (Table 1, entry 18).



Scheme 2 Substrate scope. [a]All reactions were performed with 1 (0.20 mmol) and conc. H_2SO_4 (0.20 mmol) in CH_3CN (2 mL) at 50 °C for 12 h unless otherwise noted. [b] Isolated yields. [c] 3.0 mmol scale.

With the optimized reaction conditions in hand, we subsequently investigated the generality of the Brønsted acid-promoted hydroamination reaction. As exemplified in Scheme 2, the present reaction can be extended to various β,γ-unsaturated hydrazones to give the 5-aryl or 5-alkylpyrazoline products in 60–99% yield. Substrates with either electron-donating or electron-withdrawing groups on the phenyl ring (R^1) that is attached to the C–N double bond were smoothly converted into products **2a–2j** in 73–99% yield. 2-Thienyl group was also well tolerated to provide the product **2k** in 81% yield. Notably, substrates bearing alkyl groups (R^1) at the C–N double bond moiety also participated in the reaction to give the corresponding products **2l–2q** in 65–98% yield. The effect of the substituents (R) at the alkene moiety on the reaction was next investigated. It was found that electron-rich or electron-poor aryl groups were well tolerated under the reaction conditions, producing the 5-arylpyrazoline products **2r–2w** in 85–98% yield. Furthermore, substrates bearing alkyl groups at the alkene moiety could also undergo the reaction to give the 5-alkylpyrazolines **2x** and **2y** in good yields. Nevertheless, no desired product **2z** was obtained when R group in the substrate was changed to H atom. Additionally, the substrate bearing a *gem*-dimethyl moiety adjacent to C=N bond could not produce the corresponding pyrazoline product **2aa** either. It is noteworthy that *N*-aryl, *N*-acetyl, and *N*-benzoyl substituted unsaturated hydrazones also smoothly participated in the transformation, providing the corresponding 5-arylpyrazolines **2ab–2ae** in 61–92% yield.

The structure of product **2e** (CCDC 2018227) was confirmed by single-crystal X-ray diffraction analysis (Scheme 2). To demonstrate the practical application of the method, a gram-scale reaction was carried out under standard conditions and afforded product **2a** in 92% yield (1.08 g) (Scheme 2).



Scheme 3 Control experiments.

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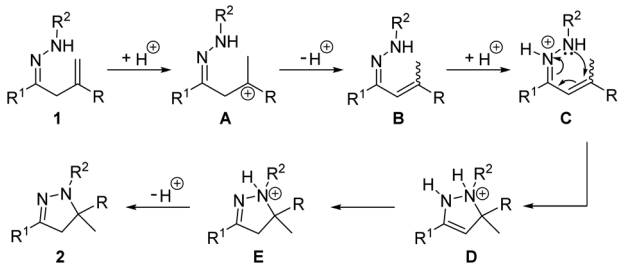

Scheme 4 Proposed mechanism.

To gain some insight into the reaction pathway, several control experiments were conducted (Scheme 3). Upon the addition of the radical scavenger butylated hydroxytoluene (BHT, 3.0 equiv.) under standard reaction conditions, the reaction still proceeded very well to give the desired product **2a** in 92% yield (Scheme 3a), suggesting that a radical pathway could not be involved in this transformation. By the treatment of **1a** with conc. H_2SO_4 (1.0 equiv.) in CH_3CN at 50 °C for a much shorter reaction time (0.5 h), two separable isomers *Z*-**3** and *E*-**3**, resulting from the isomerization of the terminal olefin moiety of **1a**, were obtained in 29% and 57% yields, respectively (Scheme 3b). Subsequent subjection of the isolated *Z*-**3** or *E*-**3** to the standard reaction conditions afforded the product **2a** in 90% and 84% yields (Scheme 3c). The results indicate that the isomeric **3** could be the reaction intermediate, and an olefin isomerization process is very likely to be involved in the reaction. No product was observed when isolated *Z*-**3** or *E*-**3** was subjected to the standard reaction conditions in the absence of H_2SO_4 (Scheme 3d), suggesting that the Brønsted acid plays an important role in the formation of the pyrazoline product from the intermediate.

Based on the above experimental results and previous reports,[12–19] a plausible reaction mechanism is proposed (Scheme 4). Initial electrophilic attack on the C–C double bond of hydrazone **1** by the proton generates carbocation **A**, which is deprotonated to afford olefin-isomerized intermediate **B**.[19a–c] Subsequent protonation of the hydrazone moiety of **B** results in cationic species **C**,[18a,b] which undergoes a 6π-azaelectrocyclization to provide intermediate **D**.[19d–g] Isomerization of **D** to **E**,[19a,h] followed by the final deprotonation to deliver pyrazoline product **2**.

Conclusions

In summary, we have developed a novel, facile, efficient, practical, and Brønsted acid-promoted hydroamination protocol that enables the synthesis of various pyrazolines from β,γ-unsaturated hydrazones. Notably, the present method can be applied to construct the biologically significant 5-arylpyrazolines that are difficult to access by the reported radical hydroaminations of β,γ-unsaturated hydrazones. Preliminary mechanistic investigations indicated that an ionic pathway could be involved in this transformation. This reaction is characterized by simple and mild conditions, broad substrate scope, high yields, excellent chemo- and regioselectivities, and amenability to gram-scale synthesis, which makes it particularly attractive and is expected to find potential applications in organic synthesis and drug discovery.

Experimental

General information

All commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a 400 MHz spectrometer. Chemical shifts (δ) were reported in ppm, and coupling constants (*J*) were given in Hertz (Hz). Data were reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet. High-resolution mass spectra (HRMS) were recorded on an AB SCIEX Triple TOF 5600+ mass spectrometer. Melting points were uncorrected. Alkenyl hydrazone substrates **1a–1ac** were prepared according to the reported methods.[17,20]

General procedure for the hydroamination reaction

To a reaction tube equipped with a magnetic stir bar were added alkenyl hydrazone **1** (0.20 mmol), conc. H_2SO_4 (11 μL, 0.20 mmol), and CH_3CN (2.0 mL). The reaction mixture was stirred at 50 °C under nitrogen atmosphere for 12 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent : petroleum ether/ethyl acetate = 10 : 1) to give product **2**.

Conflicts of interest

There are no conflicts to declare.

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