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One-Pot Synthesis of Pyrazoles through a Four-Step Cascade Sequence

Lu Hao, Jun-Jie Hong, Jun Zhu, and Zhuang-Ping Zhan*[a]

Abstract: A one-pot synthesis of 3,4,5- and 1,3,5-pyrazoles from tertiary propargylic alcohols and *para*-tolylsulfonohydrazide has been accomplished. The pyrazoles are formed through a four-step cascade sequence, including $FeCl_3$-catalyzed propargylic substitution, aza-Meyer–Schuster rearrangement, base-mediated 6π electrocyclization, and thermal [1,5] sigmatropic shift. In this reaction, the 3,4,5- and 1,3,5-pyrazoles are produced selectively according to different substituents in the starting alcohols.

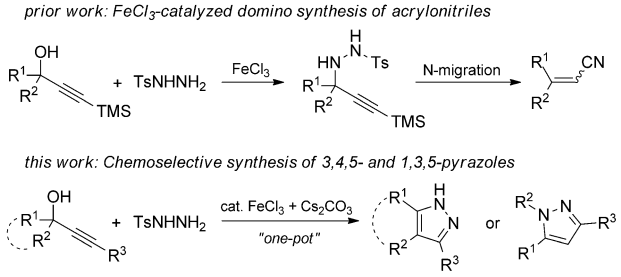
Keywords: domino reactions · heterocycles · pericyclic reaction · pyrazoles · rearrangement

Introduction

Pericyclic reactions have proven to be a powerful strategy for the synthesis of heterocycles due to their high efficiency, regioselectivity, and enantioselectivity.[1,2] For example, cycloadditions, including the well-known Diels–Alder reaction and 1,3-dipolar cycloaddition, are rapidly becoming the method of choice for the construction of heterocycles.[2] However, although cycloadditions have enjoyed great success in this arena, electrocyclization and sigmatropic shift reactions are much less utilized.[3] Accordingly, further development of pericyclic methods for heterocyclic synthesis, especially in a domino and selective manner,[4] is still an extremely attractive yet challenging task.

Pyrazole is an extensively used heterocyclic unit in medicinal, agrochemical, and ligand chemistry.[5] Selected pharmaceutical examples include the well-known drugs Celebrex, Mavacoxib, and Acomplia.[6] As a result, substantial attention has been paid to developing efficient strategies for their syntheses.[7] Two strategies are commonly used: the functionalization of pre-existing pyrazole-containing precursors through the introduction of new functional groups, and the assembly of a new pyrazole ring from acyclic precursors. In general, the latter route has greater potential for obtaining diversity rapidly in functionalized pyrazoles. Thus, new approaches allowing for the efficient assembly of different pyrazole skeletons with diverse substitution patterns are in high demand.

As a part of our studies on propargylic chemistry,[8] we have reported a novel $FeCl_3$-catalyzed domino synthesis of acrylonitriles from trimethylsilyl-substituted tertiary propargylic alcohols and *para*-tolylsulfonohydrazide (Scheme 1).[8d] In the work reported herein, we utilized the same readily available starting materials to provide an efficient access to pyrazoles. Specifically, we performed a four-step one-pot cascade process to prepare two different kinds of pyrazoles substituted at multiple sites, in moderate to excellent yields with high regioselectivity (Scheme 1).



Scheme 1. Cascade pericyclic strategies toward pyrazoles. Ts = tosyl.

Results and Discussion

Our research began with solvent and base screening (Table 1). We treated the propargylic alcohol **1a** with **2** using 10 mol% $FeCl_3$ as the catalyst at 60°C for 1 h. Then, the base was added directly and the mixture was heated to 100°C for 3 h. After careful screening, the optimal conditions were determined (Table 1, entry 8). We found that the basicity of the base plays an important role in the reaction: the use of weak and medium bases, including $NaHCO_3$ and NaOAc, gave no or low yields. On the other hand, reactions employing strong bases, such as EtONa and *t*BuOK, afforded the product in moderate yields. Notably, K_2CO_3 displayed an acceptable efficacy albeit inferior to that of Cs_2CO_3 (Table 1, entry 3). It was also found that performing the re-

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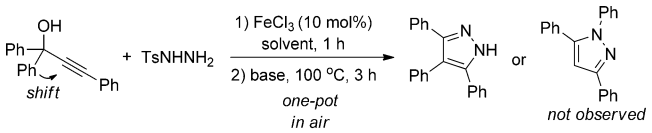
Table 1. Screening of conditions for the synthesis of pyrazoles.[a]



1a 2 3a 4a

Entry	Catalyst	Solvent[b]	Base (equiv)	Yield [%][c] of **3a**
1	$FeCl_3$	CH_3NO_2	$NaHCO_3$ (3.0)	0
2	$FeCl_3$	PhCl	NaOAc (3.0)	35
3	$FeCl_3$	PhCl	K_2CO_3 (3.0)	90
4	$FeCl_3$	PhCl	EtONa (3.0)	78
5	$FeCl_3$	PhCl	*t*BuOK (3.0)	85
6	$FeCl_3$	PhCl	Na_2CO_3 (3.0)	82
7	$FeCl_3$	PhCl	Cs_2CO_3 (3.0)	94
8	$FeCl_3$	PhCl	Cs_2CO_3 (2.2)	95
9	$FeCl_3$	PhCl	none	trace
10	$FeCl_3$	toluene	Cs_2CO_3 (2.2)	62
11[d]	$FeCl_3$	THF	Cs_2CO_3 (2.2)	trace
12	$FeCl_3$	1,4-dioxane	Cs_2CO_3 (2.2)	12
13[d]	$FeCl_3$	DCE	Cs_2CO_3 (2.2)	27
14[e]	AgOTf	PhCl	Cs_2CO_3 (2.2)	trace
15	$Cu(OTf)_2$	PhCl	Cs_2CO_3 (2.2)	34
16	$In(OTf)_3$	PhCl	Cs_2CO_3 (2.2)	47
17	$CeCl_3$	PhCl	Cs_2CO_3 (2.2)	0
18[f]	$ZnCl_2$	PhCl	Cs_2CO_3 (2.2)	trace
19	$AuCl_3$	PhCl	Cs_2CO_3 (2.2)	complex

[a] Conditions: **1a** (0.5 mmol), **2** (0.6 mmol), and catalyst (10 mol%) reacted in solvent (5 mL) in air at 60 °C for 1 h, then the base was added directly to the reaction mixture and the temperature was increased to 100 °C for 3 h. [b] THF = tetrahydrofuran; DCE = 1,2-dichloroethane. [c] Yields of isolated products based on **1a**. [d] The reactions were performed at reflux after addition of the base. [e] About 60% of the starting alcohol was recovered. [f] About 50% of the starting alcohol was recovered.

action without using base only gave a trace amount of **3a** (Table 1, entry 9). The solvent screening showed that PhCl was still the preferred solvent (Table 1, entries 10–13). Notably, the 1,3,5-pyrazole (**4a**), in which the phenyl group migrated to the adjacent N position rather than the C position, was not observed. The screening for the Lewis acid catalysts showed that $FeCl_3$ was still the preferred catalyst (Table 1, entries 14–20).

We next sought to evaluate the substrate scope of this reaction by using a variety of tertiary propargylic alcohols (Table 2). The tertiary alcohols reacted well offering a facile access to trisubstituted pyrazoles, and a range of functionalities including chloro, fluoro, nitro, ethyloxycarbonyl, methoxy, and thiophenyl groups could be well tolerated. In the examples of symmetric diaryl-substituted alcohols ($R^1 = R^2 =$ aryl), the pyrazoles were obtained in moderate to good yields (Table 2, **3a**–**3n**). On the other hand, a mixture of two isomers was generated in the reactions of asymmetric alcohols (Table 2, **3o** and **3p**). Notably, the conversion of the propargylic alcohols bearing aryl substituents on the alkyne position ($R^3 =$ aryl) proceeded very well, and led to the expected products in good to excellent yields (Table 2, **3a**–**3e** and **3i**–**3p**). By comparison, the reactions of propargylic alcohols substituted with alkyl groups ($R^3 =$ alkyl) gave relatively low yields (Table 2, **3f**–**3h**). It was noteworthy that good regioselectivity of R^2 migration was observed in the above-mentioned cases: the aryl groups migrated exclusively to the adjacent carbon atom, thereby producing the 3,4,5-pyrazoles **3** (Table 2, **3a**–**3p**).

Encouraged by these results, we next examined the reactivity of propargylic alcohols substituted with aryl and alkyl groups ($R^1 =$ aryl, $R^2 =$ alkyl). Interestingly, 1,3,5-pyrazoles **4** in which the alkyl group (R^2) migrated to the adjacent nitrogen atom were generated (Table 3, **4q**–**4t**). We also tested the reactivity of dimethyl-substituted propargylic alcohol **1u**. However, it proved to be a uniquely challenging partner and the expected product **4u** was not obtained. The chemical structure of **4q** was determined by single-crystal X-ray diffraction (Figure 1).

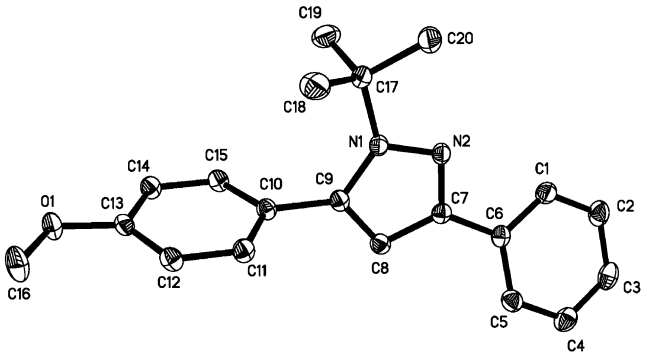
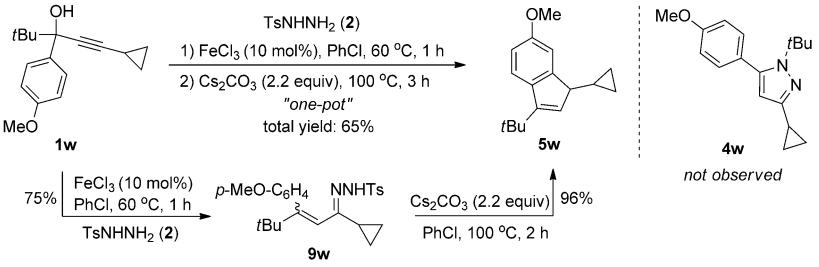


Figure 1. X-ray structure of **4q**.

When the reaction of **1w** was investigated (Scheme 2), the result was very interesting. In this reaction, indene **5w** rather than pyrazole **4w** was obtained.[9,16] Next, intermediate **9w** was isolated in 75% yield, which could be transformed into **5w** under base-mediated conditions in 96% yield. This result confirmed the participation of $TsNHNH_2$ (**2**) in the transformation of **1w** into **5w**.

The synthetic utility of this approach was further highlighted by the one-pot cascade synthesis of dibenzo-



Scheme 2. Reaction of propargylic alcohol **1w**.

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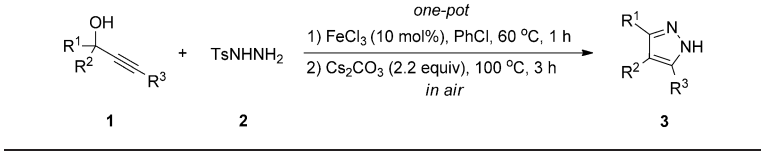
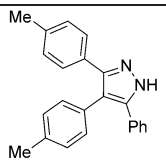
Table 2. One-pot cascade synthesis of 3,4,5-pyrazoles.[a]



1 2 3

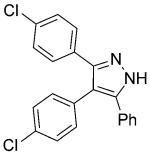
3a

3a 95 %
$R^1 = C_6H_5$
$R^2 = C_6H_5$
$R^3 = C_6H_5$



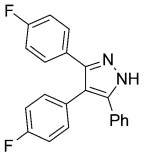
3b

3b 98 %
$R^1 = p$-Me-C_6H_4
$R^2 = p$-Me-C_6H_4
$R^3 = C_6H_5$



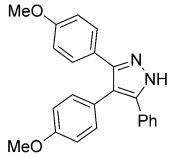
3c

3c 80 %
$R^1 = p$-Cl-C_6H_4
$R^2 = p$-Cl-C_6H_4
$R^3 = C_6H_5$



3d

3d 90 %
$R^1 = p$-F-C_6H_4
$R^2 = p$-F-C_6H_4
$R^3 = C_6H_5$

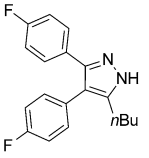


3e

3e 98 %
$R^1 = p$-MeO-C_6H_4
$R^2 = p$-MeO-C_6H_4
$R^3 = C_6H_5$

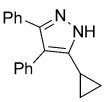
3f

3f 70 %
$R^1 = C_6H_5$
$R^2 = C_6H_5$
$R^3 = n$-butyl



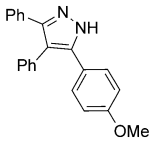
3g

3g 42 %
$R^1 = p$-F-C_6H_4
$R^2 = p$-F-C_6H_4
$R^3 = n$-butyl



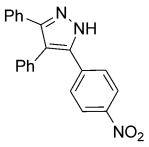
3h

3h 65 %
$R^1 = C_6H_5$
$R^2 = C_6H_5$
R^3 = cyclopropyl



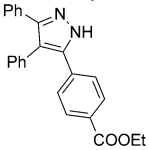
3i

3i 98 %
$R^1 = C_6H_5$
$R^2 = C$
$R^3 = p$-MeO-C_6H_4



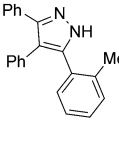
3j

3j 75 %
$R^1 = C_6H_5$
$R^2 = C_6H_5$
$R^3 = p$-O_2N-C_6H_4



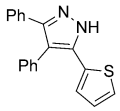
3k

3k 95 %[b]
$R^1 = C_6H_5$
$R^2 = C_6H_5$
$R^3 = p$-EtOOC-C_6H_4



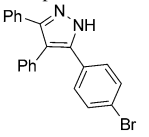
3l

3l 85 %
$R^1 = C_6H_5$
$R^2 = C_6H_5$
$R^3 = o$-Me-C_6H_4



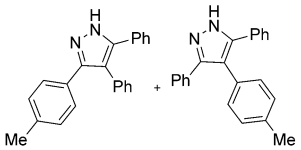
3m

3m 73 %
$R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = \alpha$-thiophenyl



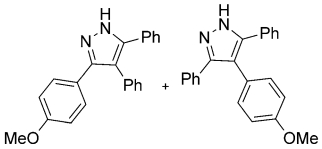
3n

3n 97 %
$R^1 = C_6H_5$, $R^2 = C_6H_5$, $R^3 = p$-Br-C_6H_4



3o

3o 98 %[c]
$R^1 = C_6H_5$, $R^2 = p$-Me-C_6H_4, $R^3 = C_6H_5$



3p

3p 98 %[c]
$R^1 = C_6H_5$, $R^2 = p$-MeO-C_6H_4, $R^3 = C_6H_5$

[a] Conditions: **1** (0.5 mmol), **2** (0.6 mmol), and $FeCl_3$ (10 mol %) reacted in PhCl (5 mL) in air at 60 °C for 1 h, then Cs_2CO_3 (2.2 equiv) was added directly to the reaction mixture and the temperature was increased to 100 °C for 3 h. Yields of isolated products based on **1**. [b] 4 Å molecular sieves were added to prevent hydrolysis of the COOEt group. [c] The isomer ratios of **3o** and **3p** were 57:43 and 60:40, respectively.

[*e*,*g*]indazole **3v** through a ring-expansion strategy of tertiary propargylic alcohol **1v** and **2** (Scheme 3). The fused heterocyclic skeleton **3v** was constructed in 60 % yield under the standard conditions.

To probe the mechanism, attempts were made to capture the reaction intermediates (Scheme 4). First, by subtle control of the reaction conditions, the propargylic substitution product (**5a**) and the aza-Meyer–Schuster rearrangement product (**9a**) were isolated [Scheme 4, Eqs. (1) and (2)]. We discovered that both **5a** and **9a** could be smoothly converted into **3a** under the standard conditions. Subsequently, the intermediate **11a** was isolated in 55 % yield [Scheme 4, Eq. (3)]. We found that **3a** could be obtained from **11a** in nearly quantitative yield under thermal conditions without adding any base [Scheme 4, Eq. (4)]. Moreover, **11a** transformed into **3a** gradually when at room temperature for over a month. These results showed that the [1,5] sigmatropic shift of **11a** into **3a** was a concerted process not affected by any other factors.

We next propose the mechanism of this reaction (Scheme 5). First, propargylic alcohol **1** reacts under iron catalysis to yield propargylic cation **7**, which is attacked regioselectively by the terminal nitrogen ($-NH_2$) of **2**, thus resulting in the substitution product **5**. Next, **5** undergoes an $FeCl_3$-catalyzed [1,3] shift of the $-NHNHTs$ group through the transition state **6**, which leads to allene **8**. Then, after rapid tautomerization from **8** to **9**, the latter transforms into **11** through a base-mediated 6π-electrocyclic ring closure.[9a] According to the type of R^2 group, the thermal [1,5] sigmatropic shift proceeds in two ways: either on the adjacent carbon atom or on the adjacent nitrogen atom. The former route produces the 4*H*-pyrazoles **12**, which subsequently experience a rapid isomerization to form 3,4,5-pyrazoles **3**, whereas the latter affords the 1,3,5-pyrazoles **4** directly.

To gain insight into the regioselectivity of the [1,5] sigmatropic shift, we performed density function theory (DFT) calculations. As shown in Scheme 6, the reaction involving shift of the phenyl group is more exothermic than that of the *t*Bu group, in line with the higher yields of the reaction of propargylic alcohols with aryl substituents over alkyl groups observed experimentally. In addition, the shift of the phenyl group to the adjacent carbon atom is thermodynamically more favorable than that to the adjacent nitrogen atom. In sharp contrast, the shift of the *t*Bu group to the adjacent nitrogen atom is thermodynamically more favorable than that to the adjacent carbon atom. To further probe the origin of the relative stability between 3,4,5- and 1,3,5-pyrazoles, we first examined the steric effect on these pyrazoles. In particular, the closest H···H distances between the phenyl and *t*Bu

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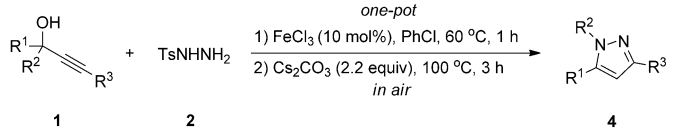
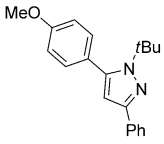
Table 3. One-pot cascade synthesis of 1,3,5-pyrazoles.[a]

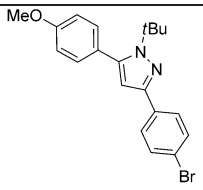


1 2 4



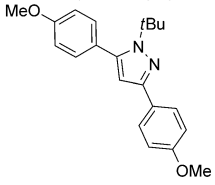
4q

4q 53 %[b]
R^1 = *p*-MeO-C_6H_4,
R^2 = *t*Bu, R^3 = C_6H_5



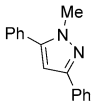
4r

4r 52 %
R^1 = *p*-MeO-C_6H_4,
R^2 = *t*Bu, R^3 = *p*-Br-C_6H_4



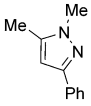
4s

4s 60 %
R^1 = *p*-MeO-C_6H_4, R^2 = *t*Bu
R^3 = *p*-MeO-C_6H_4



4t

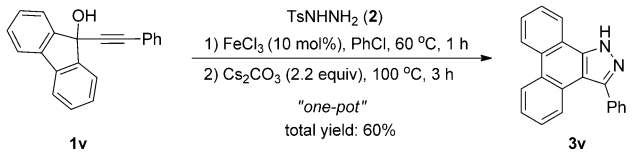
4t 17 %
R^1 = C_6H_4, R^2 = Me
R^3 = C_6H_5



4u

4u 0 %
R^1 = Me, R^2 = Me
R^3 = C_6H_5

[a] Conditions: **1** (0.5 mmol), **2** (0.6 mmol), and $FeCl_3$ (10 mol %) reacted in PhCl (5 mL) in air at 60 °C for 1 h, then the Cs_2CO_3 (2.2 equiv) was added directly to the reaction mixture and the temperature was increased to 100 °C for 3 h. Yields of isolated products based on **1**. [b] The structure of **4q** was determined by single-crystal X-ray diffraction.



1v 3v

Scheme 3. Synthesis of dibenzo[*e*,*g*]indazoles through a ring-expansion strategy.

groups in **3a′** and **4a′** are 2.237 and 2.375 Å, respectively, which indicates that the steric effect should play a role in the stability of **3a′** and **4a′**. However, the closest H···H distances between the phenyl groups in **3a** and **4a** are as far as 3.064 and 3.241 Å, respectively, thus suggesting the steric effect should not apply for **3a** and **4a**. We then examined the aromaticity of the pyrazole ring in **3a** and **4a** by computing the nucleus-independent chemical shifts (NICSs).[10] The $NICS(1)_{zz}$ values in **3a** and **4a** are −24.0 and −21.4 ppm, respectively, which indicate better conjugation of the pyrazole ring in **3a**. Thus, the interplay of the steric effect and aromaticity results in the regioselectivity of the [1,5] sigmatropic shift observed in our experiment.

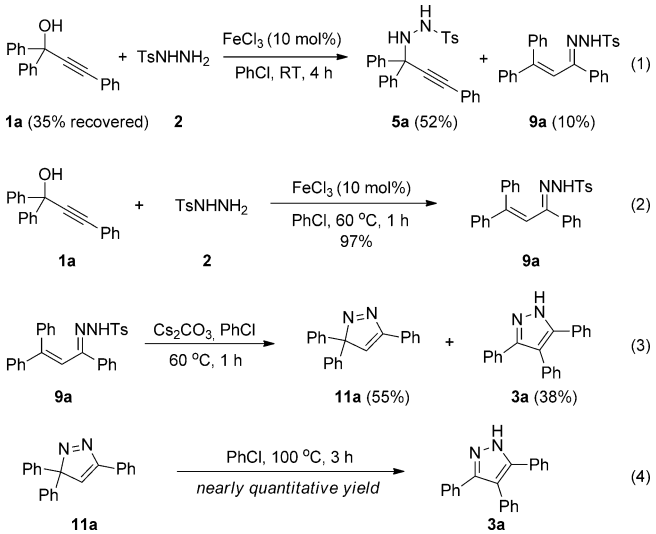
Conclusion

We have developed an expeditious one-pot protocol for the synthesis of 3,4,5- and 1,3,5-pyrazoles from readily available starting materials. The pyrazoles are formed through a four-step cascade sequence. Importantly, a cascade pericyclic strategy is incorporated into the synthetic process. Further study on this topic is in progress in our group.

Experimental Section

General procedure for the syntheses of 3a–3p, 3v, 5w, and 4q–4t: Propargylic alcohol **1** (0.5 mmol, 1.0 equiv), *para*-tolylsulfonohydrazide **2** (0.6 mmol, 1.2 equiv), and PhCl (5 mL) were added successively in air to a flame-dried 10 mL flask equipped with a magnetic bar. The mixture was stirred until **2** fully dissolved. Subsequently, $FeCl_3$ (10 mol %, 0.05 mmol) was added. The reaction mixture was stirred at room temperature in air for about 10 min until the reaction system became homogeneous. Next, the mixture was heated to 60 °C and stirred for 1 h. Then, Cs_2CO_3 (1.1 mmol, 2.2 equiv) was added directly to the reaction mixture, which was heated to 100 °C within 15 min and maintained at this temperature for 3 h. The residue was purified by column chromatography on silica gel to afford the pyrazoles.

Computational details: All structures were optimized at the M06-2X level of DFT.[11] In addition, frequency calculations were performed to confirm the characteristics of the calculated structures as minima. In the M06-2X optimizations, the standard 6-31G(d) basis set was used.[12] To assess the degree of aromaticity in 3,4,5- and 1,3,5-pyrazoles, NICS values were calculated by using the gauge including atomic orbital (GIAO) method[13] at the M06-2X level with the 6-311++G(d,p) basis set.[14] We applied the $NICS(1)_{zz}$ version, which is readily obtained as the negative of the out-of-plane tensor component of the magnetic shielding at a position 1.0 Å above or below the ring plane.[10b] This index has shown promise as a readily computable and well-performing substitute for $NICS_{zz}(0)$, the



Scheme 4. Isolation of reaction intermediates.

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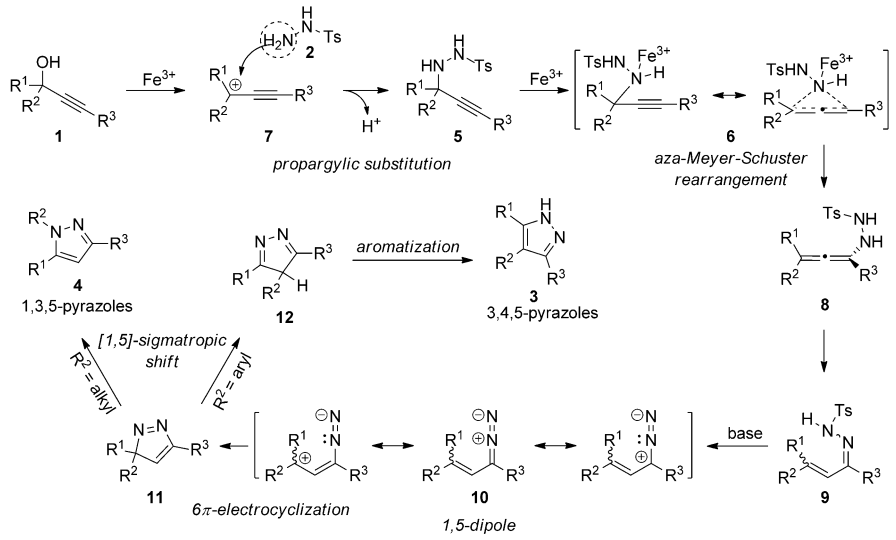
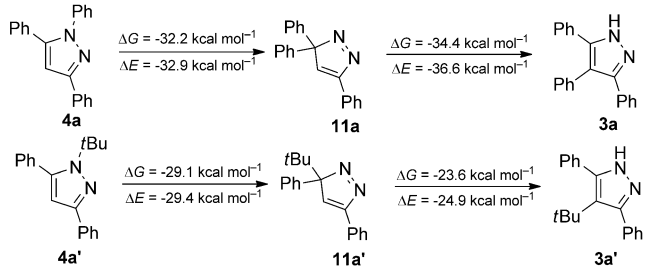


Scheme 5. Proposed mechanism for the synthesis of pyrazoles.



Scheme 6. Gibbs free energies (G) at 298 K and electronic energies (E) of the [1,5] sigmatropic shift to the adjacent nitrogen (left) and carbon (right) obtained by M06-2X calculations.

most advanced and precise NICS version. When the environments at points 1 Å above and below the ring centers are not equivalent, the averaged values are used for NICS(1)$_{zz}$. All the optimizations were performed with the Gaussian 09 software package.[15]

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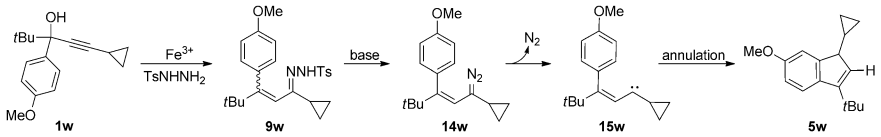

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