Organic LETTERS

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Synthesis of Polysubstituted Pyrazoles by a Platinum-Catalyzed Sigmatropic Rearrangement/Cyclization Cascade

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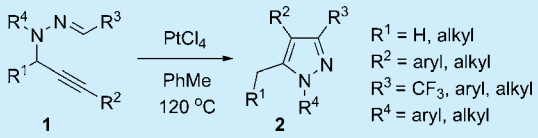
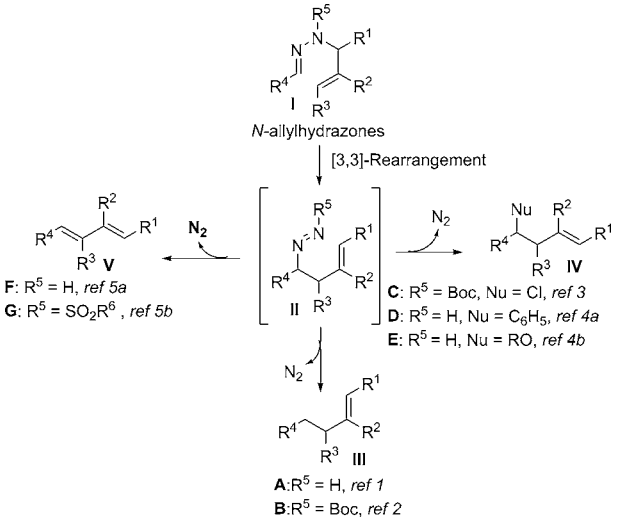
Supporting Information

ABSTRACT: A highly efficient Pt-catalyzed [3,3] sigmatropic rearrangement/cyclization cascade of *N*-propargylhydrazones is reported. The process provides expedient access to a variety of highly functionalized pyrazoles. The substrate has good substituted group compatibility, and the bioactive 3-CF_3 pyrazoles could be synthesized easily with this method.

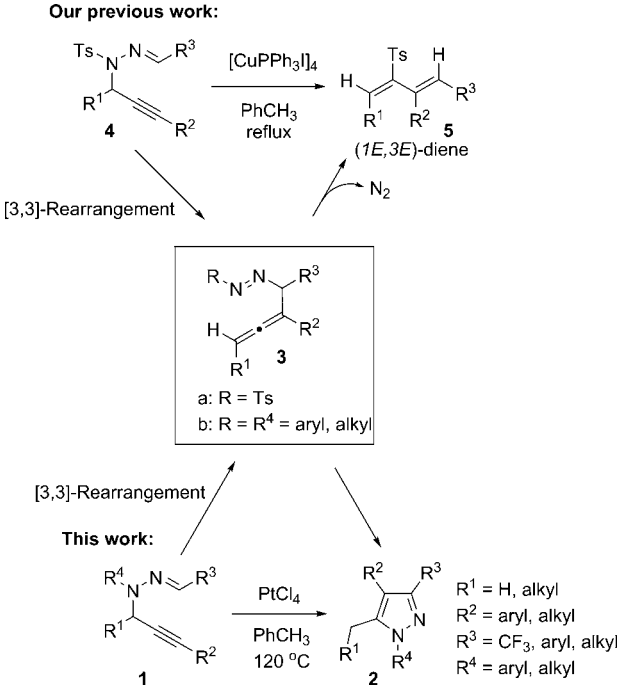


The [3,3] sigmatropic rearrangement of *N*-allylhydrazones, first reported in 1973 by Stevens and co-workers,[1] is an efficient method for the assembly of complex molecules from simple fragments such as hydrazines and aldehydes. The rearrangement of these structures usually leads to a diazo intermediate **II** (Scheme 1), which can eliminate a molecule of N_2 to generate a variety of functionalized alkenes. Since the initial discovery, various efforts have been made, mainly by Thomson and co-workers, to expand the application scope of these reactions.[2−5] In comparison, similar reactions involving *N*-propargylhydrazones were less studied. In 2013, we reported the only set of examples of the [3,3] sigmatropic rearrangement of *N*-propargylhydrazones for the stereoselective synthesis of sufonyldienes **5** (Scheme 2).[6] All of these reactions shared the same mechanistic feature that included the labile diazo intermediate invariably undergoing N_2 extrusion and generating an open-chain carbon backbone. Here, We report the synthesis of polysubstituted pyrazoles[7] from *N*-propargylhydrazones via a $PtCl_4$-catalyzed [3,3] sigmatropic rearrangement/cyclization cascade (Scheme 2), demonstrating an alternative pathway in which the diazo moiety of the intermidate **3** was retained to allow the formation of a series of highly functionalized pyrazoles.[7]

Scheme 1. [3,3]-Rearrangement of *N*-Allylhydrazones



Scheme 2. [3,3]-Rearrangement of *N*-Propargylhydrazones

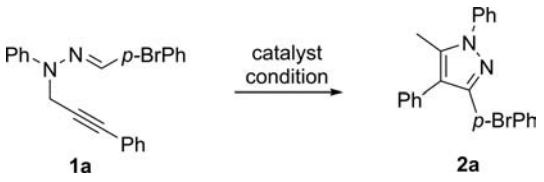


We first used the reaction conditions that we previously employed to convert tosylhydrazone **4** to diene **5** (Scheme 2) as a starting point for the optimization of reaction conditions. Hence, the model substrate **1a** was treated with a catalytic amount of $[CuPPh_3I]_4$ (5 mol %) in $PhCH_3$ under reflux for 24 h (Table 1, entry 1). However, no reaction occurred. We then tested a range of other transition-metal catalysts, including

Received: October 8, 2014
Published: November 10, 2014

dx.doi.org/10.1021/ol502968c | Org. Lett. 2014, 16, 5940−5943

Table 1. Optimization of the Reaction Conditions



entry[a]	catalyst	solvent	temp/°C	t/h	result
1	$[CuPPh_3I]_4$ (5 mol %)	$PhCH_3$	reflux	24	NR[b]
2	CuBr (10 mol %)	$PhCH_3$	120	24	NR[b]
3	$Cu(OTf)_2$ (10 mol %)	$PhCH_3$	120	24	-[c]
4	$ZnCl_2$ (10 mol %)	$PhCH_3$	120	24	-[c]
5	$NiCl_2$ (10 mol %)	$PhCH_3$	120	24	NR[b]
6	$Pd(OAc)_2$ (10 mol %)	$PhCH_3$	120	24	NR[b]
7	$PdCl_2$ (10 mol %)	$PhCH_3$	120	24	complex
8	AgOAc (10 mol %)	$PhCH_3$	120	24	NR[b]
9	AgOTf (10 mol %)	$PhCH_3$	120	24	trace
10	$PtCl_2$ (10 mol %)	$PhCH_3$	120	24	27%[d]
11	$PtCl_4$ (10 mol %)	$PhCH_3$	120	5	65%[d]
12	$PtCl_4$ (10 mol %)	$ClCH_2CH_2Cl$	120	6	48%[d]
13	$PtCl_4$ (10 mol %)	CH_3NO_2	120	6	18%[d]
14	$PtCl_4$ (10 mol %)		120	6	32%[d]
15	$PtCl_4$(10 mol %)	PhCl	120	4	45%[d]
16	$PtCl_4$ (10 mol %)	THF	120	24	trace
17	$PtCl_4$ (10 mol %)	CH_3CN	120	24	trace
18	$PtCl_4$ (10 mol %)	DMSO	120	24	trace
19	$PtCl_4$ (10 mol %)	DMF	120	24	trace
20	$PtCl_4$ (5 mol %)	$PhCH_3$	120	7	82%[d]

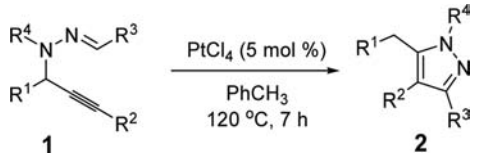
[a]Reaction conditions: **1a** (50 mg), solvent (3 mL), in Schlenk tube. [b]NR = no reaction. [c]Unstable product. [d]Isolated yield.

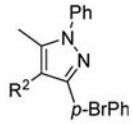
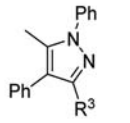
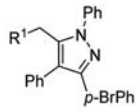
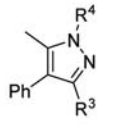
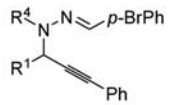
CuBr, $Cu(OTf)_2$, $ZnCl_2$, $NiCl_2$, $Pd(OAc)_2$, $PdCl_2$, AgOAc, and AgOTf, all of which either did not lead to any detectable product formation or resulted in unstable or complex byproducts (Table 1, entries 2−9). However, the treatment of **1a** with $PtCl_2$ furnished pyrazole **2a** in 27% yield (Table 1, entry 10). Experimentation with other Pt-based catalysts revealed that the choice of $PtCl_4$ could dramatically improve the yield to 65% and shorten the reaction time necessary to 5 h (Table 1, entry 11). Attempts to further enhance the efficiency of product formation by screening different solvents were unsuccessful (Table 1, entries 12−19). Additionally, lowering the usage of $PtCl_4$ to 5 mol % boosted the yield to 82% at the expense of the reaction time which was prolonged to 7 h (Table 1, entry 20). Hence, the optimum reaction conditions were determined to comprise 5 mol % of $PtCl_4$ as the catalyst, toluene as the solvent, and heating the mixture to 120 °C for 7 h.

We next evaluated the scope of the reaction under the optimal conditions by placing different substituents (R^1, R^2, R^3, R^4) on various positions of the *N*-propargylhydrazone **1** (Table 2). The alkynyl position R^2 was found to tolerate a diverse range of phenyl groups (Table 2, entries 1−4) substituted with a halogen (Br), an electron-donating group (OMe), or an electron-withdrawing group (NO_2), and alkyl or alkenyl substituents (Table 2, entries 5−6), such as butyl and cyclohexenyl. Introducing a trimethylsilyl group, however, seemed to completely abolish the pyrazole formation (Table 2, entry 7). The structure of **2b** is further confirmed by single crystal X-ray structure analysis (Figure 1).

Hydrazones derived from both aryl (including hereoaryls) and alkyl aldehydes were suitable substrates (Table 2, entries

Table 2. Synthesis of Polysubstituted Pyrazoles



entry[a]	substrate	procduct	Yield(%)[b]
1	**1a** (R^2 = Ph)		82 (**2a**)
2	**1b** (R^2 = *p*-BrPh)		70 (**2b**)
3	**1c** (R^2 = *p*-OMePh)		72 (**2c**)
4	**1d** (R^2 = *p*-NO_2Ph)		78 (**2d**)
5	**1e** (R^2 = *n*-butyl)		78 (**2e**)
6	**1f** (R^2 = cyclohexenyl)		74 (**2f**)
7	**1g** (R^2 = TMS)		NR[c]
8	**1h** (R^3 = 2-thienyl)		67 (**2h**)
9	**1i** (R^3 = 2-furyl)		68 (**2i**)
10	**1j** (R^3 = 1-naphthyl)		71 (**2j**)
11	**1k** (R^3 = *n*-pentyl)		53 (**2k**)
12	**1l** (R^1 = *n*-pentyl)		58 (**2l**)
13	**1m** (R^4 = *p*-OMePh R^3 = *p*-BrPh)		85 (**2m**)
14	**1n** (R^4 = *p*-NO_2Ph R^3 = *p*-BrPh)		NR
15	**1o** (R^4 = cyclohexyl R^3 = Ph)		38 (**2o**)
16		**4** (R^1 = Ph R^4 = Ts)	complex
17		**1p** (R^1 = H R^4 = Boc)	complex

[a]Reaction conditions: **1** (50 mg), $PhCH_3$ (3 mL), in Schlenk tube. [b]Isolated yield. [c]NR = no reaction.

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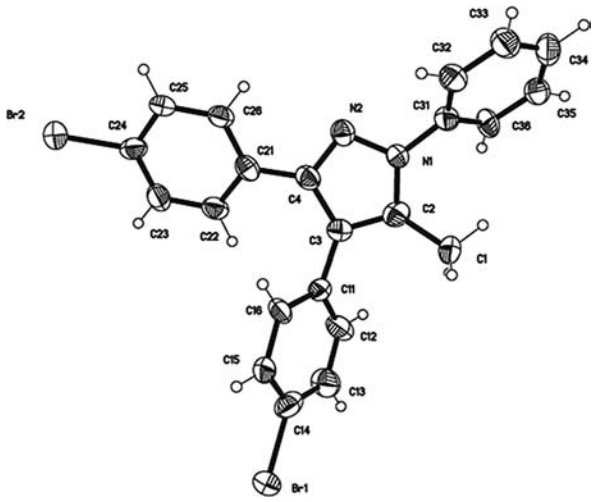
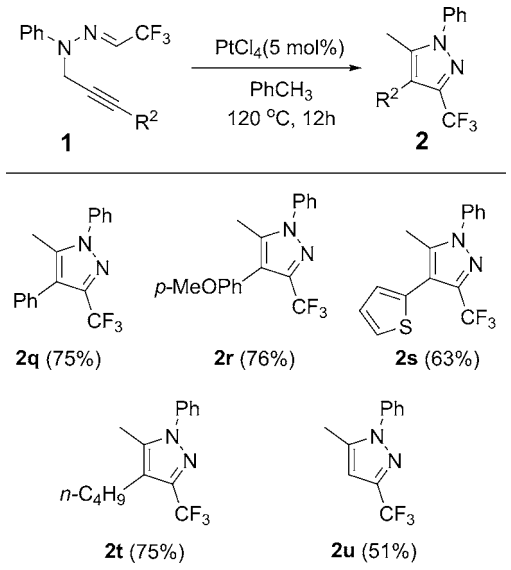


Figure 1. X-ray crystal structure of **2b**.

8−11, products **2h−2k**, 53−71% yield). Branching at the proparglic position was tolerated (R^1 = *n*-penyl), and the desired pyrazole was obtained in 58% yield (Table 2, entry 12). The reaction seemed to be very sensitive to the substituent R^4. While substrate **1m** carrying an electron-rich phenyl ring afforded the product in 85% yield (Table 2, entry 13), the ones with electron-withdrawing substituents, such as *p*-NO_2Ph, Ts, and Boc, either failed to react or led to a complex product mixture (Table 2, entries 14, 16−17). Replacing the R^4 phenyl group with a cyclohexyl ring significantly lowered the product yield to 38% (Table 2, entry 15).

3-Trifluoromethyl-substituted pyrazole is the core structure of many bioactive molecules.[8,9] As shown in Scheme 3, the current method is highly efficient for the synthesis of these structures with different substituents along the pyrazole ring, but requires a longer reaction time (12 h). Of note is that a terminal alkyne also reacted to give the desired pyrazole in 51% yield (product **2u**).

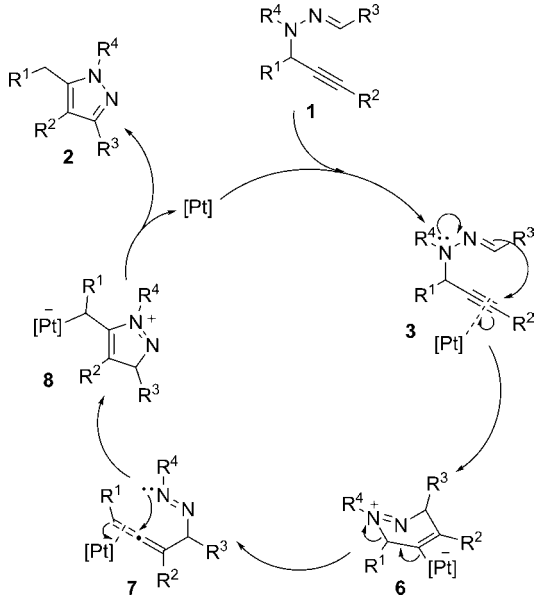
Scheme 3. Synthesis of 3-Trifluoromethylpyrazoles[a,b]



[a]Reaction conditions: **1** (50 mg), $PhCH_3$ (3 mL), in Schlenk tube. [b] Isolated yield.

A proposed mechanism for the Pt-catalyzed rearrangement/cyclization cascade is illustrated in Scheme 4. First, the Pt-based

Scheme 4. Proposed Mechanism



catalyst complexes with the triple bond of the reactant render the latter electrophilic and therefore vulnerable to the nucleophilic addition of the proximal hydrazone. The ensuing cyclization results in vinylplatinum **6**, which opens up to generate diazoallene **7**. Instead of decomposition via nitrogen extrusion, the diazo nitrogen cyclizes onto the Pt-activated allene to furnish the cyclic intermediate **8**, which then converts to the final product **2** and regenerates the Pt catalyst through proton transfer. The cyclization efficiency of **7** hinges largely on the nucleophilicity and the stability of the diazo group. If R^4 is Ts or Boc, we proposed intermediate **7** to be unstable and its nitrogen atom to exhibit weak nucleophilicity, which would lead to the complex reaction result here. In contrast, if R^4 is phenyl or alkyl, the conjugation or electron-donating effect will stabilize the intermediate **7** as well as enhance the nucleophilicity of its nitrogen atom, which will undergo a further cyclization process to furnish the cyclic intermediate **8**. In addition, the stabilization effect of the alkyl group compared to the phenyl is less, resulting in the related substrate giving the low yield of the cyclic product.

In conclusion, we have reported a novel method for the synthesis of pyrazoles from *N*-propargylhydrazones via a Pt-catalyzed [3,3] rearrangement/cyclization cascade. The method is applicable to a wide range of substrates and provides convenient access to a variety of highly functionalized pyrazoles, including medically important 3-trifluoromethyl-pyrazoles.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds and crystallographic data (CIF) of **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol502968c | *Org. Lett.* 2014, 16, 5940−5943

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (No. 21272190) and PCSIRT in University. We sincerely thank Ting Li (Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University) for his kindly help on the crystal structure analysis.

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