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Synthesis of Tri- and Tetrasubstituted Pyrazoles via Ru(II) Catalysis: Intramolecular Aerobic Oxidative C–N Coupling

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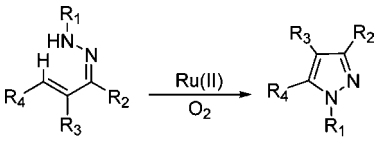
ABSTRACT



39 examples
up to 94% yield

An unprecedented ruthenium(II)-catalyzed intramolecular oxidative C–N coupling method has been developed for the facile synthesis of a variety of synthetically challenging tri- and tetrasubstituted pyrazoles. Dioxygen gas is employed as the oxidant in this transformation. The reaction demonstrates excellent reactivity, functional group tolerance, and high yields.

Pyrazoles are an important class of compounds that are extensively used in today's pharmaceutical industry.[1] Compounds containing a pyrazole scaffold are being developed for the treatment of metabolic, CNS, and oncological diseases, etc.[2] A number of pyrazole derivatives have been successfully commercialized, such as Celebrex, Viagra, and Acomplia.[3] Substituted pyrazoles have also been utilized as useful ligands for some cross-coupling reactions.[4]

Over the past decade, considerable research has focused on the development of transition-metal-catalyzed C–H bond functionalization methods that can be applied to the synthesis of biologically important aromatic and heteroaromatic compounds.[5,6] Among these, ruthenium-catalyzed

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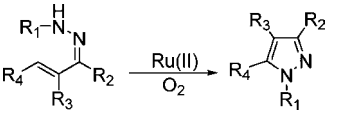
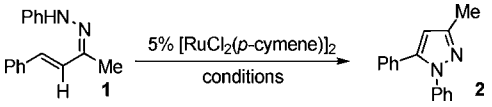
reactions have proven themselves to be highly selective and atom economical.[7,8] In this area, to date, most research has focused on the catalytic conversion of C−H bonds to C−C bonds. In contrast, the application of ruthenium catalysis to the construction of carbon−heteroatom bonds, especially for oxidative carbon−nitrogen bond formation, has been rarely reported.[9] Thus far, major research efforts into C−N oxidative coupling have focused on using other metals such as Pd, Cu, etc.[5,6] In our ongoing studies into the preparation of multisubstituted pyrazoles, we have proposed that "a ruthenium catalyst, under proper conditions, allows C−H bond cleavage via an orthometalation process that involves chelation with the nitrogen from hydrazones"[10] Consequently, the formation of a C−N bond is possible via reductive elimination to generate the corresponding pyrazole products[11] (Scheme 1). A terminal oxidant could oxidize the Ru(0) species to Ru(II) to complete the catalytic cycle. To the best of our knowledge, intramolecular oxidative carbon−nitrogen bond formation using ruthenium(II) has not yet been achieved. In this paper, we report a new example of ruthenium(II)-catalyzed oxidative C−N coupling with molecular oxygen as the oxidant for the preparation of pyrazole derivatives.

Scheme 1. Preparation of Pyrazole through Ru(II)-Mediated C−H Activation



The oxidant plays an essential role in the catalytic cycle of C−H activation. While there are many commonly used oxidants such as $PhI(OAc)_2$,[12] BQ,[13] $Cu(OAc)_2$,[14] AgOAc,[15] $K_2S_2O_8$,[16] TBHP, and Oxone, we are particularly interested here in the applicability of dioxygen,[17] since it is an ideal oxidant and offers attractive industrial prospects in terms of green and sustainable chemistry. Accordingly, to test our hypothesis, a model study was initiated with hydrazone **1** in the presence of $[RuCl_2(p\text{-cymene})]_2$ in DCE under one atmosphere of O_2. The results are shown in Table 1. Encouragingly, a 10% yield of the desired product **2** was achieved (entry 1) after stirring for 6 h at 80 °C. Encouraged by this preliminary result, we proceeded to optimize the reaction conditions. After comprehensive screening, we found DMSO to be highly efficient and superior to other solvents, such as DCM, MeCN, THF, DMF, DMA, EtOH, and 1,4-dioxane. It was observed that higher temperatures could speed up the reactions and improve the yields. There were only slight differences in terms of reaction rates and conversion ratios when higher catalyst loadings were used. Generally, a 0.05 equiv amount of $[RuCl_2(p\text{-cymene})]_2$ was sufficient to effectively promote the reaction. Moreover, we found that the yields notably increased with the addition of a base such as $NaHCO_3$. It was believed that the base would serve as a proton shuttle and assist in the transformation. Attempts to use other ruthenium catalysts, such as $RuCl_2(PPh)_3$, $RuHCl(PPh)_3$, and $Ru_3(CO)_{12}$, were not as successful as $[RuCl_2(p\text{-cymene})]_2$. Interestingly, a 36% yield of product **2** was also achieved by using air as the oxidant (entry 21). Typically, the reaction will proceed to completion in DMSO within 8 h, in a clean manner, under 1 atm of O_2 at 100 °C.

Table 1. Optimization of the Reaction Conditions



entry	condition	yield[a] (%)
1	1 atm O_2, DCE, 80 °C, 6 h	10
2	1 atm O_2, 1,4-dioxane, 80 °C, 6 h	21
3	1 atm O_2, MeCN, 80 °C, 6 h	10
4	1 atm O_2, EtOH, 80 °C, 6 h	27
5	1 atm O_2, t-AmOH, 80 °C, 6 h	11
6	1 atm O_2, DMSO, 80 °C, 6 h	35
7	1 atm O_2, DMF, 100 °C, 6 h	49
8	1 atm O_2, DMA, 100 °C, 6 h	41
9	1 atm O_2, DMSO, 100 °C, 6 h	67
10	1 atm O_2, 2.0 equiv Et_3N, DMSO, 100 °C, 6 h	71
11	1 atm O_2, 2.0 equiv DIPEA, DMSO, 100 °C, 6 h	66
12	1 atm O_2, 2.0 equiv Pyridine, DMSO, 100 °C, 6 h	47
13	1 atm O_2, 2.0 equiv DBU, DMSO, 100 °C, 6 h	59
14	1 atm O_2, 2.0 equiv DABCO, DMSO, 100 °C, 6 h	61
15	1 atm O_2, 2.0 equiv $NaHCO_3$, DMSO, 100 °C, 6 h	72[b]
16	1 atm O_2, 2.0 equiv Na_2CO_3, DMSO, 100 °C, 6 h	59
17	without Ru, 1 atm O_2, DMSO, 100 °C, 24 h	trace[c]
18	1 atm air, 2.0 equiv $NaHCO_3$, DMSO, 100 °C, 6 h	36

[a] Conversion ratio. [b] Isolated yield. [c] LC−MS analysis.

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Having identified these optimal conditions, we set out to explore the scope for this new reaction. A variety of aromatic hydrazines, α,β-unsaturated aldehydes, and ketones were surveyed to prepare different trisubstituted pyrazoles. As shown in Figure 1, not only 1,3,5-trisubstituted pyrazole derivatives (**3**–**22**) but also 1,3,4- and 1,4,5-trisubstituted pyrazole derivatives (**23**–**27**) were prepared readily from the corresponding aromatic hydrazones. The scope of the pyrazole ring substituents was found to be very broad. In terms of R_1 substituents, the *ortho*-, *meta*-, and *para*-substituted aryl groups, as well as the electron-rich and electron-deficient aryl groups, were well tolerated, while the various aryl hydrazines easily produced good to excellent yields of the corresponding pyrazole products. Notably, 2-pyridyl hydrazine was also successfully employed to provide compound **20**. It was found that R_2, R_3, and R_4 can be either H, alkyl, or aryl groups to give various substituted pyrazoles. For example, *if R_2 is H, the products will be 1,4,5-trisubstituted pyrazoles*, respectively, such as **25** and **26**. However, *when R_4 is H, the 1,3,4-trisubstituted pyrazole* **27** can be readily generated in a yield of 92%. Both alkyl and aryl groups were well tolerated to provide multifunctionalized pyrazole derivatives. It is particularly worth noting that pyrazoles (**4**–**7**, **16**, **17**, **21**) containing different heteroaromatic rings, such as pyridine, thiophene, and furan, were also smoothly prepared in good to excellent yields. Besides the alkyl and aryl substituents, vinyl functional groups were presented as well to give olefinated product **18**.

The scope of this intramolecular cyclization reaction was further expanded to the preparation of synthetically challenging tetrasubstituted pyrazole derivatives. As illustrated in Figure 2, the optimum reaction conditions also proved to be successful in providing highly diversified tetrasubstituted pyrazoles (compounds **28**–**36**) with satisfactory yields, respectively. It is noteworthy to point out that *these novel tetrasubstituted pyrazoles and most trisubstituted pyrazoles are either difficult or need extra and tedious steps to prepare via traditional methods* (Scheme 2).[18] Compared with the usual ways, our new method has the advantages of less steps, milder reaction conditions, and higher overall yields.

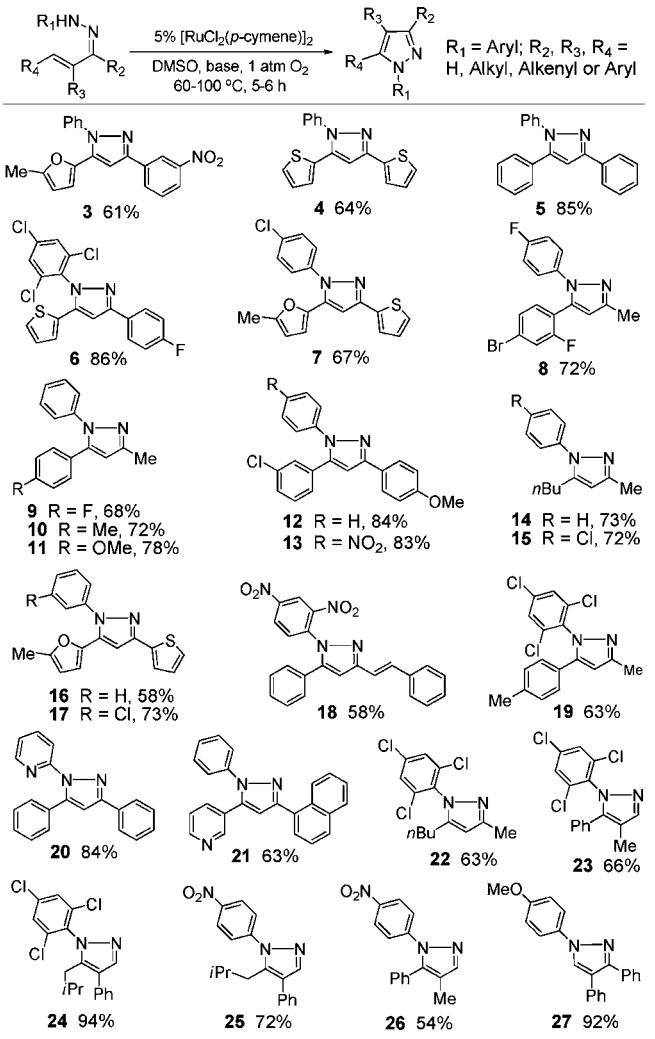

Figure 1. Synthesis of trisubstituted pyrazoles. [a]Isolated yield.

This unique method provides new opportunities for the construction of some biologically important molecules, as exemplified in Scheme 3. A sulfa nonsteroidal anti-inflammatory drug, Celebrex, and its structural analogues (**37**–**40**) were smoothly prepared in good to excellent yields.

As shown in Scheme 4, to probe the reaction mechanism, an intermolecular isotope effect study was conducted and a KIE value of 2.4 was obtained. These results indicated that C–H activation might be involved in the rate-limiting step of this transformation.[19]

Although details about the mechanism are not clear yet, on the basis of our results, a plausible mechanism for this reaction is depicted as follows: step i involves the chelation of a ruthenium to nitrogen atom from the hydrazone substrate. In the subsequent step (ii), chelate-directed C–H activation of the substrate could afford a six-membered

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(19) An other possible pathway: (i) coordination of Ru species to the carbon–carbon double bond, (ii) trans addition of the nitrogen nucleophile, (iii) elimination of RuH species, and (iv) oxidation of the Ru-H species with molecular oxygen.

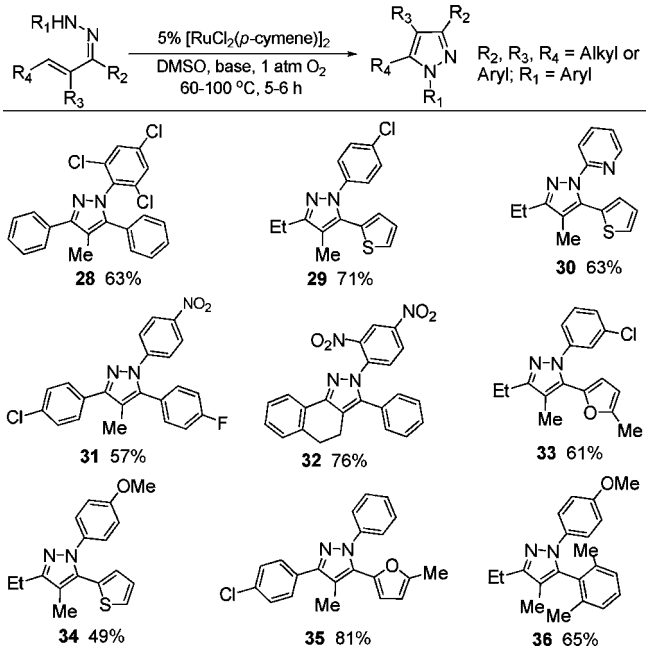
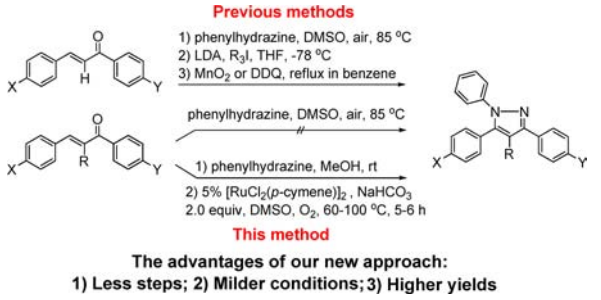


Figure 2. Synthesis of tetrasubstituted pyrazoles. [a]Isolated yield.

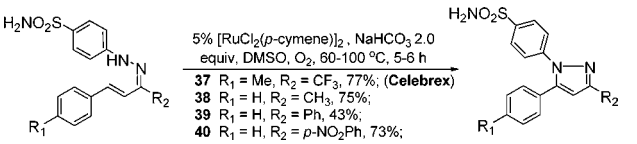
Scheme 2. Comparsions of Conventional Approaches and Our Methodology for Access to Tetrasubstituted Pyrazoles



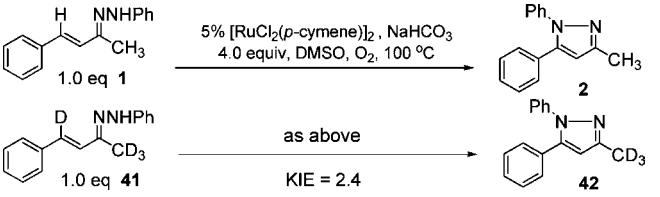
cycloruthenium(II) intermediate. The final step (iii) involves carbon−nitrogen bond-forming reductive elimination to generate the product. Molecular oxygen could be involved in the reoxidation step of Ru(0).

In summary, a novel Ru(II)-catalyzed oxidative C−N coupling method has been developed for the facile synthesis of highly diversified tri- and tetrasubstituted pyrazoles from easily accessible starting materials. Dioxygen gas

Scheme 3. Synthesis of Celebrex and Its Analogues



Scheme 4. Kinetic Isotope Effect



(1 atm) is employed as the oxidant in this transformation. This method has been found to be generally useful for making a variety of multisubstituted pyrazoles, most of which are difficult to access with conventional methods. The reaction demonstrates excellent reactivity, broad scope, high tolerance of functional groups, and high yields, which has been further exemplified in one synthetic application. By employing a combination of $[RuCl_2(p\text{-cymene})]_2$, molecular O_2, and bases, we have discovered a highly efficient catalyst system for this unique intramolecular C−N bond formation reaction. Further investigations into the mechanism and synthetic applications of this method are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.