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Oxone-mediated facile access to substituted pyrazoles

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ABSTRACT

An Oxone-mediated transition-metal-free oxidative C–N bond formation has been achieved for the regioselective synthesis of substituted pyrazoles. The reactions accompany the chelation-controlled *ortho*-oxidation of *N*-substituted aromatic ring to provide phenol derivatives in some cases. This method displays a facile access to diverse range of substituted pyrazoles from readily accessible hydrazones.

1. Introduction

Pyrazole and its derivatives are well known to be an important structural unit for the development of pharmaceuticals and agrochemicals.[1] For instances, pyrazoles exhibit antimicrobial, anti-inflammatory, analgesic, anticonvulsant, anticancer, and herbicidal activities.[1] To date, huge amount of synthetic methods of pyrazoles have been documented[2,3] including traditional approach based on the condensation of 1,3-dicarbonyl compounds with hydrazines and 1,3-dipolar cycloaddition of dipolarophiles with appropriate dipoles. However, the former affords pyrazoles as mixtures of two regioisomers when substituted hydrazines and 1,3-dicarbonyl substrates are used. The latter requires the unstable reagents such as diazo compounds.

Recently, oxidative cyclization of hydrazones **1** by hypervalent iodine (III)[4a] or DDQ[4b] to provide substituted pyrazoles **2** have been published (Eq. 1). This transformation was also achieved by transition-metal-catalyzed aerobic oxidation.[3j,u,n] More recently, I_2-mediated one-pot transformations from α,β-unsaturated aldehydes/ketones and hydrazines have also been accomplished.[5] However, there are still limitations associated with these methods, such as limited substrate scope, harsh reaction conditions, and unsatisfactory overall yields. Thus, more general and practical protocols for the synthesis of pyrazole and derivatives are still desirable. Previously, we have developed iodobenzene-catalyzed oxidative C–H amination for the construction of 1*H*-indazole core from arylhydrazones by using Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as a terminal oxidant under mild reaction conditions.[6] As a part of our continuing research on the oxidative C–N bond formation to access useful heterocycles, herein, we report a practical and regioselective synthesis of pyrazole via the oxidative annulation of allylidene- and butenylidenehydrazones under the presence of Oxone[7] as a single reagent without the use of iodine source (Eq. 2).

2. Results and discussion

The reaction conditions were evaluated by using (*E*)-1-phenyl-2-((*E*)-3-phenylallylidene)hydrazone **1a** as a model substrate (Table 1). At first we applied the conditions previously utilized for the synthesis of 1*H*-indazoles.[6] Reaction of **1a** in the presence of iodobenzene (30mol %) and Oxone (1.5 equiv) in trifluoroacetic acid (TFA) at −10 °C for 30 min afforded the desired pyrazole **2a** in 75% yield (Table 1, run 1). To our surprise, reaction of **1a** without iodobenzene under otherwise same conditions also afforded pyrazole **2a** in 54% yield along with phenol **3a** (24%) (run 2). The formation of phenol **3a** has been reduced when the same reaction was performed at 0 °C to provide 78% yield of pyrazole **2a** and still 12% of phenol **3a** (run 3). Further lowering the temperature resulted in the remarkable decrease of reactivity (run 4). Less effective results have been observed when 1.0 and 2.0 equiv of Oxone was introduced (runs 5 and 6). Interestingly, phenol **3a** was formed as a major product with the use of 30% H_2O_2 aq instead of Oxone to

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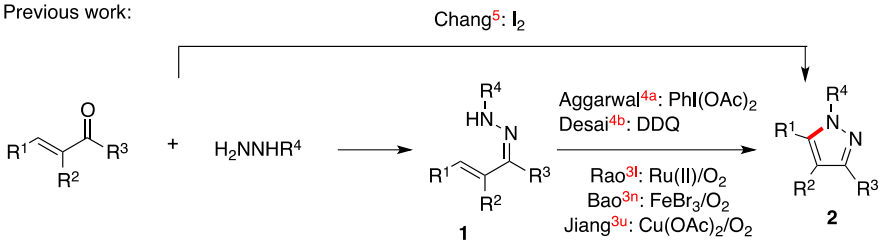

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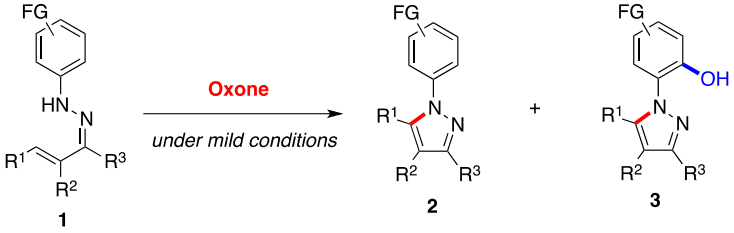
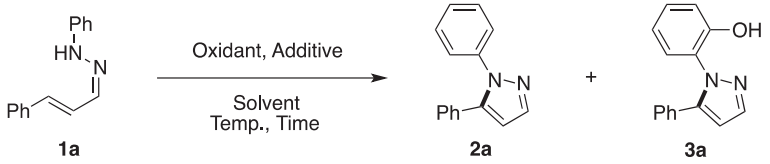


(2)

Table 1
Evaluation of the reaction conditions for the synthesis of pyrazoles[a]



Run	Oxidant (equiv)	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Yield **2a** (%)[b]	Yield **3a** (%)[b]
1	Oxone (1.5)	PhI (0.1)	TFA	−10	0.5	75	0
2	Oxone (1.5)	—	TFA	RT	0.5	54	24
3	**Oxone** (1.5)	—	TFA	**0**	**2**	**78**	**12**
4	Oxone (1.5)	—	TFA	−10	5	54	16
5	Oxone (1.0)	—	TFA	0	2	50	9
6	Oxone (2.0)	—	TFA	0	2	53	11
7	30% H_2O_2 aq (1.5)	—	TFA	RT	0.5	16	55
8	*m*CPBA (1.5)	—	TFA	RT	0.5	23	5
9	$K_2S_2O_8$ (1.5)	—	TFA	RT	0.5	Trace	0
10	70% TBHP aq (1.5)	—	TFA	RT	0.5	0	0
11	Oxone (1.5)	TsOH (1.5)	$CHCl_3$	RT	6	28	0
12	Oxone (1.5)	TsOH (1.5)	EtOH	RT	24	25	0
13	Oxone (1.5)	TsOH (1.5)	PhMe	RT	24	22	0
14	Oxone (1.5)	TsOH (1.5)	MeCN	RT	3	27	0
15	Oxone (1.5)	TFA (1.5)	MeCN	RT	3	31	0

TFA=trifluoroacetic acid, TBHP=*tert*-butylhydroperoxide, Oxone=$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.
[a] Reaction Conditions: Substrate **1a**, oxidant (1.5 equiv), in TFA (0.33 M).
[b] Isolated yield.

afford pyrazole **2a** (16%) and phenol **3a** (56%), respectively (run 7). The use of other oxidants (*m*CPBA, $K_2S_2O_8$, and TBHP) displayed the unsatisfactory transformations (runs 8–10). In addition, another solvents instead of TFA were found to be less effective (runs 11–15) to afford pyrazole **2a** as a sole product, which indicate the participation of TFA and/or trifluoroperacetic acid derived from TFA with Oxone for the formation of phenol **3a** (vide infra). The present method without the use of iodobenzene would be more practical because it can avoid the tedious chromatographic separation to remove organics derived from iodobenzene. The separation of phenol derivative was easy by extractive work-up and/or chromatography.

Another hydrazones (**1b**–**1s**)[8] were examined for the cyclization reaction under the conditions (Table 1, run 3). Substrates with electron-donating group on the *N*-substituted aromatic ring provided moderate yields of expected pyrazoles (**2b**, **2c**, and **2d**) along with phenols (**3b**, **3c**, and its regioisomer **3′c**). The preferential formation of phenol **3′c** in the transformation of hydrazine **1c** would be attributed to the steric and electronic effects (*para*-position of electron-donating group). Phenol product was not observed when hydrazine **1d** with *ortho*-substituent was employed to afford pyrazole **2d** in moderate yield, probably due to the steric congestion. Better yields were observed when substrates with electron-deficient benzene ring (**1e** and **1f**) were applied.