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When Aryldiazonium Salts Meet Vinyl Diazoacetates: A Cobalt-Catalyzed Regiospecific Synthesis of *N*-Arylpyrazoles

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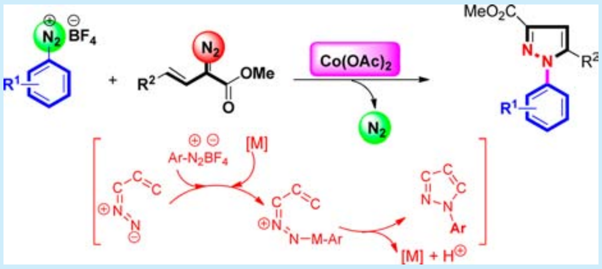
S *Supporting Information*

ABSTRACT: A cobalt-catalyzed C−N bond formation between aryl diazonium salts and vinyl diazoacetates has been developed under relatively mild conditions. The *N*-arylpyrazoles have been prepared in moderate to high yields in a regiospecific way.



Aryldiazonium salts are important active intermediates and have found wide applications in various organic transformations[1] such as in the construction of the C−Y bond (Y = Cl, Br, CN, etc.) via a Sandmeyer-type reaction,[1,2] as reactive arylhalide surrogates in Pd-catalyzed[3] as well as visible-light mediated[1b,4] C−C bond formation, and in generating C−B[5] and C−S[6] bonds (Figure 1). Recent reports highlighted the use of aryldiazonium salts as efficient radical precursors in trifluoromethylations,[8] aminosulfonylation,[9] trifluoromethylthiolation,[10] and stannylation[11] via novel Sandmeyer-type reactions. However, the utilization of aryldiazonium salts as an aryl cation or aryl-metal cation precursor for C−N bond formation is rare.[7] Clearly, it is still highly desirable to develop a novel transformation from inexpensive and readily available aryldiazonium salts.

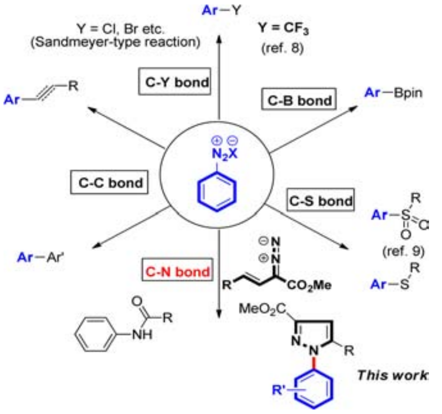
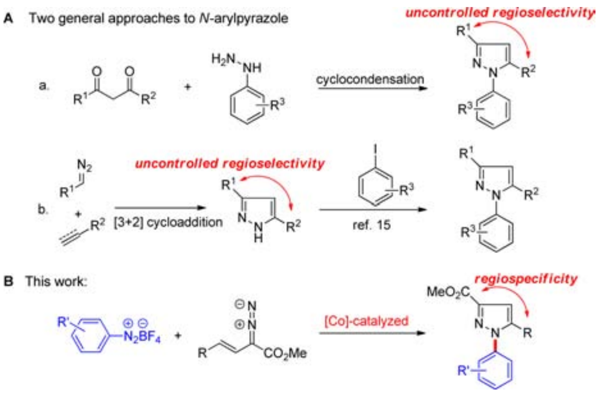


Figure 1. Aryldiazonium salts in organic transformation.

On the other hand, the *N*-arylpyrazole moiety has been found in numerous synthetic pharmaceuticals and leading compounds with a broad scope of pharmacological properties.[12] Generally, the common approach for the synthesis of *N*-arylpyrazole relies on the condensation of aryl-hydrazines with 1,3-dicarbonyl compounds or synthetic equivalents (Scheme 1A-a).[13] Alternatively, the 1,3-dipolar cycloaddition of diazo compounds or surrogates with alkynes/alkenes[14] followed by metal-catalyzed cross-coupling[15] has been another powerful tool (Scheme 1A-b). However, regioselective control is often problematic in these procedures. Nevertheless, the development of an efficient protocol for the synthesis of *N*-arylpyrazoles in a regiospecific way is still a challenging task. Herein, we describe the development of a cobalt-catalyzed approach in the use of aryldiazonium salts and vinyl diazoacetates to achieve this goal.

Scheme 1. Synthesis of *N*-Arylpyrazoles



Recently, we have been interested in the development of novel synthetic protocols with diazo compounds.[16] As often observed and also reported by Davies and others,[17] the vinyl diazoacetates are unstable and would undergo a spontaneous

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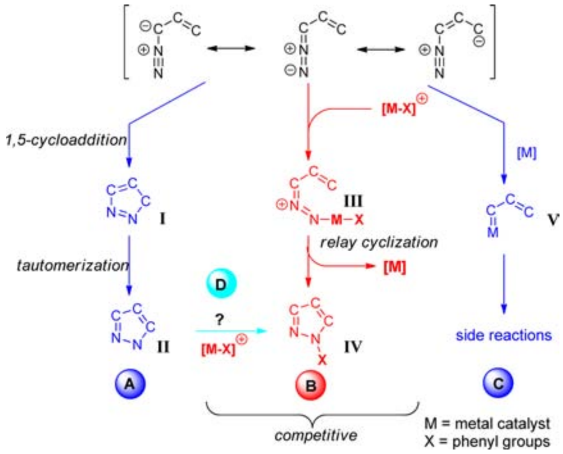
[1,5]-cycloaddition to produce pyrazole **II**, which occurred more or less as a side reaction in vinyl diazoacetates involved in transformations (Scheme 2, route A).[17c] Based on this

Scheme 2. Proposed Strategy[a]

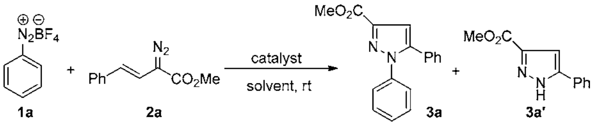


[a]The atom hydrogen and substituents have been omitted for clarity.

phenomenon and the nature of the three resonance structures of vinyl diazoacetates, we envisaged that the introduction of an *in situ* formed cation [M−X] would probably prioritize coupling with diazo to afford intermediate **III**, which then might relay the cyclization to yield **IV** along with the recovery of the metal catalyst (Scheme 2, route B). However, to realize this hypothesis, the potential reaction system would be inactive toward the rapid decomposition of vinyl diazoacetates to avoid side reactions (Scheme 2, route C). Also, this system should reduce or suppress route **A** if **II** was stable and unable to undergo direct coupling with the cation precursor (Scheme 2, route D). So with a view to maximize route **B** and increase the yield of **IV**, a suitable catalytic system must be developed not only to promote this relay cyclization but also to minimize the undesired side reactions.

Based on the above hypothesis, we utilized a diazonium salt (**1a**) and vinyl diazoacetate (**2a**) as model substrates for the initial investigation in the presence of various metal complexes (10 mol %) (Table 1). Among the metal complexes examined, the use of $Co(OAc)_2$ provided **3a** in the highest yield with also better selectivity (Table 1, entry 12) and $Co(acac)_2$ gave a slightly lower yield (Table 1, entry 13), while $Fe(acac)_3$ and $Mn(OAc)_2$ displayed moderate catalytic activity (Table 1, entries 5 and 11). However, the commonly used metal complexes for diazo decomposition such as rhodium, ruthenium, and palladium gave poor results, which probably attributed to the strong ability for rapid decomposition of the diazo moiety to bring about undesired side reactions (Table 1, entries 2 to 4). Next, after screening a variety of solvents, we were pleased to find dichloroethane (DCE) was the best choice (Table 1, entry 16), while acetonitrile (CH_3CN) afforded a slightly lower yield (Table 1, entry 17). However, the reaction was totally inert when dioxane, DMF, DMSO, and toluene were used (Table 1, entries 18 to 21). In addition, a higher temperature was detrimental to the transformation (Table 1, entry 22) and a lower catalyst loading also gave a lower yield (Table 1, entry 23). A lower reaction temperature gave almost the same result (Table 1, entry 24). It is of note that **3a** and **3a′** were obtained almost in a 1:1 ratio in very low yield without addition of any metal catalyst (Table 1, entry 1). Also, **3a′** was detected in a low ratio for most of the cobalt-catalyzed processes. Moreover, the use of $FeCl_3$ made the reaction very clean but resulted in a lower yield (Table 1, entry 6).

Table 1. Optimization of the Reaction Conditions[a]



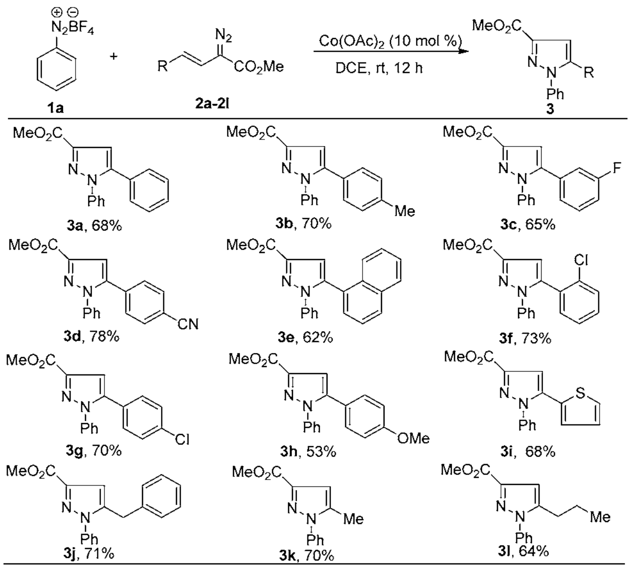
entry	catalyst	solvent	yield (%)[b]
1	no	DCM	7 (1:1)
2	$Rh(OAc)_2$	DCM	12 (10:1)
3	$[Cp^*RhCl_2]_2$	DCM	10 (5:1)
4	$[RuCl_2(p\text{-cymene})]_2$	DCM	15 (10:1)
5	$Fe(acac)_3$	DCM	45 (8:1)
6	$FeCl_3$	DCM	42
7	$Pd(TFA)_2$	DCM	8 (2:3)
8	$PdCl_2$	DCM	19 (10:1)
9	$Cu(OAc)_2$	DCM	40 (10:1)
10	CuBr	DCM	36 (7:1)
11	$Mn(OAc)_2$	DCM	50 (12:1)
12	$Co(OAc)_2$	DCM	58 (10:1)
13	$CoCl_2$	DCM	messy
14[c]	$CoBr_2$	DCM	51 (10:1)
15	$Co(acac)_2$	DCM	54 (10:1)
16	$Co(OAc)_2$	DCE	68 (15:1)
17	$Co(OAc)_2$	CH_3CN	54 (9:1)
18	$Co(OAc)_2$	dioxane	–
19	$Co(OAc)_2$	DMF	–
20	$Co(OAc)_2$	DMSO	–
21	$Co(OAc)_2$	toluene	–
22[c]	$Co(OAc)_2$	DCE	messy
23[d]	$Co(OAc)_2$	DCE	60 (15:1)
24[e]	$Co(OAc)_2$	DCE	67 (15:1)

[a]All reactions were carried out with **1a** (0.3 mmol), **2a** (0.25 mmol), metal complex (0.025 mmol, 0.1 equiv), and solvent (3 mL) under a nitrogen atmosphere at rt for 12 h unless otherwise noted. [b]Isolated yields of **3a**. The ratios in parentheses were determined by NMR analysis of crude products. [c]Reaction was performed at 60 °C for 3 h. [d]With 5 mol % $Co(OAc)_2$. [e]Reaction was performed at 0 °C for 12 h.

Under the above optimized conditions, the scope of the vinyl diazoacetates was evaluated with regard to diazonium salt **1a** as the standard substrate (Scheme 3). As observed, all of the reactions proceeded smoothly and appeared to tolerate a wide range of vinyl diazoacetates. In general, for the arylvinyl diazoacetates examined, the phenyl ring bearing electron-withdrawing substituents gave higher yields than the electron-donating substituted substrates. The thiophene vinyl diazoacetate was also subjected to this reaction and delivered the corresponding pyrazole in 68% yield (Scheme 3, **3i**). In addition, the use of alkyl vinyl diazoacetates also led to the pyrazoles in moderate yields (Scheme 3, **3j**−**3l**).

Next, we explored the reaction of different phenyl diazonium salts, such as *para*-methyl-phenyl, *para*-chloro-phenyl, *ortho*-bromo-phenyl, and 1,5-ditrifluoromethyl-phenyl diazonium salts, with a variety of vinyl diazoacetates under the optimal reaction conditions. The results were summarized in Scheme 4. In general, for the same vinyl diazoacetates employed, *para*-chloro phenyl diazonium salt gave the corresponding *N*-arylpyrazoles in higher yields than *para*-methyl phenyl diazonium salt. The highest yield was obtained from the

Scheme 3. Substrate Scope[a,b]



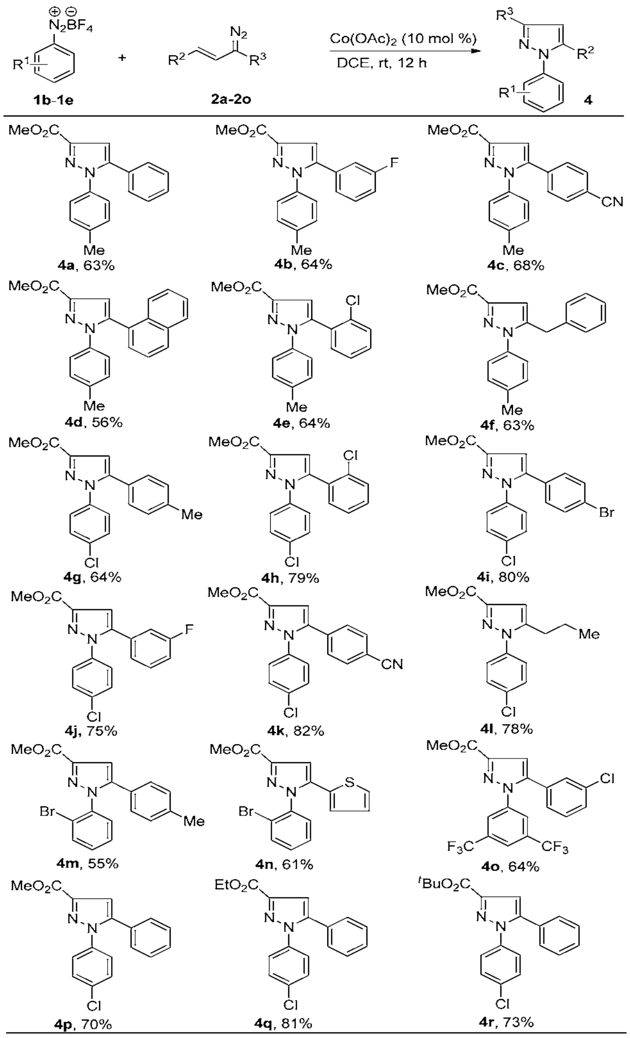
[a]All reactions were carried out with **1a** (0.3 mmol), **2** (0.25 mmol), and $Co(OAc)_2$ (0.025 mmol), in DCE (3 mL) at room temperature for 12 h. [b] Isolated yields of **3**.

reaction of *para*-chloro-phenyl diazonium salt and *para*-cyano-phenyl vinyl diazoacetate, which afforded the corresponding pyrazole in 82% isolated yield (Scheme 4, **4k**). Additionally, the alkyl vinyl diazoacetates were also tolerated in this procedure (Scheme 4, **4f**, **4l**). Remarkably, the reaction of *para*-chloro-phenyl diazonium salt with ethyl and *tert*-butyl styryldiazoacetates gave better yields than methyl styryldiazoacetate (Scheme 4, **4q** and **4r** to **4p**).

To better understand the reaction mechanism, we conducted further investigations (Scheme 5). First, diazonium salt (**1c**) treated with TEMPO and TEMPO-Ph was not isolated (Scheme 5a). Second, when TEMPO was added to the reaction mixture of **1c** and ethyl-vinyl diazoacetate, *N*-arylpyrazole (**4l**) was still isolated in 18% yield although most of vinyl diazoacetate has been oxidized to the ketone ester (Scheme 5b). These results suggested that the aryl radical is not involved as a reactive species. Third, treated **1c** with water under the optimal conditions gave phenol in high yield (Scheme 5c). The direct coupling between pyrazole (**3a′**) and **1c** was investigated. The pyrazole was not obtained, and the two staring materials had been recovered (Scheme 5d). Finally, unlike the addition of rhodium and copper catalysts to the solution of **2a**, no bubble emission was observed even with 20 mol % of $Co(OAc)_2$ and most of **2a** was recovered (Scheme 5e). In contrast, slow gas emission was observed when **1c** was treated with $Co(OAc)_2$ (Scheme 5f). These control experiments indicated that the two nitrogen atoms of the *N*-arylpyrazoles probably came from vinyl diazoacetates.

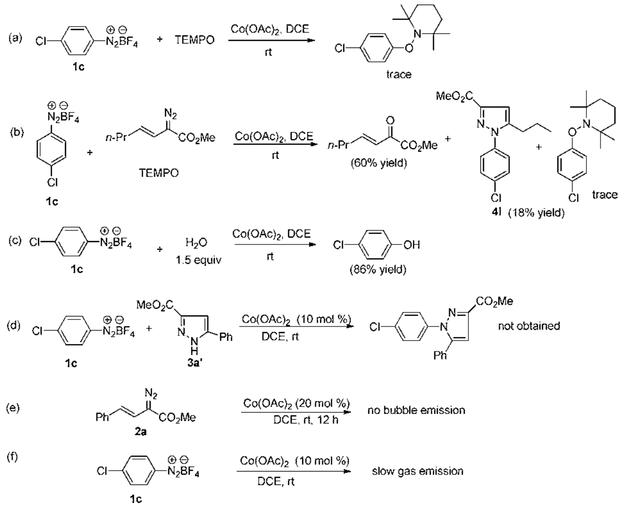
Based on the above experiments, a plausible reaction mechanism is proposed in Scheme 6. First, the oxidative addition of $Co(OAc)_2$ to phenyldiazonium salt (**1a**) generates the cationic phenyl-cobalt complex **A** and simultaneously releases one molecule of nitrogen. Second, coupling of vinyl diazoacetate (**2a**) with cation **A** gives the formation of intermediate **B**, which would subsequently undergo [1,5]-cycloaddition to afford intermediate **C**. Then subsequent tautomerization and loss of hydrogen deliver intermediate **D**. Finally, reductive elimination would furnish the target product as well as recover the cobalt catalyst.

Scheme 4. Substrate Scope[a,b]

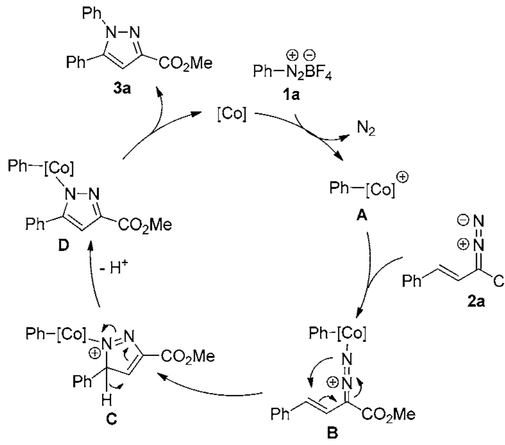


[a]All reactions were carried out with **1** (0.3 mmol), **2** (0.25 mmol), and $Co(OAc)_2$ (0.025 mmol), in DCE (3 mL) at room temperature for 12 h. [b] Isolated yields of **4**.

Scheme 5. Further Exploration



Scheme 6. Plausible Catalytic Cycle



In summary, we have demonstrated a novel strategy for the regiospecific synthesis of *N*-arylpyrazoles through the cobalt-catalyzed coupling reactions of vinyl diazoacetates and aryl diazonium salts. This protocol featured a very cheap cobalt catalyst, mild reaction conditions, easily available starting materials, and 100% regioselectivity, thus making it a genuine useful synthetic methodology toward *N*-arylpyrazoles. More importantly, a cobalt-catalyzed cation cyclization is crucial for the success of this reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures along with characterizing data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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