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Synthesis of Cinnolin-3(2*H*)-one Derivatives from Rh-Catalyzed Reaction of Azobenzenes with Diazotized Meldrum's Acid

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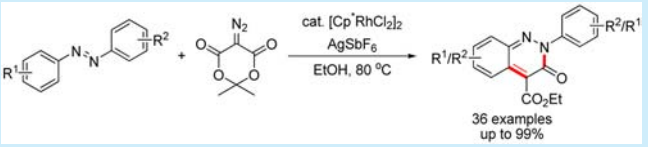
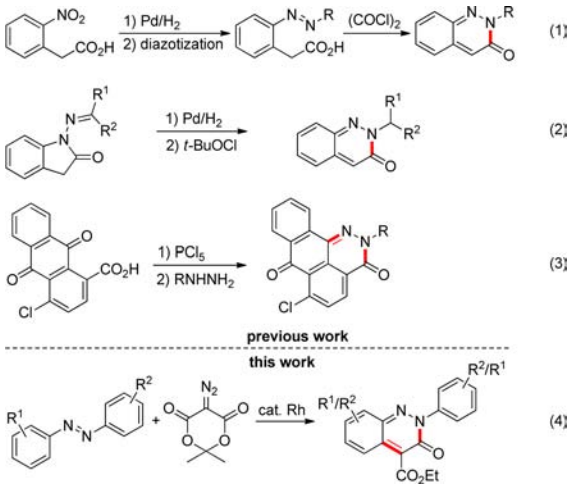
Supporting Information

ABSTRACT: A synthetic method of a wide range of cinnolin-3(2*H*)-one derivatives is developed from the reaction of symmetrical as well as unsymmetrical azobenzenes with diazotized Meldrum's acid *via* Rh-catalyzed C−H alkylation followed by cyclization.



Nitrogen heterocycles are a very significant class of compounds because of their pharmaceutical applications and biological activities.[1] In particular, cinnolin-3(2*H*)-ones are constituents of key privileged azaheterocyclic scaffolds. Thus, the establishment of robust synthetic approaches for affording substituted cinnolin-3(2*H*)-one from easily available compounds has been continuously demanded. To date, a variety of cinnolin-3(2*H*)-one derivatives could be prepared by cyclization of 2-arylazophenylacetic acid with oxalyl chloride (eq 1, Scheme 1),[2] a ring expansion of the respective 1-substituted-2-indolinones *via* an oxidative rearrangement with *tert*-butyl hypochlorite (eq 2),[3] and reaction of acid chloride obtained from 1-anthracenecarboxylic acid and PCl_5 with hydrazine (eq 3).[4] However, some of these synthetic methods are limited by their low yields. Moreover, introduction of a wide range of substituents to the cinnolin-3(2*H*)-one nucleus is difficult.

Scheme 1. Approaches for the Synthesis of Cinnolin-3(2*H*)-one Derivatives



Recently, we reported myriad C−H activations using the phosphoryl group as a directing group[5] and an efficient synthetic method of 2-aryl-2*H*-benzotriazoles from azobenzenes and *N*-sulfonyl azides *via* sequential Rh-catalyzed amidation and oxidation in one pot.[6] In our current program involved with the synthesis of nitrogen heterocycles using azobenzenes, we envisioned that reaction of azobenzenes with diazotized Meldrum's acid would provide a cinnolin-3(2*H*)-one skeleton.[7] Herein, we describe a synthetic method of a variety of cinnolin-3(2*H*)-one derivatives from the reaction of symmetrical as well as unsymmetrical azobenzenes with diazotized Meldrum's acid *via* tandem Rh-catalyzed C−H alkylation and cyclization (eq 4).

First, we initiated a Rh-catalyzed reaction of azobenzene (**1a**) with diazotized Meldrum's acid (**2a**) to obtain cinnolin-3(2*H*)-one (Table 1). A wide range of silver additives (5.0 mol %) were screened in the presence of $[Cp^*RhCl_2]_2$ (1.0 mol %) as a catalyst for this transformation. Although AgF, AgOAc, and $AgNO_3$ were totally ineffective (entries 1−3), $AgBF_4$, AgOTf, and $AgNTf_2$ delightedly produced cinnolin-3(2*H*)-one in yields ranging from 21% to 48%. Eventually, $AgSbF_6$ was found to be the additive of choice, affording cinnolin-3(2*H*)-one (**3a**) in 72% yield at 80 °C for 24 h under air (entry 7). DCE and THF were not effective (entries 8 and 9). The optimal conditions were accomplished from the reaction of azobenzene (**1a**) (0.2 mmol) with diazotized Meldrum's acid **2a** (1.2 equiv) using $[Cp^*RhCl_2]_2$ (4.0 mol %) and $AgSbF_6$ (20.0 mol %) in EtOH (2.0 mL) at 80 °C for 24 h, affording cinnolin-3(2*H*)-one **3a** in 88% yield (entry 11). The structure of **3a** was confirmed by X-ray crystallography (see the Supporting Information). To show the practicability of this cyclization method to larger scale processes, 5.0 mmol of azobenzene (0.911 g) was treated with diazotized Meldrum's acid **2a** (1.2 equiv) under the optimal conditions, leading to the formation of cinnolin-3(2*H*)-one **3a** in 83% (1.2 g) isolated yield (entry 12).

Next, the scope of symmetrical azobenzenes having a number of substituents was investigated under the optimal conditions (Scheme 2). When 2-methyl-substituted azobenzene **1b** was treated with Rh catalyst, the desired cinnolin-3(2*H*)-one **3b** was

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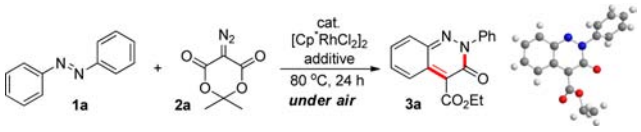
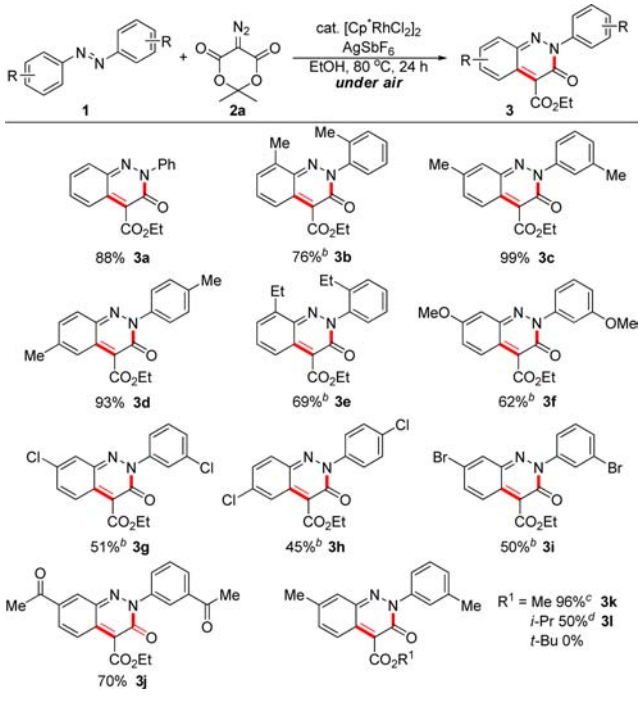
Table 1. Reaction Optimization[a]



entry	additive	solvent	yield[b] (%)
1	AgF	EtOH	0
2	AgOAc	EtOH	0
3	$AgNO_3$	EtOH	0
4	$AgBF_4$	EtOH	21
5	AgOTf	EtOH	22
6	$AgNTf_2$	EtOH	48
7	$AgSbF_6$	EtOH	72
8	$AgSbF_6$	DCE	0
9	$AgSbF_6$	THF	0
10[c]	$AgSbF_6$	EtOH	76
11[d]	$AgSbF_6$	EtOH	88 (86)[e]
12[f]	$AgSbF_6$	EtOH	84 (83)[e]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (1.0 mol %), and additive (5.0 mol %) in solvent (2.0 mL) at 80 °C for 24 h. [b]NMR yield using CH_2Br_2 as an internal standard. [c]$[Cp^*RhCl_2]_2$ (2.0 mol %) and additive (10.0 mol %). [d]$[Cp^*RhCl_2]_2$ (4.0 mol %) and additive (20.0 mol %). [e]Isolated yield. [f]Performed on a 5.0 mmol scale.

Scheme 2. Substrate Scope of Symmetrical Azobenzenes[a]

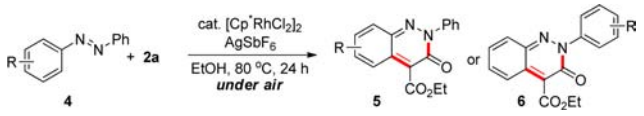


[a]Reactions were carried out with **1** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (4.0 mol %), and $AgSbF_6$ (20.0 mol %) in EtOH (2.0 mL) at 80 °C for 24 h under air. EtOH (1.0 mL). The reaction was carried out in MeOH (2.0 mL). The reaction was carried out in *i*-PrOH (1.0 mL).

obtained in 76% yield. Azobenzene **1c** having a 3-methyl group was quantitatively cyclized to produce cinnolin-3(2*H*)-one **3c**. No any cyclized compound at the 2-position was observed due to steric hindrance. 4-Methyl-substituted substrate **1d** was also converted to cinnolin-3(2*H*)-one **3d** in 93% yield. The substrate **1e** bearing a 2-ethyl substituent underwent the cyclization to furnish **3e** in 69% yield. The strongly electron-donating 3-methoxy group slightly influenced the cyclization, and the desired product **3f** was obtained in 62% yield. Chloro- or bromo-substituted azobenzenes (**1g**, **1h**, and **1i**) are applicable to the present reaction, affording the corresponding cinnolin-3(2*H*)-ones (**3g**, **3h**, and **3i**) in moderate yields. An azo compound (**1j**) having an acetyl group turned out to be compatible with the cyclization conditions, providing **3j** in 70% yield. When methanol and isopropyl alcohol were used as solvent, cinnolin-3(2*H*)-ones **3k** and **3l** having the corresponding alkoxycarbonyl group at 4-position were produced in 96% and 50% yields, respectively. However, *tert*-butyl alcohol did not give the desired product due to steric reasons.

To investigate the selectivity of Rh-catalyzed C−H activation, the optimal conditions were next applied to a wide range of unsymmetrical azobenzenes having a substituent on one aryl ring by variation of the steric and/or electronic environment (Table 2). When azobenzene **4a** having one 2-methyl group was

Table 2. Substrate Scope of Unsymmetrical Azobenzenes Having Substituent on One Aryl Ring[a]



entry	cinnolin-3(2*H*)-one **5**, **6**			ratio	yield (%)[b]
1		**5a**	-	1:0	67
2	-		**6b**	0:1	92
3		**5c**	**6c**	1:2	86
4		**5d**	**6d**	1:4.2	82
5		**5e**	**6e**	1:2.6	80
6		**5f**	-	1:0	60
7		**5g**	**6g**	1.6:1	67
8		**5h**	**6h**	1:1.4	89

[a]Reactions were carried out with **4** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (4.0 mol %), and $AgSbF_6$ (20.0 mol %) in EtOH (2.0 mL) at 80 °C for 24 h under air.

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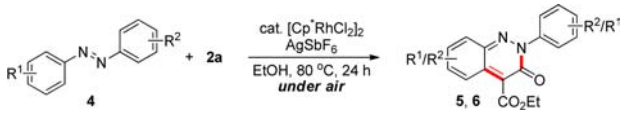
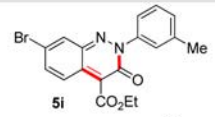
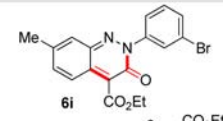
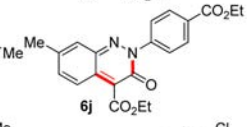
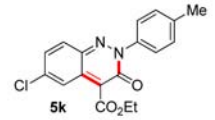
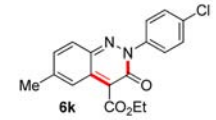
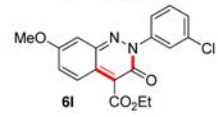
subjected to Rh catalyst, C−H alkylation followed by cyclization occurred on the methyl-substituted aryl ring, and the corresponding cinnolin-3(2*H*)-one **5a** was selectively produced in 67% yield (entry 1). Azobenzene **4b** having a 3,5-dimethylphenyl group was exclusively transformed to cinnolin-3(2*H*)-one **6b** in 92% yield due to steric reasons (entry 2). Regioselectivity of C−H activation shows a slightly different trend according to the kind and position of the substituents. In the case of 3-methyl- and 3-methoxy-substituted azobenzenes (**4c** and **4d**), C−H activation from the side of phenyl ring took place most often (entries 3 and 4). All of the isomers were easily separated by column chromatography. In contrast, azobenzene (**4e**) having an electron-withdrawing 3-bromo group was examined to disclose that the corresponding cinnolin-3(2*H*)-one **6e** was predominantly produced in 80% yield (entry 5). 3-Acetyl-substituted azobenzene (**4f**) was exclusively cyclized to cinnolin-3(2*H*)-one **5f** in 60% yield (entry 6). 4-Chloro- and 4-methyl-substituted azobenzenes (**4g** and **4h**) underwent major C−H activation on the electron-poor phenyl ring (entries 7 and 8).

With the success of the above cyclization, we next explored the substrate scope of unsymmetrical azobenzenes having substituents on two aryl rings (Table 3). When azobenzenes (**4i**, **4j**, **4k**, and **4l**) bearing electron-donating methyl and methoxy groups and electron-withdrawing bromo, ethoxycarbonyl, and chloro groups on each aryl ring were subjected to the optimal conditions, C−H activation on the electron-deficient phenyl ring took place most often, producing a wide range of cinnolin-3(2*H*)-ones in moderate to good yields ranging from 54% to 73% (entries 1−4). Azobenzene **4m** was exclusively converted to cinnolin-3(2*H*)-one **5m** in 62% yield due to steric reasons (entry 5).

Table 3. Substrate Scope of Unsymmetrical Azobenzenes Having Substituents on Two Aryl Rings[a]

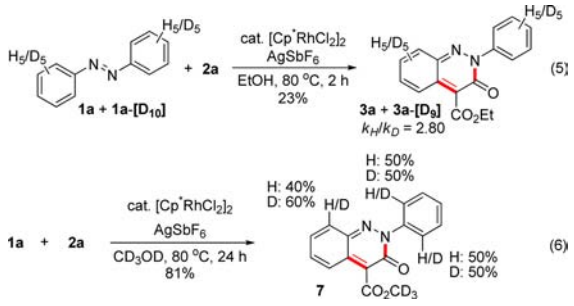


entry	cinnolin-3(2*H*)-one **5, 6**	ratio	yield (%)[b]
1	 **5i**  **6i**	1.5:1	72
2	 **5j**  **6j**	2.3:1	70
3	 **5k**  **6k**	1.4:1	73
4	 **5l**  **6l**	1.5:1	54
5	 **5m**	1:0	62

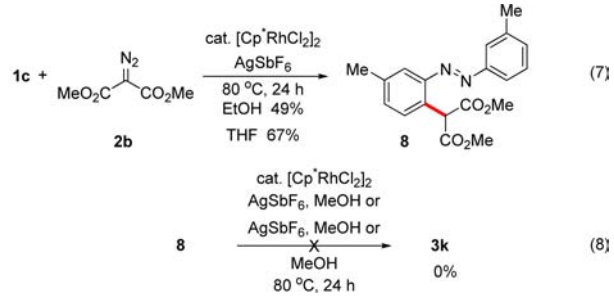
[a]Reactions were carried out with **4** (0.2 mmol), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (4.0 mol %), and $AgSbF_6$ (20.0 mol %) in EtOH (2.0 mL) at 80 °C for 24 h under air.

Next, we carried out kinetic isotope effect (KIE) studies to obtain insight into the reaction mechanism (Scheme 3). A KIE was detected (k_H/k_D = 2.80), indicating that C−H bond cleavage at the 2-position of azobenzene is most likely involved in the rate-limiting step (eq 5).[8] A catalytic C−H activation in CD_3OD was conducted, thus affording a significant D/H exchange at *ortho*-position as well as transesterified product **7** (eq 6). These results indicate that the C−H activation step is reversible and solvent is the source of the ester moiety at the 4-position of cinnolin-3(2*H*)-ones.

Scheme 3. Studies with Isotopically Labeled Compounds



When 3-methyl-substituted azobenzene **1c** was treated with dimethyl 2-diazomalonate **2b** under the optimal conditions, the alkylated product **8** was obtained in 49% yield in EtOH and 67% yield in THF (eq 7). The alkylated azobenzene **8** was not totally



ineffective under the optimal conditions or $AbSbF_6$ (20.0 mol %) or MeOH at 80 °C for 24 h, suggesting that cinnolin-3(2*H*)-one **3k** was not produced through **8** (eq 8).

Although the exact mechanism of the present reaction remains unclear, a plausible reaction mechanism is shown in Scheme 4.[8] After a rhodacyclic intermediate **A** is generated *via* electrophilic C−H bond cleavage, the diazotized Meldrum's acid **2a** is coordinated with **A** to provide the diazonium intermediate **B**. At the present stage, two pathways are feasible. In pathway a, liberation of nitrogen gas from **B** would deliver Rh-carbene **C**, which would subsequently undergo migratory insertion to provide **D**. As an alternative, intramolecular 1,2-migratory insertion of the aryl group would afford **D** (pathway b). Finally, protonolysis of **D** would afford the desired alkylated product **E**. Then, elimination of acetone followed by esterification would produce cinnolin-3(2*H*)-one **3**.

In summary, we have developed a robust synthetic method for a wide range of cinnolin-3(2*H*)-one derivatives from the reaction of symmetrical as well as unsymmetrical azobenzenes with

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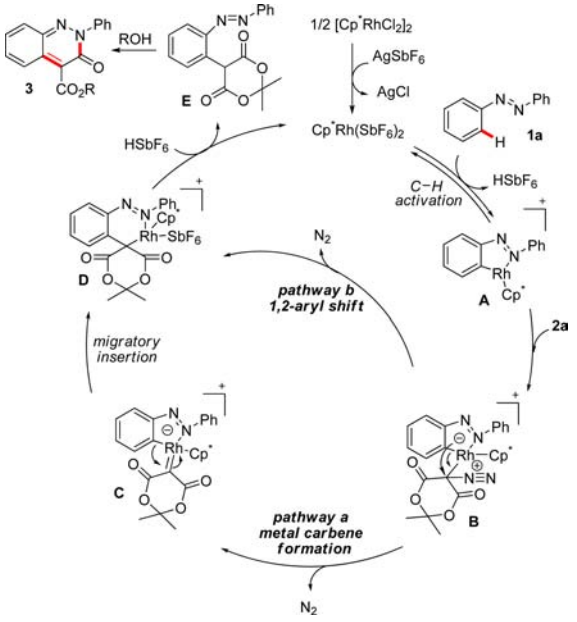
Scheme 4. Plausible Mechanism



diazotized Meldrum's acid *via* Rh-catalyzed C−H alkylation followed by cyclization.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, X-ray crystallography data (**3a**), and copies of NMR spectra for all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01052.

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Notes

The authors declare no competing financial interest.

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