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Palladium-Catalyzed Double C-H Activation: One-Pot Synthesis of Benzo[c]pyrazolo[1,2-a]cinnolin-1-ones from 5-Pyrazolones and Aryl Iodides[†]

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Received (in XXX, XXX) Xth XXXXXXXXXX 200X, Accepted Xth XXXXXXXXXX 200X

First published on the web Xth XXXXXXXXXX 200X

DOI: 10.1039/c000000x

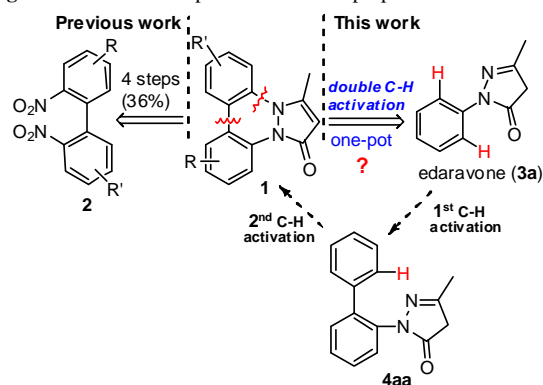
A palladium-catalyzed dual C-H activation to construct C-C/N bonds for one-pot synthesis of benzo[c]pyrazolo[1,2-a]cinnolin-1-ones is successfully developed. This approach features using a pyrazolone moiety as an internal directing group for C-H activation, and provides a flexible strategy to access this polycyclic skeleton.

Benzo[c]pyrazolo[1,2-a]cinnolin-1-ones **1** represent a unique class of polycycles possessing potential anti-inflammatory activity.¹ The synthesis of these compounds was initially reported in 1960s through a four-step synthetic process from 2,2'-dinitrophenyl **2** in 36% overall yield (Figure 1).^{1a,b} However, very limited pharmacological studies have been reported so far largely due to the difficulty in synthesis, especially the harsh reaction conditions and limited availability of the starting materials **2** (Figure 1). Therefore, to fully disclose the pharmacological potential of benzo[c]pyrazolo[1,2-a]cinnolin-1-ones, new and flexible synthetic methods are highly desirable.

In view of the advances in the directing-group (DG) assisted palladium-catalyzed C-H activation,² especially the achievements in the synthesis of many natural and synthetic complex molecules through a multiple C-H activation process,^{3,4} we envisioned that benzo[c]pyrazolo[1,2-a]cinnolin-1-ones **1** might be prepared from 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (**3a**) and aryl iodides through a Pd-catalyzed double C-H activation process. Although many *N*-heterocycles are known capable of directing C-H activations,^{5,6} to the best of our knowledge, Pd-catalyzed C-H activation directed by a pyrazol-5(4H)-one moiety (as in **3a**) has not been reported yet. Herein, we wish to report a Pd-catalyzed one-pot synthesis of benzo[c]pyrazolo[1,2-a]cinnolin-1-ones **1** through a double C-H activation approach from diversified 1-aryl-1H-pyrazol-5(4H)-ones and aryl iodides. Notably, compound **3a** itself is a

neuroprotective drug marked as Edaravone^{7,8} in 2001 in Japan for neurological recovery following acute brain ischemia and subsequent cerebral infarction. Derivatives of **3a** are also rare due to its limited synthetic starting materials, aryl hydrazines.⁹ Therefore, our current C-H activation study on compound **3a** will not only lead to facile synthesis of target skeleton **1**, but also generate new analogues of **3a**.

Figure 1 Conventional processes and our proposal.



To test our assumption, we first treated pyrazol-5(4H)-one **3a** with phenyl iodide **5a** under Pd(OAc)₂/AgOAc in refluxing TFA, a widely used procedure¹⁰ for C-H activation. It was found that arylation product **4aa** was formed as the major product in 2.5 h, and the expected cyclization product **1a** appeared when the reaction time was extended to 3 h. Further extension of the reaction time did not significantly increase the yield of **1a**, instead dual arylation product **6** was formed (Scheme 1). Although our target compound **1a** was not obtained as the major product, this result confirmed the feasibility of using pyrazol-5(4H)-one moiety as an internal component of the substrate/product to direct the double C-H activation process.

To promote compound **1a** as the major product and to suppress formation of the dual arylation product **6**, we decided to investigate the two C-H activation steps separately. First, we investigated the Pd-catalyzed C-H activation/arylation on the model reaction of **3a** with iodobenzene (**5a**). Systematic screening of various Pd catalysts, amount of iodobenzene, solvents and reaction temperature (see ESI[†], Table 1) disclosed that the highest yield (82%) of the arylated product **4aa** could be obtained when the reaction was conducted using 5 equiv of iodide **5a** in TFA (0.2 M) at 120 °C for 1.5 h with Pd(OAc)₂ (10 mol %) as the catalyst, and AgOAc (1.5 equiv) as silver salt.

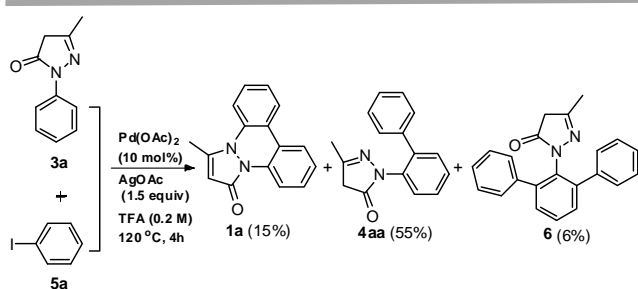
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[†] Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data of all new compounds, CCDC 965248. See DOI: 10.1039/c000000x/

With the optimized reaction conditions for the first C-H activation, we explored the substrate scope and limitation. It was found that various pyrazol-5(4H)-one derivatives and substituted iodides were well tolerated providing corresponding arylated products **4** in moderate to high yields (See ESI[†], Table 2). Next, we set out to explore the optimal conditions for the second C-H activation/intramolecular C-N bond formation to complete the construction of benzo[c]pyrazolo[1,2-a]cinnolin-1-ones **1**. With Pd(OAc)₂ as the catalyst, different bases, oxidants as well as various concentrations of the reaction solution were tested (See ESI[†], Table 3). It was found that high conversion of **4aa** to **1a** (74%) could be achieved when the reaction was conducted in a sealed tube with Pd(OAc)₂ (10 mol %) as the catalyst, K₂S₂O₈ (1.5 equiv) as the oxidant and K₂CO₃ (2 equiv) as the base in refluxing TFA (0.1 M). Encouraged by the results, we further evaluated the one-pot process to prepare **1a** directly from **3a** and **5a** by conducting the first C-H activation/arylation reaction followed by directly subjecting the reaction mixture to the optimized second C-H activation/cyclization condition. To our delight, compound **1a** was obtained in 76% yield through the one pot process, which is even more efficacious than that from two separate reactions.

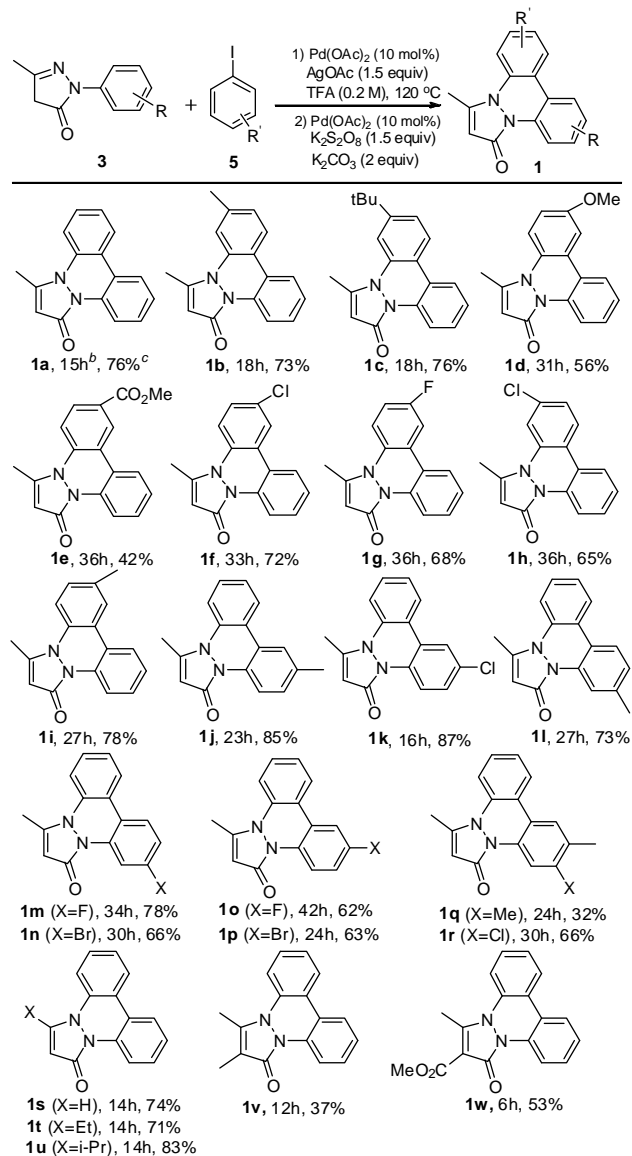


Scheme 1 Reaction of pyrazol-5(4H)-one **3a** and iodide **5a**.

To determine the generality and limitation of this one-pot double C-H activation process, diversified pyrazol-5(4H)-ones **3** and iodides **5** were tested, and the results were summarized in Scheme 2. It was found that a *para*-substituent on the aryl iodides has minor effect and compounds **1a-c** were obtained in nearly identical yields (73-76%). Similar to the observations from the first step/arylation, the second C-H activation/cyclization at the less steric site was favored¹¹ and no other regioisomers of compounds **1d-g** were isolated. Longer reaction time was necessary for those substrates bearing an electron-withdrawing substituent (**1e-h**, **1m-n**) and for those bearing multiple substituents (**1r**, **1q**). In addition, substitution on the pyrazol-5(4H)-one ring was explored as well (**1s-w**). Substrates with non-substitution or with an alkyl group at C-3 gave corresponding products **1s-u** in 71-83% yield, whereas a C-4 substituent led to lower yield (**1v**, 37%). In the case of substrate bearing an ester substituent, product **1w** was obtained in 53% yield. Although the yield is moderate, the ester function provides an additional platform for further structural manipulation. All the structures were fully characterized and further confirmed by the X-ray single-crystal analysis of compound **1n** (see ESI[†]).

To gain insights into the reaction mechanism, additional

experiments were performed. It has been reported previously that structure **3a** is stable in CHCl₃, and readily tautomerizes to **3a'** in DMSO.⁸ To test the real isomer involved in our reaction cycle, we conducted ¹H-NMR analysis of **3a**, and found it indeed existed as **3a** in CDCl₃, but immediately converted to **3a'** when a few drops of TFA was added to the CDCl₃ solution (Scheme 3, also See ESI[†]).

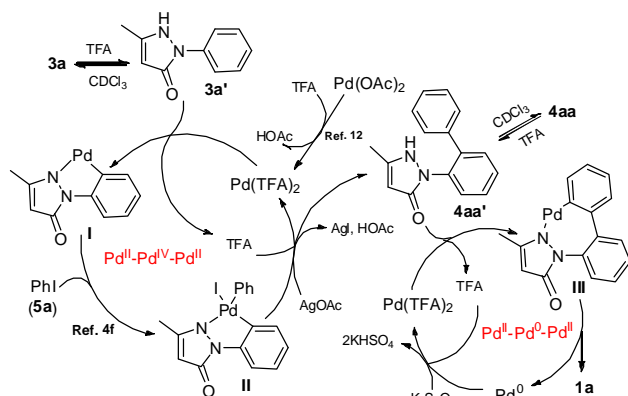


^a All reactions were carried out with pyrazol-5(4H)-ones **3** (0.5 mmol) and aryl iodides **5** (2.5 mmol) in a sealed tube under the optimized conditions; ^b Time for two steps; ^c Isolated yield.

Scheme 2 One-pot synthesis of Benzo[c]pyrazolo[1,2-a]cinnolin-1-ones.^a

Meanwhile, two additional substrates, 4,4-dimethyl-1-phenyl-1H-pyrazol-5(4H)-one and or *N*-methyl 1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one, were employed as substrates for the Pd-catalyzed C-H activation/arylation. Only the former substrate went through the reaction to provide the arylated product in 72% yield, whereas the reaction with the later substrate did not occur (See ESI[†]). This result suggested that the imino *N*-2 other than the carbonyl-*O* in pyrazol-5(4H)-ones **3** acted as the directing group in current reaction.

Based on these experimental outcomes and by referring to the leading references,^{4b,f,12,13} a tentative mechanism was proposed (Scheme 3, based on the model reaction of **3a** and **5a**). First, substrate **3a** tautomerized to **3a'** in TFA and then underwent the first C-H activation to generate a palladacycle intermediate **I**. Oxidative addition^{4f} of iodide **5a** to the palladacycle **I** yielded a Pd^{IV} species **II** which then underwent a reductive elimination in the presence of AgOAc to produce compound **4aa'** and AgI, along with regeneration of the Pd^{II} species for next catalytic cycle. Compound **4aa'** shifted to the tautomer **4aa** in CDCl₃. Meanwhile, further C-H activation and palladation of **4aa'** resulted in a seven-membered palladacycle **III**, which was then followed by a reductive elimination/C-N bond formation to produce Pd⁰ and the cyclized product **1a**. With the assistance of K₂S₂O₈, the produced Pd⁰ was then oxidized to Pd^{II} for further reaction.



Scheme 3 Proposed mechanism.

In conclusion, we have successfully developed a novel one-pot cascade synthesis to conveniently construct the unique class of benzo[c]pyrazolo[1,2-a]cinnolin-1-ones in good yields. This strategy includes two-step/double C-H activation process: first C-H activation/arylation coupled with second C-H activation/intramolecular C-N bond formation. This approach not only offers the first example using the pyrazolone moiety as an internal directing group for C-H activation/functionalization, and also provides a new access to re-investigate this polycyclic skeleton since its first synthesis reported in 1960s.

This work was supported by grants from Chinese NSF (81125021, 81373277), and grants from the "Interdisciplinary Cooperation Team" Program for Science and Technology Innovation (CAS) were also appreciated.

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