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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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A palladium-catalyzed dual C–H activation to construct C–C/C–N bonds for one-pot synthesis of benzo[*c*]pyrazolo[1,2-*a*]cinnolin-1-ones is successfully developed. This approach involves 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 the 1960s through a four-step synthetic process from 2,2′-dinitrobiphenyl **2** in 36% overall yield (Fig. 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** (Fig. 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.

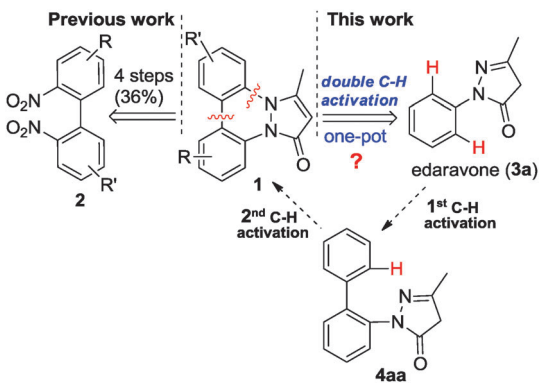

Fig. 1 Conventional processes and our proposal.

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-1*H*-pyrazol-5(4*H*)-one (**3a**) and aryl iodides through a Pd-catalyzed double C–H activation process. Although many N-heterocycles are known to be capable of directing C–H activation,[5,6] to the best of our knowledge, Pd-catalyzed C–H activation directed by a pyrazol-5(4*H*)-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-1*H*-pyrazol-5(4*H*)-ones and aryl iodides. Notably, compound **3a** itself is a neuroprotective drug marketed as Edaravone[7,8] in 2001 in Japan and used 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**.

To test our assumption, we first treated pyrazol-5(4*H*)-one **3a** with phenyl iodide **5a** in the presence of $Pd(OAc)_2$/AgOAc in refluxing TFA, a widely used procedure[10] 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(4*H*)-one moiety as an internal

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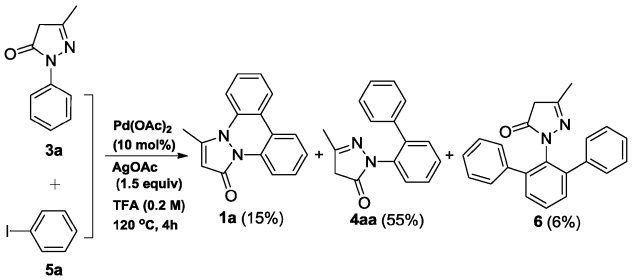


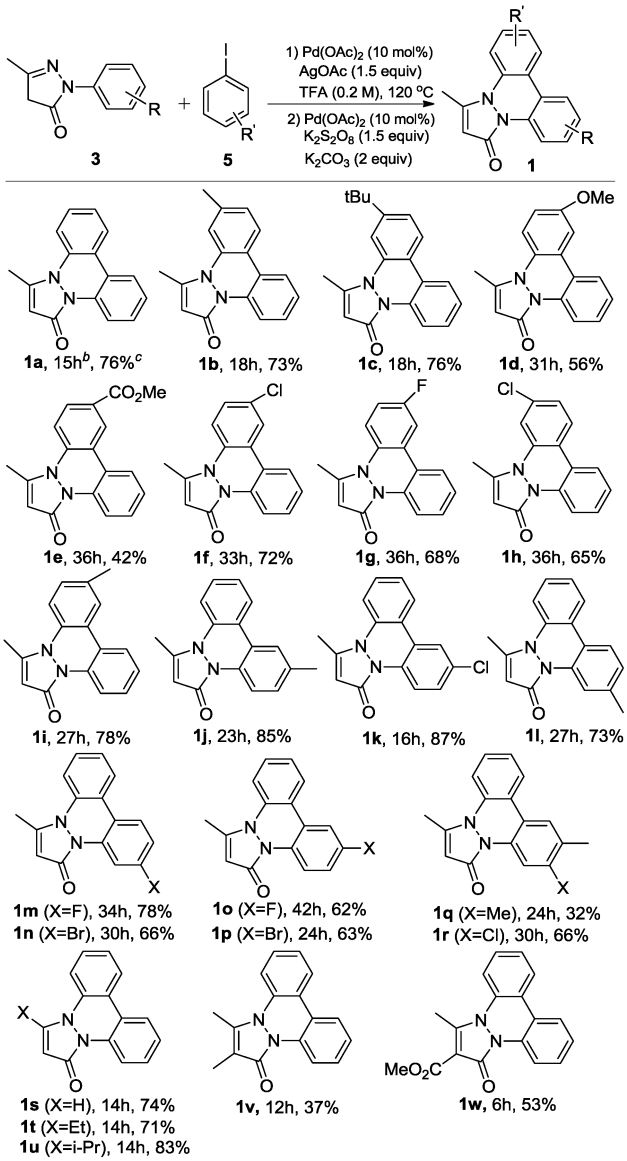
Scheme 1 Reaction of pyrazol-5(4*H*)-one **3a** and iodide **5a**.

component of the substrate/product to direct the double C–H activation process.

To promote compound **1a** as the major product and to suppress the 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 S1) 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 the silver salt.

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(4*H*)-one derivatives and substituted iodides were well tolerated providing corresponding arylated products **4** in moderate to high yields (see ESI,† Table S2). 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 S3). 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, $K_2S_2O_8$ (1.5 equiv.) as the oxidant and K_2CO_3 (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 obtained from two separate reactions.

To determine the generality and limitation of this one-pot double C–H activation process, diversified pyrazol-5(4*H*)-ones **3** and iodides **5** were tested, and the results are summarized in Scheme 2. It was found that a *para*-substituent on the aryl iodides has a 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 favored[11] and no other regioisomers of compounds **1d–g** were isolated. A longer reaction

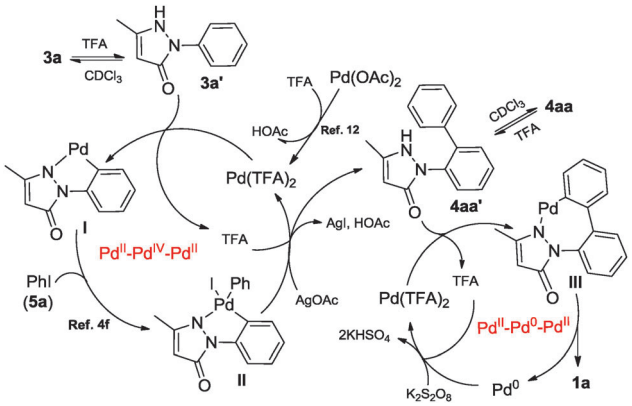


[a] All reactions were carried out with pyrazol-5(4H)-ones **3** (0.5 mmol) and aryl iodides **5** (2.5 mmol) in a sealed tube under the optimized conditions; [b] Time for two steps; [c] Isolated yield.

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

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(4*H*)-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% yields, whereas a C-4 substituent led to lower yield (**1v**, 37%). In the case of substrates 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 was reported previously that



Scheme 3 Proposed mechanism.

compound **3a** is stable in $CHCl_3$, and readily tautomerizes to **3a′** in DMSO.[8] To test the real isomer involved in our reaction cycle, we conducted ^{1}H-NMR analysis of **3a**, and found it indeed existed as **3a** in $CDCl_3$, but immediately converted to **3a′** when a few drops of TFA was added to the $CDCl_3$ solution (Scheme 3, also see ESI†).

Meanwhile, two additional substrates, 4,4-dimethyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and *N*-methyl 1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one, were employed as substrates for the Pd-catalyzed C–H activation/arylation. Only the former substrate underwent the reaction to provide the arylated product in 72% yield, whereas the reaction with the latter substrate did not occur (see ESI†). This result suggested that the imino N-2 other than the carbonyl-*O* in pyrazol-5(4*H*)-ones **3** acted as the directing group in the 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 the next catalytic cycle. Compound **4aa′** shifted to the tautomer **4aa** in $CDCl_3$. 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 Pd^0 and the cyclized product **1a**. With the assistance of $K_2S_2O_8$, the produced Pd^0 was then oxidized to Pd^{II} for further reaction.

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 a 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, but also provides a new access to re-investigate this polycyclic skeleton since its first synthesis reported in the 1960s.

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Notes and references

1 (*a*) E. Andre, A. Georges and A. Serge, *C. R. Seances Acad. Sci., Ser. C*, 1967, **264**, 1855; (*b*) E. Andre and I. Georges, *Bull. Soc. Chim. Fr.*, 1964, **11**, 2897; (*c*) E. Andre and P. Rene, *Bull. Soc. Chim. Fr.*, 1962, 292.
2 For recent reviews on C–H activation, see: (*a*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*b*) K. Muniz, *Angew. Chem., Int. Ed.*, 2009, **48**, 9412; (*c*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (*d*) P. Sehnal, R. J. K. Taylor and I. J. S. Fairlamb, *Chem. Rev.*, 2010, **110**, 824; (*e*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*f*) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (*g*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*h*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*i*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*j*) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (*k*) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936; (*l*) B.-J. Li and Z.-J. Shi, *Chem. Soc. Rev.*, 2012, **41**, 5588; (*m*) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177.
3 (*a*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (*b*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (*c*) J. Wencel-Delord and F. Glorius, *Nature*, 2013, **5**, 369.
4 For selected examples of C–C & C–N formation, see: (*a*) C. Zhu, R. Wang and J. R. Falck, *Chem.–Asian J.*, 2012, **7**, 1502; (*b*) B.-J. Li, S.-L. Tian, Z. Fang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1115; (*c*) D.-D. Li, T.-T. Yuan and G.-W. Wang, *Chem. Commun.*, 2011, **47**, 12789; (*d*) J.-H. Chu, P.-S. Lin, Y.-M. Lee, W.-T. Shen and M.-J. Wu, *Chem.–Eur. J.*, 2011, **17**, 13613; (*e*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350; (*f*) G.-W. Wang, T.-T. Yuan and D.-D. Li, *Angew. Chem., Int. Ed.*, 2011, **50**, 1380; (*g*) J. Karthikeyan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2011, **50**, 9880; (*h*) J. Karthikeyan, R. Haridharan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 12343; (*i*) L. Wang, W. Guo, X.-X. Zhang, X.-D. Xia and W.-J. Xiao, *Org. Lett.*, 2012, **14**, 740.
5 (*a*) D. Shabashov and O. Daugulis, *Org. Lett.*, 2005, **7**, 3657; (*b*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2007, **129**, 11904.
6 (*a*) N. R. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 11234; (*b*) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331; (*c*) C. S. Yeung and V. M. Dong, *Synlett*, 2011, 974; (*d*) D. Kalyani, K. B. McMurtrey, S. R. Neufeldt and M. S. Sanford, *J. Am. Chem. Soc.*, 2011, **133**, 18566; (*e*) S. R. Neufeldt and M. S. Sanford, *Adv. Synth. Catal.*, 2012, **354**, 3517.
7 (*a*) T. Watanabe, M. Tahara and S. Todo, *Cardiovasc. Ther.*, 2008, **26**, 101; (*b*) R. Tabrizch, *Curr. Opin. Invest. Drugs*, 2000, **1**, 347; (*c*) Y.-J. Jin, T. Mima, V. Raicu, K. C. Park and K. Shimizu, *Neurosci. Res.*, 2002, **43**, 75; (*d*) The Edaravone Acute Brain Infarction Study Group (Chair: E. Otomo, MD), *Cerebrovasc. Dis.*, 2003, **15**, 222.
8 S. Pal, J. Mareddy and N. S. Devi, *J. Braz. Chem. Soc.*, 2008, **19**, 1207.
9 For selected examples, see: (*a*) M. Desroses, M.-C. Jacques-Cordonnier, S. Llona-Minguez, S. Jacques, T. Koolmeister, T. Helleday and M. Scobie, *Eur. J. Org. Chem.*, 2013, 5879; (*b*) M. S. Chande, P. A. Barve and V. Suryanarayan, *J. Heterocycl. Chem.*, 2007, **44**, 49; (*c*) Z.-L. Tao, W.-Q. Zhang, D.-F. Chen, A. Adele and L.-Z. Gong, *J. Am. Chem. Soc.*, 2013, **135**, 9255; (*d*) N. Uramaru, H. Shigematsu, A. Toda, R. Eyanagi, S. Kitamura and S. Ohta, *J. Med. Chem.*, 2010, **53**, 8727; (*e*) L. Liu, M. H. Norman, M. Lee, N. Xi, A. Siegmund, A. A. Boezio, S. Booker, D. Choquette, N. D. D' Angelo, J. Germain, K. Yang, Y. Yang, Y. Zhang, S. F. Bellon, D. A. Whittington, J.-C. Harmange, C. Dominguez, T.-S. Kim and I. Dussault, *J. Med. Chem.*, 2012, **55**, 1868.
10 O. Daugulis and V. G. Zaitsev, *Angew. Chem., Int. Ed.*, 2005, **44**, 4046.
11 M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries and P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.*, 2002, **124**, 1586.
12 (*a*) C. S. Yeung, X. Zhao, N. Borduas and V. M. Dong, *Chem. Sci.*, 2010, **1**, 331; (*b*) W.-W. Chan, Z. Zhou and W.-Y. Yu, *Chem. Commun.*, 2013, **49**, 8214.
13 H. Li, R.-Y. Zhu, W.-J. Shi, K.-H. He and Z.-J. Shi, *Org. Lett.*, 2012, **14**, 4850.

