ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 3545–3547

www.rsc.org/chemcomm

COMMUNICATION

Pd-catalyzed and CsF-promoted reaction of bromoalkynes with isocyanides: regioselective synthesis of substituted 5-iminopyrrolones†

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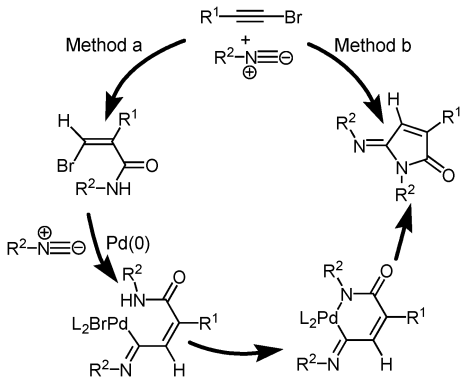
Received 9th December 2011, Accepted 20th February 2012
DOI: 10.1039/c2cc17717j

The palladium-catalyzed and CsF-promoted annulation reaction of bromoalkynes and isocyanides regioselectively affords a diverse set of 5-iminopyrrolone derivatives. This chemistry presumably proceeds through the bromoacrylamide intermediates, which can be readily prepared from the nucleophilic addition reaction of isocyanides to bromoalkynes in the presence of CsF.

The development of general and efficient methodologies for the synthesis of complex molecular skeletons is the central focus of modern organic chemistry. Haloalkynes are attractive starting materials in palladium-catalyzed transformations because they are highly reactive and readily available from the inexpensive acetylides. Plus, they can tolerate various reaction conditions and generally do not require additional oxidant or base.[1] Previously, we have demonstrated that the conjugated *cis*-bromo-alkenynes and 7-alkynyl norbornanes could be prepared from the stereo-selective bromoalkynylation of internal alkynes and norbornene derivatives.[2] Herein, we wish to report the first synthesis of 5-iminopyrrolones *via* palladium-catalyzed annulation reaction of bromoalkynes and isocyanides. This chemistry presumably proceeds through the intermediacy of haloacrylamides, which could be readily prepared from the nucleophilic addition reaction of isocyanides to bromoalkynes.

Polysubstituted iminopyrrolinone derivatives are the core structures of numerous natural products, pharmaceuticals and organic materials.[3] Consequently, the synthesis of iminopyrrolinone heterocycles has attracted great attention, and a number of methodologies have been reported, yet an efficient and general approach is still in demand.[4] Isocyanides are versatile synthons in synthetic organic chemistry, and a few transition-metal-catalyzed reactions involving isocyanides have been disclosed. It appears that the coordination between isocyanides and transition metals may enhance the reactivity of isocyanides, providing more opportunities for novel methodologies development.[5,6] For instance, Yamamoto *et al.*[7] and de Meijere *et al.*[8] independently reported the copper-catalyzed reaction of alkynes with isocyanides for the synthesis of 2,4-di-EWG-substituted pyrroles, whereas the phosphine-catalyzed reaction of isocyanides with alkynes affords the 2,3-di-EWG-substituted pyrroles.



Scheme 1 New reaction hypothesis.

Recently, our group reported the first synthesis of amides *via* the palladium-catalyzed coupling reaction of aryl halides and isocyanides.[9] Interestingly, highly functionalized *cis*-haloalkenes can also be prepared by the acetification and iodation reaction of haloalkynes in a regio- and stereo-selective fashion.[10] Encouraged by these results, we decided to investigate the reaction of isocyanides and haloalkynes in the presence of appropriate bases and transition metals, which not only provides an efficient strategy for the synthesis of haloacrylamide skeletons, but also allows us to study the migratory insertion reaction of isocyanides into palladium species (Scheme 1). To the best of our knowledge, no example of palladium-catalyzed cyclization of haloalkynes with isocyanides has been described in the literature. The major challenge in this hypothesis is the control of chemo- and regioselectivity, since the examples of regioselective reactions involving haloalkynes are still limited.[11]

To our delight, the CsF-promoted nucleophilic addition reaction of isocyanides to bromoalkynes afforded good to excellent yields of functionalized *cis*-bromoacrylamides (Scheme 2).[12] For instance, phenylethynyl bromide was allowed to react with *tert*-butyl isocyanide in the presence of 1.2 equiv. of CsF in DMSO at 90 °C for 12 h. This reaction afforded 87% yield of the desired *N*-*tert*-butyl-3-bromo-2-phenylacrylamide product (Scheme 2, **3a**).[13] With this result in hand, various aryl halides and alkyl ethynyl bromides were employed in this transformation

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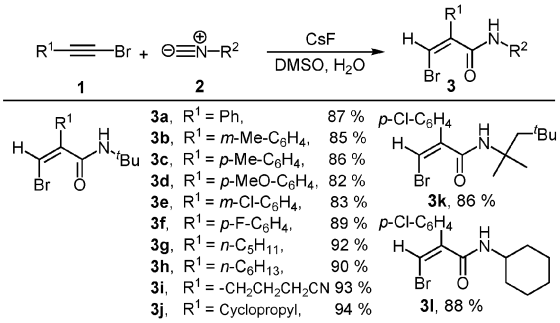
† Electronic supplementary information (ESI) available: Experimental section, characterization of all compounds, copies of ^{1}H and ^{13}C NMR spectra for isolated compounds. CCDC 847837. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17717j



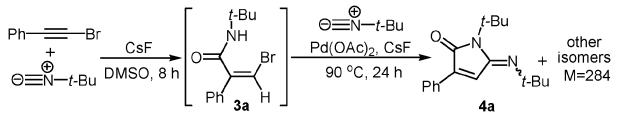
[a] Haloalkyne (1.0 mmol), isocyanide (2.0 mmol), CsF (1.2 equiv), 0.1 mL of H_2O in 2.0 mL DMSO at 90 °C for 8-12 h. Isolated yields are given.

Scheme 2 CsF-promoted reaction of haloalkynes with isocyanides[a].

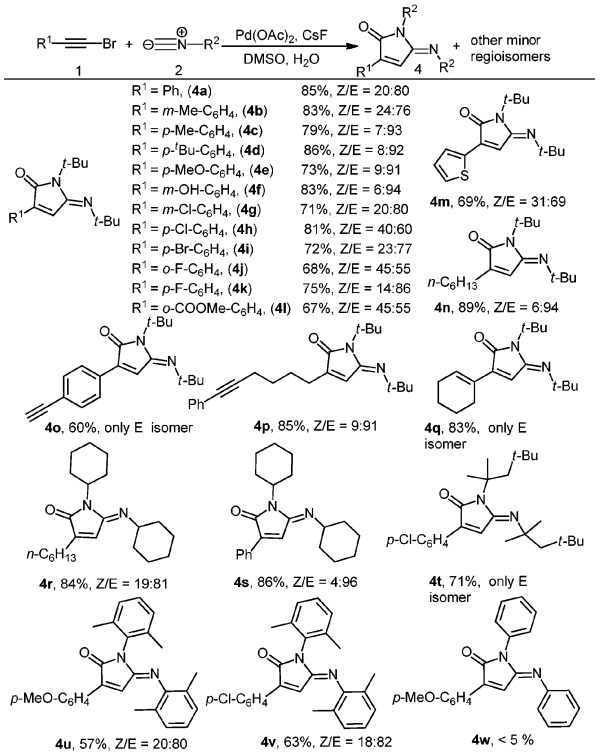
to investigate the reaction scope and limitations. In all of the examples investigated, good yields and high selectivities were obtained, which indicates the exceptional generality of this novel methodology. As a matter of fact, bromoalkynes in which the phenyl ring bears various functional groups like Me, OMe, F and Cl were very well tolerated in this reaction (Scheme 2, **3b** to **3f**). Alkyl-substituted alkynylbromides such as 1-pentyl bromide and (2-bromoethynyl)-cyclopropane also afforded the desired product in excellent yields. Interestingly, sterically-hindered isocyanides like 2-isocyano-2,4,4-trimethylpentane and isocyanocyclohexane could also be employed in this transformation and these reactions afforded the acrylamide products in 86% and 88% yields, respectively (Scheme 2, **3k** and **3l**).

Bromoacrylamides are an important class of Br-containing amides in organic chemistry, and also potential precursors for the synthesis of numerous natural products and potent pharmaceuticals.[14] With a viable route to the functionalized bromoacrylamides, we are then working on exploring their potential applications as building blocks for the synthesis of highly substituted heterocycles. During the course of these studies, we discovered that the Pd-catalyzed one-pot annulation of phenylethynyl bromide with *tert*-butyl isocyanide gave 5-iminopyrrolinone **4a** and other regioisomers (Scheme 3).

With these results in hand, we envisioned that the *in situ* bromo-substituted acrylamides could react with palladium(0) species and generate the highly reactive vinylpalladium intermediates, which subsequently should react with another isocyanide to afford the biologically-interesting 5-iminopyrrolone derivatives in a one pot process. The reaction scope and limitation are summarized in Scheme 4. Generally, this reaction proceeds smoothly under the optimal conditions to afford various polysubstituted 5-iminopyrrolones in a regioselective manner in good to excellent yields. With regard to phenylethynyl bromides, both electron-rich and electron-poor functional groups can be tolerated and the reaction efficiency and selectivity are exceptional (Scheme 4, **4b–4l**). In particular, the reactivity of the cyclization reaction of alkyl-substituted



Scheme 3 One-pot synthesis of 5-iminopyrrolinone from bromoalkyne and isocyanide.



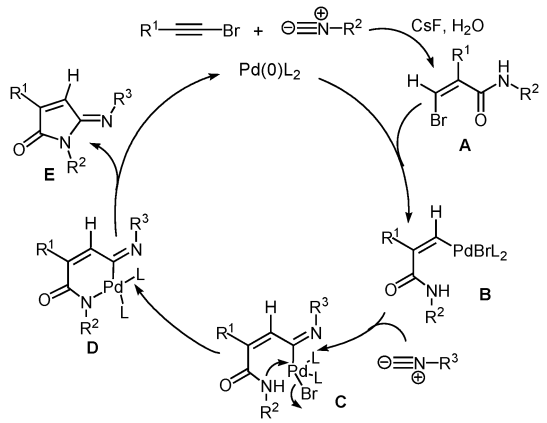
[a] Bromoalkyne (1.0 mmol), isocyanide (3.0 mmol), $Pd(OAc)_2$ (5 mol %), CsF (1.5 equiv), 0.1 mL of H_2O in 2.0 mL DMSO at 90 °C for 8-12 h. Yields of isolated products. *Z*/*E* configuration of the imino bond was detected by GC.

Scheme 4 Palladium-catalyzed synthesis of iminopyrrolinones from haloalkynes and isocyanides[a].

ethynyl bromide appears to be higher than that of the aryl-substituted ethynyl bromide, presumably due to the fact that a less hindered group is in favour of nucleophilic addition reaction and migratory insertion of isocyanides (Scheme 4, **4n, 4p** and **4q**). It is worth noting that the ethynyl bromide substrates containing reactive groups such as C–C double/triple bonds can also be employed in this transformation and the desired products (**4o–4q**) were obtained in reasonable to good yields. In order to confirm the structure of the products obtained, the molecular structure of compound **4d** was established by X-ray crystallography (see ESI†).

With the use of various isocyanides as substrates, this transformation can also be performed in one pot to afford the corresponding iminopyrrolinone products in good yields (Scheme 4, **4r–4v**). However, the isocyanides with less hindered substituents such as 1-isocyanobenzene or 2-isocyanoacetate gave a very low yield (Scheme 4, **4w**). We guess that when the reaction took place over a long reaction time at higher temperatures, decomposition or hydroxylation of 1-isocyanobenzene occurred prior to completion of the annulation reaction.

The postulated reaction mechanism is depicted in Scheme 5.[9,15,16] The catalytic cycle was initiated by the nucleophilic addition of isocyanides to bromoalkynes, which gave the bromoacrylamides **A** in the presence of CsF. Subsequently, bromoacrylamide **A** underwent oxidative addition reaction to afford vinylpalladium complex **B**. Subsequently, another isocyanide could undergo 1,1-insertion reaction to afford



Scheme 5 Proposed mechanism for annulation reaction.

intermediate **C**. Possibly, the amine group of intermediate **C** could coordinate to the palladium metal and a subsequent proton abstraction should afford the palladium metallacycle intermediate **D**. The reductive elimination of metallacycle intermediate **D** would afford the annulated product **E**.

In conclusion, we have developed a new strategy for the synthesis of bromoacrylamides and polysubstituted iminopyrrolinones in good to excellent yields from readily available starting materials. This chemistry proceeds smoothly under the optimal reaction conditions and various functional groups can be tolerated with exceptional selectivity. The methodology is highly practical and it provides a straightforward approach to a series of 5-iminopyrrolones and haloacrylamides in a regioselective manner. Current efforts aiming at broadening the scope of the catalytic system and exploring synthetic applications are still ongoing.

We thank the National Natural Science Foundation of China (20932002 and 21172076), National Basic Research Program of China (973 Program) (2011CB808600), Doctoral Fund of Ministry of Education of China (20090172110014), Guangdong Natural Science Foundation (10351064101000000) and the Fundamental Research Funds for the Central Universities (2010ZP0003) for financial support.

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