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Pd(II)-Catalyzed alkyne annulation through allylic isomerization: synthesis of spiro-cyclopentadiene pyrazolones†

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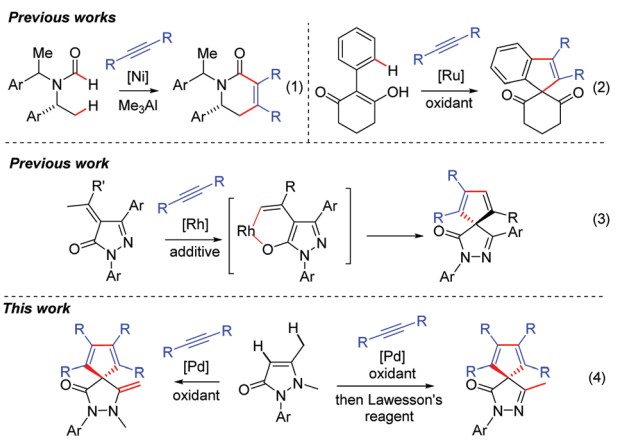
The Pd(II)-catalyzed activation of Csp^2–H bond and double alkyne annulation which proceeds *via* allylic isomerization is reported for the first time. This reaction of antipyrines with alkynes provides an efficient synthetic route for the biologically important spiro-cyclopentadiene pyrazolones. In the presence of Lawesson's reagent, this Pd(II)-catalyzed annulation reaction affords another spiro-cyclopentadiene pyrazolone which displays very good fluorescence properties.

In the past few decades, transition-metal-catalyzed hetero atom directed C–H bond activation and oxidative alkyne annulation reactions have emerged as a powerful tool for the construction of a wide range of heterocycles.[1] Jiao and co-workers developed a Pd-catalyzed reaction to activate two C(sp^2)–H bonds and alkyne annulation for the synthesis of aromatic carbocycles.[2] Nakao and co-workers developed a Ni-catalyzed alkyne annulation reaction of formamides *via* functionalization of one C(sp^3)–H bond and one C(sp^2)–H bond (Scheme 1, eqn (1)).[3] Lam and co-workers performed the alkyne annulation *via* C(sp^2)–H bond activation, sequential keto enol tautomerization and C(sp^3)–H bond activation for the synthesis of spirocycles (Scheme 1, eqn (2)).[4] Yao *et al.* reported a Rh-catalyzed alkyne annulation *via* enol directed formal C(sp^3)–H bond activation of α-arylidene pyrazolones for the synthesis of spiro-pyrazolones (Scheme 1, eqn (3)).[5] In continuation of our work on metal-catalyzed reactions,[6] herein, we report an unprecedented alkyne annulation reaction which involves the activation of one olefinic C(sp^2)–H bond, and the annulation proceeds *via* the allyl bond isomerization (Scheme 1, eqn (4)). This Pd-catalyzed annulation reaction of antipyrines and alkynes provides an efficient route to access 4-spiro-5-pyrazolones. The 4-spiro-5-pyrazolones and their derivatives have attracted considerable attention recently, due to their interesting biological activities. These compounds exhibit miticidal activity, inhibit type-4 phosphodiesterases and they are also used as PPARα antagonists (Fig. 1).[7] Therefore, a new efficient method to access this core structure is highly desirable. Furthermore, we developed an unprecedented Pd(II)-catalyzed Lawesson's reagent mediated cascade annulation reaction of antipyrines with alkynes for the synthesis of spiro-pyrazolones which proceeds *via* 1,2-methyl shift (Scheme 1, eqn (4)).

Initially, antipyrine **1a** and alkyne **2a** were chosen to optimize the reaction conditions for the synthesis of the spiro compound **3aa**. As shown in Table S1 (ESI†), among the metal complexes studied for this annulation reaction, $Pd(OAc)_2$ catalyst along with the additive $Cu(OAc)_2$, provided the highest yield of **3aa** (48%) in 1,4-dioxane (entry 3). Then, studies on solvents revealed toluene and ^{t}AmOH as the most suitable solvents that provided 74% and 79% yields of **3aa**, respectively (entries 9 and 11). These optimized reaction conditions were then tested to study the substrate scope of various substituted pyrazolones **1a–k** with alkyne **2a** which is shown in Table 1.



Scheme 1 Examples of various alkyne annulation reactions.

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† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H NMR, ^{13}C NMR and HRMS spectrum of the synthesized compounds. CCDC 1944638 and 2079413. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc02155a

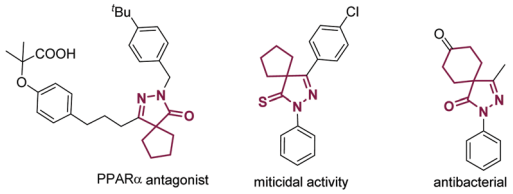
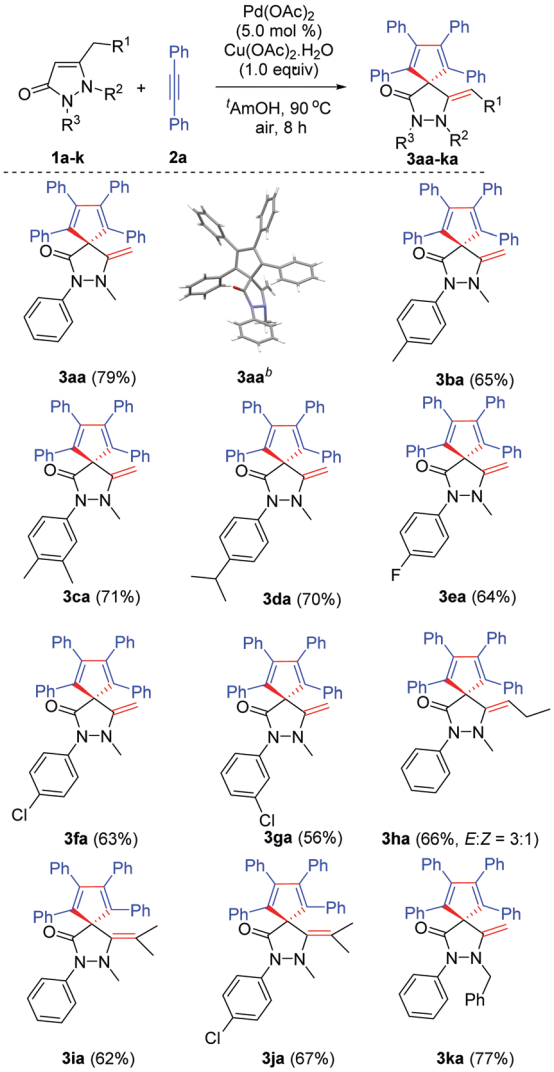


Fig. 1 Representative bioactive spiro-pyrazolones.

The pyrazolones possessing electron-donating and electron-withdrawing substituents such as methyl, isopropyl, fluoro and chloro on the 2-phenyl ring **1b**, **1d–g** were tested with **2a**. These reactions provided the spiro compounds **3ba**, **3da–ga** with yields in the range of 56–70%, irrespective of the position of the substituent on the phenyl ring. Similarly, dimethyl substituted pyrazolone **1c** was also found to be a good substrate to provide **3ca** in 71% yield. Then, the annulation reaction of pyrazolones containing substituents at 5-position of the pyrazolone ring was studied. Thus, the studied typical pyrazolones substituted at 5-position with *n*-propyl and iso-propyl groups **1h–j** were also found to be suitable substrates to perform this annulation reaction to afford **3ha–ja** in 62–67% yields. The spiro compound **3ha** was a mixture of both the geometrical isomers ($E:Z$ = 3 : 1) which was determined by the NOE spectrum. Finally, pyrazolone substituted with a benzyl group at 1-position **1k** was tested for the annulation reaction with **2a** to afford **3ka** in 77% yields. The structures of all the compounds were determined with the help of NMR spectroscopy and finally confirmed by single X-ray crystallography studies of compound **3aa**.[8]

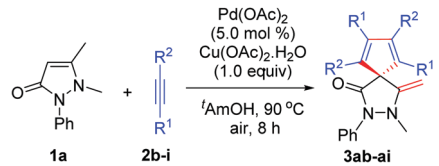
Table 1 Scope of antipyrines **1a–k** with **2a**[a]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv.) in ^{t}AmOH (5.0 mL) at 90 °C for 8 h under air. [b] For clarity one molecule is shown (for details see ESI).

Then the scope of the alkynes **2b–i** was studied with antipyrine (**1a**) as shown in Table 2. The symmetrically substituted alkynes, substituted with electron-releasing and electron-withdrawing substituents such as methyl, methoxy and fluoro at 4-position of the phenyl ring **2b–d** afforded the spiro compounds **3ab–ad** with yields in the range of 66–76%. Similarly, symmetrical disubstituted alkyne substituted with an electron-withdrawing fluoro substituent at the 3-position of the phenyl ring **2e** was also found to be a suitable substrate for this reaction to provide **3ae** in 73% yield. The reaction of the aryl and alkyl group substituted alkyne **2f** with **1a** was highly regioselective to provide only one isomer of the spiro compound **3af**. However, alkyne **2g** substituted with a phenyl group and an ethyl group afforded a 3 : 1 mixture of spiro compound **3ag**. The regioselectivity of these unsymmetrical alkynes is similar to the previously reported metal-catalyzed alkyne annulation reactions, where the sterically hindered phenyl ring containing centre of the alkyne binds with the metal during the insertion of alkyne in the C–M bond, leading to the preferential formation of one isomer.[9] Finally, the dialkyl substituted alkynes **2h–i** were tested for this annulation reaction, and they also turned out to be suitable substrates for this annulation reaction to provide spiro compounds **3ah–ai**, though

Table 2 Scope of alkynes **2b–i** with **1a**[a]



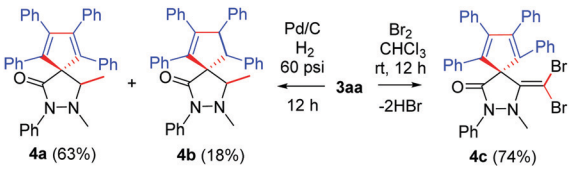
3ab ($R^1 = R^2$ = 4-Me-Ph, 76%)
3ac ($R^1 = R^2$ = 4-MeO-Ph, 70%)
3ad ($R^1 = R^2$ = 4-F-Ph, 66%)
3ae ($R^1 = R^2$ = 3-F-Ph, 73%)
3af (R^1 = Me, R^2 = Ph, 58%)
3ag (R^1 = Et, R^2 = Ph, 55%, r.r. = ~ 3:1)[b]
3ah ($R^1 = R^2$ = *n*-Propyl, 55%)
3ai ($R^1 = R^2$ = *n*-Butyl, 52%)

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv.) in ^{t}AmOH (5.0 mL) at 90 °C for 8 h under air. [b] Major isomer is shown, ratio of regioisomers (r.r.) was determined by ^{1}H NMR.

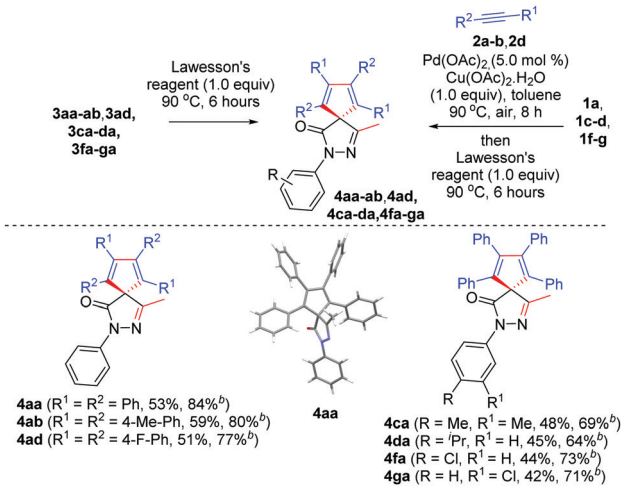
with comparatively less yields (52–55%). The terminal alkynes, trimethyl(phenylethynyl)silane, methyl 3-phenylpropiolate and 1-methyl-2,5-diphenyl-1,2-dihydro-3*H*-pyrazol-3-one were not found to be suitable substrates for this reaction.

To see the synthetic utility of the spiro product, we performed some of the transformation reactions of **3aa**. As shown in Scheme 2, the hydrogenation reaction of **3aa** in the presence of Pd/C as the catalyst provided a mixture of hydrogenated products **4a** and **4b**, which could be separated using silica gel column chromatography. Hydroboration of **3aa** with borane complex and subsequent reduction of the resultant boron complex in the presence of Pd/C in methanol provided the same exocyclic double bond reduced product **4a**. Interestingly, the bromination reaction of **3aa** provided a geminal dibromo spiro compound **4c**. This dibromo compound **4c** was formed from **3aa** *via* bromination–dehydrobromination and subsequent repeated bromination–dehydrobromination of the resulted monobromo olefin. This dibromo compound would be a suitable synthon for further functionalization. Next, we attempted to transform the pyrazolone **3aa** to its corresponding thiopyrazolone by treatment with Lawesson's reagent in toluene. Interestingly, instead of providing the thiopyrazolone, this reaction provided the spiro-cyclopentadiene pyrazolone **4aa** in 84% yield (Scheme 3). Further studies revealed that **4aa** could also be synthesized in one pot from **1a** and **2a**, using the optimized reaction conditions and toluene as the solvent, followed by the addition of Lawesson's reagent into the reaction mixture (Scheme 3). Owing to the importance of these spiro-pyrazolones,[7] we studied these novel one-pot and two-steps reactions to synthesize some of the representative spiro-pyrazolones which is shown in Scheme 3. The one pot synthesis provided inferior yields of spiro compounds (42–59%) as compared to the two-steps reaction (64–84%). The structure of these compounds was determined using NMR spectroscopy and confirmed using X-ray crystallography studies of compound **4aa**.[10] Moreover, treatment of **1a** alone under standard conditions in D_2O for 4 h provided deuterated **1a**, where the fourth C–H bond of **1a** is exchanged with D atom (35%).

Recently, the polyarylated compounds have attracted considerable attention owing to their notable photochemical properties, which make them useful compounds for organic semiconductors. Therefore, a preliminary study of the optical properties of all the synthesized compounds was carried out.[11] The absorption bands of all the synthesized spiro-pyrazolones appeared in the region 320–360 nm. Among all the compounds studied, only compounds shown in Scheme 3 exhibited intense fluorescence in the range from 438 to 457 nm with quantum efficiency (Φ) of 48% (**4aa**), 75% (**4ab**), 64% (**4ad**), 52% (**4ca**), 61% (**4da**), 30% (**4fa**) and 47% (**4ga**) (Fig. 2).



Scheme 2 Transformation of 4-spiro-5-pyrazolone.



Scheme 3 LR-mediated synthesis of spiro-pyrazolones. [a] Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv.) in toluene (5.0 mL), 90 °C for 8 h under air, then Lawesson's reagent (0.5 mmol), 90 °C for 6 h. [b] Yield from two-step reaction performed in toluene starting with **3** at 90 °C for 6 h.

A plausible mechanism for the formation of **3aa** is proposed in Scheme 4. Initially, direct activation of the olefinic C(sp^2–H) bond of antipyrine forms the Pd(II) complex **A**. Then, metal–alkyne coordination followed by insertion of the alkyne into the Pd–C bond results in the Pd(II) complex **B**. Subsequent allylic isomerization affords π-allylpalladium species **C**.[12] Insertion of one more molecule of an alkyne into the Pd–C bond of **C** affords a six membered Pd-complex **D**. Finally, reductive elimination and subsequent oxidation of the metal in the presence of air and $Cu(OAc)_2$ provides **3aa** and the active catalyst. Again, [3+2] cycloaddition of **3aa** with LR generates **E**, which on subsequent 1,2-methyl shift followed by elimination of phosphorous sulphide **G**[13] finally led to the formation of **4aa**.

In conclusion, we have developed a new Pd-catalyzed alkyne annulation reaction, where annulation proceeds *via* the activation of one olefinic C(sp^2–H) bond followed by the rearrangement of one allylic C(sp^3–H) bond. This annulation reaction of antipyrines and disubstituted alkynes provides an efficient method for the synthesis of 4-spiro-5-pyrazolones which are the key structural motif of several bioactive compounds.

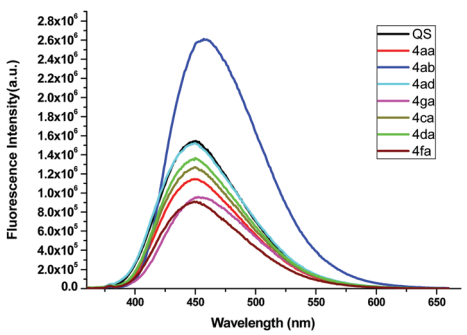
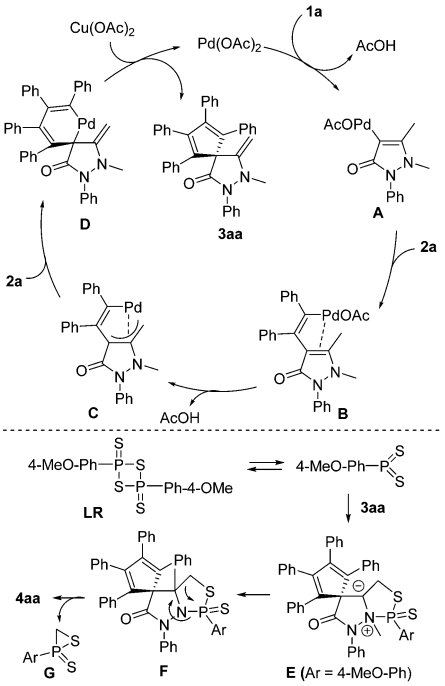


Fig. 2 Fluorescence (2.0×10^{-5} M, excitation at 340 nm) spectra of spiro-pyrazolones **4** in toluene using quinine sulfate (QS) as the standard.



Scheme 4 Possible reaction mechanism.

Moreover, we have developed another unprecedented Lawesson's reagent mediated and Pd-catalyzed annulation reaction for the synthesis of spiro-cyclopentadiene pyrazolones which exhibited fluorescence properties.

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Conflicts of interest

There are no conflicts to declare.

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