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Rh(III)-catalyzed oxidative C–H annulation of 6-arylpyridazin-3(2*H*)-ones: direct access to diarylpyridazino[6,1-*a*]isoquinolin-5-ium-3-olates

Chaitanya Ittamalla,[ae] N. S. S. Mukundram,[b] Jyothirmai Nagireddy,[c] B. Sridhar[d] and B. V. Subba Reddy *[ae]

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A novel strategy has been developed for the synthesis of diarylpyridazino[6,1-*a*]isoquinolin-5-ium-3-olate frameworks through a Rh(III)-catalyzed C–H annulation of 6-arylpyridazin-3(2*H*)-ones with internal alkynes by means of C–H bond activation. This is the first report on *ortho*-C–H bond annulation of 6-arylpyridazin-3(2*H*)-ones with alkynes to afford angularly fused heterocycles in good yields with high functional group tolerance. This method offers a facile and practical approach to structurally diverse mesoionic scaffolds of pharmaceutical relevance.d6ra01670g-s

Introduction

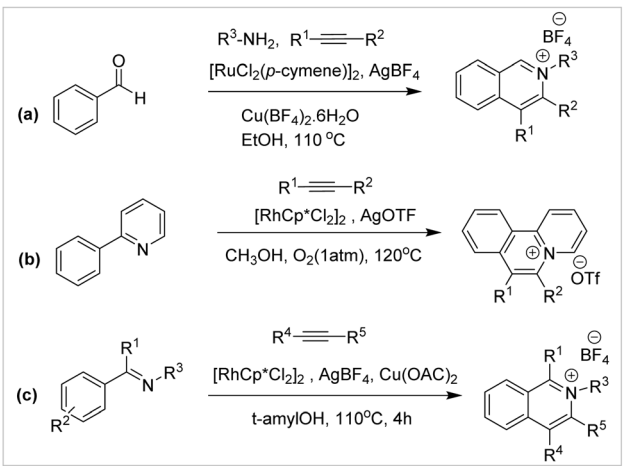
In recent years, transition metal-catalyzed *ortho*-C–H bond functionalization has emerged as a powerful synthetic strategy in organic synthesis, enabling the formation of C–C, C–N, and C–X bonds without the need of pre-functionalization of the substrate.[1] For instance, substrate-directed C–H functionalization offers significant advantages by providing direct access to diverse substitution patterns and thus facilitating the construction of *N*-containing heterocycles, which are key components of many biologically active molecules. This method overcomes significant challenges associated with conventional approaches.[2]

In particular, Rh(III)-catalyzed directed C–H bond activation of aromatic rings with alkynes has received special attention due to its high atom efficiency in constructing a diverse range of fused polycyclic aromatic frameworks.[3,4] On the other hand, isoquinolinium salts are an important class of compounds that are widely utilized for the synthesis of several biologically active compounds.[5] As a result, many efforts have been made to develop efficient methods for the synthesis of these compounds (Scheme 1).[6,7]

In particular, transition metal-catalyzed annulation of aryl halides with alkynes is a commonly used strategy for the synthesis of isoquinolinium salts.[8,9] Furthermore, mesoionic compounds are distinct types of heterocycles, which belong to the class of non-benzenoid aromatics such as sydnones and munchnone *etc* (Fig. 1).[10]

Interestingly, these mesoionic compounds are key building blocks for many biologically active compounds, which possess wide applications such as dyes, insecticides, pharmaceuticals.[11] Recently, ruthenium-catalyzed alkenylation of 6-aryl(dihydro) pyridazin-3(2*H*)-ones with alkynes has been reported to give *N*-alkenylated products (**I**) and *C*-alkenylated products (**II**) under different atmospheric conditions (Scheme 2).[12]

However, there are no reports on the annulation of 6-arylpyridazin-3(2*H*)-ones with internal alkynes to generate a novel class of mesoionic compounds. Interestingly, these mesoionic compounds are used as precursors for dyes, insecticides and pharmaceuticals.[13]



Scheme 1 Previous reports on the synthesis of isoquinolinium salts.

[a]*Fluoro & Agrochemicals, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India. E-mail: basireddy.iict@csir.res.in; Web: https://www.iict.res.in/*

[b]*Polymers and Functional Materials, India*

[c]*Centre for NMR Spectroscopy, India*

[d]*Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad–500 007, India*

[e]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002, India*

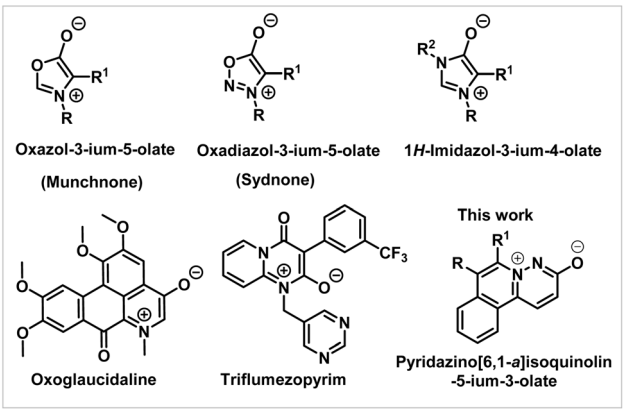
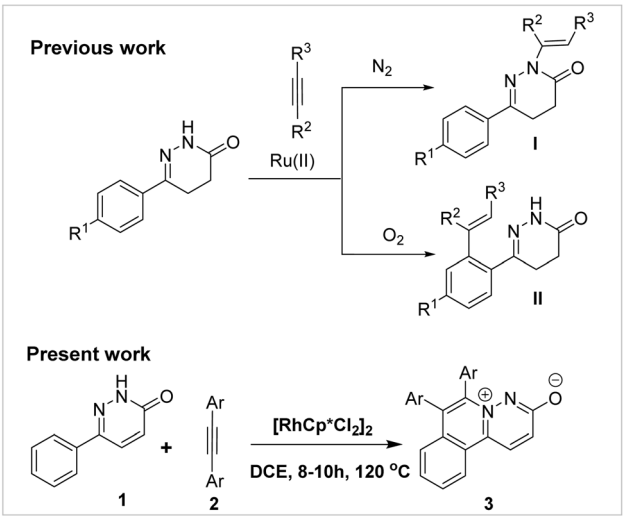


Fig. 1 Examples of bioactive mesoionic compounds.



Scheme 2 Previous and present work.

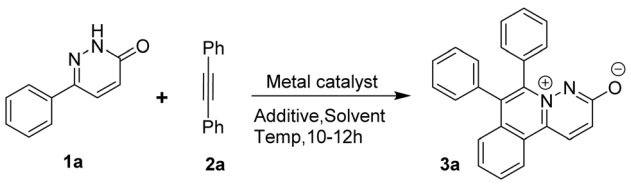
Results and discussion

Following our interest on C–H functionalization of *aza*-aromatic systems,[14] we herein report a novel strategy for the oxidative annulation of 6-arylpyridazin-3-oneswith internal alkynes using a catalytic system comprising of $[Cp^*RhCl_2]_2$, $AgSbF_6$ & $Cu(OAc)_2\cdot H_2O$ to afford a novel class of mesoionic isoquinolinium derivatives. A model reaction between 6-phenylpyridazin-3(2*H*)-one (**1a**) and 1,2-diphenylethyne (**2a**) was performed under different experimental conditions (Table 1).

Initially, the annulation was carried out using a 5 mol% of $[Cp^*RhCl_2]_2$, 30 mol% of $AgSbF_6$ and 0.5 equiv. of AgOAc in DCE at 80 °C under inert conditions. Interestingly, a novel mesoionic compound, *i.e.* 6,7-diphenylpyridazino[6,1-*a*]isoquinolin-5-ium-3-olate **3a** was isolated in 55% yield (entry 1, Table 1). To improve the yield, the temperature was increased ranging from 80° to 120 °C. To our delight, the yield was enhanced from 55% to 75% respectively (entries 1, 2 and 3, Table 1). To optimize the role of additive, the reaction was further carried out using $Cu(OAc)_2\cdot H_2O$ under similar conditions. Remarkably, the product **3a** was obtained in 92% yield (entry 4, Table 1). The use of either $AgSbF_6$ or $Cu(OAc)_2.H_2O$ alone was found to be less effective (entries 5 & 6, Table 1). To realize the effect of solvent, the reaction was conducted in different solvents (entries 7–10, Table 1). Among them, DCE gave the best result. To understand the role of catalyst, the reaction was performed using other metal catalysts such as $[Ru(p\text{-cym})Cl_2]_2$ & $Pd(OAc)_2$ (entries 11 and 12, Table 1). However, the use of $[Ru(p\text{-cym})Cl_2]_2$ gave the product **3a** in low yield compared to $[RhCp^*Cl_2]_2$, whereas $Pd(OAc)_2$ failed to give the desired product under similar conditions.

Having the optimized reaction conditions in hand, we examined the scope and generality of this process. The reaction

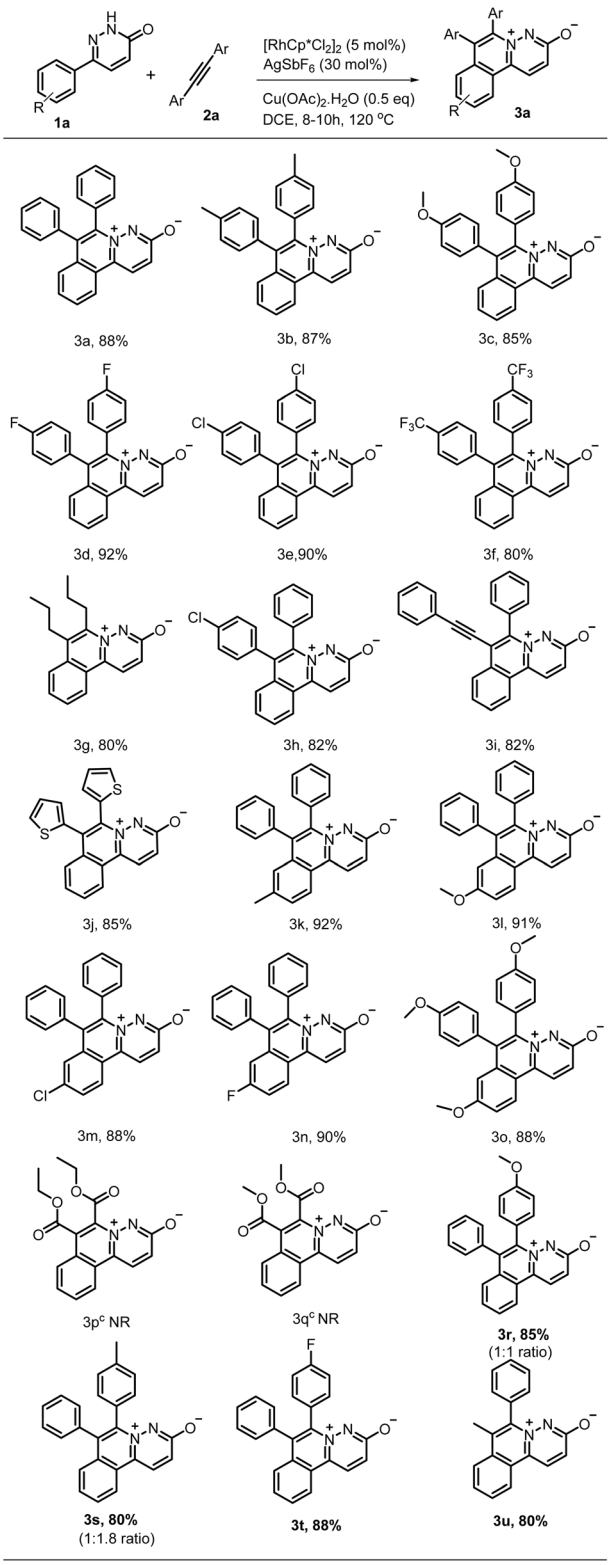
Table 1 Optimization of reaction conditions[a,b]



Entry	Catalyst	Activator	Oxidant	Solvent	Temp.(°C)	Yield (%)[b]
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$	AgOAc	DCE	80	55
2	$[RhCp^*Cl_2]_2$	$AgSbF_6$	AgOAc	DCE	100	70
3	$[RhCp^*Cl_2]_2$	$AgSbF_6$	AgOAc	DCE	120	75
4	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	DCE	120	92
5	$[RhCp^*Cl_2]_2$	—	$Cu(OAc)_2.H_2O$	DCE	120	Trace
6	$[RhCp^*Cl_2]_2$	$AgSbF_6$	—	DCE	120	40
7	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	MeOH	120	75
8	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	EtOH	120	70
9	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	Toluene	120	65
10	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	ACN	120	62
11	$[Ru(p\text{-cym})Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	DCE	120	75
12	$Pd(OAc)_2$	$AgSbF_6$	$Cu(OAc)_2.H_2O$	DCE	120	—

[a] Reaction conditions: **1a** (1.0 equiv), **2a** (1.2 equiv.), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (30 mol%), $Cu(OAc)_2$ (0.5 equiv.), DCE (5.0 mL) at 120 °C for 8–10 h in a sealed tube. [b] Isolated yield after purification.

Table 2 Annulation of arylpyridazin-3(2*H*)-ones with alkynes[a,b]



[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$(5 mol%), $AgSbF_6$(30 mol%), $Cu(OAc)_2$ (0.5 equiv.), DCE (5.0 mL) at 120 °C for 8–10 h in a sealed tube. [b] Isolated yield after purification. [c] No reaction.

between various internal alkynes **2a–i** and different pyridazinones was studied systematically. The results are summarized in Table 2. A variety of diaryl acetylenes bearing an electron withdrawing and donating substituents at the *para*-position of phenyl ring afforded the corresponding products in good to excellent yields (entries **3b**, **3c**, **3d** & **3e**, Table 2). The structure of **3d** was confirmed by NMR spectroscopy and single crystal X-ray crystallography (Fig. 2a).[15]

Conversely, the substrate bearing $-CF_3$ group at the *para*-position and dialkylacetylene also gave the desired product relatively in low yield (entries **3f** & **3g**, Table 2). Interestingly, the reaction was quite successful with 1,4-diphenylbutadiyne furnishing the required product in good yield (entry **3i**, Table 2). Nevertheless, the substrate derived from thiophene afforded the respective product in good yield (entry **3j**, Table 2). Furthermore, we evaluated the scope of this process with various pyridazinones bearing different substituents such as methyl, methoxy, fluoro and chloro on benzene ring. It is noteworthy to mention that these groups are well tolerated under the reaction conditions and the corresponding products were isolated in excellent yields (entries **3k**, **3l**, **3m** & **3n**, Table 2). However, a few unsymmetrical alkynes gave the product as a mixture of regioisomers in different ratio (**3r** in 1 : 1 ratio, **3s** in 1 : 1.8 ratio). Where as the unsymmetrical alkyne bearing substituents like 4-chlorophenyl, 4-fluorophenyl and methyl furnished the desired product with high regioselectivity due to electronic effects (entries **3h**, **3i**, **3t**, & **3u**, Table 2). The structures of compounds **3i** and **3u** were confirmed through extensive 2D NMR analysis. For compound **3i**, NOE correlations between H12 ↔ H25, 29 and H15 ↔ H8, along with HMBC correlations between H25, 29 ↔ C23, established the structure of **3i**. Similarly, for compound **3u**, NOE correlations between 23-methyl ↔ H12, 23-methyl ↔ H18, 22, and H15 ↔ H8 confirmed the regioisomer. The spectral data and interpretation of nOes are presented as Fig. Sx–Sy and Tables S1 and S2 in SI. In addition to this, the structures of **3h** and **3t** were established by single crystal X-ray crystallographic studies (Fig. 2b and 2c).[15] It was observed that the reaction did not proceed either with diethyl or with dimethyl acetylene carboxylate (entries **3p** and **3q**, Table 2).

Based on experimental results and previous reports,[16,17] a plausible reaction mechanism is proposed in Scheme 3. The catalyst, $[RhCp^*Cl_2]_2$ is activated by $AgSbF_6$ to generate a highly reactive monomeric Rh(III) species, which coordinates with a nitrogen atom of the substate **1a** along with *ortho*-C–H bond cleavage to form a five-membered rhodacycle (**I**). In the second step, the alkyne **2a** coordinates with a rhodacycle (**I**) to form a ternary complex (**II**). Then, a migratory insertion of alkyne into Rh–C bond generates a seven-membered rhodacycle (**III**). Finally, the reductive elimination occurs to give the intermediate **IV** along with Rh(I) species, which can undergo oxidation by Cu(II) to complete the catalytic cycle, while Cu(II) is reduced to Cu(I) or Cu(0). Finally, the anion (acetate) abstracts the proton from hydroxyl group, probably due to its basicity to produce the mesoionicisoquinoline**3a** (Scheme 3).

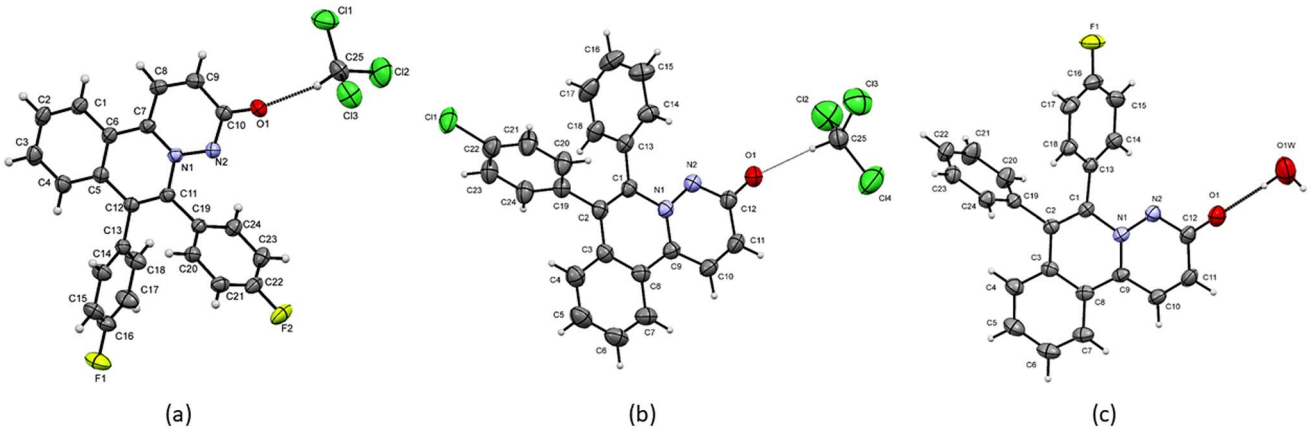
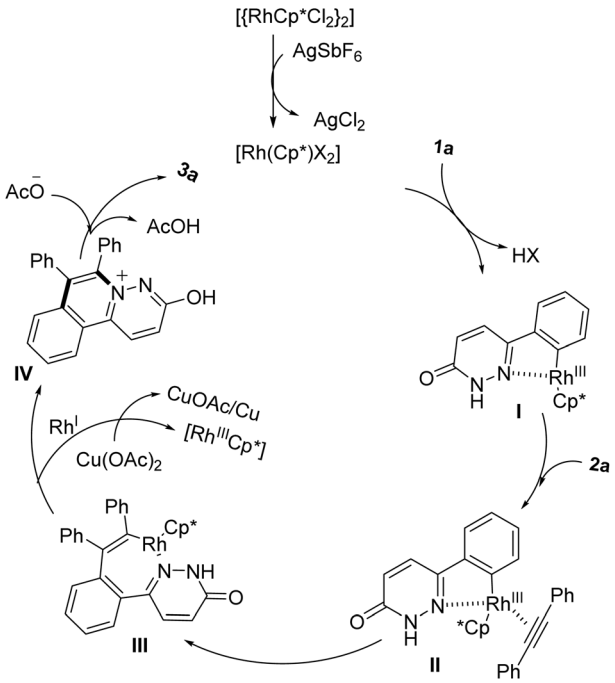


Fig. 2 (a) ORTEP diagram of **3d**; (b) ORTEP diagram of **3h**; (c) ORTEP diagram of **3t**.



Scheme 3 A plausible reaction mechanism.

Conclusions

We have successfully developed a novel approach to the synthesis of mesoionic isoquinolin-5-ium-3-olate frameworks through a transition metal catalyzed oxidative C–H annulation of 6-arylpyridazin-3(2*H*)-ones with diarylacetylenes. The catalytic system comprises 5 mol% Rh(III), 30 mol% $AgSbF_6$ and 0.5 equiv of $Cu(OAc)_2 \cdot H_2O$ and acts as a trifunctional catalyst. This approach offers several advantages including operational simplicity, broad substrate scope, and excellent functional group tolerance. The end products are more relevant to pharmaceuticals and agrochemicals and also serve as versatile precursors for novel heterocycles through dipolar cycloadditions.

Experimental section

All solvents were dried by a standard literature procedure. Crude products were purified by column chromatography on silica gel of 60–120 or 100–200 mesh. Thin layer chromatography (TLC) plates were visualized by exposure to ultraviolet light at 254 nm, and by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solvents were concentrated on rotary evaporator at 35–40 °C. Melting points (mp) were measured on Buchi B-540. ^{1}H & ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on 300, 400 or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (J) are quoted in hertz (Hz). ORBITRAP and ESI mass spectrometer were used for recording the HRMS.

Experimental procedure for the synthesis of 3a

To an oven dried sealed tube equipped with a stir bar were charged with 6-phenylpyridazin-3(2*H*)-one (**1a**, 1.0 equiv.), biphenyl acetylene (**2a**, 1.2 equiv.) in 3 mL of DCE, followed by addition of [Cp*RhCl2]2catalyst (5 mol%), AgSbF6(30 mol%) and Cu(OAc)2.H2O (0.5 equiv.) at room temperature. The resulting mixture was stirred at 120 °C for 8–10 h and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (MeOH/Chloroform) to afford the pure product **3a**.

Conflicts of interest

The authors declare that no conflict of interest.

Data availability

CCDC 2480463 (**3d**), 2548013 (**3h**), and 2548012 (**3t**) contain the supplementary crystallographic data for this paper.[15a,b,c]

Data is available in the supplementary information (SI) file along with this article. Supplementary information: copies of ^{1}H

&^{13}C NMR spectra of products are provided in the supplementary information. See DOI: https://doi.org/10.1039/d6ra01670g.

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