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Synthesis of 2-Pyridones and Iminoesters via Rh(III)-Catalyzed Oxidative Coupling between Acrylamides and Alkynes

Yan Su, Miao Zhao, Keli Han, Guoyong Song,* and Xingwei Li*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, P. R. China 116023

xwli@dicp.ac.cn; songgy129@gmail.com

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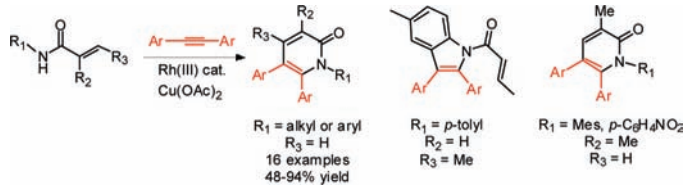
ABSTRACT



Catalytic oxidative coupling between acrylamides and alkynes was achieved using 0.5 mol % loading of $[RhCp^*Cl_2]_2$ with $Cu(OAc)_2$ as an oxidant. 2-Pyridones, iminoesters, and substituted indoles could be obtained as a result of the electronic and steric effects of the substituents in the acrylamides.

Pyridones are a valuable building block in natural product synthesis,[1] and they represent one of the most important classes of heterocycles that are known to exhibit a wide range of biological activities.[2] Consequently, various methods have been developed, and the construction of substituted 2-pyridone rings is generally achieved using acyclic starting materials with a Michael addition being the key step.[3] However, they typically involve harsh conditions and can be incompatible with sensitive functional groups. Metal catalysis is one of the most straightforward methods for constructing pyridone rings.[4] For example, Padwa developed an important methodology of 2-pyridone synthesis starting from diazo compounds using Rh(II) catalysts.[5] A well-known strategy to construct 2-pyridone rings is based on a [2 + 2 + 2] cycloaddition between alkynes and isocyanates, and these reactions can be catalyzed by Rh(I),[6] Co(I),[7] and Ru(II)[8] complexes. Tanaka recently developed synthetic methods to access substituted 2-pyridones via intramolecular hydrovinylation of *N*-alkenyl alkynylamides using Au(I) or

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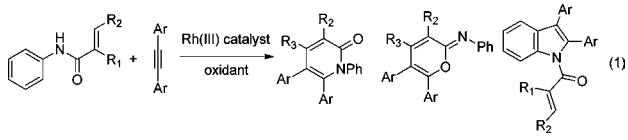
Pd(II) catalysts.[9] Very recently, Tsuji reported a related 2-quinolones synthesis via Ir(I)-catalyzed annulation reactions between carbamoyl chlorides and alkynes.[10]

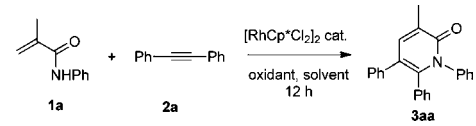
In the past decade, catalytic activation of C−H bonds has become an increasingly important strategy for the elaboration of readily available simple substrates in an atom-economic fashion.[11] Recently, the groups of Jones, Fagnou, Miura and Satoh, Glorius, Rovis, and Li have independently reported Rh(III)-catalyzed oxidative coupling between alkynes and arenes bearing heteroatom directing groups.[12−14] The C−H activation of arenes is directed to the *ortho* positions, and this method allows the synthesis of various heterocycles including indoles,[13j] pyrroles,[13c] isoquinolones,[13a,d,e,14] isoquinolines,[13h,m] and isocoumarins.[13f] Our[14] and other's[13a,d,e] recent studies indicated that isoquinolones can be efficiently synthesized from the oxidative coupling reactions between alkynes and benzamides using Rh(III) catalysts and Cu(II) or Ag(I) oxidants. Along the same lines, an efficient and selective synthesis of related 2-pyridones via oxidative insertion of alkynes into acrylamides would constitute a powerful method (eq 1).



We reasoned that when *N*-aryl acrylamides are used as substrates C−H activation can take place either in the aryl ring or at the β position of the olefin unit. Therefore, pyridones, iminoesters, and *N*-acyl indoles are the three possible products (eq 1), as a result of different chemoselectivity. We now report the synthesis of all these three categories of products in Rh(III)-catalyzed oxidative coupling, and the product formation is controlled by the steric and electronic effects of the substituent in the *N*-aryl ring and in the olefin unit.

We commenced our studies with the screening of reaction conditions for the coupling between *N*-phenyl methacrylamide and PhC≡CPh. Our previous studies indicated that oxidative coupling between PhC≡CPh and the structurally related *N*-phenyl benzamide can be successfully achieved using $[RhCp^*Cl_2]_2$ as a catalyst and Ag_2CO_3 as an oxidant.[14] Indeed, 2-pyridone **3aa** was isolated in 68% yield when this combination was used in MeCN at 110 °C (entry 1, Table 1). The yield was significantly improved when acetone was used as a solvent even at a lower temperature (entry 3). However, a rather high loading (4 mol %) of $[RhCp^*Cl_2]_2$ is necessary for a full conversion when Ag_2CO_3 was used. Moving to $Cu(OAc)_2$ as an oxidant, we were delighted to find that **3aa** was isolated in 94% yield using only 0.5 mol % loading of the catalyst when the reaction was conducted in acetone (entry 4). Reactions performed using benchtop acetone without the extrusion of air afforded products in nearly indentical yields.

Table 1. Synthesis of Pyridone **3aa** under Different Conditions[a]



entry	cat. loading	oxidant	temp (°C)	solvent	yield
1	4 mol %	Ag_2CO_3	110	MeCN	68%
2	4 mol %	Ag_2CO_3	90	acetone	86%
3	4 mol %	Ag_2CO_3	100	acetone	92%
4	0.5 mol %	$Cu(OAc)_2$	100	acetone	94%

[a] Conditions: **1a** (5.0 mmol), diphenylacetylene (1.3 equiv), oxidant (1.5 equiv of Ag_2CO_3 or 2.2 equiv of $Cu(OAc)_2$), catalyst, solvent (3 mL), 12 h, isolated yield.

The coupling of various acrylamides with internal alkynes was examined under the optimized conditions (Scheme 1). Substrate **1a** reacted similarly with a symmetrically substituted diaryl alkyne to give **3ab** in high yield. A thiophenyl-substituted alkyne can also be used but with lower reactivity, and **3ac** was isolated in 53% yield. Surprisingly, dialkyl-substituted alkynes such as 4-octyne only gave complicated reactions with unidentifiable products. In contrast, mixed alkyl- and aryl-substituted unsymmetrical alkynes are suitable coupling partners. Thus PhC≡CMe readily participated in this reaction, and products **3jd** and **3jd′** were isolated as a mixture of regioisomers (7:1 ratio) in excellent yield.[15] The selectivity was slightly decreased when PhC≡C^{n}Pr was employed to give **3ke** and **3ke′** in a 5:1 ratio, where the

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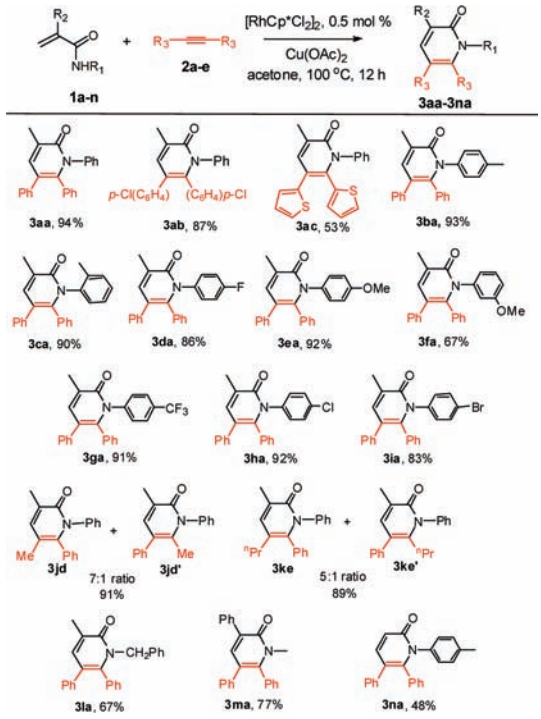
(15) The regiochemistry of the major isomer **3jd** was confirmed by the correlation between the pyridine ring C−*H* and the two C*H*$_3$ groups in NOESY spectroscopy (see Supporting Information).

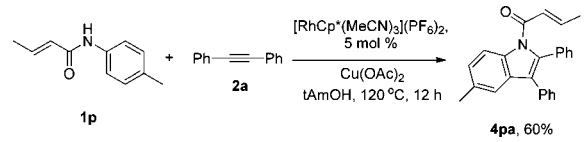
Scheme 1. Oxidative Coupling of *N*-Substituted Acrylamides and Internal Alkynes[a]



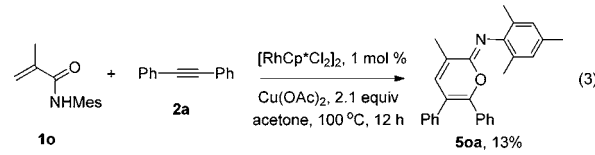
[a] Reaction conditions: acrylamide, alkyne (1.5 equiv), 2.2 equiv of $Cu(OAc)_2$, 0.5 mol % of catalyst, acetone, 100 °C, 12 h, isolated yield.

decreased selectivity is plausibly ascribed to the increased steric bulk of the ^{n}Pr group. However, essentially no coupling occurred when PhC≡CSiMe$_3$ was used under the same conditions. The scope of the acrylamide was further defined using PhC≡CPh as the coupling partner. Methacrylamides bearing a wide variety of *N*-aryl groups can be applied. Both electron-donating (**3ba**, **3ca**, **3ea**) and -withdrawing (**3da**, **3ga**, **3ha**, **3ia**) *N*-aryl groups in methacrylamides can be tolerated, and the 2-pyridone products were isolated in excellent yield. These products were fully characterized; the carbonyl group resonates within a narrow range of δ 162−163 in the ^{13}C NMR spectra, and it offers diagnostic handles for structure elucidation. The isolation of **3ca** in high yield indicates that the steric bulk of the *N*-*o*-tolyl group can be tolerated. Furthermore, the N-substituent is not limited to an aryl group, and *N*-benzyl-substituted acrylamide (**1l**) reacted similarly to give pyridone **3la** in good yield.

The effects of the substituent in the olefin unit of the acrylamide were further explored. The substituent at the α-position seems to have a big effect. *N*-Methyl 2-phenylacrylamide reacted similarly with PhC≡CPh to give **3ma** in 77% yield (Scheme 1). However, when acrylamide with an unsubstituted olefin unit (**1n**) is used, a sluggish reaction was observed and **3na** was isolated in only 48% yield. The substituent at the β-position has an even more pronounced effect. When a phenyl group is introduced into the β-position of acrylamide (*trans*-cinnamide), no coupling product could be detected, and the starting materials were fully recovered. In contrast, when *trans*-crotylamide **1p** was subjected to the standard reaction conditions, incomplete conversion was observed, and the major product (**4pa**) was identified as an indole on the basis of its characteristic ^{1}H and ^{13}C NMR data (eq 2). No full conversion could be reached even though the reaction was conducted at a high (4 mol %) loading of $[RhCp^*Cl_2]_2$ in acetone or MeCN. Eventually a full conversion could be reached when $[RhCp^*(MeCN)_3](PF_6)_2$ (5 mol %) was used as a catalyst in ^{t}AmOH at 120 °C, and **4pa** was isolated as the major product in 60% yield. Synthesis of indoles or pyrroles via Rh(III)-catalyzed oxidative coupling has been reported.[13c,j]



During our exploration of the scope of the acrylamide that bears a bulky *N*-aryl group, substrate **1o** with an *N*-mesityl substituent has been applied. As expected, this reaction was slow with low conversion, and only one product was detected and isolated in 13% yield. Interestingly, this product was identified as an iminoester **5oa** (eq 3). In the ^{13}C NMR spectrum, the *C*═N resonates at δ 151.9, to the higher field of the carbonyl signals in pyridones **3aa**−**3na**. In addition, the iminoester ring proton (*para* to the oxygen) resonates as a quartet (δ 6.78, $^4J_{H-H}$ = 1.5 Hz) in the ^{1}H NMR spectrum. The highly bulky N-substituent renders any C−N bond formation unfavorable, and consequently C−O bond formation occurred, where apparent NH to OH tautomerization of the acrylamide is involved. This interesting strategy to construct heterocycles that involves tautomerization of amides and anilines has been increasingly explored in both intramolecular and cross-coupling reactions in palladium or copper catalysis.[16]



In addition to the formation of iminoester through steric control of the *N*-aryl group, the selectivity of pyridone versus iminoester formation could also be tuned by the electronic effects of the *N*-aryl group. We reasoned that introduction of an electron-withdrawing group into the *N*-aryl group of acrylamides should enhance the acidity of the NH proton, and consequently, NH to OH tautomerization of the amide functionality is expected to proceed at a lower kinetic barrier. As a result, the likeliood of oxidative C−O bond formation that yields an iminoester is enhanced. Indeed, the reaction of **1q** and PhC≡CPh under the standard conditions afforded both 2-pyridone **3qa** and iminoester **5qa** in 52% and 21%

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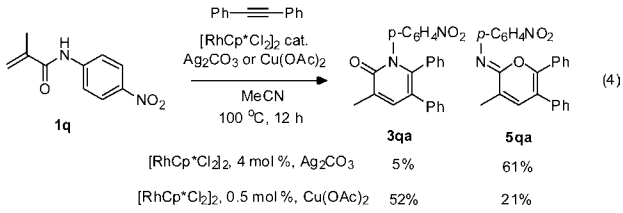
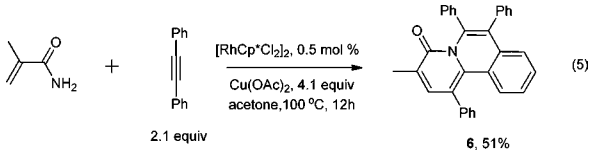
isolated yield, respectively (eq 4). The selectivity of iminoester versus pyridone can be further improved when a combination of $[RhCp^*Cl_2]_2$ (4 mol %) and Ag_2CO_3 (1.5 equiv) was used, and iminoester **5qa** was isolated as the major product in 61% yield.



(4)

In addition to the coupling of alkynes with secondary acrylamides, the coupling of primary methacylamide and PhC≡CPh proceeded smoothly under the same conditions. Interestingly, tricyclic product **6** was obtained in 51% yield (eq 5), which corresponds to the oxidative incorporation of two alkyne units, and thus 4 equiv of $Cu(OAc)_2$ was provided. Formation of **6** is proposed to involve the formation of a 2-pyridone intermediate that bears an NH group, followed by oxidative insertion of the second equivalent of PhC≡CPh. A similar type of reaction has been reported by us and others.[13e,14]



(5)

In conclusion, we have successfully developed Rh(III)-catalyzed oxidative coupling between acrylamide and alkynes. In most cases, the coupling reaction proceeded smoothly with 0.5 mol % loading of $[RhCp^*Cl_2]_2$ in common solvents. Products in three categories, namely, 2-pyridone, iminoesters, and a substituted indole, have been obtained as a result of the electronic and steric effects of the substituents in the *N*-aryl groups and in the olefin unit. In most cases 2-pyridones were obtained as the oxidative coupling product. The formation of iminoesters was favored for a substrate bearing a bulky *N*-aryl group. Both 2-pyridone and iminoester products were obtained for an acrylamide bearing a nitro-functionalized *N*-aryl group. The β-substituents of the acrylamides showed pronounced effects. No coupling reaction was detected for an *N*-aryl *trans*-cinnamide, while the coupling of *N*-aryl *trans*-crotylamide (**1p**) afforded an indole product, where C−H activation occurred at the *ortho* position in the *N*-aryl ring, instead of at the β vinylic position. An amount of 2 equiv of alkynes was oxidatively incorporated to give a tricyclic product when simple methacrylamide was used. The versatility and the wide scope of this coupling reaction should find applications in the synthesis of complex organic molecules such as natural products.

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Supporting Information Available: Detailed synthetic procedures, characterization data, and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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