ORGANOMETALLICS

A Nickel-Based, Tandem Catalytic Approach to Isoindolinones from Imines, Aryl Iodides, and CO

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S Supporting Information

ABSTRACT: We describe herein a modular nickel-catalyzed synthesis of isoindolinones from imines, aryl iodides, and CO. This reaction is catalyzed by Ni(1,5-cyclooctadiene)₂ in concert with chloride salts and postulated to proceed via a tandem nickel-catalyzed carbonylation to form *N*-acyl iminium chloride salts,



followed by a spontaneous nickel-catalyzed cyclization. A range of aryl iodides and imines have been found to be viable substrates in this reaction, providing a modular route to generate substituted isoindolinones with high atom economy.

ransition-metal-catalyzed carbonylation reactions have seen growing use in synthetic chemistry.¹ In addition to simple esters, amides, ketones, and related carboxylic acid derivatives, there has been significant recent application of carbonylations to the assembly of more elaborate carbocyclic and heterocyclic products. Examples of these can range from carbonylative cyclizations² to ring expansions,³ Pauson-Khand type reactions,⁴ and others.⁵ One important class of heterocyclic products toward which carbonylations have been applied are isoindolinones. These heterocycles represent the core unit in a variety of natural products and other pharmaceutically relevant compounds, including antitumor, anesthetic, anti-inflammatory, and antidiabetic agents and others.⁶ A number of approaches have been reported for the carbonylative synthesis of isoindolinones with ortho-functionalized aryl halides, including those with o-imino- and o-vinylsubstituted arenes (Scheme 1a).⁷ However, similar to other approaches to isoindolinones, these often require the initial assembly of the appropriate aryl-tethered precursors for cyclization.

In considering the structure of isoindolinones, we postulated that a more modular approach to these products might be via the carbonylative coupling of aryl halides and imines. Watson and co-workers demonstrated that nickel catalysts can mediate the cyclization of synthetic N-benzoylaminals to isoindolinones (Scheme 1b).⁸ An alternative would be to generate the N-acyl iminium salt intermediates via carbonylation. We have recently reported that palladium catalysts can be employed to generate acid chlorides from aryl iodides, which are reactive with even weak nucleophiles such as imines.⁹ However, these palladium systems are potent carbonylation catalysts and mediate a second, spontaneous carbonylation of the N-acyl iminium salt to form mesoionic 1,3-oxazolium-5-oxides 1 (i.e., Münchnones, Scheme 1c).¹⁰ Relative to palladium, nickel catalysts often show diminished reactivity in carbonylations.¹¹ This suggests that nickel catalysts may be better suited to mediate a tandem carbonylation/C-H functionalization reaction (Scheme 1d),

Scheme 1. Catalytic Synthesis to Isoindolinones

a) Carbonylative Approaches to Isoindolinone Synthesis



b) Nickel-Catalyzed Cyclization Route to Isoindolinones



c) Palladium Catalyzed Synthesis of Münchnones



rather than the double-carbonylative formation of 1. We describe herein the successful realization of this goal and an efficient, tandem catalytic approach to isoindolinones.

Our initial studies of this transformation examined the carbonylative coupling of 4-iodotoluene and imine (Table 1). The use of the catalyst nickel(0) bis(cyclooctadiene) (Ni- $(COD)_2$) led to only trace amounts of isoindolinone **2a** and

Received: March 15, 2015

Table 1. C	atalyst Des	ign for C	Carbonyl	ative 1	lsoind	oli	none
Synthesis ^{<i>a</i>}							

+	$CO + N^{-Bn} - \frac{10 \text{ mo}}{10 \text{ mo}}$	$\frac{DD}{DD}^{2}$ $\frac{DD}{DD}^{2}$ $\frac{DD}{D}^{2}$ $\frac{DD}{D}^{2}$ $\frac{DD}{D}^{2}$	O N-Bn p-	o tolyl N Bn
	120°C	, 24 h	2a p-tolyl	3a
entry	L	additive	3a (%)	2a (%)
1	-	-	28	2
2	PPh ₃	-	-	-
3	P'Bu ₃	-	-	-
4	P(o-tolyl) ₃	-	-	3
5	-	Bu ₄ NCl	17	79
6	-	CsC1	16	5
7	-	Ph ₄ PCl	28	69
8	PCy ₃	Bu ₄ NCl	0	0
9	DPPE	Bu ₄ NCl	0	0
10	DPPF	Bu ₄ NCl	5	0
11	PPh ₃	Bu ₄ NCl	3	7
12	P'Bu ₃	Bu ₄ NCl	5	10
13	P(o-tolyl) ₃	Bu ₄ NCl	13	60
14	tBu ₂ P	Bu ₄ NCl	4	11
15	XantPhos	Bu ₄ NCl	23	48
16 ^b	-	Bu ₄ NCl	17	79 (78)°

^{*a*}Conditions unless specified otherwise: *p*-tolyl-I (44 mg, 0.20 mmol), imine (21 mg, 0.10 mmol), $Et^{i}Pr_{2}N$ (16 mg, 0.12 mmol), additive (0.10 mmol), $Ni(COD)_{2}$ (3 mg, 0.01 mmol), CO (4 atm), CD₃CN (0.7 mL), 120 °C for 24 h. NMR yields. ^{*b*}CO (1 atm). ^{*c*}Isolated yield given in parentheses.

instead generated amide **3a** in low yield. The addition of various ligands to this reaction also did not afford significant amounts of **2a**. We have previously noted in our studies of palladium-catalyzed carbonylation that chloride sources can facilitate coupling with weakly nucleophilic substrates by allowing the in situ generation of acid chlorides.^{9a} As was hoped, the addition of tetrabutylammonium chloride to the catalytic reaction with simple Ni(COD)₂ catalyst resulted in the high-yield formation of isoindolinone **2a** as the major reaction product. Most added ligands retard the formation of **2a**, with only the bulky and weak donor P(*o*-tolyl)₃ leading to yields approaching that of simple Ni(COD)₂. These results suggest that the active catalyst for this system is unligated nickel(0).¹² Decreasing the reaction pressure to 1 atm does not appear to influence the product yield (entry 16).

With the optimized reaction conditions in hand, we explored the substrate diversity of the aryl halide reaction partner (Table 2). Both electron-rich (2e) and electron-deficient (2b,c,f-h)aryl iodides can participate in this reaction and lead to products in good yields. In addition to simple para-substituted aryl iodides, symmetrically disubstituted aryl iodides are viable substrates in this chemistry (2i). On the other hand, orthosubstituted aryl iodides such as 2-iodotoluene and 2-iodoanisole failed to produce any of the corresponding isoindolinone products under these conditions. Simple meta-substituted aryl iodides lead to a mixture of isomeric products (2i). Table 2. Aryl Iodide Diversity in Isoindolinone Synthesis^a



^aConditions: Ar-I (1.00 mmol), imine (105 mg, 0.50 mmol), $Et^{i}Pr_{2}N$ (77 mg, 0.60 mmol), $Bu_{4}NCl$ (134 mg, 0.50 mmol), $Ni(COD)_{2}$ (14 mg, 0.05 mmol), CO (1 atm), MeCN (2 mL), 120 °C for 24 h. Isolated yields.

The compatibility of this reaction with imines was also examined (Table 3). A number of *N*-alkyl (2k,l)- and *N*-benzyl-

Table 3. Imine Diversity in Isoindolinone Synthesis^a



^aConditions: *p*-tolyl-I (218 mg, 1.00 mmol), imine (0.50 mmol), $Et^{i}Pr_{2}N$ (77 mg, 0.60 mmol), $Bu_{4}NCl$ (134 mg, 1.0 mmol), $Ni(COD)_{2}$ (14 mg, 0.05 mmol), CO (1 atm), MeCN (2 mL), 120 °C for 24 h. Isolated yields. ^bReaction performed on a 4 mmol scale.

substituted (2n,o) imines can undergo carbonylative cyclization to form isoindolinones. However, *N*-aryl-substituted imines yield only starting material under these conditions, presumably due to their decreased nucleophilicity for *N*-acyl iminium salt formation (vide infra). The imine carbon can tolerate a range of aromatic units, including those with electron-withdrawing (2o) and electron-donating (2m,n) arenes, or heteroaryl units (2q). As shown with isoindolinone 2p, ^tBu-substituted imines can also be employed in this chemistry. This reaction can be applied to a gram-scale synthesis of isoindolinones (e.g., 2o).

While the mechanism of this transformation is still under investigation, on the basis of preliminary studies we postulate a dual role of the nickel catalyst in this reaction (Scheme 2a).

Scheme 2. Mechanism of Isoindolinone Synthesis



b) Control experiments for isoindolinone formation



The required use of chloride in catalysis (Table 1) is similar to that observed with palladium systems that lead to acid chloride synthesis.⁹ Thus, although it is possible that an in situ generated nickel aroyl complex (II) can react directly with the imine, the critical role of chloride in this chemistry is more consistent with the nickel-catalyzed formation of acid chloride. As shown in Scheme 2b, acid chloride can rapidly react with an imine, forming an *N*-acyl iminium chloride. Unlike the case for traditional Pictet–Spengler reactions, **4a** does not undergo cyclization, even upon heating at 120 °C, and instead slowly decomposes to yield amide **3a**. However, the addition of Ni(COD)₂ to **4a** leads to the formation of isoindolinone in a yield similar to that noted in catalysis (Scheme 2b). As noted by Watson, the nickel catalyst could play several roles in this cyclization, including that of a Lewis acid (e.g., III) or a more

direct role in facilitating C–H bond functionalization.⁸ While we at present cannot distinguish between these mechanisms, the conversion of N-acyl iminium chloride to the more electrophilic iodide or triflate salt also leads to cyclization, consistent with a Lewis acidic role of the nickel catalyst.

In conclusion, we have developed a nickel-catalyzed process for the synthesis of highly substituted isoindolinones from aryl iodides, imines, and carbon monoxide. This reaction is believed to proceed via the in situ generation of an *N*-acyl iminium chloride, which can further undergo a nickel-mediated annulation. Overall, this process provides a modular synthesis of isoindolinones from available substrates and is directly amenable to structural diversification.

ASSOCIATED CONTENT

S Supporting Information

Text and figures giving experimental procedures, characterization data, and NMR spectra for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00215.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This publication was made possible by funding through an NPRP award (5-156-1-037) from the Qatar National Research Fund (member of Qatar Foundation). The statements made herein are solely the responsibility of the authors.

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(12) *Caution*! Ni(CO)₄ is a potential product generated in nickelbased carbonylations and is extremely toxic and volatile. Precautions must be taken to avoid all contact with the reaction mixture prior to quenching. All manipulations of the catalysis solutions after CO introduction were therefore rigorously performed in sealed vessels and under an isolated atmosphere with no contact to air or person. To remove Ni(CO)₄, all volatiles from the reaction were immediately transferred in vacuo on a Schlenk line into a liquid N₂ cooled solvent trap charged with excess PPh₃ and then exposed to water, as noted: Dorta, R.; Stevens, E. D.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. J. Am. Chem. Soc. **2005**, 127, 2485–2495.