Synthesis of Carbonyl-Containing Oxindoles via Ni-Catalyzed Reductive Aryl-Acylation and Aryl-Esterification of Alkenes

Zhengtian Ding and Wangqing Kong *

Abstract: Carbonyl-containing oxindoles are ubiquitous core structures present in many biologically active natural products and pharmaceutical molecules. Nickel-catalyzed reductive aryl-acylation of alkenes using aryl anhydrides or alkanoyl chlorides as acyl sources is developed, providing 3,3-disubstituted oxindoles bearing ketone functionality at the 3-position. Moreover, nickel-catalyzed reductive aryl-esterification of alkenes using chloroformate as ester sources is further developed, affording 3,3-disubstituted oxindoles bearing ester functionality at the 3-position. This strategy has the advantages of good yields and high functional group compatibility.

Keywords: nickel catalysis; reductive coupling reaction; aryl-acylation; aryl-esterification; oxindoles

1. Introduction

Carbonyl-containing oxindoles are ubiquitous core structures present in many natural products and pharmaceutical molecules, such as Convolutamydine A, Coixpirolactam A, AG-041R, Surugatoxin, and JMX0254, which show a wide range of biological activities (Figure 1) [1–5]. In addition, this framework is a very attractive synthon for the synthesis of other structurally complex indole alkaloids [6–12]. Consequently, it is highly desirable to develop efficient methods to access carbonyl-containing oxindoles from readily available chemical materials.

Figure 1. Carbonyl-containing oxindoles in natural products and pharmaceuticals.

On the other hand, nickel-catalyzed reductive cross-coupling reactions pioneered by Weix [13] and Gong [14] et al., have received considerable attention over the past decade as they represent a powerful tool for the construction of diverse C-C bonds [15–30].

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Compared with the classical redox-neutral protocol, this strategy allows reactions to proceed under mild conditions with high functional group tolerance, without the need for pre-preparation of sensitive organometallics. Furthermore, Ni-catalyzed reductive cyclization/cross-coupling reactions have also been developed, in which two C–C bonds are forged in one pot and the C(sp\(^3\)) electrophilic fragment is generated in situ via intramolecular addition of a C(sp\(^2\)) electrophile to an alkene. This method shows attractive application in the rapid construction of diverse functionalized heterocycles with sterically congested quaternary carbon stereocenters [31–47]. In 2019, our group reported a Ni-catalyzed reductive aryl-acylation of alkenes for the synthesis of carbonyl-containing oxindoles by using isobutyl chloroformate as carbonyl source (Scheme 1A) [49]. However, this strategy is limited to the synthesis of dialkyl ketones. Subsequently, Wang et al., reported a nickel-catalyzed reductive aryl-acylation of alkenes by using ortho-pyridinyl esters as the acyl sources (Scheme 1B) [50]. However, this method is restricted to the synthesis of aryl-alkyl ketones, and the use of acid anhydride as the acyl source failed to obtain the product. In order to overcome the shortcomings of the above methods, we hope to develop a general method to synthesize various carbonyl-containing oxindoles. Herein, we report Ni-catalyzed reductive aryl-acylation and aryl-esterification of alkenes, providing 3,3-disubstituted oxindoles bearing ketone and ester functionalities at the 3-position (Scheme 1C).

Scheme 1. The state of the art of Ni-catalyzed reductive aryl-acylation of alkenes. (A) Ni-catalyzed reductive aryl-acylation of alkenes [49]. (B) Ni-catalyzed reductive aryl-acylation of alkenes [50]. (C) Ni-catalyzed reductive aryl-acylation and aryl-esterification of alkenes (This work).
2. Results

Our initial studies commenced with the cyclization/cross-coupling reaction of N-(2-bromophenyl)-N-methylmethacrylamide (1a) and benzoic anhydride (2a) utilizing NiBr₂ as a catalyst, Mn as a reductant, and K₃PO₄ as a base in DMA at 80 °C. We expect that the reaction efficiency will be strongly ligand-dependent. As Table 1 shows, this turned out to be the case. After screening a variety of ligands (entries 1–8), we found that a rigid phenanthroline framework with electron-deficient carbonyl groups at the 4-positions (L₈) was particularly suitable for our purpose, providing the desired ketone 3a in 57% yield along with the reductive Heck product 4a in 21% yield (entry 8). Different solvents were next investigated (entries 9–11), and MeCN was identified as the most effective solvent, affording 3a in 67% isolated yield, while the reductive Heck product 4a was reduced to 2% (Table 1, entry 10). The use of Zn₀ instead of Mn₀ resulted in little change in the yield of 3a, but more side product 4a was observed (compare entry 10 with 12). The reaction can be carried out at 60 °C without affecting the outcome of the reaction (entry 13). Finally, the best result was achieved using TBAB as an additive, providing 3a in 85% yield with excellent chemoselectivity (entry 14). The reaction was carried out using 5 mol% nickel catalyst with only a slight decrease in product yield (entry 15). Finally, a series of control experiments confirmed that product was not formed in the absence of Ni₀ catalyst and Mn₀ (entries 16–17).

Table 1. Optimization of the reaction conditions.

| Entry | Ligand | Solvent | Reductant | Yield of 3a (%) | Yield of 4a (%) |
|-------|--------|---------|-----------|----------------|---------------|
| 1     | L₁     | DMA     | Mn        | <1             | 6             |
| 2     | L₂     | DMA     | Mn        | <1             | <1            |
| 3     | L₃     | DMA     | Mn        | 5              | 35            |
| 4     | L₄     | DMA     | Mn        | 10             | <1            |
| 5     | L₅     | DMA     | Mn        | 12             | <1            |
| 6     | L₆     | DMA     | Mn        | <1             | <1            |
| 7     | L₇     | DMA     | Mn        | <1             | <1            |
| 8     | L₈     | DMA     | Mn        | 57             | 21            |
| 9     | L₈     | DMF     | Mn        | 52             | 11            |
| 10    | L₈     | MeCN    | Mn        | 67             | 2             |
| 11    | L₈     | THF     | Mn        | 48             | <1            |
| 12    | L₈     | MeCN    | Zn        | 65             | 24            |
| 13    | L₈     | MeCN    | Mn        | 67             | <1            |
| 14    | L₈     | MeCN    | Mn        | 85             | <1            |
| 15    | L₈     | MeCN    | Mn        | 85             | <1            |
| 16    | L₈     | MeCN    | Mn        | 0              | 0             |
| 17    | L₈     | MeCN    | Mn        | 0              | 0             |

a Reaction conditions: 1a (0.10 mmol), 2a (0.20 mmol), NiBr₂ (0.01 mmol), ligand (0.02 mmol), reductant (0.30 mmol), and K₃PO₄ (0.20 mmol) were carried out in solvent (2 mL) at 80 °C for 36 h. b Isolated yields. c 60 °C. d TBAB (0.05 mmol) was used. * NiBr₂ (0.005 mmol), L₈ (0.01 mmol) was used. † Without NiBr₂.
With the optimal conditions in hand, we turned our attention to validating the generality of the arylation protocol for the preparation of 3,3-disubstituted oxindoles with ketone functionalities at the 3-position (Scheme 2). The substrate scope with respect to alkene-tethered aryl bromides 1 was first investigated. Different substitution patterns with electron-donating or electron-withdrawing groups on the aniline part were well tolerated, furnishing the corresponding oxindoles 3a–3l in 51–90% yields. N-benzyl protected substrate was also accommodated, providing 3j in 85% yield. The benzyl group can be easily removed to allow access to the N–H oxindole. The influence of the Cα substituents (R3) of the acrylamide double bond on the reaction outcome was examined. Methoxymethyl, benzyl, n-hexyl, and isopropyl all proceeded smoothly to give the corresponding oxindoles 3k–3n in 60–77% yields. Remarkably, the pyridine backbone was also perfectly accommodated, furnishing aza-oxindole 3o in 61% yield. In addition to aryl bromides, aryl triflates are also suitable electrophiles, as shown in the formation of 3p and 3q. We further investigated the scope of acid anhydrides. Both electron-deficient and electron-rich aryl anhydrides are well compatible with this reaction (3r–3t). Finally, phenylacetyl chloride was also found to be a suitable electrophile, providing the dialkyl ketone 3u in 61% yield after slightly modifying the reaction conditions.

Scheme 2. Ni-catalyzed reductive arylation of alkenes. a Aryl triflates instead of aryl bromides. b 80 °C. c Reaction conditions: N-(2-iodophenyl)-N-methylmethacrylamide (0.10 mmol), 2-phenylacetyl chloride (0.30 mmol), NiBr2 (0.01 mmol), L8 (0.02 mmol), Mn (0.30 mmol), MgCl2 (1.5 equiv), and K3PO4 (0.20 mmol) were carried out in MeCN (2 mL) at 40 °C for 36 h.

Encouraged by these results, we further hoped to achieve reductive aryl-esterification of alkenes. However, using the arylation reaction conditions in Scheme 3, the corresponding ester product 6a could not be obtained. A judicious screening of all the reaction parameters (see Table S1 in Supporting Information) revealed that a combination of NiBr2 (10 mol%), 2,2′-bipyridine (20 mol%), Mn (3.0 equiv), and TBAB (0.5 equiv) in MeCN at
100 °C afforded 6a in 75% isolated yield. With this reliable set of conditions in hand, we set out to explore the preparative scope of our catalytic aryl-esterification reaction. The aromatic ring of the aniline moiety with both electron-donating groups (Me, OMe) as well as electron-withdrawing groups (F, CF$_3$) at the para-position was well tolerated to afford the corresponding oxindoles 6b–6e in good yields. The meta- and ortho-substituted anilides generally react well to deliver the corresponding product 6f–6j in good yields. Remarkably, pyridine backbone was also compatible to afford aza-oxindole 6k, which has received particular attention due to its prominence in natural product and drug discovery programs. The cyclizative cross-coupling reaction of N-benzyl acetanilide with aryl chloroformate 5a proceeded efficiently to provide 6l. The influence of the C$_\alpha$ substituents (R$_3$) of the acrylamide double bond on the reaction outcome was examined. Methoxymethyl, benzyl, n-hexyl, and isopropyl substituents were well compatible (6m–6p). Finally, the transformation is not limited to aryl chloroformates, and alkyl chloroformates can also react smoothly to obtain the corresponding alkyl esters (6q–6s).

Scheme 3. Ni-catalyzed reductive aryl-esterification of alkenes. a 0.4 mmol chloroformate was used.

3. Discussion

To gather direct evidence on the reaction intermediates involved in this transformation, we prepared σ-alkyl-Ni(II) complex 7 according to our previous report. The stoichiometric reaction of 7 with 5a affords 6a in 21% yield (Scheme 4). The control experiment without nickel catalyst did not consume aryl bromide 1a (Table 1, entry 16), indicating that the formation of aryl manganese species is unlikely. Taken together, we consider σ-alkyl-Ni(II)species 7 to be the key intermediate for this transformation.
4.2. General Procedure for the Synthesis of Esters

An oven-dried sealed tube equipped with a PTFE-coated stir bar was charged with NiBr₂ (10 mol%), 1,10-phenanthroline-5,6-dione (L8) (20 mol%), 1 (0.1 mmol, 1.0 equiv), manganese powder (3.0 equiv), TBAB (0.5 equiv), and K₃PO₄ (2.0 equiv). The sealed tube was evacuated and backfilled with argon (this process was repeated three times) and then MeCN (0.05 M) was added. This reaction mixture was stirred at room temperature for 15 min and then aryl anhydride 2 (2.0 equiv) was added. The reaction was heated at 60 °C for 36 h until the reaction was complete (monitored by TLC). The resulting mixture was evacuated and backfilled with argon (this process was repeated three times) and then MeCN (0.05 M) was added. This reaction mixture was stirred at room temperature for 15 min and then acid chloride 5a (2.0 equiv) was added. The reaction was heated at 100 °C for 36 h until the reaction was complete (monitored by TLC). The resulting mixture was purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:20~1:5. The corresponding products were obtained, which regenerates the catalytically active nickel(0) upon Mn reduction.

Scheme 5. Proposed reaction mechanism.

4. Materials and Methods

4.1. General Procedure for the Synthesis of Ketones

On the basis of the experimental observations and previous studies [31–50], a plausible reaction mechanism is proposed (Scheme 5). Oxidative addition of catalytically active nickel(0) A to aryl bromide 1 affords aryl-Ni(II) intermediate B, which undergoes intramolecular migratory insertion to give σ-alkyl-Ni(II) species C. Reduction of the intermediate C with Mn(0) affords σ-alkyl-Ni(I) intermediate D, which undergoes further oxidative addition to acid chloride 5 (or acid anhydride 2) to form σ-alkyl-Ni(III)-carbonyl species E. Reductive elimination of intermediate E provides the final product and nickel(I) F, which regenerates the catalytically active nickel(0) upon Mn reduction.

Scheme 4. Mechanistic study.
was purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:20–1:5 (v/v) to afford the corresponding products 3.

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An oven-dried sealed tube equipped with a PTFE-coated stir bar was charged with NiBr\(_2\) (10 mol%), bpy (L1) (20 mol%), acrylamide 1 (0.1 mmol, 1 equiv), manganese powder (3 equiv), and TBAB (0.5 equiv). The sealed tube was evacuated and backfilled with argon (this process was repeated three times) and then MeCN (0.025 M) was added. This reaction mixture was stirred at room temperature for 15 min and then acid chloride 5 (2–4 equiv) was added. Then, the reaction was heated at 100 °C for 36 h until the reaction was complete (monitored by TLC). The resulting mixture was purified by chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1:20–1:5 (v/v) to afford the corresponding products 6.

5. Conclusions

In summary, we have developed a nickel-catalyzed reductive arylacylation of alkenes using aryl anhydrides or alkanoyl chlorides as acyl sources, providing 3,3-disubstituted oxindoles bearing ketone functionality at the 3-position. Moreover, we further developed a nickel-catalyzed reductive arylesterification of alkenes using chloroformate as ester sources, affording 3,3-disubstituted oxindoles bearing ester functionality at the 3-position. This strategy has the advantages of good yields and high functional group compatibility. Future development of the asymmetric version is underway in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27185899/s1, Table S1: Optimization reaction conditions for the synthesis of esters, NMR data of known compounds matched those reported in the literature [51–56], \(^1\)H NMR, \(^13\)C NMR, and \(^19\)F NMR spectra of all reported products.

Author Contributions: Conceptualization, Z.D.; methodology, Z.D.; validation, Z.D. and W.K.; resources, Z.D.; data curation, Z.D.; writing-original draft preparation, Z.D.; writing-review and editing, W.K.; visualization, Z.D. and W.K.; supervision, W.K.; project administration, W.K.; funding acquisition, W.K. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

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