

Nickel-Catalyzed Formal Aminocarbonylation of Unactivated Alkyl lodides with Isocyanides

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 ABSTRACT: Herein, we disclose a Ni-catalyzed formal amino-carbonylation of primary and secondary unactivated aliphatic
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carbonylation of primary and secondary unactivated aliphatic iodides with isocyanides to afford alkyl amide, which proceeds via the selective monomigratory insertion of isocyanides with alkyl iodides, subsequent β -hydride elimination, and hydrolysis process. The reaction features wide functional group tolerance under mild

 $\begin{array}{cccc}
R' & & & & I \\
R & & & & & \\
R' & & & & & \\
R' & & & & \\
H_3O^+ & & & & \\
H_3O^+ & & & \\
\end{array}$ Unactivated alkyl iodides

conditions. Additionally, the selective, one-pot hydrolysis of reaction mixture under acid conditions allows for expedient synthesis of the corresponding alkyl carboxylic acid.

ransition-metal-catalyzed three-component coupling reactions represent one of the most frequently applied methods for introducing a carbonyl group in organic synthesis.¹ Among such various types of carbonylative transformations, palladium-catalyzed aminocarbonylation reactions in particular are synthetically useful for expedient access to amides.² Nevertheless, the user-friendly method mainly focuses on the formation of (hetero)aromatic amide derivatives because of the facile oxidative addition of aryl (pseudo)halide. Despite the prevalence of alkyl amide in numerous biologically active compounds, medicines, agrochemicals, and polymers,³ the reported Pd-catalyzed aminocarbonylation of unactivated alkyl halide still requires the use of high-pressure CO gas, high energy irradiation, or toxic organotin initiators via radical processes, as well as a multiple CO insertion pathway.⁴ More recently, several earth-abundant transition-metal-catalyzed aminocarbonylations of unactivated alkyl halides have provided a robust platform to form alkylated amide synthesis; however, elevated pressure of CO gas is still required for this successful transformation.⁵ Therefore, seeking an easily accessible and environmentally benign CO surrogate to realize this transformation still remains highly desirable.⁶

Isocyanides are broadly utilized as an easily accessible carbon monoxide synthon possessing both electronic and sterically tunable properties.⁷ Not surprisingly, the Pdcatalyzed aminocarbonylation of aryl halides with isocyanides has been extensively accomplished (Scheme 1a).⁸ In contrast, the carbonylation of alkyl electrophiles with isocyanides was less explored and mostly restricted to activating alkyl electrophiles. The Zhu and Yang groups realized Pd-catalyzed aminocarbonylation using the activated alkyl electrophiles including allyl acetates,^{9,10} α -haloketones,¹¹ and α -phosphate benzyl chlorides¹² to afford amide moieties, where the isocyanide served as both the carbonyl and amine source (Scheme 1a). To the best of our knowledge, the carbonylation of unactivated alkyl halide with isocyanide remains elusive,

Scheme 1. Overview of Aminocarbonylation with Isocyanide

(a) Previous work:

Palladium-catalyzed aminocarbonylation of aryl electrophile with isocyanide.



mainly due to the inherent properties of the relatively slow oxidative addition of alkyl halide with low-valent palladium catalyst and the susceptibility of undesired β -H elimination of alkyl palladium intermediate to generate a dehalogenated alkene side product. We have recently achieved a nickel-catalyzed highly regioselective allylic carbonyl Negishi reaction to access the α,β -unsaturated ketones with broad functional group tolerance under mild conditions.¹³ Leveraging nickel as

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a transition metal catalyst circumvents the overcarbonylation of isocyanide and unselective regioisomers based on the alkyl zinc nucleophiles encountered in palladium catalysis.¹⁴ Thereby, we reasoned nickel catalysis to be an ideal tool for unactivated alkyl halide aminocarbonylations with isocyanide to tackle the above-mentioned challenges.¹⁵ Implementing isocyanides in such Ni-catalyzed carbonylation reactions remains limited,^{13,16} mainly owing to the propensity of the imidoylnickel intermediate toward migratory insertion with additional isocyanide to form poly(iminomethylene)s which was broadly applied in polymer chemistry.¹⁷ Herein, we report the Ni-catalyzed formal aminocarbonylation of unactivated alkyl iodide with isocyanide with broad substrate scope under mild conditions, and the selective acidic in situ hydrolysis of the reaction mixture can provide an expedient way for alkyl carboxylic acid synthesis.

We initiated the aminocarbonylation using commercially available primary iodoheptane 1a as starting material and tertbutyl isocyanide as the carbonyl source. To our delight, the reaction proceeded extremely well with treatment of 10 mol % of Ni(COD), and 2.0 equiv of NaO^tBu at 50 °C in toluene, affording the desired amide 3a in quantitative yield (99% isolated yield). Nevertheless, the standard conditions were not suitable for the secondary tert-butyl 4-iodopiperidine-1carboxylate (1q), the amides product (3q) was obtained in trace amount (8%), and the major side product was tert-butyl 3,6-dihydropyridine-1(2H)-carboxylate (3q') in 42% yield, which was generated via the undesired β -hydride elimination pathway as previously mentioned (Table 1, entry 1). The investigation of ligand effect revealed that the incorporation of an electron-rich NHC ligand was crucial to promote the aminocarbonylation presumably due to the acceleration of the 1,1-migratory insertion rate of the alkyl nickel intermediate to isocyanide (Table 1, entries 2-3). By further reducing the

Table 1. Optimization of the Ni-Catalyzed Aminocarbonylation of 1q with t BuNC^{*a*}

Boc N	10 mo 20 mc 1.2 e	I% NI(COD)₂ I% IMes [:] HCI Boc N quiv ^f BuNC [юс_й_л
1	2.0 ed ^t BuOH 100	quiv NaO ^r Bu H/H ₂ O = 10/1) °C, 12 h	т ^и ви 9 3q	ل 3q'
Entry	Ligand	Solvent	3q [%] ^b	3q' [%] ^b
1 ^c	_	toluene	8	42
2 ^{<i>c</i>}	SIPr ·HCl	toluene	27	23
3 ^c	IMes·HCl	toluene	30	26
4	IMes·HCl	toluene	51	17
5 ^{<i>c</i>,<i>d</i>}	IMes·HCl	toluene	4	67
6	IMes·HCl	dioxane	0	47
7	IMes·HCl	^t BuOH	59	31
8 ^e	IMes·HCl	^t BuOH	69	10
9	IMes·HCl	${}^{t}BuOH/H_{2}O = 10/1$	92 (92) ^f	5
10	IMes·HCl	$MeOH/H_2O = 10/1$	22	75
11	IMes·HCl	${}^{i}PrOH/H_{2}O = 10/1$	27	12

^{*a*}Reaction conditions: **1q** (0.1 mmol), *tert*-butyl isocyanide (0.12 mmol), Ni(COD)₂ (0.01 mmol), IMes·HCl (0.02 mmol), NaO^{*t*}Bu (0.2 mmol), ^{*t*}BuOH (1.0 mL), H₂O (0.1 mL) at 100 °C, 12 h. Then 1 M HCl (1.0 mL), rt, 5 min. ^{*b*}Corrected GC yield with dodecane as an internal standard. ^{*c*}1.5 equiv *tert*-butyl isocyanide. ^{*d*}*tert*-Butyl 4-bromopiperidine-1-carboxylate was used as the starting material. ^{*e*}2.0 equiv of H₂O were added. ^{*f*}Isolated yield.

amount of tert-butyl isocyanide, a higher yield of desired amide 3q (51%) was provided (Table 1, entry 4). When tert-butyl 4bromopiperidine-1-carboxylate was selected as the alkyl electrophile component, the undesired β -H elimination became the prominent pathway; only 4% of desired product 3q was observed (Table 1, entry 5). It was found that the sterically bulky ^tBuOH was a superior solvent (Table 1, entries 6-7). To our delight, addition of 2.0 equiv of water significantly reduced the byproduct 3q' (Table 1, entry 8). The optimized ratio of ^tBuOH and water was 10:1 (v/v), yielding 3q in 92% isolated yield, while only 5% alkenes could be observed in the GC (Table 1, entry 9). It is possible that the addition of water may accelerate the rate of migratory insertion of isocyanide, which is driven by the hydrolysis of ketenimine intermediate in situ. Other common alcoholic solvents (MeOH, ⁱPrOH) were detrimental (Table 1, entries 10-11).

With the optimized conditions in hand, we turned our attention to examine the substrate scope of the nickel-catalyzed aminocarbonylation of unactivated alkyl iodides with isocyanides (Scheme 2). Primary and secondary alkyl iodides bearing different functional groups offered the amides in moderate to excellent yields. Alkenes (1c, 1d) and an alkyne (1e) were well tolerated, providing the respective amides in good yields. It is worth noting that no cyclized products were detected. When the 6-bromohex-1-ene was utilized as the starting material, the isolated yield of amide 3d was obtained in 70% isolated yield, which revealed that the primary alkyl bromide was also a potentially available substrate for this Nicatalyzed formal aminocarbonylation protocol. A substrate with silvl ether (1f) could be perfectly accommodated to afford 3f in 98% isolated yield. Intriguingly, free aliphatic alcohol (1g) gave the desired product 3g under this basic condition in moderate yield. In addition, substrates containing Bpin functionality (1h) could also be tolerated under standard condition, which could be further converted to other functionalities via the diverse borane chemistry. The reactive aromatic bromide and iodide were unreactive to provide the desired 3i and 3j in 84% and 81% isolated yield, respectively, which clearly demonstrated the broad functional tolerance in this nickel chemistry. As shown for product 3l and 3m, the conditions permitted the coupling of other sterically hindered isocyanides Subsequently, derivatives of biologically active natural products were all suitable under the standard conditions to generate 3k, 3n-3p in 47% to 99% yield, demonstrating the potential utility in complex molecular synthesis.

We next applied a catalytic combination comprised of 10 mol % Ni(COD)₂ and 20 mol % IMes·HCl to the crosscoupling of the secondary alkyl iodides with alkyl isocyanides (Scheme 2). Piperidines (1q, 1r, 1s) with different protecting groups (such as Boc, Ts, and Cbz) which are widely applied in medicinally vital structures could also be tolerated well in this reaction. Other alkyl iodides containing heterocycles could also be employed such as tetrahydropyran (1u) and N-Boc acetidine (1v). This protocol allowed acyclic secondary alkyl iodide 1w to convert into amide 3w in 78% yield. A diverse array of isocyanides proceeded in the aminocarbonylation vielding the corresponding tertiary amides 3x-3aa in 53% to 92% yields. Currently, the substrate scope of isocyanides is restricted to the tertiary isocyanides. Unfortunately, no desired aminocarbonylative amide products (3ab-3ad) were obtained when the primary 1-isocyanododecane, secondary cyclohexyl iscaynide, and phenyl isocyanide were employed as a C-1



Scheme 2. Scope of Ni-Catalyzed Aminocarbonylation of Alkyl Iodides with Isocyanides

^{*a*}Primary alkyl iodide 1 (1.0 equiv), 2 (1.5 equiv), Ni(COD)₂ (10 mol %), NaO^tBu (2.0 equiv), toluene (0.1 M), 50 °C, 12 h. Then 1 M HCl, rt, 5 min. ^{*b*}Secondary alkyl iodide 1 (1.0 equiv), 2 (1.2 equiv), Ni(COD)₂ (10 mol %), IMes·HCl (20 mol %), NaO^tBu (2.0 equiv), ^{*b*}BuOH/H₂O = 10/ 1 (v/v, 0.1 M), 100 °C, 12 h. Then 1 M HCl, rt, 5 min. ^{*c*}6-Bromohex-1-ene was used as the starting material.

component. When the tertiary (3-iodo-3-methylbutyl)benzene was employed as the starting material, the reaction failed to afford the desired amide product **3ae**, which demonstrated the necessity of β -hydride in this protocol.

The validity of our synthetic strategy is illustrated in Scheme 3. The *tert*-butyl group could be smoothly deprotected *in situ* upon treatment of the reaction mixture with $Sc(OTf)_3$ after solvent exchange to afford the unsubstituted amide in 69% isolated yield (Scheme 3, condition A),⁶ which are ubiquitous motifs in countless biologically relevant molecules and are difficult to obtain from alkyl halides. The expedient conversion

of alky halide **1a** into alkyl carboxylic acid **5** resulted in a 52% yield upon treatment of the reaction with 12 M HCl, which provides an alternative way for alkyl carboxylic acid synthesis,¹⁸ which is widely synthesized via the *in situ* generation of a strong basic organometallic reagent, with subsequent trapping with CO_2 with limited functional group tolerance (Scheme 3, condition B).

The "radical clock" experiment was designed for mechanistic studies (Scheme 4). **1ab** was selected as the model substrate under standard conditions. It was found that 41% ring-opening product **3ab**' was observed along with 18% normal product

Scheme 3. Direct Formation of Primary Amide and Alkyl Carboxylic Acid from Alkyl Iodide







3ab remained (confirmed by ¹H NMR), which clearly indicated that an alkyl radical intermediate was involved in this reaction (Scheme 4a). However, when iodide 1d acted as the substrate, no cyclized product 3d' was formed (Scheme 4b). The TEMPO trapped radical product was not observed when 3.0 equiv of TEMPO was employed as a radical scavenger; amide 3a was obtained in 64% isolated yield (Scheme 4c).

Based on these experimental results and prior work on crosscoupling reaction with isocyanides, we propose the following catalytic mechanism: radical 1' is formed from alkyl iodides 1 via a single electron transfer (SET), which is followed by radical rebound to provide nickel species **B**. Then intermediate **D** is furnished by the migratory insertion of ¹BuNC into **C**, which then undergoes subsequent β -hydride elimination to provide the key intermediate, ketenimines 6.^{9–12} Hydrolysis of 6 under acidic aqueous workup furnishes the desired amide 3 (Scheme 5).

In conclusion, we have developed a nickel-catalyzed direct transformation from unactivated alkyl iodides to amides via the formal aminocarbonylation, utilizing the isocyanides as both a carbonyl source and amine source. The broad scope of the reaction is highlighted by the tolerance of iodine and bromine atoms and the Bpin group, providing a handle for subsequent conversions. Besides, one-pot formation from unactivated alkyl iodides to primary amides and carboxylic acids is achieved, demonstrating the potential impact of our aminocarbonylation Scheme 5. Mechanistic Hypothesis



procedure. Further investigations on nickel-catalyzed carbonylation with isocyanide are underway in our lab.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01022.

Synthetic procedures and analytical data of all compounds (PDF)

Primary NMR FID files for compounds 1k, 1n, 1o, 1p, 3a-z, 3aa (ZIP)

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Notes

The authors declare no competing financial interest.

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