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Palladium Catalyzed Synthesis of Indolizines via the Carbonylative Coupling of Bromopyridines, Imines and Alkynes

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We report herein the development of a palladium-catalyzed, multicomponent synthesis of indolizines. The reaction proceeds via the carbonylative formation of a high energy, mesoionic pyridine-based 1,3-dipole, which can undergo spontaneous cycloaddition with alkynes. Overall, this provides a route to prepare indolizines in a modular fashion from combinations of commercially available or easily generated reagents: 2-bromopyridines, imines and alkynes.

Introduction

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Metal catalyzed carbonylations offer an efficient platform to assemble carbonyl-based products from feedstock chemicals.¹ In addition to their classical use in carboxylic acid, ester, amide or ketone synthesis, there has been recent research effort directed toward employing carbonylations to generate products that are themselves reactive.^{2,3} These highlight an additional useful feature of carbon monoxide, its energetics, where its conversion to carboxylic acid derivatives is often exergonic. Carbonylations have been exploited to access various reactive acylating electrophiles and even non-CO containing products.⁴ Our lab has reported several examples of the latter, wherein the carbonylative formation of 1,3-dipoles (e.g. Münchnones) can be coupled with cycloaddition reactions to afford heterocycles (Fig. 1a).^{4e-g} In these, carbon monoxide is initially incorporated into the reactive 1,3-dipole, yet is ultimately converted to CO2 to drive the assembly of heterocycles from combinations of reagents.

Considering the high value of carbonyl-based building blocks, the use of carbonylation reactions to effectively assemble other classes of reactive substrates could be of synthetic utility. One possibility is the pyridine-based 1,3-dipole **1** (Fig. 1b).⁵ **1** has been recently described as a reactive version of the mesoionic dye Besthorn's Red,⁶ and can undergo 1,3-dipolar cycloaddition with alkynes to generate indolizines. These heterocycles, and their reduced derivatives, represent the core of a wide variety of pharmaceutically relevant molecules and natural products,^{7,8} and their extended conjugation has made them attractive as components in electronic materials.⁹ Indolizines are classically prepared by cyclizations of substituted pyridines¹⁰⁻¹² or pyrroles.¹³ While some variants of these substrates can be easily

a. Carbonylative munchnone formation



b. Pyridine-based mesoionic 1,3-dipole



c. This work: Carbonylative, multicomponent synthesis of indolizines



Figure 1. Carbonylative approaches to 1,3-dipoles and their use in multicomponent heterocycle synthesis.

generated, they more often require the build-up of the appropriate substituted core for cyclization, which adds synthetic steps, creates waste, and can limit their ease of diversification. Similarly, a limitation of the use of **1** in indolizine synthesis is the initial formation of the 1,3-dipole itself from 2-pyridyl acid chlorides, which must first be synthesized, and, due to their incorporation of both nucleophilic and electrophilic components, have limited scope and stability. Only certain variants of the 1,3-dipole **1** can therefore be accessed.

We hypothesized that carbonylations might provide a solution to these challenges. The mesoionic core of **1** contains a carbonyl-unit, which could in principle be derived by

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palladium catalyzed carbonylation (Fig. 1c). In addition to representing a new route to exploit carbonylation in synthesis, this would allow the formation of 1,3-dipole 1 from combinations of reagents that are all by themselves stable, functional group compatible, and readily available: halopyridines, imines and carbon monoxide. We describe in this report our development of a palladium catalyzed route to such a synthesis. Coupling the formation of 1 with cycloaddition has opened a new multicomponent synthesis of indolizines, where these heterocycles can now be formed from three simple, easily diversified reagents.

Results and discussion

The carbonylative generation of 1,3-dipole **1** presents several design challenges. Imines are rarely employed in carbonylation chemistry due to their weak nucleophilicity and poor reactivity with the palladium-acyl intermediates generated in this chemistry. We envisioned that this might be addressed by instead using carbonylations to build-up *in situ* acid chloride electrophiles. Recent studies have shown that such a transformation is viable using sterically encumbered phosphines such as P^tBu₃ on palladium catalysts to favor the challenging reductive elimination of these products.^{2b} However, the carbonylative formation of acid chlorides with coordinating substrates such as 2-bromopyridines has not been previously reported, and even simple aryl bromides require

 Table 1. Catalyst development for the carbonylative formation of 1,3-dipole 1.



2-bromopyridine (9.5 mg, 0.06 mmol), imine (8.4 mg, 0.04 mmol), NEtiPr₂ (6.2 mg, 0.048 mmol,), C₆D₆ (0.75 mL), Bu₄NCl (17 mg, 0.06 mmol), Pd₂dba₃ (1.0 mg, 0.001 mmol), L (0.004 mmol; 0.002 mmol bidentate) [a] 7.5h [b] 80 °C [c] 0.04 mmol 2-bromopyridine. [d] 0.04 mmol 2-bromopyridine, 0.06 mmol imine.

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imine

p-

pressing conditions (110°, 20 atm CO) to be converted to carid

chloride products.^{2d} The latter could prove problematics for the

tolyl(H)C=N(benzyl) in the presence of a chloride source

(Bu₄NCl, Table 1). Using Pd(P^tBu₃)₂ as catalyst, which was

previously noted to allow acid chloride generation,^{2e} does

indeed lead to the in situ build-up of dipole 1a in low yield (38%)

at 100° (entry 1), but we noted the growth of other decomposition products upon extended reaction. In order to

improve the yield of **1a**, the influence of ligands on the reaction was examined. The use of Pd_2dba_3 without added ligand (entry

2) or with various common phosphines (entries 3-6) leads to decreased product yield. Simple bidentate ligands also inhibit

catalysis (entries 7,8). However, we were pleased to find that

large bite angle ligands such as DPE-Phos and Xantphos

significantly increase catalytic activity, with the latter forming

1a in near quantitative yield (94%, entry 10). Similar yields were

noted at 80 °C (entry 11). Xantphos is a rigid, large bite angle

bidentate ligand that can create steric strain in Pd(II) and

potentially favor reductive elimination (vide infra).¹⁴ In addition

to the formation of 1,3-dipole 1a, this reaction can be coupled

with a cycloaddition. Thus, the palladium catalyzed build-up of

1a, followed by the addition of the electron deficient alkyne

dimethylacetylene dicarboxylate (DMAD) leads to the overall

one-pot formation of indolizine **2a** in 76% yield (Figure 2). The multicomponent reaction of 2-bromopyridine, imine, carbon

monoxide and the less electron deficient alkyne ethyl 3-phenyl-2-propynoate can even be performed in a single operation to

access indolizine in good yield (Fig. S1). While these

experiments use imine as the limiting reagent, only slightly

diminished yield are observed when a stoichiometric amount of

imine is used (entry 12), and 1a can be formed in high yield with

indolizine structures. As shown in Table 2, a range of C-aryl

substituted imines can be used in this reaction. This includes

simple phenyl substituted (2b) and electron-rich (2c,d) imines,

which lead to the corresponding indolizine in good yield. Imines

with electron withdrawing substituents can also be employed,

although these require extended reaction times to build-up the

1,3-dipole (2e). Sterically hindered 2-naphthyl, 2-tolyl and even

2,6-disubstituted imines are similarly viable substrates (**2f-h**). In the latter two cases, cycloaddition requires elevated

temperatures and longer reaction times. Heteroaryl-

substituted products are also accessible, such as those with

Me

With a modular method to generate indolizines in hand, we next explored if this system could offer access to various

2-bromopyridine as the limiting reagent.

2-bromopyridine

To probe this potential, we first examined the carbonylative

and

the

formation of a reactive 1,3-dipole 1.

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Me



1) 2-bromopyridine (79 mg, 0.50 mmol), imine (0.75 mmol), Pd_2dba_3 CHCl₃ (13 mg, 0.025 mmol); Xantphos (14 mg, 0.05 mmol); N^iPr_2Et (77 mg, 0.6 mmol); Bu_4NCl (208 mg, 0.75 mmol); 5 atm CO; 10 mL C_6H_6 , 2) dimethylacetylene dicarboxylate (85 mg, 0.6 mmol), 1 h, rt [a] 24h [b] Step 2: 12 h [c] 100 °C, 3.5h [d] Step 2: 48 h at 80 °C [e] 21 h, CH₃CN instead of C_6H_6 , 0.25 mmol Bu_4NCl

thiophene and furan substituents (**2j,k**). The reaction can even allow the use of *C*-alkyl imines, which have proven problematic in related carbonylations due to their ability to readily convert to enamides upon N-acylation.^{5c} However, rapid intramolecularcyclization with the pyridine in the more polar acetonitrile solvent followed by alkyne cycloaddition can afford the isopropyl-substituted indolizine (**2i**).

In addition to the imine, cycloaddition with variously substituted alkynes can be used to modulate the 1- and 2indolizine substituents. Examples include the terminal alkyne ethyl propiolate (**2I**) or internal alkynes such as ethyl 3-phenyl-2-propynoate (**2m**). The more electron rich phenyl acetylene also undergoes cycloaddition with catalytically formed **1** to afford indolizine (**2n**), as does dimethylamino-substituted phenyl acetylene in lower yield (**2o**). More pressing conditions are required for the more electron rich alkynes (16 h for **2I**, 80° for **2m** and **2n**) but lead to the formation of the corresponding indolizines in good yields. Notably, only one regioisomeric product is formed with these unsymmetrical alkynes, where the



Conditions of Table 2 with alkyne (0.6 mmol) [a] 1.5 eq. imine (157 mg, 0.75 mmol), 1 eq. pyridine (79 mg, 0.5 mmol) [b] Cycloaddition for 16h at rt [c] Cycloaddition for 2 d at 80 °C or 150 °C for **20** [d] 24h [e] 5 eq NEt'Pr₂

larger substituent is incorporated into the 1-position. This is consistent with steric bias in 1,3-dipole 1 directing the larger alkyne substituent away from R^{2,5} The 2-bromopyridine structure can also be tuned. Thus, pyridines with donor or electron withdrawing substituents in the 5-position can be incorporated in the reaction (2p-r). The extended conjugation in 2-bromoquinolineis also tolerated, leading to tricyclic product 2s. It is even possible to use a more sterically hindered 3-substituted bromopyridine to generate 8-substituted indolizine 2t. These bromopyridine derivatives are all significantly less expensive and more easily handled than the corresponding acid chlorides or even parent carboxylic acids. Together, this palladium catalyzed carbonylation offers a route to generate indolizines where every substituent can be systematically modulated in a one pot reaction from stable and available reagents.

We have performed several experiments to explore the mechanism of this reaction. Catalysis in the absence of a

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chloride source significantly diminishes the yield of 1a, and instead leads to the recovery of starting materials (Fig. 3a). Low product yields were also observed upon replacing chloride with other salt additives (e.g. Bu₄NOTf: 18%). These observations suggest that chloride is required for an efficient reaction, and are consistent with in situ carbonylative acid chloride formation.¹⁵ Competition reaction with two imines varying only in the para-substituent on the C-aromatic ring leads to selective incorporation of the more electron rich imine into the product (Fig. 3b), which supports its role as a nucleophile in the reaction. It is notable, however, that no acid chloride is observed on monitoring the reaction by ¹H NMR analysis, nor when performing the reaction in the absence of an imine trap (Fig. S2). This implies that if acid chloride is generated, it either rapidly adds back to palladium, or, in the presence of an imine trap, is converted to the 1,3-dipole. Carbon monoxide pressure can influence the reaction, where performing the reaction at 1 atm CO leads to lower product yields (Fig. 3c), and consistent with



Figure 3. Mechanistic experiments on the palladium catalyzed synthesis of 1,3-dipole 1 and indolizines.

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the ability of carbon monoxide ligand to favor, reductive DOI: 10.1039/D0SC03977B elimination and stabilize Pd(0). On the basis of these experiments, we postulate that the catalytic formation of 1,3-dipole 1 proceeds as shown in Fig. 3d. In this, 2-bromopyridine oxidative addition to Pd(0) followed by CO insertion leads to the formation of the palladium-acyl complex 4. In presence of a chloride source, anion exchange can allow the reversible reductive elimination of acid chloride (path A). The re-addition of acid chloride to Pd(0) is presumably rapid, but can be inhibited by nucleophilic trapping with the imine to generate an N-acyl iminium salt for cyclization to 1,3dipole 2. The efficiency of the Xantphos ligand in catalysis may be tied to its large bite angle (111°),¹⁴ which creates significant steric and electronic strain in 4 and can favor reductive elimination of a reactive acid chloride intermediate. Nevertheless, the ability of this system to proceed to product in the absence of chloride implies that the imine can react with other electrophilic intermediates in the reaction, such as the palladium-acyl complex 4 (path B) or potentially an acid bromide, albeit at a slower rate than with acid chloride.

Conclusions

In conclusion, a palladium catalyzed, multicomponent synthesis of indolizines from 2-bromopyridines, CO, imines and alkynes has been developed. In this, carbon monoxide is not incorporated into the final product, but instead serves to first build-up the high energy 1,3-dipole 1, and is then liberated with the nitrogen unit from the imine as an isocyanate. From a synthetic perspective, the reaction has opened a route to prepare indolizines from combinations of stable, tunable reagents, and with the ability to modulate all substituents by variation of the pyridine, imine and alkyne employed. Considering the utility of 1,3-dipoles in synthesis, we anticipate this chemistry could offer a modular route to access a range of fused-ring heterocyclic products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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A palladium catalyzed, multicomponent synthesis of indolizines is described via the carbon monoxide driven generation of reactive, pyridine-based 1,3-dipoles.