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Expedient Synthesis of *N*-Acyl Anthranilamides and β-Enamine Amides by the Rh(III)-Catalyzed Amidation of Aryl and Vinyl C–H Bonds with Isocyanates

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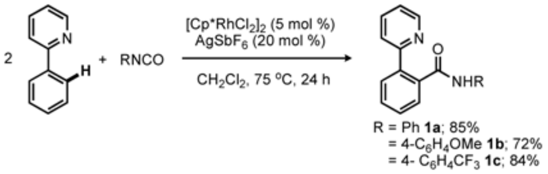
Abstract

A Rh(III)-catalyzed protocol for the amidation of anilide and enamide C–H bonds with isocyanates has been developed. This method provides direct and efficient syntheses of *N*-acyl anthranilamides, enamine amides, and pyrimidin-4-one heterocycles.

Transition-metal catalyzed C–H bond functionalization reactions have emerged as effective strategies for streamlining chemical synthesis by avoiding tedious and costly substrate pre-activation steps. While the development of methods for the functionalization of C–H bonds with alkenes and alkynes has been extensively investigated,[1] the identification of related procedures for additions across polar C–N π-bonds has seen considerably less progress.[2] Given the ubiquity of amines in bioactive molecules and drugs, the installment of nitrogen-based functional groups into molecules through the direct addition of C–H bonds to unsaturated C–N multiple bonds represents a worthwhile pursuit with profound synthetic potential.

Recently, we showed that $[Cp^*RhCl_2]_2/AgSbF_6$ mixtures are capable of catalyzing the addition of 2-arylpyridines to *N*-Boc and *N*-sulfonyl imines via C–H functionalization to afford α-branched amine products.[2a,3] Building on this result, we focused on expanding this reactivity to include the insertion of C–H bonds across isocyanates towards the synthesis of amides.[4] Initially, we demonstrated the feasibility of this transformation by successfully employing the 2-pyridyl directing group (eq 1), but immediately refocused our efforts to the use of the *N*-acyl amino directing group present in anilides and enamides for the synthesis of *N*-acyl anthranilamides and enamine amides.



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Supporting Information. Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

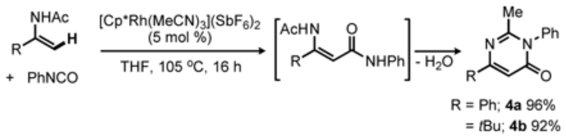
The atom-economical synthesis of *N*-acyl anthranilamides from readily available anilides and isocyanates is of significant practical utility given that this structural motif is found in numerous drugs and drug candidates.[5] Anthranilamides are typically prepared from the corresponding anthranilic acids; however, this approach is inherently restricted by the limited selection of commercially available anthranilic acids.[6] *N*-Acyl enamine amides obtained from enamides and isocyanates are also useful intermediates because they can readily be reduced to β-amino amides, which are present in important drugs as well as β-peptides.[7] Moreover, both *N*-acyl anthranilamides and enamine amides are poised to undergo cyclodehydration reactions to provide quinazolinone and pyrimidinone frameworks, which are also a common feature in approved drugs and drug candidates.[8] Herein we report the first examples of the coupling of anilides and enamides with isocyanates to form amides. This unprecedented method enables the efficient preparation of *N*-acyl anthranilamides and enamine amides from readily available starting materials.

Our initial investigations focused on the identification of a suitable catalyst and reaction conditions for the selective coupling of phenyl isocyanate with the vinylic C–H bond in *N*-acetyl enamine **2a** to afford the amidation product **3a**.[9,10] Although the use of 2.5 mol % of $[Cp^*RhCl_2]_2$ proved unsuccessful in catalyzing this reaction (Table 1, entry 1), employing a mixture of 2.5 mol % of $[Cp^*RhCl_2]_2$ and either 10 mol % of $AgSbF_6$ or $AgB(C_6F_5)_4$ in THF at 75 °C provided an excellent combined yield of amidation products.[11] However, the ratio of the desired amidation product **3a** to the cyclodehydrated pyrimidin-4-one **4a** remained low (Table 1, entry 2 and 3). Notably, comparable catalyst activity was achieved through the use of the more practical Rh(III) precursor $[Cp^*Rh(MeCN)_3](SbF_6)_2$,12 which was used for all subsequent optimization (Table 1, entry 4). When conducted in the absence of the Rh(III) catalyst, preferential reaction between the amide functionality of the substrate and the isocyanate occurred rather than the desired C–C bond formation (Table 1, entry 5). In addition, as shown in entries 6 to 8, a variety of acids and bases, as well as Lewis acids, did not promote the desired reaction. Alternative solvents, such as CH_2Cl_2 and *t*BuOH, provided good yields of the amidation products **3a** and **4a**, but did not improve the product ratios (Table 1, entries 9 to 11). Variable substrate stoichiometries were investigated; the highest yields were observed for reactions employing 2 equiv of the enamide relative to phenyl isocyanate (Table 1, entry 12).[13] The selective formation of either **3a** or **4a** was ultimately achieved by conducting the reaction at room temperature or 105 °C, respectively (Table 1, entries 13 and 14).

Having defined a highly effective catalyst system and reaction conditions for the selective amidation of *N*-acyl enamine **2a** with phenyl isocyanate, we sought to further explore the reaction scope for other enamides and anilides with a broad range of isocyanates (Table 2). In addition to employing phenyl isocyanate, the amidation of **2a** with primary and secondary alkyl isocyanate substrates provided amide products **3b** and **3c** in excellent yields (96 and 84%, respectively) when employing 5 mol % of Rh in THF at room temperature. Addition of the sterically-demanding tertiary 1-adamantyl isocyanate was also successful, albeit in a modest yield (**3d**; 40%). An isocyanate derived from the readily available amino acid phenylalanine was readily accommodated (**3e**; 65%), and served to highlight potential opportunities for the incorporation of chiral components in more complex synthesis. In addition to **2a**, enamides derived from 1-acetyl-cyclohexene and cyclohexanone were readily converted to the amides **3f** and **3g** in good yields (80% and 76%, respectively).

Literature methods are available for the efficient cyclodehydration of *N*-acyl anthranilamides and enamine amides to quinazolinone and pyrimidinones, respectively.[14] However, we postulated that by conducting the Rh(III)-catalyzed reaction at high temperature, both the isocyanate coupling and cyclization might be accomplished in a single step. Indeed, heating enamides **2a** (R = Ph) and **2b** (R = *t*Bu) with phenyl isocyanate at 105

°C in the presence of 5 mol % of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ directly provided the corresponding pyrimidin-4-ones **4a** and **4b** in excellent yields (eq 2).[15] When monitored by ^{1}H NMR, the initial enamine amide products (**3**) are formed along with the heterocycles (**4**) at early conversion. Notably, heating the isolated amide **3a** in the absence of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ resulted in negligible conversion to **4a** suggesting that cyclodehydration of **3a** to **4a** is facilitated by the rhodium catalyst rather than being solely thermally-induced.[16]

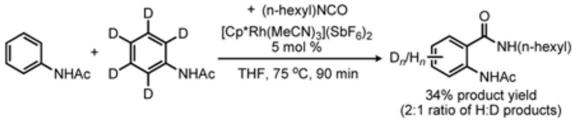


(2)

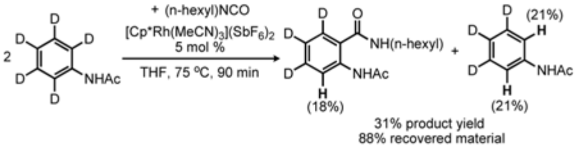
The substrate scope was extended further to include anilides to provide direct access to anthranilamide derivatives from readily available anilines and isocyanates (Table 2). Although the reaction did not proceed at room temperature, good yields were obtained at 75 °C (**3h**–**3t**). Consistent with the substrate scope for enamides (**3a**–**3g**), primary, secondary, and tertiary alkyl isocyanates all readily coupled with acetanilide (**3i**–**3t**). Significantly, alternative more bulky anilide acyl groups, such as *i*Pr and *i*Bu, provided good yields of anthranilamides **3k** and **3l** (77% and 72%, respectively). Electron-rich or electron-poor acetanilides featuring *meta*- or *para*-substitution provided the desired anthranilamide products with good to excellent yields (**3m**–**3p;** 44–97%). Moreover, *meta*-substituted acetanilides exclusively provided the less substituted anthranilamide products (**3o** and **3p**). *N*-acylamino substituted nitrogen and oxygen heterocycles were also evaluated and provided anthranilimides that incorporate indole (**3s**) and benzofuran (**3t**) functionality, with two regioisomeric products obtained for the substituted benzofuran substrate (**3t**).

The product regiochemistry observed for the isocyanate additions to aromatic substrates is most consistent with a Rh-mediated C–H cleavage step directed by a Lewis basic group instead of a more traditional electrophilic aromatic substitution mechanism. Specifically, *ortho*-functionalization rather than *meta*-substitution is observed for 2-phenylpyridine, and exclusive *ortho*-substitution, as opposed to *ortho*-/*para*-product mixtures, is observed for anilides.

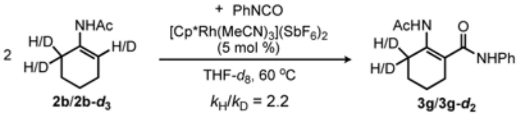
To provide preliminary insight into the reaction mechanism for the Rh(III)-catalyzed addition of isocyanates to acetanilides, deuterium kinetic isotope effects (DKIE) were also investigated. When a competition reaction was conducted with an equimolar ratio of deuterio- and protio-acetanilide, a ≥2-fold product ratio favoring the protio-derived product was observed at early conversion (eq 3).[13] However, when acetanilide-d_5 was subjected to the standard reaction conditions modest deuterium exchange was observed at the *ortho*-positions of both the unreacted anilide (21% H) and the product *N*-acyl anthranilamide (18% H) (eq 4), thus complicating the interpretation of the data presented in eq 3. The DKIE was therefore also evaluated for the reaction of phenyl isocyanate with *N*-cyclohexenyl acetamide **2b** and the analogous deuterated enamide **2b-d_3**. Indeed, a comparison of the initial rates of enamine amide product formation at early conversions revealed a DKIE of 2.2 (eq 5).[13] Importantly, no background H/D exchange was observed for unreacted **2b-d_3** under these reaction conditions. Although elucidation of the rate law for the reaction is necessary to interpret this result properly, a primary isotope effect is consistent with rate-limiting C-H bond activation rather than direct π-bond addition to the isocyanate electrophile.[17] We plan to carry out a more thorough kinetic examination of the reaction to confirm this inference.



(3)



(4)



(5)

In summary, we have identified [Cp*Rh(MeCN)$_3$](SbF$_6$)$_2$ as an effective catalyst for the addition of anilide and enamide C–H bonds across a broad range of isocyanates to afford valuable *N*-acyl anthranilamides and enamine amides. Studies are on-going to better understand the reaction mechanism as well as to apply the method to natural product and drug synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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5. Typing the name of these drug and drug candidates into Pub-chem provides the compound structure, bioactivity, full list of literature, and access to ongoing clinical trials, applications, and usage: betrixaban (CID 10275777) and tariquidar (CID 148201).
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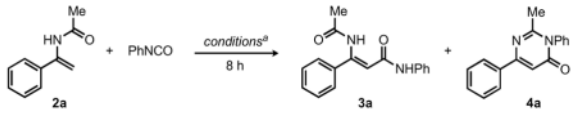
15. Cyclization occurs more slowly for the less acidic *N*-hexyl or *N*-cyclohexyl amides obtained from alkyl isocyanates.
16. The cyclodehydration of isolated **3a** to **4a** was achieved in an 80% ^1H NMR yield (relative to 2,6-dimethoxytoluene) when treated with 5 mol % $[Cp^*Rh(MeCN)_3](SbF_6)_2$ in THF at 105 °C for 16 h.
17. Kinetic isotope studies for Rh(III)-catalyzed C–H/alkyne couplings have been shown to be consistent with rate-limiting C–H bond activation steps, see: Guimond N, Gorelsky SI, Fagnou K. J Am Chem Soc. 2011; 133:6449–6457. [PubMed: 21452842] (b) reference 3a. (c) reference 10b.

Table 1

Reaction Optimization



entry	catalyst	solvent	temp	yield[b]
1	$[Cp^*RhCl_2]_2$	THF	75	0
2[c]	$[Cp^*RhCl_2]_2$, $AgSbF_6$	THF	75	93 (1:8)
3[c]	$[Cp^*RhCl_2]_2$, $AgB(C_6F_5)_4$	THF	75	94 (1:3)
4	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	THF	75	94 (1:3)
5	-	THF	75	0
6[d]	$AgSbF_6$	THF	75	0
7[e]	AcOH or TFA	THF	75	0
8[e]	NEt_3, K_3PO_4, or KO(*t*Bu)	THF	75	0
9	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_2Cl_2	75	85 (3:1)
10	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	*t*BuOH	75	75 (1:8)
11	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	toluene	75	30 (1:1)
12[f]	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	THF	75	78 (1:2)
13	***$[Cp^*Rh(MeCN)_3](SbF_6)_2$***	***THF***	***rt***	***96 (15:1)***
14	***$[Cp^*Rh(MeCN)_3](SbF_6)_2$***	***THF***	***105***	***99 (1:50)***

[a] Conditions: PhNCO:**2a** = 1:2, 0.05 mmol (0.1 mM) PhNCO scale, 5 mol % of Rh, 8 h.

[b] Determined by ^1H NMR relative to 2,6-dimethoxytoluene as an internal standard. Ratio of **3a:4a** is indicated in parentheses.

[c] Addition of 10 mol % of Ag salt.

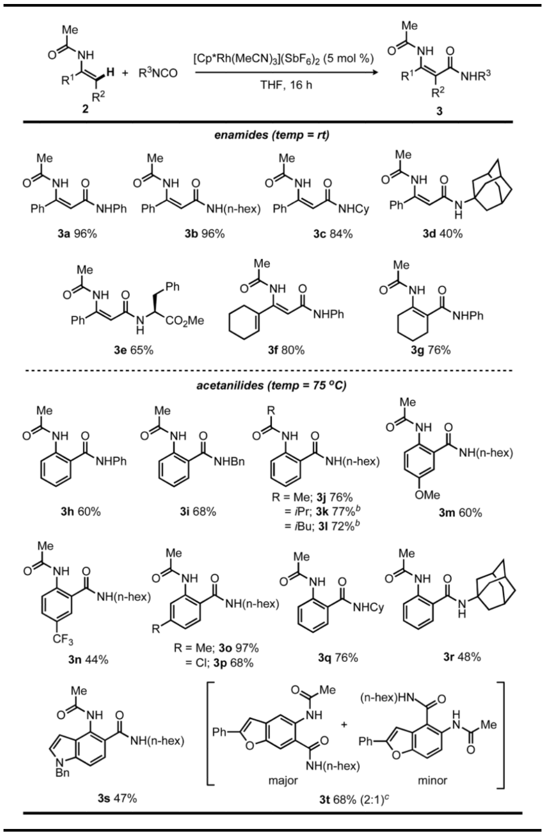
[d] 20 mol % of $AgSbF_6$ employed.

[e] 20 mol % of acid or base employed.

[f] PhNCO:**2a** = 2:1.

Table 2

Substrate Scope[a]



[a] Conditions: R^3NCO:**2** = 1:2, 0.25 mmol (0.25 mM) R^3NCO scale, 5 mol % of Rh, 16 h; yields represent isolated material.

[b] Reaction conducted at 120 °C for 24 h. ^1H NMR yield relative to 2,6-dimethoxytoluene.

[c] Reaction conducted at 120 °C.