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Letter

Base-Promoted Tandem Synthesis of 3,4-Dihydroisoquinolones

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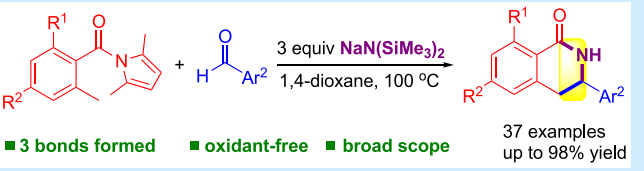
ABSTRACT: Using benzaldehydes, $NaN(SiMe_3)_2$, and *N*-acylpyrroles, an operationally simple tandem method to produce a wide array of 3,4-dihydroisoquinolones is presented (37 examples, yields up to 98%). A unique feature of this method stems from the sequential aminobenzylation of aldehydes and transamidation of the corresponding *N*-(trimethylsilyl)imines in one pot. In this process, three new bonds are generated (one C−C and two C−N bonds).



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3,4-Dihydroisoquinolones are common scaffolds found widely in naturally occurring alkaloids[1] and pharmaceuticals (Scheme 1).[2−4] Compounds containing 3,4-dihydroisoquinolone cores

Scheme 1. Representative Biologically Active Compounds Containing 3,4-Dihydroisoquinolone Cores

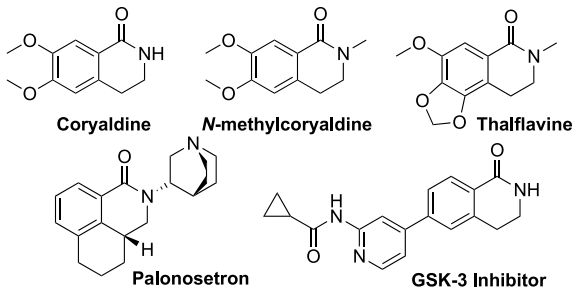
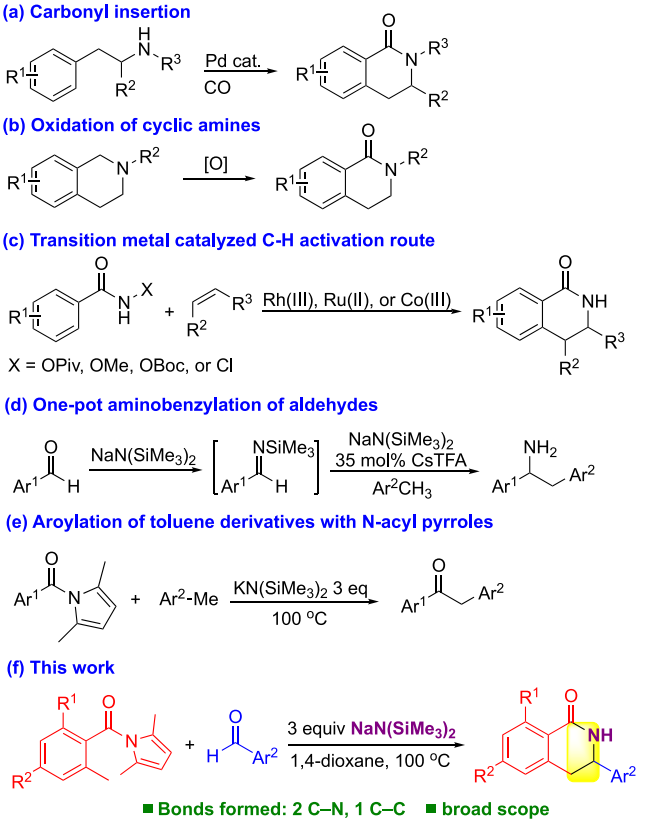


exhibit a variety of biological activities, such as anti-HIV,[5] antidepressant,[6] anticancer,[7] antioxidant,[8] antithrombotic,[9] and antibacterial properties.[10] They are also known as EZH2 inhibitors,[11] PARP inhibitors,[12] and cyclin-dependent kinase inhibitors.[13] Consequently, the development of efficient methods for the synthesis of this important *N*-heterocycle core has attracted much attention.

Traditional approaches to access 3,4-dihydroisoquinolones mainly rely on intramolecular cyclization of activated amide or amide precursors, including carbamates,[14−16] isocynates,[17,18] ureas,[19] and azidoamides.[20,21] However, most of these methods suffer from limited substrate scope resulting from the use of strongly acidic conditions. Recently, significant effort has been devoted to the preparation of 3,4-dihydroisoquinolones, with representative methods including (1) palladium catalyzed carbonyl insertion (Scheme 2a);[22−24] (2) oxidation of cyclic amines (Scheme 2b);[25−27] and (3) [4 + 2] cycloaddition of activated arylamides with alkenes via transition-metal-catalyzed C−H activation (Scheme 2c).[28−30] Despite substantial progress, most of these methods still leave room for improvement to address the use of prefunctionalized

Scheme 2. Methods for the Synthesis of 3,4-Dihydroisoquinolones and Relevant Prior Works



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substrates, expensive metal catalysts and ligands, the need for excess oxidants, or tedious procedures. The development of greener and more practical methods for the synthesis of 3,4-dihydroisoquinolones, therefore, remains in demand.

Our team has a long-standing interest in Brønsted base [$MN(SiMe_3)_2$, M = Li, Na, K, and Cs] promoted functionalization of weakly acidic C−H bonds in toluene derivatives.[31−33] As shown in Scheme 2d, we advanced an $MN(SiMe_3)_2$-mediated C−N and C−C bond-forming process by reaction of $MN(SiMe_3)_2$ with aryl aldehydes to generate *N*-TMS imines. The $MN(SiMe_3)_2$ simultaneously acts as a base in the deprotonation of toluene derivatives' weakly acidic $C(sp^3)$−H bonds. The resulting benzylic organometallic reacts with the *N*-TMS imine to give an amine after hydrolysis. Other groups have used different bases in related strategies,[34−38] including use of enantioenriched ligands for the base by the Kobayshi group.

In combination with reversible toluene deprotonation, we have examined different electrophiles, including methyl esters, Weinreb amides, and *N*-acyl pyrroles, to make ketones (Scheme 2e).[39,40] It is well-known that the carbonyl group of *N*-acyl pyrroles is significantly more electrophilic than those of standard amides[41] because the lone pair of the pyrrole nitrogen is also delocalized into the aromatic π-system. In the case of 2,5-disubstituted *N*-acyl pyrroles, the substituents force the pyrrole out of planarity from the carbonyl group. Based on our ketone synthesis (Scheme 2e), we were curious if 3,4-dihydroisoquinolones could be accessed from 2-methyl benzamide derivatives through an initial aminobenzylation followed by transamidation (Scheme 2f). Herein, we report the net [4 + 2] annulation composed of an initial amino-benzylation of aldehydes and transamidation of the *N*-acyl pyrrole for the synthesis of 3,4-dihydroisoquinolones (Scheme 2f). This one-pot procedure results in the formation of 3 new bonds (2 × C−N, C−C) and a heterocyclic scaffolding.

At the outset of our studies, the reaction of the model substrate, 2,5-dimethyl-*N*-2′,4′,6′-trimethylbenzolpyrrole **1a**, and benzaldehyde **2a** was conducted in toluene at 100 °C for 12 h with $NaN(SiMe_3)_2$ (Table 1). To our delight, the target product **3aa** was produced in 77% isolated yield (Table 1, entry 1). Screening solvents [toluene, CPME (cyclopentyl methyl ether), DME, THF, and 1,4-dioxane] indicated that reactions in 1,4-dioxane showed the best performance, furnishing the cyclization product in 83% yield (entry 5). Different main group cations can have a profound impact on reactivity and chemoselectivity.[42] Thus, it was not surprising that the choice of silylamide base for our reaction was critical. Unlike $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$ failed to promote the reaction (entry 6) and $LiN(SiMe_3)_2$ exhibited inferior performance (60% yield, entry 7). Increasing the amount of benzaldehyde **2a** to 1.2 equiv improved the yield of **3aa** (entries 5 vs 8, from 83% to 88%). Furthermore, excess base was essential for this protocol. Lowering the equivalents of $NaN(SiMe_3)_2$ to 2 gave 55% yield, while almost no product was detected with 1 equiv of $NaN(SiMe_3)_2$ (entries 9 and 10 vs 8). It should be noted that 1.2 equiv of the silyl amide is needed to convert the aldehyde to the imine. The pyrrolide anion (formed as a byproduct) is insufficiently basic to deprotonate the benzylic methyl group, resulting in consumption of an equivalent of base. Thus, the use of 3 equiv of base ensures that any trace protic impurities in the solvent can also be deactivated. The optimized conditions (Table 1, entry 8) were then carried forward to explore the substrate scope.

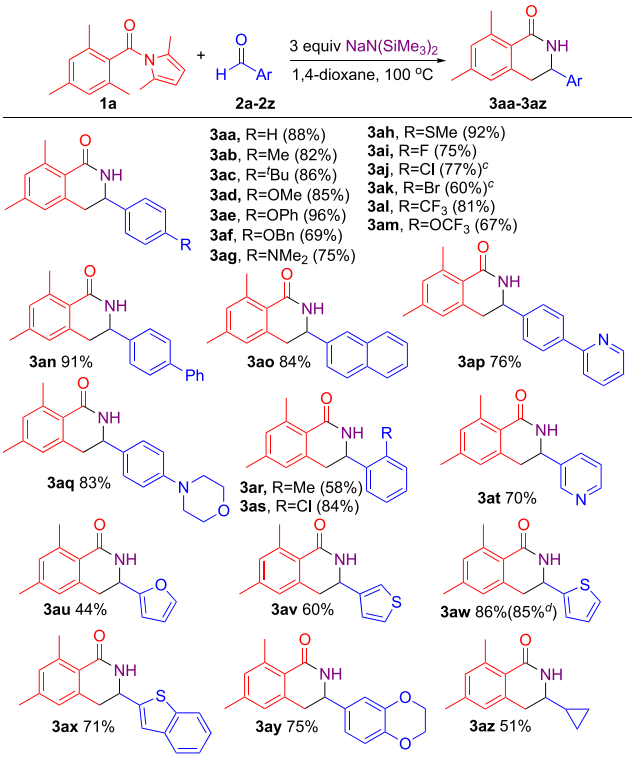
As depicted in Table 2, a wide range of aryl aldehydes were compatible with the reaction and afforded the 3,4-dihydroisoquinolone products in good to excellent yields. Benzaldehydes containing alkyl groups (4-Me and 4-^{t}Bu) gave products **3ab** and **3ac** in 82% and 86% yield, respectively. Benzaldehydes bearing electronically diverse substituents, including electron-

Table 1. Reaction Optimization[a]

Entry	Solvent	Base	1a:2a	Yield[b] (%)
1	Toluene	$NaN(SiMe_3)_2$	1:1	77
2	CPME	$NaN(SiMe_3)_2$	1:1	61
3	DME	$NaN(SiMe_3)_2$	1:1	trace
4	THF	$NaN(SiMe_3)_2$	1:1	60
5	1,4-Dioxane	$NaN(SiMe_3)_2$	1:1	83
6	1,4-Dioxane	$KN(SiMe_3)_2$	1:1	trace
7	1,4-Dioxane	$LiN(SiMe_3)_2$	1:1	60
8	1,4-Dioxane	$NaN(SiMe_3)_2$	1:1.2	88
9[c]	1,4-Dioxane	$NaN(SiMe_3)_2$	1:1.2	55
10[d]	1,4-Dioxane	$NaN(SiMe_3)_2$	1:1.2	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), base (0.6 mmol), solvent (2 mL), 12 h. [b]Isolated yields. [c]2 equiv of $NaN(SiMe_3)_2$. [d]1 equiv of $NaN(SiMe_3)_2$.

Table 2. Scope of Arylaldehyde[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), arylaldehyde (0.24 mmol), $NaN(SiMe_3)_2$ (1.0 mol/L in THF, 0.6 mL, 0.6 mmol), 1,4-dioxane (0.1 M), 100 °C, 12 h. [b]Isolated yield. [c]80 °C. [d]Reaction conducted on 5 mmol scale.

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donating 4-OMe, 4-OPh, 4-OBn, 4-NMe_2, and 4-SMe, gave the products (**3ad**, **3ae**, **3af**, **3ag**, **3ah**) in 69−96% yield. Benzaldehydes with electronegative or electron-withdrawing substituents (4-F, 4-Cl, 4-Br, 4-CF_3, 4-OCF_3) resulted in product generation in 60−81% yield (**3ai**, **3aj**, **3ak**, **3al**, **3am**). However, 4-iodobenzaldehyde was not a suitable substrate in this protocol and decomposed under the reaction conditions. Additionally, substrates possessing 4-Ph (**3an**), 2-naphthyl (**3ao**), heterocyclic 2-pyridyl (**3ap**), and morpholino (**3aq**) groups furnished products in 76−91% yield. Sterically hindered aryl aldehydes bearing 2-Me and 2-Cl groups were found to be suitable substrates, affording the cyclized products **3ar** and **3as** in 58−84% yields. Interestingly, heterocyclic nicotinealdehyde, furfural, 3-thiophenaldehyde, 2-thiophenaldehyde, 1-benzothiophene-2-carbaldehyde, and 1,4-benzodioxan-6-carboxaldehyde also participated in this reaction, giving the products **3at**−**3ay** in 44−86% yields.

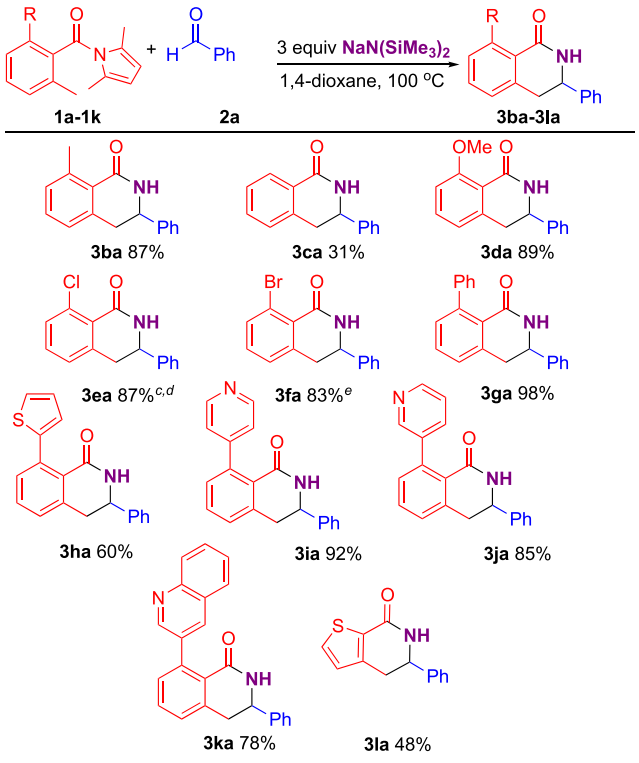
It is noteworthy that the reaction was also applicable to cyclopropanecarboxaldehyde to furnish desired **3az**, albeit with diminished efficiency (51% yield). No desired product was observed with terephthalaldehyde. To test the scalability of our method, 5 mmol of **1a** was reacted with 1.2 equiv of 2-thiophenaldehyde (**2w**), and the target product **3aw** was isolated in 85% yield (1.09 g).

The scope of 2,5-dimethyl-*N*-acylpyrroles was next explored with benzaldehyde (**2a**) (Table 3). As expected, 2,6-dimethyl-substituted *N*-acyl pyrrole showed similar reactivity to the model reaction (87% yield). In this study, it was found that substrates bearing substituents at the 6-position are critical for high yield. The less sterically encumbered substrate **2c** displayed 31% yield in the formation of **3ca**. The origin of the reactivity difference is not clear but may result from directed ortho metalation (although no such products were observed). Replacement of one of the methyl groups of **1b** with electron-donating OMe (**1d**) or electron-withdrawing Cl or Br (**1e**, **1f**) groups restored the reactivity, providing the target product **3da**−**3fa** in 83−89% yields. Unfortunately, a 6-iodo substituent was not tolerated in this reaction due to decomposition. Additionally, use of substrates with various 2-aryl substituents [2-Ph, 2-(2-thienyl), 2-(4-pyridinyl), 2-(3-pyridinyl), or 2-(3-quinolyl)] furnished the product **3ga**−**3ka** in 60−98% yields. Notably, a heterocyclic substrate bearing a thienyl group produced a 48% yield of **3la**. When 2-ethyl-*N*-acylpyrrole was also utilized in this transformation, no desired product was observed under various reaction conditions. Overall, a variety of 3,4-dihydroisoquinolones were synthesized via our transition-metal-free annulation reaction with readily available aryl aldehydes and 2,5-dimethyl-*N*-acylpyrroles.

The key steps in a proposed mechanism are shown in Scheme 3. Rapid reaction of the aldehyde with the silyl amide base is followed by an aza-Peterson elimination to generate the *N*-$SiMe_3$ imine. At the same time, deprotonation of the methyl group next to the amide ensues. The reaction of the metalated amide with the imine generates a C−C bond and reveals a nucleophilic nitrogen that is positioned to undergo transamidation with the *N*-acyl pyrrole, forming the second C−N bond. Aqueous workup provides the observed annulated product.

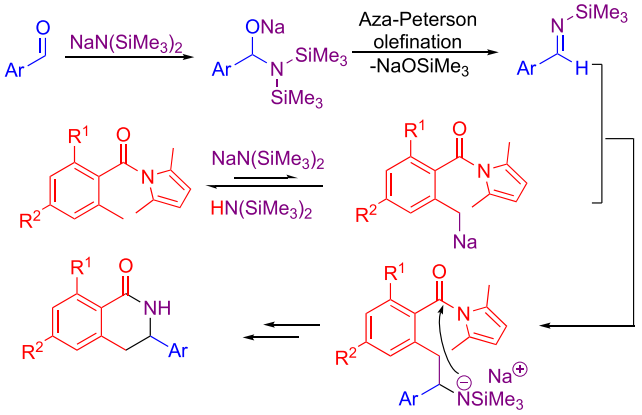
In conclusion, we have advanced a novel $NaN(SiMe_3)_2$-mediated tandem aminobenzylation/transamidation reaction under transition-metal-free conditions. This method provides an efficient and straightforward strategy for the synthesis of 3,4-dihydroisoquinolones. The broad scope and good functional group compatibility of this protocol make it an attractive alternative to previously reported methods. The 3,4-dihydroisoquinolone derivatives prepared in this study belong to a class of scaffolds relevant to pharmacologically important compounds and natural products. Due to its ability to access bioactive heterocycles in a single step, we envision that this tandem reaction will find application in chemical sciences and medicinal chemistry.

Table 3. Scope of 2,5-Dimethyl-*N*-acylpyrroles[a,b]



[a]Reaction conditions: 2,5-dimethyl-*N*-acylpyrroles (0.2 mmol), **2a** (0.24 mmol), $NaN(SiMe_3)_2$ (1.0 mol/L in THF, 0.6 mL, 0.6 mmol), 1,4-dioxane (0.1 M), 100 °C, 12 h. [b]Isolated yield. [c]1,4-Dioxane was replaced with DME. [d]80 °C. [e]60 °C

Scheme 3. Key Steps in the Proposed Mechanism



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■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03167.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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