Organic Letters
Letter
pubs.acs.org/OrgLett

Three-Component Functionalized Dihydropyridine Synthesis via a Formal Inverse Electron-Demand Hetero-Diels–Alder Reaction

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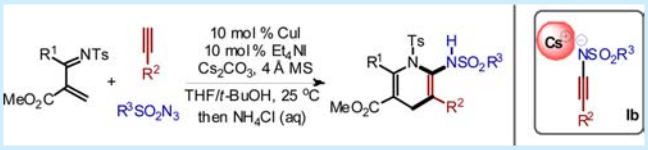
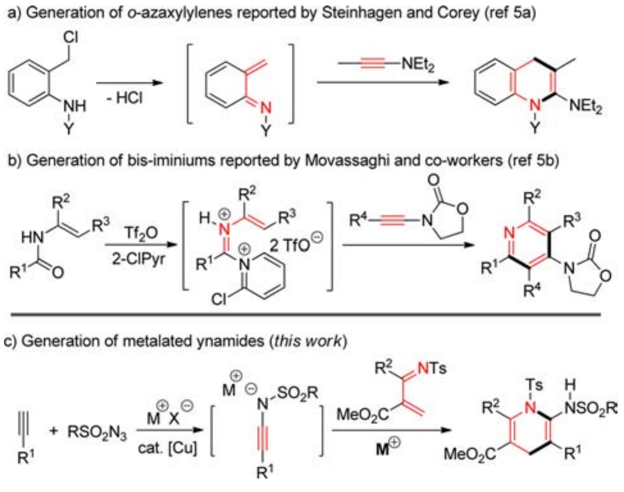
ABSTRACT: A mild three-component synthetic approach to versatile 2-amino-1,4-dihydropyridines from terminal alkynes, sulfonyl azides, and *N*-sulfonyl-1-aza-1,3-butadienes was successfully developed and relied on the in situ generation of metalated ynamide intermediates **Ib** to achieve a formal inverse electron-demand hetero-Diels–Alder reaction. Experimental results suggest that alkali metal cations (Li^+ and Cs^+ ions) might play a critical role to achieve the cycloaddition process.



The hetero-Diels–Alder (HDA) reaction of azadienes has recently emerged as a promising approach to six-membered aza-heterocycles.[1] In this regard, the inverse electron-demand Diels–Alder (IEDDA) reaction of electron-deficient azadienes[2] with alkynes has been met with limited success to deliver dehydro-[4 + 2] adducts,[3] partially due to geometric constrictions arising from the lineal disposition imposed by the *sp*-hybridization of the triple bond carbons.[4] The reported types of these IEDDA reactions nearly all employ in situ generated azadienes to cyclize with a preorganized substituted alkyne.[5] In 1999, Steinhagen and Corey presented a versatile route to dihydroquinolines through a IEDDA reaction between *o*-azaxylylenes and ynamines (or alkoxyacetylenes) (Scheme 1a).[5a] In 2007, Movassaghi and co-workers uncovered an acid-mediated formal aza-[4 + 2] cycloaddition of enamides and ynamides to provide a direct synthesis of pyridines relying on the formation of bis-iminium intermediates from enamides (Scheme 1b).[5b] Notably, in 2012, Kozmin and Rawal and co-workers developed a silver-catalyzed tandem formal IEDDA/retro-Diels–Alder reaction sequence of phthalazines and siloxy alkynes, giving rise to siloxy naphthalenes and anthracenes.[5c] Despite this significant progress, the development of novel IEEDA approaches, such as using simpler alkynes, for the assembly of six-membered heterocycles remains desirable.

Scheme 1. Formal Dehydro-IEDDA Reactions upon in Situ Generation of Azadienes or Dienophiles



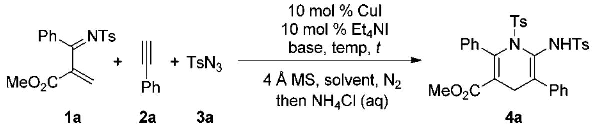
During the past decade, ynamides have emerged as powerful and versatile building blocks in a variety of ring-forming transformations.[6,7] As a complementary alternate to substituted ynamides, we have recently developed a mild procedure to generate lithiated ynamides[8] by the Cu-catalyzed azide–alkyne cycloaddition (CuAAC) reaction[9] in the presence of stoichiometric amounts of LiOH.[10] The resulting lithiated ynamide intermediates could react with ynals to give polysubstituted alkenes in high *E*/*Z* selectivity through a cascade [2 + 2]/retro-[2 + 2] reaction, simultaneously enabling the incorporation of the sulfonyl amide moiety.[10a,b] Herein, we wish to report a Cu-catalyzed three-component reaction of terminal alkynes, sulfonyl azides, and *N*-sulfonyl-1-aza-1,3-butadienes[11] for the direct synthesis of 2-amino-1,4-dihydropyridines[12] through a formal IEDDA reaction of electron-deficient 1-azadienes with transient metalated ynamides (Scheme 1c).

An initial trial was conducted with the mixtures of methyl 2-(phenyl(tosylimino)methyl)acrylate (**1a**), ethynylbenzene (**2a**), and tosyl azide (**3a**), using CuI (10 mol %) and Et_4NI (10 mol %) as the catalysts in the presence of 4 Å molecular sieves under N_2 atmosphere (Table 1). While 2,6-lutidine was completely ineffective to give any desired cyclization products, LiOH could enable the direct formation of 2-amino-1,4-dihydropyridine **4a** in 49% isolated yield after 48 h (Table 1, entries 1 and 2). To improve the chemical yield, two other inorganic bases were examined. Whereas *t*-BuOLi sharply accelerated the conversion of substrates, the desired product **4a** was only obtained in 24% yield along with a lot of undetermined byproducts (entry 3). Gratifyingly, cesium carbonate (Cs_2CO_3) significantly elevated

Received: June 3, 2015
Published: June 26, 2015

DOI: 10.1021/acs.orglett.5b01622
Org. Lett. 2015, 17, 3536–3539

Table 1. Optimization of Reaction Conditions[a]



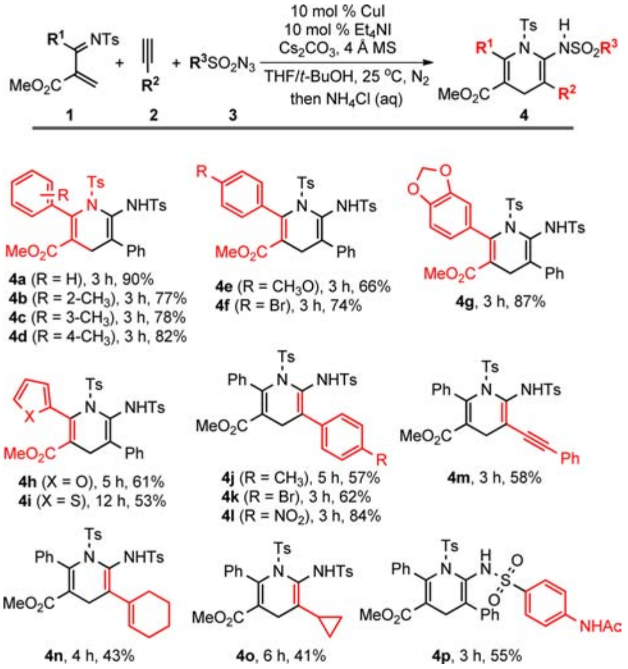
entry	solvent	temp (°C)	base (equiv)	t (h)	yield (%)[b]
1	THF	10	LiOH (1.5)	48	49
2	THF	10	2,6-lutidine (1.5)	48	
3	THF	10	*t*-BuOLi (1.5)	1	24
4	THF	10	Cs$_2$CO$_3$ (1.5)	6	64
5	THF:*t*-BuOH[c]	10	Cs$_2$CO$_3$ (1.5)	6	81
6	toluene	10	Cs$_2$CO$_3$ (1.5)	24	44
7	DCE	10	Cs$_2$CO$_3$ (1.5)	24	62
8	THF:*t*-BuOH[c]	10	Cs$_2$CO$_3$ (3.0)	4	88
9	THF:*t*-BuOH[c]	25	Cs$_2$CO$_3$ (3.0)	3	90
10	THF:*t*-BuOH[c]	35	Cs$_2$CO$_3$ (3.0)	2	78
11	THF:*t*-BuOH[c]	25	K$_2$CO$_3$ (3.0)	12	9
12	THF:*t*-BuOH[c]	25	NaOH (3.0)	10	12

[a] Reaction conditions: (1) **1a** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), CuI (10 mol %), and Et$_4$NI (10 mol %) in solvent (5.0 mL) under N$_2$, then base (1.5 equiv or 3.0 equiv); (2) saturated aqueous NH$_4$Cl (10 mL). [b] Isolated yield of **4a**. [c] v/v = 10:1. Et$_4$NI = tetraethylammonium iodide.

the reaction yield to 64% (Table 1, entry 4). Using 1.5 equiv of Cs$_2$CO$_3$, subsequent investigation of solvent effects (Table 1, entries 5–7) indicated the mixtures of THF and *tert*-butyl alcohol (v/v = 10:1) to be the best choice. Intriguingly, increasing the amount of Cs$_2$CO$_3$ to 3.0 equiv would favor the formation of **4a** (entry 8). It was observed that the temperature has a critical effect on this reaction (Table 1, entries 8–10): while the yield of **4a** slightly increased to 90% by elevating the temperature to 25 °C, further increase in temperature led to a complicated conversion and dropped the product yield to 78% (2 h). Nevertheless, other inorganic base like K$_2$CO$_3$ and NaOH proved to be ineffective for this conversion (entries 11 and 12), suggesting that metal cations might play a distinct role herein. Finally, the structure of **4a** was unambiguously determined by single-crystal X-ray diffraction analysis.

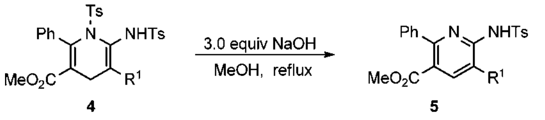
The scope of this reaction was then explored with a range of accessible 1-azadienes **1** (Scheme 2). Variation of R^1 showed that the substitution patterns of aryl moieties had little effect on this cycloaddition reaction, delivering desired products **4b–d** in similar yields from ortho-, meta-, and para-substituted arenes, respectively. Substituted benzene rings bearing an electron-donating group (−OMe) or an electron-withdrawing group (−Br) were tolerated to form products **4e** and **4f**. Other aromatic rings, including benzo[*d*][1,3]dioxol-5-yl, 2-furyl, and 2-thienyl groups could also be introduced to accomplish this conversion successfully, providing access to the desired dihydropyridines **4g**, **4h**, and **4i** in reasonably good yields. However, a range of terminal alkynes were also examined for this three-component reaction. Aromatic alkynes containing −CH$_3$, −Br, and −NO$_2$ groups at the 4-position of benzene rings underwent this reaction smoothly, affording the targeted products **4j–l** in moderate to good yield. Alkynyl-substituted dihydropyridine **4m** could also be obtained by using a buta-1,3-diyn-1-ylbenzene as the substrate. Other aliphatic alkynes including 1-ethynylcyclohex-1-ene and ethynylcyclopropane were also suitable substrates for this conversion to give products **4n** and **4o** successfully, albeit in lower yields. Nevertheless, it was unsuccessful to isolate the desired product from the reaction of hex-1-yne in which a complicated mixture was formed. Moreover, variation of the sulfonyl azide component (R^3 = 4-AcNHC$_6$H$_4$) was also tolerated; the corresponding product **4p** was obtained in 55% yield.

Scheme 2. Synthesis of Dihydropyridines 4[a]



[a] Reaction conditions: (1) **1** (0.2 mmol), **2** (0.3 mmol), **3** (0.3 mmol), CuI (10 mol %), 4 Å MS (100 mg), and Et$_4$NI (10 mol %) in THF/*t*-BuOH (v/v = 10:1) under N$_2$ at 25 °C, then Cs$_2$CO$_3$ (0.6 mmol); (2) saturated aqueous NH$_4$Cl (10 mL). The yields are of the isolated products.

Functionalized pyridines **5** were easily derived from **4** by NaOH (3 equiv) in methanol with retained ester groups in 67–91% yield:



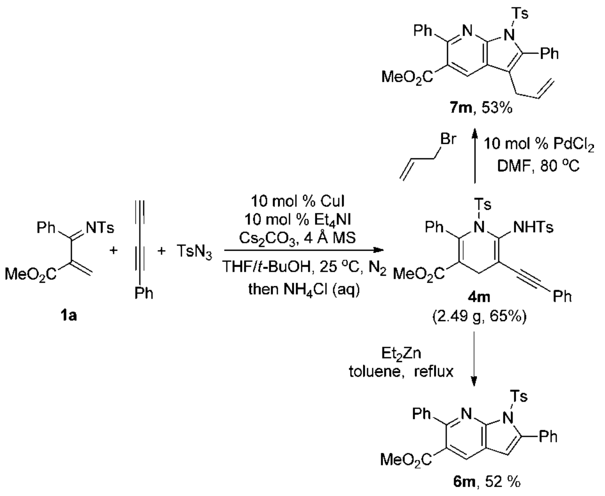
4 **5** (1)

5a R^1 = Ph, 91%
5i R^1 = 2-thienyl, 79%
5k R^1 = 4-BrC$_6$H$_4$, 83%
5m R^1 = Ph—≡—, 67%

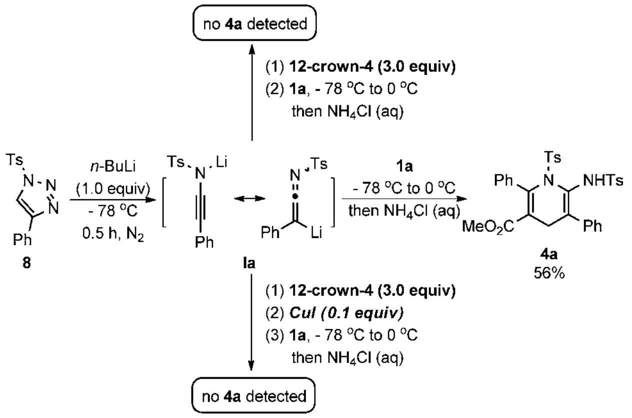
However, the present cycloaddition process could be easily carried out on a multigram scale, for example, to produce versatile dihydropyridine **4m** in 65% yield (Scheme 3). Upon treatment with Et$_2$Zn (2.2 equiv), dihydropyridine **4m** underwent an aromatization/cyclization cascade smoothly, resulting in the formation of *N*-tosyl-7-azaindole **6m** in 52% yield. The reaction of **4m** and 3-bromoprop-1-ene catalyzed by PdCl$_2$ in DMF at 80 °C directly furnished 7-azaindole **7m** in 53% yield through a palladium-catalyzed desulfonation/cyclization/coupling sequence. Notably, 7-azaindole is one class of azaindole compounds, which constitute essential subunits in many pharmaceutically important compounds and have also found applications in material synthesis and coordination chemistry.[13]

To gain preliminary understanding of possible pathways of the multicomponent reaction of 1-azadienes **1**, terminal alkynes **2**,

Scheme 3. Formation of 7-Azaindoles 6m and 7m



Scheme 4. Preliminary Mechanistic Investigations

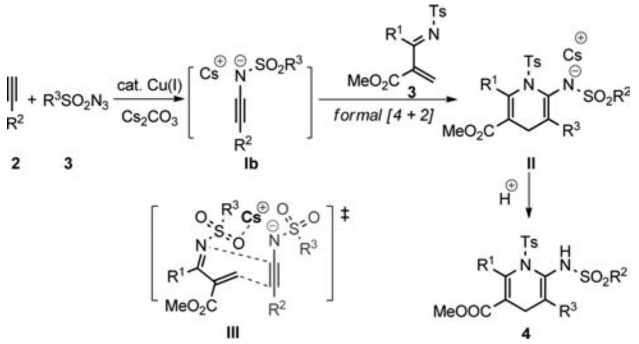


and sulfonyl azides **3**, several control experiments of 1-sulfonyltriazole **8** and **1a** were conducted (Scheme 4). After decomposition of **8** by *n*-butyllithium at −78 °C, as expected, the resulting lithium ynamidate **Ia** reacted with azadiene **1a** smoothly, leading to the formation of dihydropyridine **4a** in 56% yield. However, in the presence of 3 equiv of [12]crown-4, no desired **4a** was observed regardless of the absence or the presence of catalytic amounts of CuI.[14] These results suggested that lithium cation is presumably required for the current cycloaddition process as Lewis acid, while previous reports on the Lewis acid-catalyzed formal IEDDA reaction of azadienes employed transition-metal salts[5c] or boron-containing compounds[15] as the catalysts.

A plausible pathway for this tandem reaction is depicted in Scheme 5. Initial CuI-catalyzed cascade reaction of terminal alkyne **2** and azide **3** in the presence of stoichiometric amounts of Cs_2CO_3 generates cesium ynamidate **Ib**, which undergoes cyclization with 1-azadiene **3** to afford [4 + 2] cycloadduct **II**. Given the critical effect of lithium cation on delivering product **4a** in control experiments, a transient complex **III** would be involved in this formal cycloaddition step, wherein the cesium cation acts as a Lewis acid to facilitate the formation of **II**. Finally, the protonation of **II** with aqueous NH_4Cl then furnishes the targeted product **4**.

In conclusion, we have developed a three-component reaction of terminal alkynes, sulfonyl azides, and *N*-sulfonyl-1-aza-1,3-butadienes, providing access to densely functionalized 1,4-dihydropyridine compounds, which constitute a versatile scaffold for the synthesis of pyridine and 7-azaindole derivatives. Mechanically, this synthetic procedure proceeds through a formal IEDDA reaction of electron-deficient 1-azadienes with metalated ynamide intermediates arising from a Cu-catalyzed azide−alkyne reaction in the presence of stoichiometric amounts of Cs_2CO_3. Experimental results suggest that alkali metal cations (Li^+ and Cs^+ ions) might play a critical role in this formal [4 + 2] cycloaddition process.

Scheme 5. Proposed Reaction Pathway



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data of **4a**, experimental procedures, and characterization data of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01622.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21372196) and the Zhejiang Provincial Natural Science Foundation of China (R4110055) for financial support.

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DOI: 10.1021/acs.orglett.5b01622
Org. Lett. 2015, 17, 3536−3539