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Copper-catalyzed reaction of secondary propargylamines with ethyl buta-2,3-dienoate for the synthesis of 1,6-dihydropyridines

Chao Liu,[a] Gaigai Wang,[a] Yuqing Wang,[a] Olga P. Pereshivko*[a] and Vsevolod A. Peshkov*[a],[b]

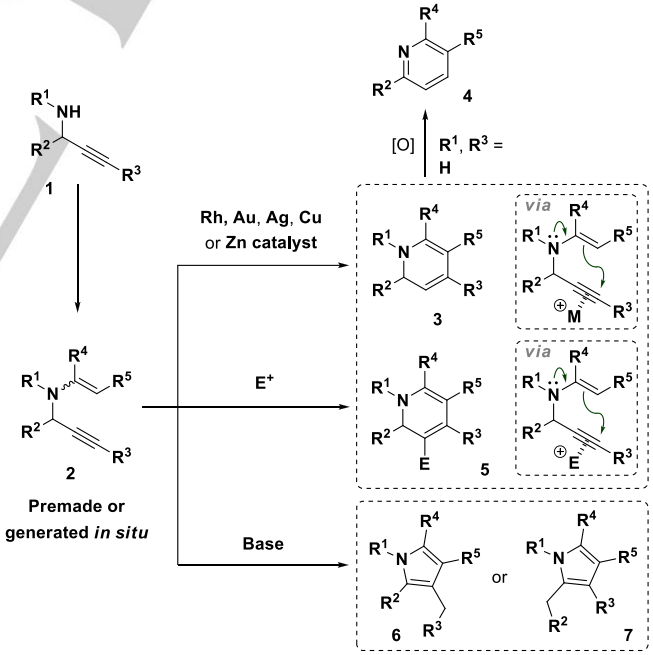
Abstract: A copper(I) bromide-catalyzed reaction of A^3-coupling-derived propargylamines with ethyl buta-2,3-dienoate for the fast assembly of a 1,6-dihydropyridine core is described. The developed protocol was tested on a variety of secondary propargylamines and the possibility of a one-pot synthesis of 1,6-dihydropyridine through the A^3-coupling and subsequent ethyl buta-2,3-dienoate incorporation was investigated.

Introduction

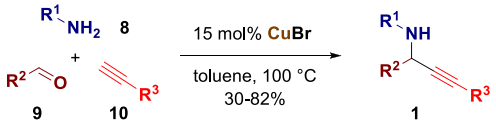
Propargylic compounds are convenient building blocks for the generation of a large variety of heterocyclic molecules.[1] For example, 1,5-enynes **2** derived from propargylamines or amides **1** are known to undergo 6-endo-dig cycloisomerizations into dihydropyridines (DHPs) **3** under rhodium,[2] gold,[3] silver,[4] copper[5] and zinc[6] catalysis (Scheme 1). Furthermore, for the substrates derived from terminal primary propargylamines, the initially obtained dihydropyridines **3** could be in situ oxidized into pyridines **4**.[4b] Analogously to metal-catalyzed transformations, electrophile-mediated cyclizations of **2** occur in 6-endo-dig fashion producing dihydropyridines **4** (Scheme 1).[7,8] In contrast, base-mediated transformations of 1,5-enynes **2** selectively deliver isomeric pyrroles **6** or **7** depending on the applied reaction conditions (Scheme 1).[5a,9,10]

Results and Discussion

Despite that the above procedures collectively cover broad substrate scope towards divergent products, most of them suffer from various limitations. In particular, the most common drawbacks for the reactions leading to dihydropyridines **3** include the necessity to use expensive catalysts as well as tedious preparation of starting materials that imposes additional restrictions on the substrate's substitution pattern. For example, recent copper-catalyzed protocol of Oguri and coworkers[4a] was mainly tested for the terminal propargylenamines **2** unsubstituted at the propargylic position. We decided to address this issue by taking an advantage of a metal-catalyzed three-component coupling of amines, aldehydes and alkynes (A^3-coupling) that has been recently emerged as a major tool for the generation of various classes of propargylamines.[11] Consecutively, we have prepared a number of secondary propargylamines **1** by the copper(I) bromide-catalyzed A^3-coupling of primary amines **8**, aldehydes **9** and terminal alkynes **10** (Scheme 2).[12] Next, we attempted to react propargylamine **1a** with various electron-deficient alkynes **11a-c** aiming to generate 1,5-enynes **2** (Scheme 3). Using ethyl propiolate (**11a**) and diethyl acetylenedicarboxylate (**11b**), 1,5-enynes **2a** and **2b** were obtained in 75% and 98%, respectively. In contrast, treatment of **1a** with ethyl but-2-ynoate (**11c**) failed to yield the expected enyne **2c**, which could be attributed to a lower electrophilicity of **11c** compared to **11a** and **11b**. Nevertheless, both **2a** and **2b** could be successfully converted into corresponding dihydropyridines **3a** and **3b** with the aid of cationic copper(I) complex $[Cu(MeCN)_4]PF_6$ following a modified Oguri's protocol (Scheme 3).



Scheme 1. Cyclizations of 1,5-enynes **2**.



Scheme 2. Synthesis of starting propargylamines **1**.

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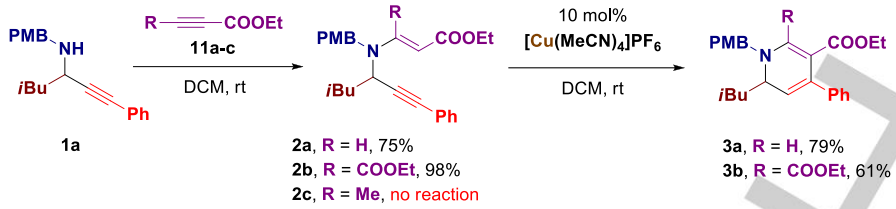
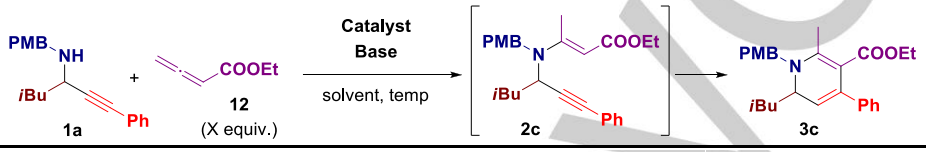


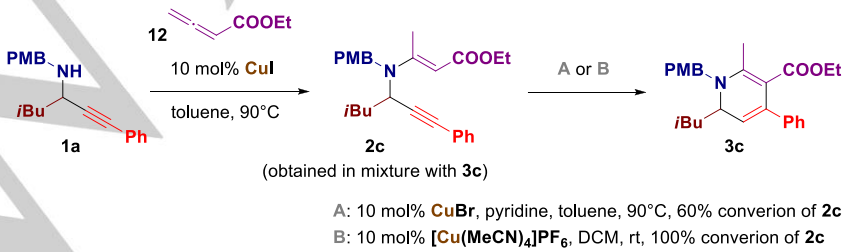
Scheme 3. Two-step synthesis of dihydropyridines **3a** and **3b** based on Oguri's Cu-catalyzed protocol.

Table 1. Screening the conditions for the reaction of propargylamine **1a** and ethyl buta-2,3-dienoate (**12**)[a]



Entry	X, equiv	Catalyst, mol%	Base	Solvent	Dilution	Temp., °C	Time, h[b]	Conversion of **1a**,[c] %	Yield,[c] %	
									3c	**2c**
1	1.2	-	-	toluene	0.2 M	110	40 min	29	-	27
2	1.2	-	-	toluene	0.2 M	90	40	90	7	43
3	1.2	$[Cu(MeCN)_4]PF_6$, 10	-	DCM	0.1 M	rt	2	84	9	59
4	1.2	$[Cu(MeCN)_4]PF_6$, 10	-	DCM	0.1 M	rt	6	90	30	37
5	1.2	$Cu(OTf)_2$, 15	-	toluene	0.2 M	110	40 min	95	32	-
6	1.5	$Cu(OTf)_2$, 10	-	toluene	0.2 M	90	2	100	33	-
7	1.5	AgOTf, 10	-	toluene	0.2 M	90	2	81	38	-
8	1.5	CuI, 10	-	toluene	0.2 M	90	2	100	39	33
9	1.5	CuBr, 10	-	toluene	0.2 M	90	2	100	62	-
10	1.5	CuBr, 10	-	1.4-dioxane	0.2 M	90	2	100	45	-
11	1.5	CuBr, 10	-	DMF	0.2 M	90	2	100	51	-
12	1.5	CuBr, 10	-	toluene	0.4 M	90	2	100	66	-
13[d]	1.5	CuBr, 10	Et_3N	toluene	0.4 M	90	2	100	74	-
14[d]	1.5	CuBr, 10	Pyridine	toluene	0.4 M	90	2	100	78 (76)[e]	-
15[d]	1.5	-	Pyridine	toluene	0.4 M	90	2	100	3	82

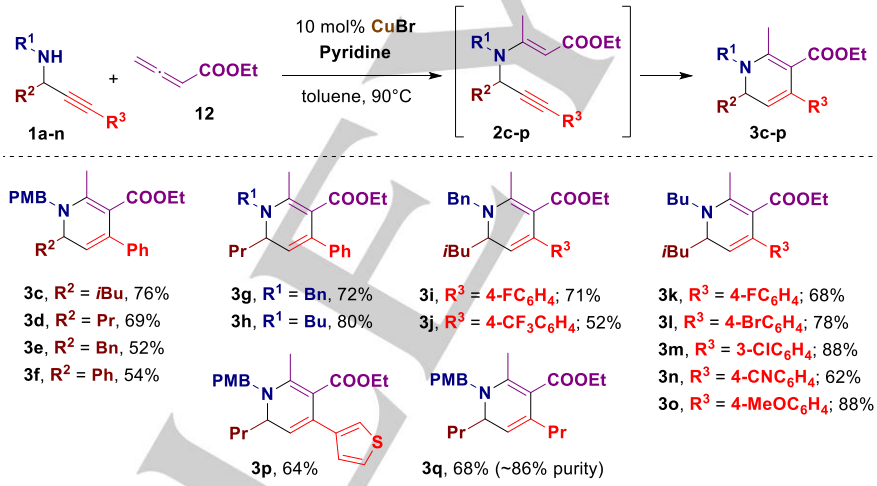
[a] All reactions were conducted on 0.2 mmol scale. [b] The reaction time is in hours, unless otherwise indicated. [c] Determined by ^1H NMR using 3,4,5-trimethoxybenzaldehyde as an internal standard. [d] The reactions were conducted in the presence of 1 equiv of base. [e] Isolated yield for a 0.5 mmol scale reaction is given in parenthesis.



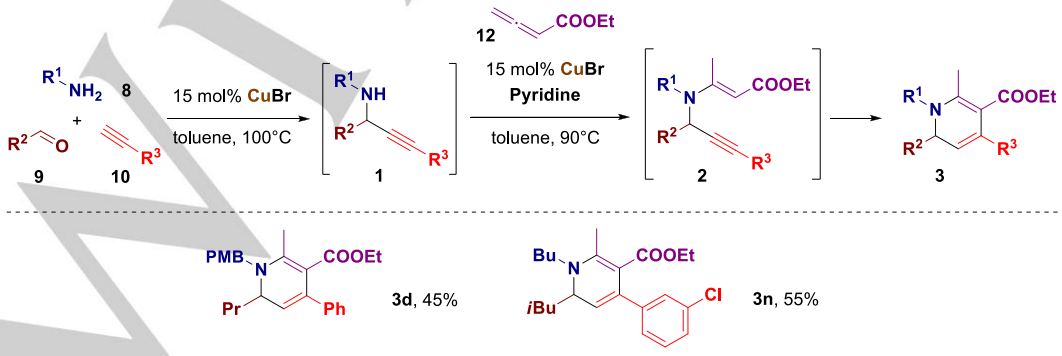
Scheme 4. Stepwise synthesis of dihydropyridine **3c**.

It is well known, that secondary propargylamines can undergo additions to a number of heteroallenes allowing to assemble a variety of heterocycles through the subsequent transition metal-catalyzed or electrophile-mediated cyclizations.[13-15] Considering this, we decided to investigate an addition of propargylamine **1a** to ethyl buta-2,3-dienoate (**12**) in an attempt to overcome the limitation arisen from the inability of former to react with electron-deficient alkyne **11c** (Table 1). We were pleased to find that buta-2,3-dienoate (**12**) turned out to be a stronger electrophile than ethyl but-2-ynoate (**11c**). However, reacting **1a** with **12** in toluene at 110°C for 40 min resulted in only a poor conversion of **1a**, yielding 1,5-enyne **2c** in only 27% (Table 1, entry 1). Conducting the reaction at 90°C over extended time of 40 h led to an improved conversion, producing 1,5-enyne **2c** along with corresponding dihydropyridine **3c** in 43% and 7% yield, respectively (entry 2). Encouraged by this result, we decided to evaluate the reaction of **1a** and **12** in the presence of various catalysts aiming for the direct synthesis of dihydropyridine **3c**. Initially, we have attempted to utilize cationic tetrakis(acetonitrile)copper(I) hexafluorophosphate complex. Carrying out the reactions in DCM at rt delivered dihydropyridine **3c** in up to 30% yield albeit in a mixture with uncyclized enyne **2c** and unreacted propargylamine **1a** (entries 3 and 4). Next, we decided to evaluate copper(II)[16] and silver(I)[17] triflates that were proved to be promising catalysts in a number of heterocyclizations involving triple bond. Using toluene as reaction media at the temperature of 110 or 90°C, dihydropyridine **3c** was obtained with the yields ranging from 32% to 38% (entries 5-7). Consequently, we have turned our attention to copper(I) iodide and copper(I) bromide that were also reported as efficient triple bond activators.[18] While copper(I) iodide produced a mixture of **2c** and **3c** (entry 8), copper(I) bromide delivered dihydropyridine **3c** in a 62% yield as a sole reaction product (entry 9). Changing toluene to other solvents led to decreased yield of **3c** (entries 10 and 11), while lowering toluene's volume resulted in a small improvement (entry 12). Finally, introducing 1 equiv of a mild organic base led to another substantial upgrade of the reaction outcome allowing to obtain **3c** in up to 76% isolated yield (entries 13 and 14). To investigate the role of base, we conducted a control experiment in the absence of copper catalyst (entry 15). This resulted in a complete conversion of propargylamine **1a** into 1,5-enyne **2c** underlying a beneficial influence of base on the addition of **1a** to buta-2,3-dienoate (**12**).

Interestingly, the copper(I) bromide/pyridine-catalyzed conditions found above turned out to be unsuitable for the stepwise synthesis of **3c**. When the mixture of 1,5-enyne **2c** and dihydropyridine **3c** obtained by the copper(I) iodide-catalyzed



Scheme 5. Copper-catalyzed synthesis of dihydropyridines **3** from secondary propargylamines **1** and ethyl buta-2,3-dienoate (**12**).



Scheme 6. One-pot A^3-coupling/ethyl buta-2,3-dienoate addition for the synthesis of dihydropyridines **3**.

reaction (Table 1, entry 8) was resubjected to the copper(I) bromide-catalyzed protocol in the presence of pyridine base no full conversion of **2c** into **3c** could be achieved (Scheme 4, conditions A). In contrast, treating the same mixture with cationic $[Cu(MeCN)_4]PF_6$ catalyst could effectively drive the cycloisomerization of **2c** to completion (Scheme 4, conditions B). To sum up, our procedure allows to efficiently assemble dihydropyridines **3** directly from propargylamines **1** through a one-pot addition to buta-2,3-dienoate (**12**) and subsequent cycloisomerization while Oguri's protocol appears to be a better choice for accessing **3** from premade 1,5-enynes **2**.

Scheme 5 summarizes the scope of our new copper-catalyzed protocol for the direct synthesis of 1,6-dihydropyridines **3** from secondary propargylamines **1** and ethyl buta-2,3-dienoate (**12**). Examining the substrates substituted differently at the propargylic position, it can be concluded that the aliphatic substituents give slightly better results as compared to benzylic and aromatic (Scheme 5, products **3c** and **3d** versus **3e** and **3f**). As for the nitrogen atom, both alkyl and benzyl substituted substrates produced dihydropyridines **3d,g,h** in consistently good yields. With regard to the triple bond, both aromatic and heteroaromatic substituents were well tolerated allowing to obtain products **3i-p** in up to 88% yield. Substrates bearing electron-deficient aromatic groups on the triple bond produced dihydropyridines **3j** and **3n** in moderate yields of 52% and 62%, respectively. Utilizing aliphatic propargylamine led to unclean reaction delivering dihydropyridine **3q** in a mixture with unidentified impurities.

Finally, we have explored the possibility of merging A^3-coupling and ethyl buta-2,3-dienoate incorporation in a two-step one-pot process, since both of these transformations are operated under copper(I) bromide catalysis. As a result of these efforts, 1,6-dihydropyridines **3d** and **3n** were prepared in 45% and 55% yields, starting directly from amines **8**, aldehydes **9** and alkynes **10** with no need in isolating intermediate propargylamines **1** (Scheme 6).

Conclusions

In summary, we have elaborated a copper-catalyzed protocol for the synthesis of 1,6-dihydropyridines that involves the addition of secondary propargylamines to ethyl buta-2,3-dienoate and subsequent cycloisomerization of resulting 1,5-enynes. This novel process is complementary to the known syntheses of pyridine derivatives from either premade 1,5-enynes[2,3,4a,5,7,8] or from those that are generated *in situ* from propargylamines and electron-deficient alkynes.[4b,6]

Experimental Section

General remarks

Unless otherwise specified, the starting materials and solvents were purchased from commercial sources and used as received. Melting points were measured using INESA WRR apparatus. Infrared (FT-IR) spectra were recorded neat on a Bruker Vertex 70. ^{1}H (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded using a Bruker Avance III HD instrument. The ^{1}H and ^{13}C chemical shifts are reported relative to TMS using the residual $CDCl_3$ signal as internal reference. HRMS were performed on a Bruker micrOTF-Q III.

General procedure for copper-catalyzed synthesis of dihydropyridines 3 from secondary propargylamines 1 and ethyl buta-2,3-dienoate (12)

Propargylamine **1** (0.8 mmol) was places in a screw cap vial followed by addition of toluene (1 mL), ethyl buta-2,3-dienoate **12** (135 mg, 1.2 mmol), CuBr (11.5, 0.08 mmol), and pyridine (63 mg, 0.8 mmol). The resulting mixture was flashed with argon, sealed and stirred at 90°C for 2 h. Upon completion of this time, the mixture was diluted with ethyl acetate and transferred to the round bottom flask. Then the silica gel was added and the mixture was concentrated under reduced pressure. Column chromatography on silica gel using petroleum ether-ethyl acetate (49:1→9:1) as eluent provided dihydropyridine **3**.

Acknowledgements

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Keywords: allenes • copper • cyclization • 1,6-dihydropyridines • propargylamines

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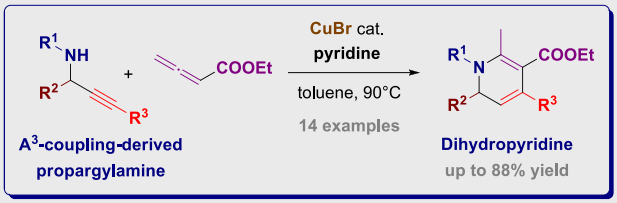

A copper(I) bromide-catalysed reaction of A^3-coupling-derived propargylamines with ethyl buta-2,3-dienoate for the fast assembly of a 1,6-dihydropyridine core is described. The possibility of a one-pot synthesis of 1,6-dihydropyridine through the A^3-coupling and subsequent ethyl buta-2,3-dienoate incorporation was investigated.

1,6-Dihydropyridines

Chao Liu, Gaigai Wang, Yuqing Wang, Olga P. Pereshivko, Vsevolod A. Peshkov**

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Copper-catalyzed reaction of secondary propargylamines with ethyl buta-2,3-dienoate for the synthesis of 1,6-dihydropyridines