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Synthesis of 1,4-Dihydropyridazines from Propargylic Alcohols and Hydrazones via a Cs_2CO_3-mediated Process

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An efficient catalyst-free annulation process between propargylic alcohols and hydrazones has been reported. Under the optimized conditions, a wide variety of propargylic alcohols bearing an aromatic group or an aromatic heterocyclic group and hydrazones were well tolerated to afford the corresponding 1,4-dihydropyridazines in moderate to good yields via a Cs_2CO_3-mediated process.

Keywords: Pyridazine | Drug | Propargylic alcohol

Pyridazines and its derivatives have been proven to be the core units of many commercial drugs and related candidates (Figure 1), which deserve chemists' attention.[1] For instance, chloridazon[2] and pyridate[3] are extensively employed for weed control. Minaprine[4] is recognized as selective GABA-A receptor antagonists, which is an antidepressant. Moreover, the calcium-sensitizing inotropic agent levosimendan and cardiotonic vasodilator pimobendan are present in the market.

Among pyridazine derivatives, 1,4-dihydropyridazines are a class of compounds that is receiving much attention for their versatile pharmacological activities such as anti-inflammatory[5] and antihypertensive.[6] For these reasons, a variety of strategies have been developed for the synthesis of 1,4-dihydropyridazines and the reports of the synthetic methods of 1,4-dihydropyridazine rings could be classified in four methods: 1) from the reaction of 1,2-diaza-1,3-butadienes with activated methine compounds,[7] 2) from the reactions of tetrazines with unsaturated compounds,[8] 3) from the acid-catalyzed reaction of α,β-unsaturated ketones and hydrazones,[9] and 4) from the reaction based on cyclopropenecarboxylic acids[10] or 1,2-diazepin-4-ones.[11] Our group has been making great efforts to synthesize heterocycles by using propargylic alcohols as the substrates.[12] As part of our continuing work in this area, we herein report the synthesis of highly arylated 1,4-dihydropyridazines from propargylic alcohols and hydrazones via a Cs_2CO_3-mediated process.

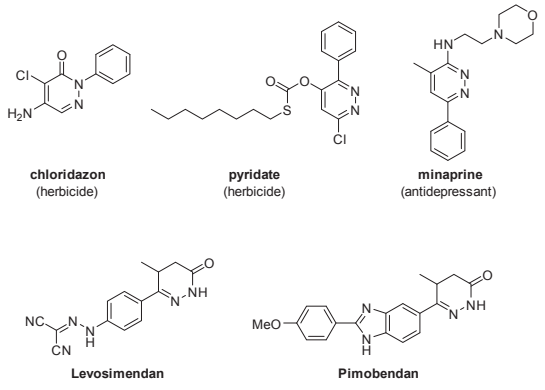
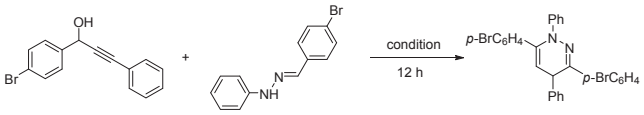


Figure 1. Several herbicides and drugs.

Initially, substrates **1a** and **2a** were treated with Cs_2CO_3 (1.5 equiv) in dichloromethane (DCM) under room temperature (r.t.), which, however, gave no product at all (Table 1, Entry 1). The solvent 1,2-dichloroethane (DCE) or 1,4-dioxane led to the recovery of the starting materials (Table 1, Entries 2 and 3). To our delight, the reaction performed in CH_3CN can result in 42% yield of the aimed product (Table 1, Entry 4). The test of the other solvents such as CH_3NO_2, THF, and PhCl was unsuccessful (Table 1, Entries 5–7). In contrast, the use of dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) as solvents could increase the reaction yield to 65% and 54%, respectively (Table 1, Entries 8 and 9). Bases screening indicated that bases including K_2CO_3, CsF, NaH, *t*-BuOK, and NaOH either did not lead to any detectable product formation or decreased the yield (Table 1, Entries 10–14). Furthermore, the amounts of Cs_2CO_3 were also tested, and the results reveal that reducing the amounts of Cs_2CO_3 to 1 equiv led to the decreasing yield of the aimed product (Table 1, Entry 15), and raising the amounts gave a more excellent reaction yield (Table 1, Entry 16). Hence, the optimal reaction conditions for this reaction were determined

Table 1. Optimization of reaction conditions[a]

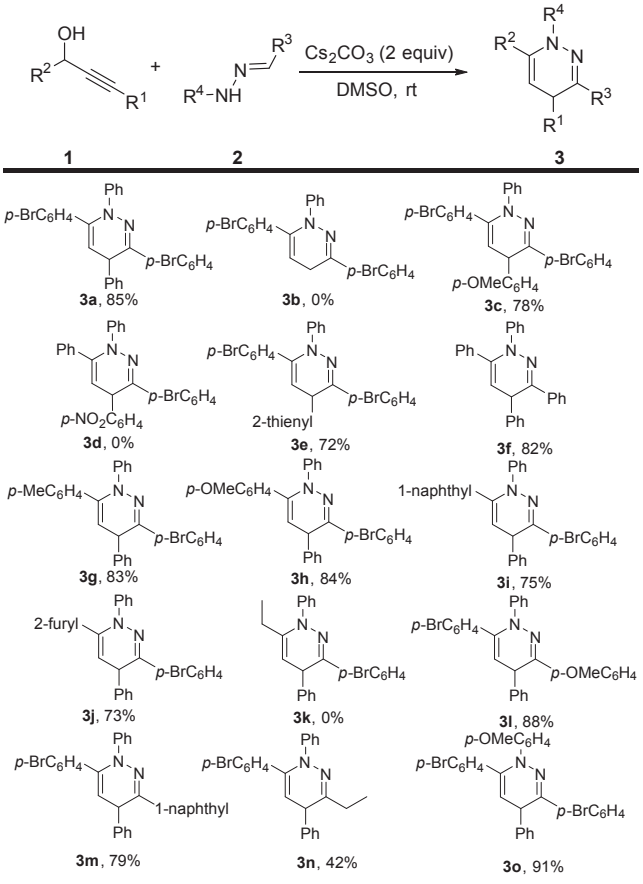


1a 2a 3a

Entry	Base (equiv)	Solvent	Yield[b]/%
1	Cs_2CO_3 (1.5 equiv)	DCM	n.r.[c]
2	Cs_2CO_3 (1.5 equiv)	DCE	n.r.
3	Cs_2CO_3 (1.5 equiv)	1,4-dioxane	n.r.
4	Cs_2CO_3 (1.5 equiv)	CH_3CN	42
5	Cs_2CO_3 (1.5 equiv)	CH_3NO_2	n.r.
6	Cs_2CO_3 (1.5 equiv)	THF	n.r.
7	Cs_2CO_3 (1.5 equiv)	PhCl	n.r.
8	Cs_2CO_3 (1.5 equiv)	DMSO	65
9	Cs_2CO_3 (1.5 equiv)	DMF	54
10	K_2CO_3 (1.5 equiv)	DMSO	n.r.
11	CsF (1.5 equiv)	DMSO	15
12	NaH (1.5 equiv)	DMSO	38
13	*t*-BuOK (1.5 equiv)	DMSO	47
14	NaOH (1.5 equiv)	DMSO	36
15	Cs_2CO_3 (1.0 equiv)	DMSO	52
16	Cs_2CO_3 (2.0 equiv)	DMSO	85

[a]Reaction conditions: **2a** (0.3 mmol), **1a** (0.36 mmol), solvent (5 mL), room temperature (r.t.), in schlenk tube. [b]Isolated yield. [c]n.r.: no reaction.

Table 2. The synthesis of 1,4-dihydropyridazine[a,b]



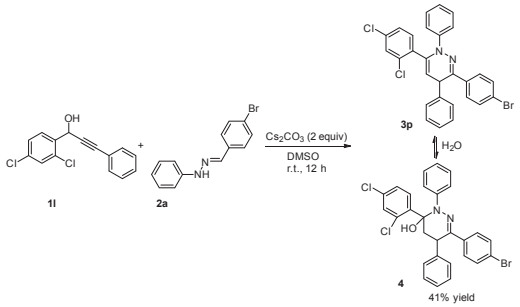
[a]Reaction conditions: **2** (0.3 mmol), **1** (0.36 mmol), solvent (5 mL), room temperature (r.t.), in schlenk tube. [b]Isolated yield.

to be performing the reaction in DMSO at room temperature with Cs_2CO_3 (2.0 equiv) as the base for about 12 h (Table 1, Entry 16).

We next evaluated the scope of the reaction under the optimal conditions by placing different substituents (R^1, R^2, R^3, R^4) on various positions of propargylic alcohols **1** and hydrazones **2** (Table 2). First of all, we tested the influence of R^1 on propargylic alcohols **1**. A terminal alkyne ($R^1 = H$) was not tolerated in this reaction, which could not lead to the aimed product (Table 2, product **3b**, 0% yield). The alkynyl position R^1 was found to the tolerate phenyl group substituted with an electron-donating group (OMe) (Table 2, product **3c**, 78% yield), but the phenyl group substituted with an electron-withdrawing group (NO_2) seemed to completely abolish the 1,4-dihydropyridazine formation, which gave 0% yield of product **3d**. The investigation of the R^1 group also revealed that heteroaryl-substituted substrate **1e** could react smoothly to give the aimed product **3e** in 72% yield.

Next, the R^2 group at the propargylic position was examined. The substrate bearing a phenyl group could react smoothly to give the aimed product **3f** in 82% yield.

Similarly, substrates bearing *p*-MeC_6H_4 and *p*-$OMeC_6H_4$ groups at the propargylic position also gave product **3g** and **3h** in 83% and 84% yields, respectively. In addition, 1,4-dihydropyridazines **3i** was obtained in good reaction yield as well. Moreover, 2-furyl-substituted substrate could also react smoothly to give product **3j** in 73% yield. However, the disappointing thing was that the ethyl substituent was not tolerated in this reaction (Table 2, product **3k**, 0% yield).



Scheme 1. The reaction of substrate **1l** and **2a**.

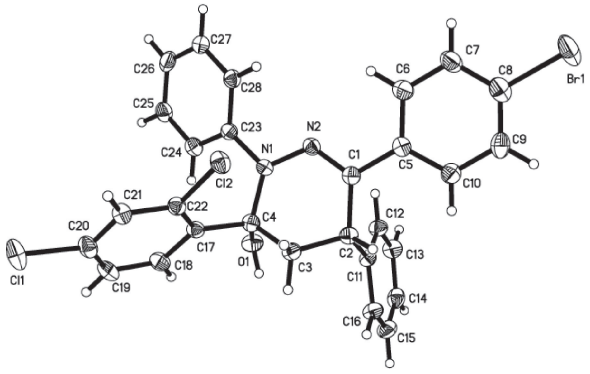


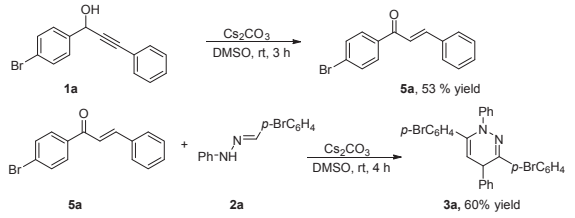
Figure 2. X-ray crystal structure of product **4**.

Finally, we investigated the influence of R^3 and R^4 on hydrazones **2**. When R^3 were *p*-$OMeC_6H_4$ and 1-naphthyl, corresponding 1,4-dihydropyridazines were formed in 88% and 79% yields, respectively. Of note is that hydrazone derived from propanal as a substituent was also tolerated and the related substrate was transformed into the aimed product **3n** in 42% yield. Additionally, replacing the R^4 phenyl group with *p*-$OMeC_6H_4$ also gave the aimed product **3o** in 91% yield.

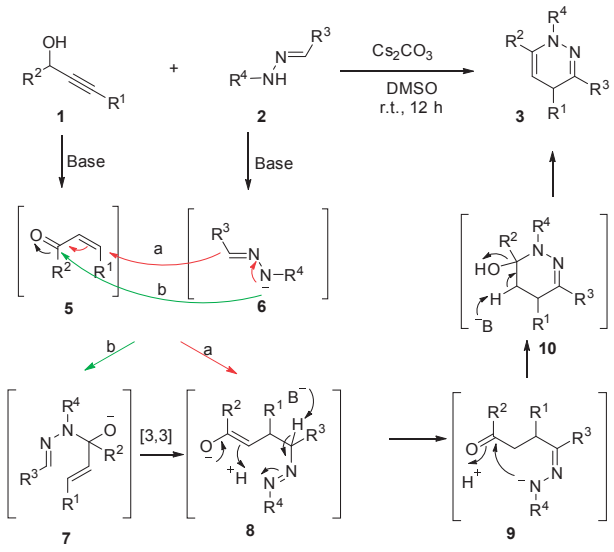
Note that when propargylic alcohols **1l** and hydrazone **2a** were tested as the substrates to synthesize product **3p** under the optimal conditions (Scheme 1), 6-hydroxyl-1,4,5-trihydropyridazine **4** was isolated in 41% yield and the definite structure of **4** was confirmed by single-crystal X-ray diffraction analysis (Figure 2). We conjectured that **4** came from the hydrolysis of **3p** when the crude product was purified by silica gel column chromatography, and the transformation of **3p** to **4** was reversible.

As a note, under the optimal conditions, propargylic alcohol **1a** could smoothly convert to α,β-unsaturated ketone **5a**, and we could obtain the final product **3a** from the reaction between **5a** and **2a** in 60% yield (Scheme 2).

Based on the experimental results presented above and our previous reports, a proposed reaction mechanism is depicted in Scheme 3. Firstly, under the base condition, propargylic alcohol **1** was transformed to α,β-unsaturated ketone **5**[13] and hydrazone **2** converted to intermediate **6**. There are two possible reaction



Scheme 2. Control experiment.



Scheme 3. Proposed mechanism.

routes for the further step. One is the Michael addition reaction process (path a), which will result in intermediate **8**. The other is nucleophilic addition from nitrogen anion of **6** to carbonyl group of **5** (path b), which gave intermediate **7** and then transformed to intermediate **8** via a [3,3] rearrangement process. Eventually, product **3** is obtained by the condensation of intermediate **9**. In the case of $R^1 = H$ and $R^2 =$ ethyl, the α,β-enone formation step may be inhibited, resulting in no aimed product of **3b** and **3k**.

In conclusion, we have reported a highly efficient method for the synthesis of 1,4-dihydropyridazines from propargylic alcohols and hydrazones via a Cs_2CO_3-mediated process. This protocol provided an alternative way to synthetize 1,4-dihydropyridazines.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.160397.

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