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Synthesis of 1,2-Dihydrocyclobuta[b]quinoline Derivatives from Isocyanophenyl-Substituted Methylenecyclopropanes

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Abstract. A new protocol to synthesize 1,2-dihydrocyclobuta[b]quinoline derivatives from isocyanophenyl-substituted methylenecyclopropanes via a formal insertion of isocyanide carbon into a C-C bond has been developed. The reaction proceeds smoothly in the presence of silver carbonate (5 mol%) upon heating in a highly atom economic manner and exhibits broad substrate scope, giving the desired products in moderate to excellent yields. Furthermore, several transformations of the obtained products have been also demonstrated.

Keywords: isocyanide; methylenecyclopropane; quinoline; aromatic heterocycles.

Isocyanides as pivotal species in organic chemistry have been widely used to synthesize a diversity of nitrogen-containing compounds, especially in the preparation of aromatic heterocycles.[1] They have exhibited versatile reaction properties in organic synthesis. For example, the α proton next to isocyano moiety has high acidity due to the electron-withdrawing effect of the isocyano moiety,[2] and thus isocyanides can serve as nitrilium ylides after abstraction of the α-H group.[3] Moreover, they can also undergo radical insertion,[4] form metal carbenes with a transition metal catalyst,[5] insert into a C-heteroatom bond,[6] undergo dimerization,[7] and act as a zwitterion to accept nucleophilic attack,[8] or even function as a cyanide resource in further chemical transformations.[9] Among these interesting transformations, the insertion into a C-heteroatom bond has been well investigated, but the insertion into a C-C bond is still undeveloped due to the unpolarized high C-C bond energy.[10]

During the past decades, multi-component reactions have been developed significantly and utilized as a powerful protocol to rapidly construct complex molecules.[11] Alternatively, employing mono-component intramolecular cyclization reactions is also a good strategy to effectively construct polycyclic structural motifs.

Methylenecyclopropanes (MCPs), classical highly strained small ring compounds, are efficient building blocks in organic synthesis due to their ready accessibility as well as diverse reactivity driven by the relief of ring strain. The ring opening reactions of MCPs are synthetically useful in the construction of complex product structures, and have been studied extensively.[12] Especially, MCPs could be used as a C_3 synthon to construct polycyclic systems, which have attracted a lot of attention from organic chemists in the past decades.[13] More recently, several novel formal intramolecular [3+2] cascade cycloadditions of MCPs with alkynes or the in situ generated ketenimines, isocyanates and isothiocyanates have been also developed for the diversified synthesis of fused polycyclic compounds.[14] For example, we have previously reported a visible-light-induced trifluoromethylation of isocyanophenyl-substituted alkylidenecyclopropanes to access 2-trifluoromethylquinoline derivatives using Togni reagent via an intramolecular radical cyclization with arene.[15] This interesting transformation encouraged us to further explore the new chemistry of isocyanophenyl-substituted alkylidenecyclopropanes or methylenecyclopropanes in the construction of heterocycles.

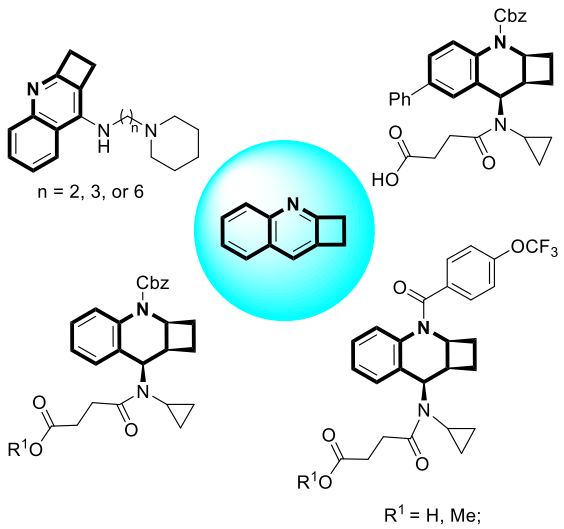

Figure 1. 1,2-Dihydrocyclobuta[b]quinoline structural motifs found in biologically active molecules.

1,2-Dihydrocyclobuta[b]quinolines have recently attracted a lot of attention because their highly strained heterocyclic systems are very useful in organic synthesis.[16] Moreover, they are special building blocks found in a sort of non-imidazole histamine H_3 antagonist molecules and chemoattractant receptor-homologous

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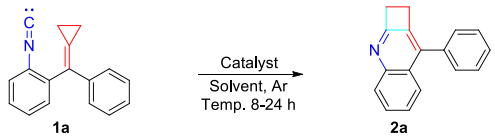
molecule expressed on T-helper-type-2-cells (CRTH2) receptor modulator (Figure 1).[17] In general, the previously reported preparation methods were carried out under harsh conditions, giving the products only in low yields.[18] Therefore, the development of convenient and efficient synthetic methods for this type of heterocyclic compounds is highly desirable at the present stage. Herein, we wish to report a formal intramolecular [3+1] cyclization reaction to acquire 1,2-dihydrocyclobuta[b]quinoline derivatives using isocyanophenyl-substituted methylenecyclopropanes as substrates upon heating in the presence of metal Lewis acid.

We initiated our investigation by heating a mixture of isocyanophenyl-substituted methylenecyclopropane **1a** and Ag_2CO_3 (20 mol%) in 1,4-dioxane at 80 °C and only trace amount of the desired 1,2-dihydrocyclobuta[b]quinoline derivative **2a** was detected (Table 1, entry 1). To our delight, when the reaction was carried out at 100 °C and 120 °C, the desired product **2a** was isolated in 23% and 86% yields, respectively (Table 1, entries 2-3). In the absence of Ag_2CO_3, the reaction still could proceed smoothly, giving **2a** in 52% yield, but suggesting that the addition of Ag_2CO_3 could indeed improve the reaction outcome (Table 1, entry 4). Concerning the background reaction (entry 4), we have confirmed that after all of the starting materials were consumed, the desired product **2a** was still provided in only 52% yield. The higher reaction temperature can also promote the decomposition of starting materials. Thus, raising the reaction temperature or prolonging the reaction time can not further enhance the yield of the desired product, and these operations cannot achieve a highly effective catalyst-free reaction. In addition, starting materials **1d** and **1i** from Table 2 have been also chosen for the reaction carried out under a catalyst-free condition, but no better result was obtained either (45% and 50% yields). Next, we screened several other metal salts such as CuBr, $Cu(OTf)_2$, $AgNTf_2$ and CF_3COOAg, but no better results could be achieved (Table 1, entries 5-8). Reducing the Ag_2CO_3 loading to 10 mol% or 5 mol% gave **2a** in 90% and 95% yields, respectively (Table 1, entries 9-10). The examination of solvent effect revealed that 1,2-dichloroethane (DCE), acetonitrile and toluene are not suitable for this reaction (Table 1, entries 11-13). The use of N,N-dimethylformamide (DMF) also gave **2a** in a relatively lower yield (Table 1, entry 14). We have also used the non-metallic Lewis acid $BF_3{\cdot}Et_2O$ (0.2 equiv) as the catalyst in this reaction, but it only leads to decomposition of the starting materials without formation of **2a** under the standard reaction conditions (entry 15).

Table 1. Optimization of the reaction conditions for the synthesis of **2a**.[a, b, c]

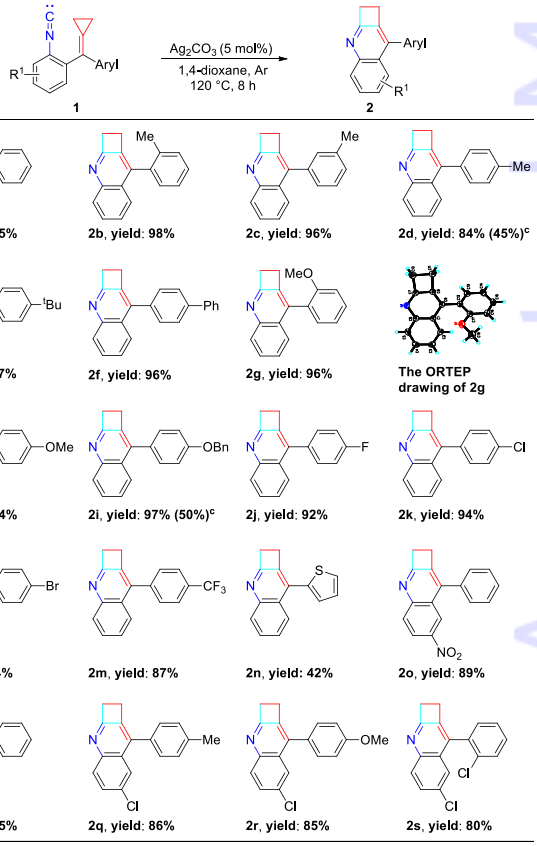


1a **2a**

Entry[a]	**1a** (equiv.)	Catalyst (equiv.)	Temp. (°C)	Solvent	**2a** Yield[b](%)
1	1.0	Ag_2CO_3 (0.20)	80	1, 4-dioxane	trace
2	1.0	Ag_2CO_3 (0.20)	100	1, 4-dioxane	23
3	1.0	Ag_2CO_3 (0.20)	120	1, 4-dioxane	86
4	1.0	-	120	1, 4-dioxane	52
5	1.0	CuBr (0.20)	120	1, 4-dioxane	47
6	1.0	$Cu(OTf)_2$ (0.20)	120	1, 4-dioxane	67
7	1.0	$AgNTf_2$ (0.20)	120	1, 4-dioxane	76
8	1.0	CF_3COOAg (0.20)	120	1, 4-dioxane	81
9	1.0	Ag_2CO_3 (0.10)	120	1, 4-dioxane	90
10	1.0	Ag_2CO_3 (0.05)	120	1, 4-dioxane	95
11	1.0	Ag_2CO_3 (0.05)	120	DCE	14[c]
12	1.0	Ag_2CO_3 (0.05)	120	CH_3CN	33[c]
13	1.0	Ag_2CO_3 (0.05)	120	Toluene	21
14	1.0	Ag_2CO_3 (0.05)	120	DMF	79
15	1.0	$BF_3 \cdot OEt_2$ (0.20)	120	1, 4-dioxane	-

[a] Reaction conditions: **1a** (0.10 mmol) and catalyst in solvent (1.0 mL) upon heating for 8-24 hours under an argon atmosphere.
[b] Isolated yields.
[c] Yields were determined by ^1H NMR spectroscopy (internal standard: 1, 3, 5-trimethoxybenzene).

Table 2. Reaction scope: Synthesis of 1,2-dihydrocyclobuta[b]quinoline derivatives.[a, b]

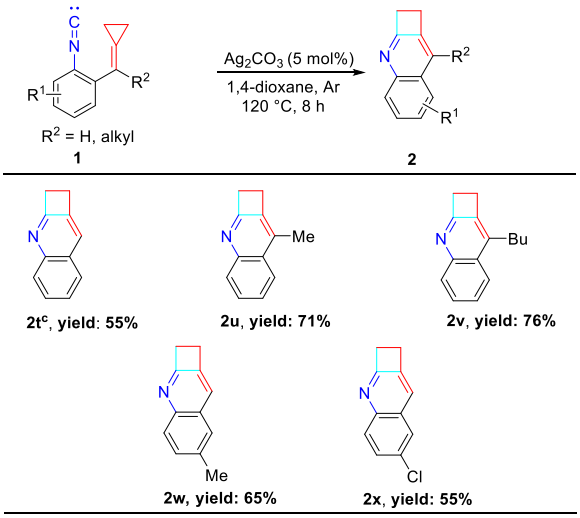


[a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv.) and Ag_2CO_3 (5 mol%) in 1,4-dioxane (2.0 mL) upon heating at 120 °C for 8 hours under an argon atmosphere.
[b] Isolated yields.
[c] The isolated yield under catalyst-free condition.

With the optimal reaction conditions (1.0 equiv. **1**, 5 mol% Ag_2CO_3 in 1,4-dioxane at 120 °C under an argon atmosphere) in

hand, we next surveyed the substrate scope with a range of different isocyanophenyl-substituted methylenecyclopropanes in this reaction. The results are summarized in Tables 2 and 3, respectively. As for substrates **1b**-**1m**, the reactions proceeded efficiently regardless of whether the aryl groups contained electron donating or withdrawing substituents, providing the corresponding products **2b**-**2m** in good to excellent yields. In addition, heteroaromatic group was also tolerated in the reaction, affording the desired product **2n** in 42% yield. The lower yield of **2n** was mainly due to the instability of thiophene-substituted substrate **1n** under the standard conditions. Nitryl or Cl substituent could be also introduced at the phenylisocyanide moiety, giving the corresponding products **2o**-**2s** in good yields. All these results suggested that the electronic effects on both of aromatic rings did not have significant impact on the reaction yield. The structure of **2g** was unambiguously confirmed by X-ray diffraction analysis, and its ORTEP drawing is shown in Table 2.[19]

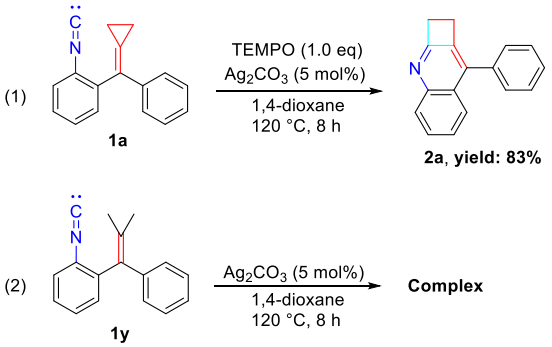
Table 3. Reaction scope: Synthesis of 1,2-dihydrocyclobuta[b]quinoline derivatives.[a, b, c]



[a] Unless otherwise specified, the reaction conditions are **1** (0.20 mmol, 1.0 equiv.) and Ag_2CO_3 (5 mol%) in 1,4-dioxane (2.0 mL) at 120 °C for 8 hours under an argon atmosphere.
[b] Isolated yield.
[c] The reaction temperature is 140 °C, the reaction time is 24 hours .

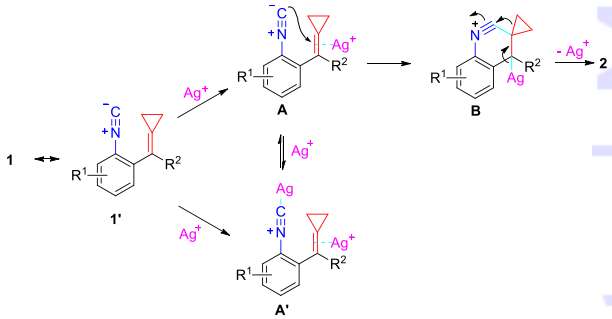
We further investigated substrates **1** containing aliphatic group or H atom in this reaction. As shown in Table 3, when R^2 is H atom, methyl or butyl group, the desired products **2t**-**2v** were furnished in moderate yields. For substrates **1w** and **1x**, in which R^2 is H atom, and the phenylisocyanide moiety was substituted by Me or Cl at the *para*-position, the reaction also proceeded smoothly, giving the desired products **2w** and **2x** in moderate yields.

To get more insights into the reaction mechanism of this novel formal [3+1] cyclization reaction, a well-known radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.0 eq) was added into the reaction of **1a** under the standard conditions and the desired product **2a** was obtained in 83% yield along with the recovery of TEMPO in 94% yield (Scheme 1, eq. 1), suggesting a non-radical reaction pathway. The use of substrate **1y** with isocyanophenyl- and dimethyl-substituted alkene only gave complex product mixtures under identical conditions (Scheme 1, eq. 2), indicating that the cyclopropane moiety in MCPs is essential to this transformation.



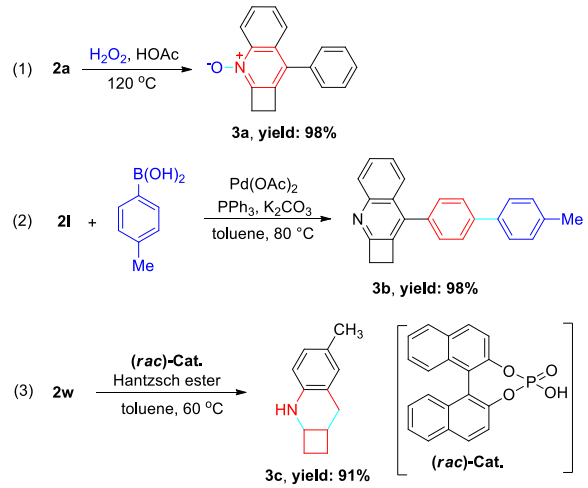
Scheme 1. Control experiments.

On the basis of above results and the previous reports,[20] a plausible reaction mechanism for this formal [3+1] cyclization of isocyanophenyl-substituted methylenecyclopropane to construct 1,2-dihydrocyclobuta[b]quinoline derivative has been outlined in Scheme 2. Initially, the C=C double bond of MCP in **1** (or its resonance structure **1'**) was activated by silver (I) ion to give an intermediate **A** or **A**' and there might exist an equilibrium between the intermediate **A** and the intermediate **A**' (see Page S67 in the Supporting Information). Subsequently, the intermediate **A** underwent an intramolecular nucleophilic attack to afford intermediate **B**.[21] Then, the elimination of Ag^+ and cyclopropane ring expansion furnished the corresponding product **2**.



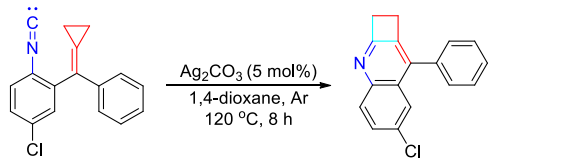
Scheme 2. A plausible reaction mechanism for the formation of **2**.

To further illustrate the synthetic utility of product **2**, we have conducted several transformations of **2a**, **2l** and **2w**. Carrying out the reaction of **2a** in H_2O_2/HOAc at 120 °C afforded the N-oxidation product **3a** in 98% yield (Scheme 3, eq. 1).[22] The reaction of **2l** with 4-tolylboronic acid under Suzuki-Miyaura cross coupling reaction conditions[23] produced the corresponding arylation product **3b** in 98% yield (Scheme 3, eq. 2). When diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (Hantzsch ester) was used as a hydride source and binaphthyl phosphoric acid was used as a Brønsted acid catalyst, the corresponding reduction product **3c** derived from hydrogen transfer was obtained in 91% yield (Scheme 3, eq. 3),[24] providing a key precursor for bioactive molecules.



Scheme 3. Further transformations of the obtained products **2**.

The formal [3+1] cyclization reaction could also be carried out on larger scale as illustrated in Scheme 4. Using 3.5 mmol of isocyanophenyl-substituted methylenecyclopropane **1p** (940 mg) gave 1,2-dihydrocyclobuta[b]quinoline derivative **2p** in 84% yield (790 mg) under the standard conditions.



1p (940 mg, 3.5 mmol) **2p** (790 mg, yield: 84%)

Scheme 4. A scale-up reaction of **1p** for the synthesis of **2p**.

In conclusion, we have developed a novel formal [3+1] cyclization reaction of isocyanophenyl-substituted methylenecyclopropanes upon heating in the presence of Ag_2CO_3 (5 mol%) via the formal insertion of isocyanide carbon into a C-C bond, affording diversified 1,2-dihydrocyclobuta[b]quinoline derivatives. The reaction proceeds efficiently through an excellent atom economic manner and exhibits broad substrate scope under convenient conditions, giving the desired products in moderate to excellent yields. Several useful transformations of the corresponding products have been also demonstrated in this context. The potential utilization and further investigation of the reaction mechanism is in progress.

Experimental Section

General Procedure for Synthesis of 2

A 10 mL flame-vacuum dried screwed-tube equipped with a magnetic stirring bar was charged with **1** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.01 mmol, 0.05 equiv) and 1,4-dioxane (2.0 mL) under argon atmosphere. The reaction mixture was stirred at 120 °C for 8-24 hours in a pre-heated oil bath. After the starting material **1** was consumed completely (using TLC to monitor the reaction proceeding), the reaction mixture was cooled to ambient temperature. Then, organic solvent was removed under reduced pressure and the resulting residue was purified through a silica-gel column chromatography to provide the desired product.

Acknowledgements

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An Update

Synthesis of 1,2-Dihydrocyclobuta[b]quinoline Derivatives from Isocyanophenyl-Substituted Methylenecyclopropanes

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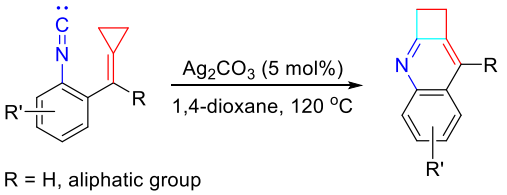

R = H, aliphatic group
or substituted aromatic groups
R' = NO_2, Me, Cl

24 examples
up to 98% yield

Formal [3+1] cyclization reaction
Broad substrate scope