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1-(Arylsulfonyl)cyclopropanol, a new cyclopropanone equivalent and its application to prepare 1-alkynyl cyclopropylamine

Jie Liu, Yan An, Hai-Ying Jiang, Zili Chen *

Department of Chemistry, Renmin University of China, Beijing 100872, China

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Abstract

Cyclopropanone derivative 1-(arylsulfonyl)cyclopropanol **4** simply prepared from the reaction of cyclopropanone ethyl hemiacetal **3** with sodium arylsufinate in the presence of formic acid is a new cyclopropanone equivalent to react with terminal acetylenes, and disubstituted amines in water catalyzed by $AuCl_3$, to provide an unprecedented synthesis of 1-alkynyl cyclopropylamines in moderate yields.

Keywords: Cyclopropanone; 1-Alkynyl cyclopropylamine; $AuCl_3$; Terminal alkyne

1. Introduction

The cyclopropyl group is found as a basic structural element in a wide range of naturally occurring compounds in plants and in microorganisms, and as a privileged unit in medicinal chemistry since it possesses unique spatial and electronic properties in conjunction with high metabolic stability.[1] The cyclopropane chemical reactivity not only closely resembles that of an olefinic double bond but moreover also involves rearrangements of particular synthetic importance: that is, ring-opening and expansion reactions, and it has established its potential as useful building blocks in organic synthesis.[2]

Most synthetic strategies for constructing cyclopropyl group in organic compounds resorted to carbene addition to an alkene, for example, Simmons–Smith cyclopropanation,[3] sulfur ylide chemistry[4] or the transition metal catalyzed cyclopropanation of an alkene with α-diazocarbonyl compounds.[5] Developing new approach of cyclopropanation therefore can enhance the flexibility to construct these important structural entities.

Cyclopropanone, which is formed from ketene and diazomethane in inert solvent at −78 °C,[6] seems to be a feasible precursor to incorporate a cyclopropyl group in organic compounds, but is not sufficiently stable to permit useful synthetic applications. Two cyclopropanone derivatives, hydrated cyclopropanone **2**[7] and cyclopropanone hemiacetal **3**,[8] (Fig. 1) have been developed to provide a convenient source of the parent ketone. However, their utility was dwarfed either by their volatility and low stability, or by their decreased reactivity, (EtO^- is not a good leaving group[9]). In this Letter, a new cyclopropanone surrogate and its application in the synthesis of 1-alkynyl cyclopropylamines are reported. Although some methods have been reported to incorporate a cyclopropyl group into an amine group either directly[10] or indirectly,[11] to the best of our knowledge, there is no procedure allowing the simple construction of alkynyl-substituted cyclopropylamines.[12]

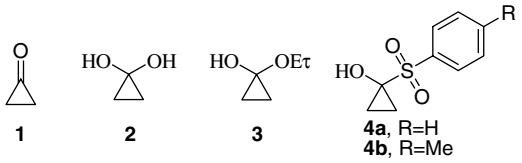

Fig. 1. Cyclopropanone and its derivatives.

* Corresponding author. Tel./fax: +86 10 62516660.
E-mail address: zilichen@ruc.edu.cn (Z. Chen).

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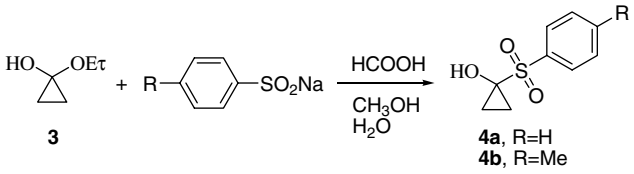


Scheme 1. Synthesis of 1-(arylsulfonyl)cyclopropanol.

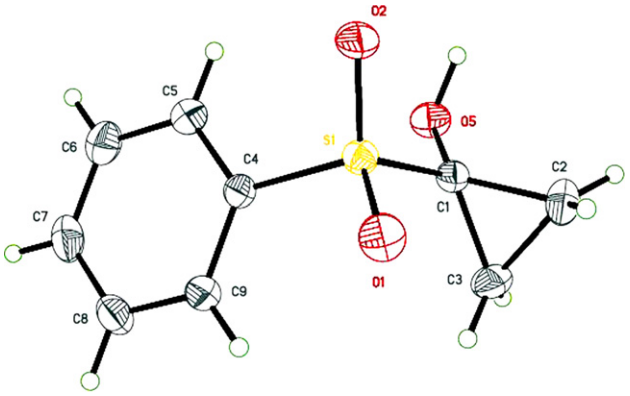


Fig. 2. The X-ray crystal structure of compound **4a**.

2. Results

Cyclopropanone derivative 1-(benzenesulfonyl) cyclopropanol **4a** can be simply prepared by the reaction of cyclopropanone ethyl hemiacetal **3** with sodium benzenesulfinate in a mixture of solvents, CH_3OH:H_2O (1:2) in the presence of 10 equiv HCOOH as a catalyst (Scheme 1). Extraction of the water diluted reaction mixture with dichloromethane followed by recrystallization gave compound **4a** as a colorless crystal in 63% yield. Increasing the equivalents of HCOOH significantly reduced the reaction time. Compound **4b** can be prepared by the same method. The effort to synthesize 1-(benzenesulfonyl) cyclobutanol failed,[13] perhaps because of less **I** strain in cyclobutanone.

The new compounds were quite stable and could be kept at 0 °C for several months without explicit decomposition.[14] Their structures were characterized by ^1H and ^{13}C NMR spectral data including the ^1H H-2/H-3 signals (t, 1.2–1.6 ppm) and ^{13}C C-2/C-3 signals (13.5 ppm). The structure of **4a** was also confirmed by X-ray crystallography (Fig. 2).[15]

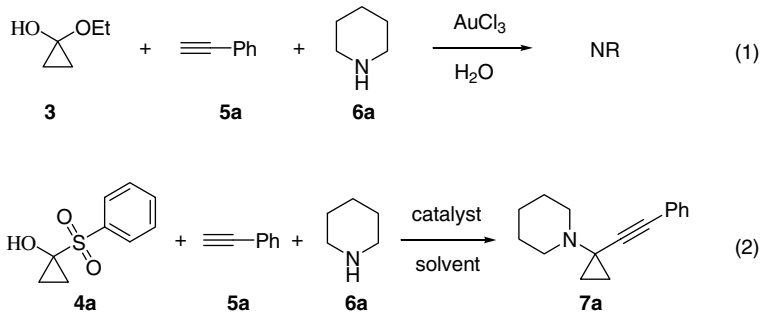
Table 1
Three components coupling of **4a**, phenyl-acetylene, and piperidine

	Catalyst (mol %)	Solvent/ additive	**5/6/4a** (equiv)	Time (h)/ temp	Yield[a]
1	$AuCl_3$ (1)	H_2O	1.5/1/1	12/rt	30
2	$AuCl_3$ (1)	H_2O	1.5/0.9/1	12/rt	13
3	$AuCl_3$ (1)	H_2O	2/1.5/1	12/rt	42
4	$AuCl_3$ (1)	H_2O	2/2/1	12/rt	36
5	$HAuCl_4$ (1)	H_2O	2/1.5/1	12/rt	<10
6	$NaAuCl_4$ (1)	H_2O	2/1.5/1	12/rt	13
7	$AuCl_3$ (1)	C_2H_5OH	2/1.5/1	12/rt	27
8	$AuCl_3$ (1)	CH_3CN	2/1.5/1	12/rt	11
9	$AuCl_3$ (1)	CH_2Cl_2	2/1.5/1	12/rt	5
10	$AuCl_3$ (2)	H_2O	2/1.5/1	12/rt	56
11	$AuCl_3$ (2)	H_2O	2/1.5/1	12/rt	62[b]
12	$AuCl_3$ (2)	H_2O	2/1.5/1	12/35 °C	55
13	$AuCl_3$ (5)	H_2O	2/1.5/1	12/rt	34
14	$AuCl_3$ (2)	H_2O/Na_2CO_3	2/1.5/1	12/rt	31
15	$AuCl_3$ (2)	H_2O/Et_3N	2/1.5/1	12/rt	34

[a] Isolated yields based on compound **4a**.
[b] Compound **4a** was added in three batches.

When we explored the reaction of **4a** with phenylacetylene and piperidine in water with 1 mol % $AuCl_3$ as catalyst,[16] the compound *N*-piperidinyl-1-(phenylethynyl) cyclopropane **7a** was obtained in 30% yield (Table 1, entry 1). In contrast, cyclopropanone hemiacetal **3a** afforded no product under the same condition (Scheme 2, Eq. 1). The effect of the amount of amine on the yield was then tested. When 1.5 equiv piperidine was employed with 2 equiv phenylacetylene, **7a** was obtained in 42% yield (Table 1, entry 3). Further increasing the amount of the amine was proved fruitless.

Subsequently, other gold salts such as $HAuCl_4$ and $NaAuCl_4$ were investigated and showed much lower catalytic activity than $AuCl_3$ (Table 1, entries 5 and 6); whereas the copper and silver salts, such as CuI,[17] CuCl, and AgI,[18] were totally inactive. In solvent screening experiments, water was found to be superior to other protic or nonprotic solvent, such as C_2H_5OH, CH_3CN, and CH_2Cl_2 (Table 1, entries 7–9). A number of additives such as Et_3N and Na_2CO_3 were evaluated (Table 1, entries 14 and 15), but all of them lowered the yield. Optimization of reaction temperature and the amount of $AuCl_3$ identified a set of



Scheme 2. The coupling reaction of **3** or **4a**, phenylacetylene and piperidine.

Table 2
Coupling reaction[a] of compound **4** with a series of terminal alkynes and disubstituted amines[b]

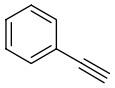
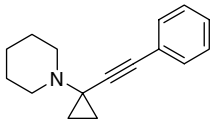
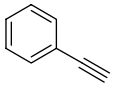
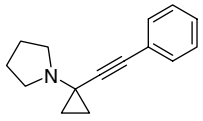
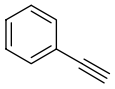
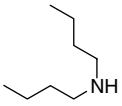
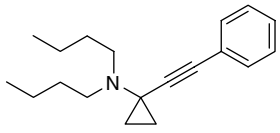
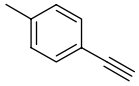
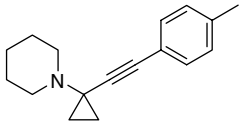
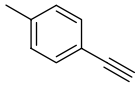
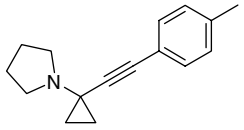
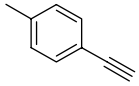
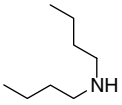
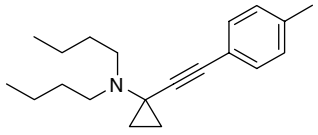
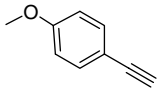
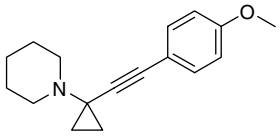
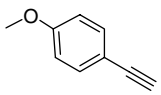
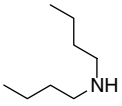
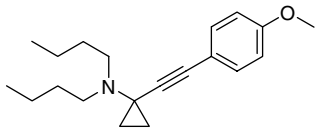
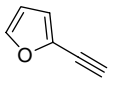
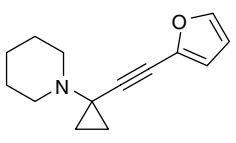
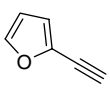
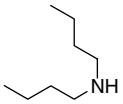
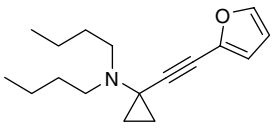
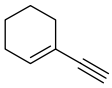
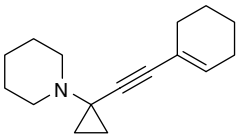
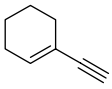
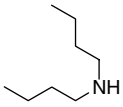
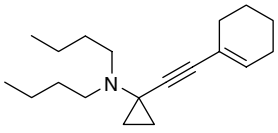
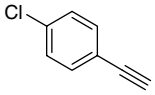
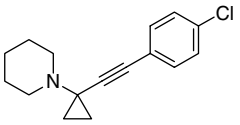
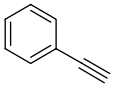
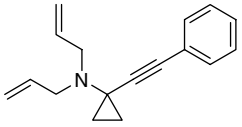
Entry	Alkyne **5**	Amine **6**	Product (yield %)
1			 **7a** 62% (34%[C])
2			 **7b** 55%
3			 **7c** 65%
4			 **7d** 54%[d]
5			 **7e** 57%[d]
6			 **7f** 64%[d]
7			 **7g** 70%
8			 **7h** 64%
9			 **7i** 30%

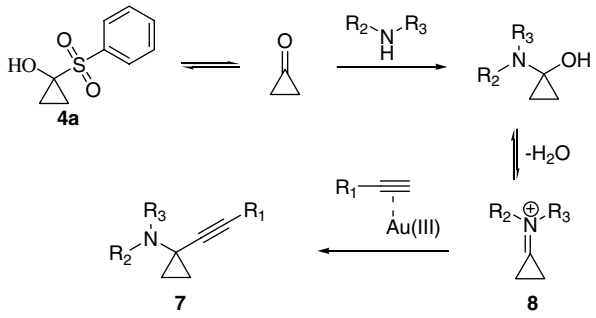
Table 2 (*continued*)

Entry	Alkyne **5**	Amine **6**	Product (yield %)
10			 **7j** 32%
11			 **7k** 41%
12			 **7l** 48%
13			 **7m** 42%
14			 **7n** 55%

[a] All reactions were carried out at 0.5 mmol scale with alkyne/amine/**4a** = 2/1.5/1 (**4a** was added in three batches), using 2 mol % of $AuCl_3$ as catalyst in 1 mL water at rt for 12 h.
[b] Unless noted, isolated yields were based on **4a**.
[c] Compound **4b** was used as substrate.
[d] Reaction temperature was improved to 35 °C to enhance the solubility of *p*-methyl phenylacetylene in water.

conditions (2 mol % of $AuCl_3$, water, rt Table 1, entry 10) to give the desired product in 55% yield. To prevent the possible decomposition during the course of the reaction, **4a** was added in three batches. This way, the reaction yield was slightly improved (Table 1, entry 11).

As shown in Table 2, a range of 1-alkyne cyclopropyl amine products[19] were easily obtained utilizing the optimized reaction conditions with Au(III) catalyst (2 mol % of $AuCl_3$, alkyne/amine/**4a** = 2/1.5/1, 0.5 M in water, addition of **4a** in three batches, rt, 12 h). Both aromatic and hetero-aromatic terminal alkynes including those bearing functional groups such as alkoxy, chloro, and methyl, were able to undergo the corresponding three-component-coupling reaction. Aryl alkynes with electron-donating groups (Table 2, entries 4–8) displayed relatively high reactivity and gave higher conversion. However, other aryl alkynes such as 4-chlorophenylacetylene (Table 2, entry 13) with electron-withdrawing substituent and hetero-aromatic 2-furyl ethyne (Table 2, entries 9 and 10) exhibited relatively low reactivity. Alkene substituted alkynes also worked effectively in this reaction (Table 2, entries 11 and 12). But aliphatic alkynes such as 3-phenyl-1-propyne only gave trace amount of the desired product. The corresponding amine also plays a crucial role in the reaction: whereas dialkylamines reacted smoothly in these conditions, the dibenzyl amine afforded the corresponding product in very low yield (7%), possibly due to the steric hindrance. Amide



Scheme 3. Proposed mechanism.

compounds and 1° amine such as aniline were inert to these reactions. When 1-toluene sulfonyl cyclopropanol **4b** was employed as a reactant, the reaction yield (Table 2, entry 1, yield in parentheses) was lower than that of **4a**.

Presumably, the mechanism in this reaction could be similar to the coupling reaction of $AuCl_3$ activated terminal alkyne with aldehydes.[16] Cyclopropanone, in situ generated from compound **4a** (Scheme 3), would react with disubstituted amine to provide imine cation **8**, which then could couple with terminal alkynes to yield product **7**.

3. Conclusion

In summary, a new cyclopropanone derivative 1-arylsulfonyl cyclopropanol was developed in a simple and expedient method. Unlike previous cyclopropanone derivatives, this new surrogate exhibited relatively higher reactivity. It can be used to construct 1-alkynyl cyclopropylamines in moderate yields, from terminal alkynes, and disubstituted amines in water with $AuCl_3$ as the catalyst. Further work directed to study the reactivity of the new compound **4a**, particularly its applications either as a cyclopropanone equivalent or as a new synthetic subunit is in progress.

Acknowledgements

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Supplementary data

Supplementary data associated with this article include brief experimental details, X-ray structure, and other spectra data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.093.

References and notes

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13. A new product, which had similar polarity with 1-(benzenesulfonyl) cyclopropanol, could be detected in TLC. It was not stable enough for separation or further purification.
14. It was found that compound **4a** could be kept in bottle at rt for three weeks without explicit decomposition.
15. The spectral data of 1-(benzenesulfonyl) cyclopropanol **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, $J = 6.9$ Hz, 2H), 1.66 (t, $J = 6.9$ Hz, 2H), 3.95 (s, 1H), 7.58 (m, 2H), 7.68 (m, 1H), 7.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 13.6, 71.3, 129.0, 129.1, 133.9, 137.0. Supplementary data have been deposited with the CCDC in the CIF format with the deposition number CCDC 667597.
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19. General procedure for the coupling reaction of 1-benzenesulfonyl cyclopropanol **4a** with the terminal alkynes, and disubstituted amines catalyzed by $AuCl_3$. To a solution of a terminal alkyne (1 mmol), and a disubstituted amine (0.75 mmol) in water (1 mL), was added 1-benzenesulfonyl cyclopropanol **4a** (33 mg, 0.17 mmol) followed by $AuCl_3$ (3 mg, 0.01 mmol, 2% equiv). After 4 h, another batch of **4a** (33 mg, 0.17 mmol) was added. And the third batch of **4a** (33 mg, 0.17 mmol) was added 8 h later. The reaction mixture was stirred at rt for 12 h under N_2, and extracted with EtOAc (3×10 mL). The combined organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was then purified by flash chromatograph on silica gel to give the desired 1-alkynyl cyclopropyl amine (PE/EA = 50/1). The spectral data of *N*-piperidinyl-1-(phenylethynyl) cyclopropane **7a**: ^{1}H NMR ($CDCl_3$, Me_4Si) δ 0.89 (t, $J = 4.3$ Hz, 2H), 0.99 (t, $J = 4.3$ Hz, 2H), 1.45 (t, $J = 4.4$ Hz, 2H), 1.56 (m, 4H), 2.70 (t, $J = 4.7$ Hz, 4H), 7.24–7.30 (m, 3H), 7.41 (t, $J = 3.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 17.8, 24.6, 26.3, 38.0, 51.8, 82.6, 89.7, 123.8, 127.9, 128.4, 131.9.