Tetrahedron 66 (2010) 321–328

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Gold-catalyzed cyclization of 1-alkynyl cyclopropyl *tert*-butyl carbonate to construct multifunctionalized vinyl cyclopropane derivatives

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A R T I C L E I N F O

Article history:
Received 27 August 2009
Received in revised form 22 October 2009
Accepted 27 October 2009
Available online 29 October 2009

Keywords:
Vinyl cyclopropane
Cyclic carbonate
Gold-catalyzed reaction
6-*endo-dig* Process

A B S T R A C T

A convenient new method was developed to prepare two types of vinyl cyclopropane derivatives through gold-catalyzed cyclization of 1-alkynyl cyclopropyl *tert*-butyl carbonates **2**. Different from the previous reported 5-*exo-dig* route, the 6-*endo-dig* addition is the preferred pathway to provide six-membered cyclized carbonates. Two factors, including stereoelectronic effect and steric effect might affect the regioselectivity. Therefore, low steric aliphatic substrates afforded only six-membered isomers. The synthetic utility of compound **3** was also explored to afford a series of β-carbonyl cyclopropanol derivatives.

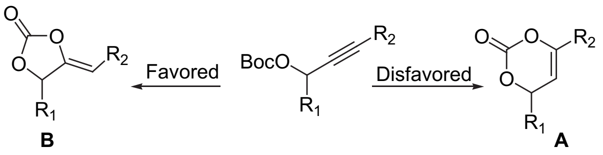
1. Introduction

Vinyl cyclopropane species are found as the important structural elements in a wide range of bioactive natural, non-natural compounds.[1,2] With a unique combination of a reactive double bond and an unstable three-membered ring in one molecule, these species can be employed as C5 or C3 building blocks in many metal-catalyzed inter- or intramolecular (5+2,[3]3+2,[4] 4+1)[5] cycloaddition reactions to construct cyclopentene or cycloheptene derivatives of various structural characteristics and functionalities.[6]

Methods for the preparation of vinyl cyclopropane derivatives are very limited. The reported results generally proceed via two similar transformations, including addition of carbene to the conjugated diene[7] or the reaction of α-vinyl carbenoid with an isolated olefin.[8] However, the synthetic utilities of these transformations often suffered from the tedious preparation of the diene or carbene reactants, and from the difficulties to introduce structural or functional diversity. Therefore, developing new approaches to construct these important synthetic entities would greatly broaden their application in organic synthesis.

Gold (I) complexes have emerged as an efficient and mild catalyst for the transformation of substrates possessing alkyne or alkene functionality into a range of useful structural motifs. As part of a program directed toward the development of new gold-catalyzed reactions, we want to report herein a convenient new method to prepare multifunctionalized vinyl cyclopropane derivatives via gold-catalyzed cyclization of 1-alkynyl cyclopropyl *tert*-butyl carbonates.

In previous reports, most of the metal-catalyzed cyclization of propargylic carbonates, as indicated in Scheme 1, are favored to proceed in an intramolecular 5-*exo-dig* process to afford five-membered ring products **B**.[9] For example: Gagosz group has reported that Au(I)-catalyzed 5-*exo-dig* cyclization of propargylic *tert*-butyl carbonates to give five-membered 4-alkylidene-1,3-dioxolan-2-ones even from an internal alkyne.[10] Whereas in this paper, gold-catalyzed reaction of 1-alkynyl cyclopropyl *tert*-butyl carbonates **2** mainly provided six-membered isomers **3** (**A** type products, Scheme 1) via a 6-*endo-dig* route. The unusual regioselectivity might be owing to the special stereoelectronic effect in the cyclopropane-containing system.



Scheme 1. Metal-catalyzed cyclization of propargylic carbonates.

The starting 1-alkynyl cyclopropyl *tert*-butyl carbonate **2** can be readily prepared from the reaction of 1-alkynyl cyclopropanol with *tert*-butoxyl carbonate in CH_2Cl_2.[11] Subsequent gold-catalyzed

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0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.10.087

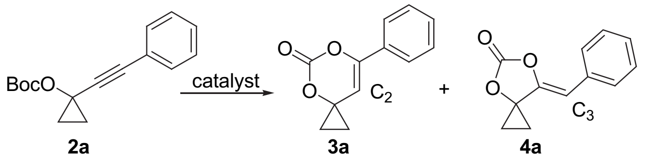
cyclization of compound **2** afforded two types of vinyl cyclopropane derivatives. The structure of the minor product **4a** was identified to be a five-membered spiro-cyclopropyl alkylidene-1,3-dioxolan-2-one derivative by X-ray crystallography.[12] The structure of **3a** was then determined to be a six-membered isomer.

A range of five- or six-membered carbonate bearing vinyl cyclopropanes were then prepared. Synthetic utility of major products **3** was also explored to provide cyclopropane-containing β-hydroxy ketone derivatives **5**.[13] These compounds represent a useful source to prepare cyclopentanone and other elaborated structures.[14]

2. Results and discussions

In the preliminary studies, the reaction of 1-phenyl alkynyl cylcopropyl *tert*-butyl carbonate **2a** was chosen as the model system to investigate the reaction condition. As shown in Table 1, when 0.5 mmol **2a** was treated with 2 mol % equivalent of $AuPPh_3Cl/AgBF_4$ in CH_2Cl_2 at rt for 50 h, two cyclized products **3a** and **4a** were obtained in a total yield of 76% (3a/4a=1.5/1).

Table 1
Reaction optimization of gold-catalyzed cyclization of 1-phenyl ethynyl cyclopropyl *tert*-butyl carbonate **2a**[a]



	Catalyst	*T* (h)	Sol/temp	Yield (%)[b] (ratio **3a**/**4a**)[c]
1	$AuPPh_3Cl/AgBF_4$	50	DCM/rt	76 (1.5/1)
2	$AuPPh_3Cl/AgSbF_6$	15	DCM/rt	65 (1.9/1)
3	$AuPPh_3Cl/AgPF_6$	48	DCM/rt	0
4	$Au(PPh_3)NTf_2$	72	DCM/rt	11 (2.6/1)
5	$AuPPh_3Cl/AgOTf$	2	DCM/rt	88 (2.4/1)
6	$AuPPh_3Cl/AgOTf$	2	DCE/rt	78 (1.8/1)
7	$AuPPh_3Cl/AgOTf$	40	THF/rt	60 (1.6/1)
8	$AuPPh_3Cl/AgOTf$	38	Toluene/rt	50 (2.6/1)
9	$AuPPh_3Cl/AgOTf$	40	CH_3CN/rt	0
10	$AuPPh_3Cl/AgOTf$	20	Et_2O/rt	Trace
11	$AuCl_3$	30	DCM/rt	0
12	$PtCl_2$	48	DCM/rt	0
13	AgOTf	48	DCM/rt	0
14	$Cu(OTf)_2$	48	DCM/rt	0

[a] All reactions were carried out at 0.5 mmol scale, using 2 mol % of gold catalyst in 2 mL solvent at rt.
[b] Separated yield.
[c] The ratio **3a**/**4a** was based on the separated yields.

The ^1H and ^{13}C NMR spectra data for compound **3a** and **4a** are very similar. Only one obvious difference exists between the chemical shift of **3a**'s hydrogen at C2 position (5.52 ppm, **3a**) and that of **4a**'s C3 hydrogen (5.15 ppm, **4a**). The structure of **4a** was then identified to be 7-benzylidene-4,6-oxa-5-carbonyl-spiro[2,4]-heptane by X-ray crystallography (Fig. 1). Then, the structure of **3a** can be deduced to be 7-phenyl-4,6-oxa-5-carbonyl-spiro[2,5]-7-octene.

A series of experiments were performed to optimize this reaction. Different silver salts were tested, it was found that $AuPPh_3Cl/AgPF_6$ and $Au(PPh_3)NTf_2$ have low activities (entries 3 and 4, Table 1). With $AuPPh_3Cl/AgPF_6$ as catalyst, the desired product was obtained in 65% yield with **3a**/**4a**=1.9/1 (entry 2, Table 1). The best catalyst, as shown in Table 1, was proved to be $AuPPh_3Cl/AgOTf$ (entry 5, Table 1), which provide **3a** and **4a** in 88% with a ratio of 2.4/1. Several solvents were also screened. CH_3CN and Et_2O were found to be ineffective (entries 9 and 10, Table 1). When DCE, THF, and toluene were used as the solvent, the reaction yields were lower than that in DCM (entries 6–8, Table 1). $AuCl_3$ and other non-gold catalysts, such as $PtCl_2$, AgOTf, and $Cu(OTf)_2$ were then investigated. These catalysts were proved to be inferior to the Au(I) complexes and afforded no product (entries 11–14, Table 1). The optimal reaction condition was then determined to be 2 mol % of $AuPPh_3Cl/AgOTf$ in CH_2Cl_2 at rt.

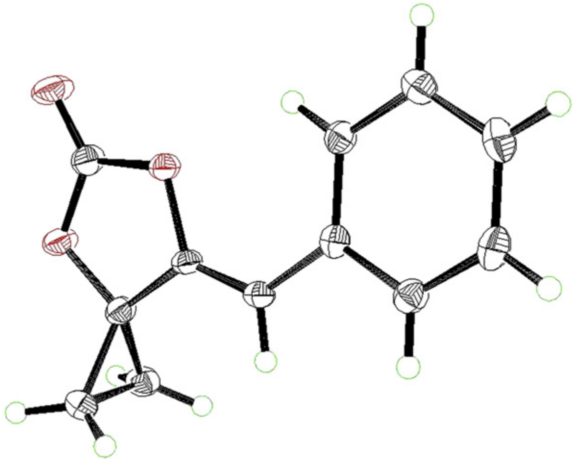


Figure 1. The X-ray diffraction structure of compound **4a**.

With the optimized condition in hand, we explored the scope and the limitation of this reaction. As shown in Table 2, a range of 1-alkynyl cyclopropyl *tert*-butyl carbonates were prepared through the reaction of the corresponding 1-alkynyl cyclopropanols with *tert*-butyl carbonate.

Compound **2** were then treated with $AuPPh_3Cl/AgOTf$ to prepare vinyl cyclopropane derivatives **3** and **4**. Both aromatic and aliphatic alkynyl substrates exhibited good reactivities. Two types of vinyl cyclopropane derivatives were readily obtained in moderate to good yields. Aryl alkynyl cyclopropyl *tert*-butyl carbonates bearing electron-donating groups, such as methyl, ethyl, *n*-butyl, and methoxy substitutes (Table 2, entries 2–5), displayed relative high reactivities and gave higher conversion. While other aryl alkynyl substrates with electron-withdrawing chloro or fluoro groups had relative low reactivities (Table 2, entries 6–9). Aliphatic alkynyl substrates also worked effectively in this reaction (Table 2, entries 10 and 11), which nevertheless, only gave the six-membered cyclization products.

The regioselectivity for the aromatic alkynyl substrates ranged from 1.5/1 to 6/1. Electron rich substrates seem to have a better selectivity for the formation of the major isomers (Table 2, entries 2–5), as compared with the lower **3**/**4** ratio obtained in their electron deficient counterparts (Table 2, entries 6–9). The highest ratio was obtained in substrate **2g** (Table 2, entry 5), which has an electron-donating *p*-methoxy substitutes on the phenyl group. However, the aliphatic substrates only gave the single major products.

We assumed that the regioselectivity might be affected by two factors. The first is the stereoelectronic effect. In substrate **2**, angle θ for C2–C1–O is larger than the normal bond angle in an sp^3 hybridized carbon (109.5°), because of the existence of a small, strained bond angle in cyclopropane (Scheme 2). Therefore, S_N2 addition of the carbonate oxygen onto the gold activated triple bond is favored to proceed through a 6-*endo-dig* route (Scheme 2, route a). However, high steric aromatic group would affect the attack of the carbonyl oxygen, and favored the 5-*exo-dig* pathway to construct minor five-membered isomer (Scheme 2, route b). Aliphatic substrates, which have no high steric aromatic group, would therefore give only the major products.

The quench step of the gold-catalyzed cyclization reaction was then investigated (Scheme 3). When 3 equiv of D_2O was added into