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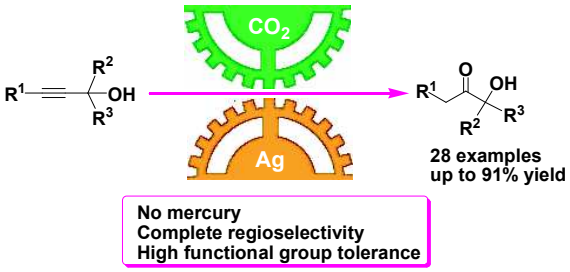

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ARTICLE TYPE

Efficient synthesis of tertiary α-hydroxy ketones through CO_2-promoted regioselective hydration of propargylic alcohols

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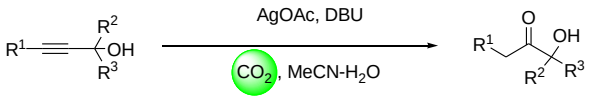
A carbon dioxide-promoted and silver acetate-catalyzed hydration of propargylic alcohols for the efficient synthesis of tertiary α-hydroxy ketones has been developed. The reaction is proposed to proceed via a tandem process of carbon dioxide incorporation into propargylic alcohols and subsequent hydrolysis.

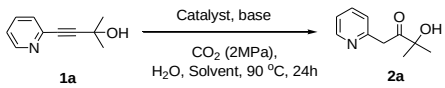
The catalytic hydration of alkynes is an important and atom-economic reaction that provides one of the most straightforward and efficient methodologies to generate useful carbonyl compounds.[1] Transition-metal-catalyzed hydration of alkynes has long been known since Kucherov found that mercury(II) salts can efficiently catalyze the hydration of alkynes in aqueous sulphuric acid solution.[2] However, associating with high toxicity of mercury salts, the Kucherov reaction is not practical in modern industrial application. Therefore, much effort has been devoted to developing less toxic and more efficient catalysts for the reaction in recent years. A wide range of transition metals including Pd,[3] Pt,[4] Fe,[5] Au,[6] Ag,[7] Ir[8] and Ru[9] have been investigated for the hydration of alkynes. These catalyst systems are proved to be efficient for simple nonfunctionalized alkynes. However, few of them could be applicable for efficient hydration of propargylic alcohols. These α-hydroxy group functionalized alkynes either showed low activity or led to other reactions including the Meyer-Schuster and Rupe rearrangements under mercury-free conditions.[4c, 6a, 6b, 6f, 7b,7c] Thus, the direct hydration of propargylic alcohols remains a continuing challenge. It should be noted that the mercury-catalyzed hydration of propargylic alcohols is one of most important applications of alkyne hydration of all, because it offers α-hydroxy ketones as important building blocks for more elaborated molecules.[10] And recently, α-hydroxy ketones have attracted tremendous interest in biologically active natural product research and synthetic chemistry.[11] Therefore, the development of novel mercury-free processes for the efficient hydration of propargylic alcohols to produce α-hydroxy ketones is highly desirable. Herein, we present a carbon dioxide (CO_2)-promoted and silver acetate-catalyzed hydration of propargylic alcohols for convenient synthesis of tertiary α-hydroxy ketones under mild reaction conditions (Scheme 1).

During the course of our investigating the optimal reaction conditions for the synthesis of 2,2,5-trimethyl-4-(pyridin-2-yl)furan-3(*2H*)-one from 2-methyl-4-(pyridin-2-yl)but-3-yn-2-ol (**1a**) and acetonitrile under CO_2 atmosphere, 3-hydroxy-3-methyl-1-(pyridin-2-yl)butan-2-one (**2a**) was observed as a by-product in some cases.[12] Surprisingly, the α-hydroxy ketone was selectively formed in 76% isolated yield when silver acetate was used as catalyst under 2 MPa of CO_2 at 70 °C in the presence of 0.5 equiv of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) (Table 1, entry 1).



Scheme 1 Transformation of propargylic alcohols into tertiary α-hydroxy ketones.

Table 1 Optimization of reaction conditions[a]



1a **2a**

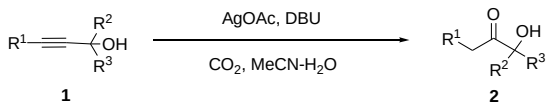
Entry	Catalyst	Base	Solvent v/v	Yield/%[b]
1[c]	AgOAc	DBU	MeCN	76
2	AgOAc	DBU	MeCN/H_2O = 10:3	91
3[d]	AgOAc	DBU	MeCN/H_2O= 10:3	72
4	AgCl	DBU	MeCN/H_2O= 10:3	18[e]
5	$AgNO_3$	DBU	MeCN/H_2O= 10:3	8[f]
6	Ag_2CO_3	DBU	MeCN/H_2O= 10:3	17
7	$AgBF_4$	DBU	MeCN/H_2O= 10:3	14
8	AgOAc	DIEA	MeCN/H_2O= 10:3	9[g]
9	AgOAc	DABCO	MeCN/H_2O= 10:3	27
10	AgOAc	Et_3N	MeCN/H_2O= 10:3	49
11	AgOAc	DBU	1,4-Dioxane/H_2O= 10:3	30
12	AgOAc	DBU	THF/H_2O= 10:3	10
13	AgOAc	DBU	CH_2Cl_2/H_2O= 10:3	trace
14	AgOAc	DBU	DMF/H_2O= 10:3	trace
15	AgOAc	DBU	H_2O	24
16[h]	AgOAc	DBU	-	11
17[i]	AgOAc	DBU	MeCN/H_2O= 10:3	73
18[j]	AgOAc	DBU	MeCN/H_2O= 10:3	n.r.[k]
19	AgOAc	-	MeCN/H_2O= 10:3	n.r.
20	-	DBU	MeCN/H_2O= 10:3	n.r.

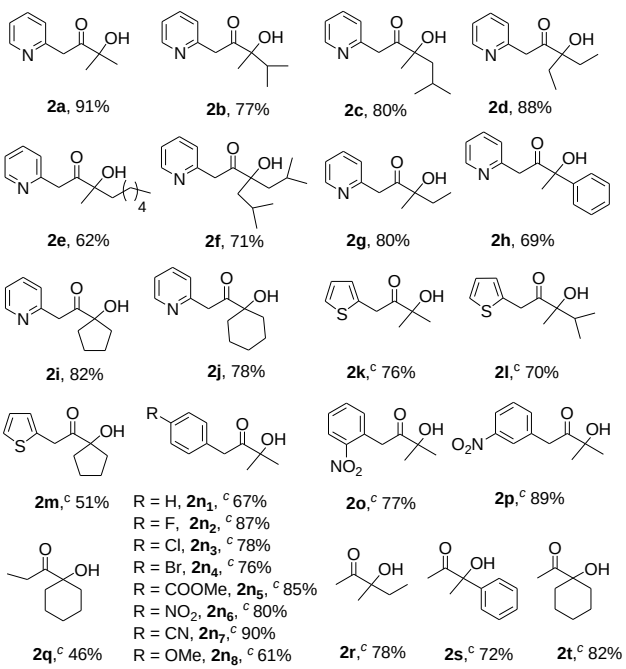
[a] Reaction conditions: **1a** (0.5 mmol), catalyst (10 mol %), base (0.25 mmol), solvent (1.3 mL), CO_2 (2 MPa), 90 °C, 24 h. [b] Isolated yield. [c] Ref. 12, catalyst (10 mol %), H_2O (1 mmol), MeCN (1 ml), 70 °C. [d] The reaction was carried out at 120 °C. [e] 66% of **1a** was recovered and 8% yield of 2,2,5-trimethyl-4-(pyridin-2-yl)furan-3(*2H*)-one was isolated. [f] 61% of **1a** was recovered and 12% yield of 2,2,5-trimethyl-4-(pyridin-2-yl)furan-3(*2H*)-one was isolated. [g] 36% yield of (*Z*)-4,4-dimethyl-5-((pyridin-2-yl)methylene)-1,3-dioxolan-2-one was obtained as major product. [h] 1 mmol of H_2O was added. [i] At 1 MPa of CO_2. [j] The reaction was carried out under a nitrogen pressure of 2 MPa in the absence of CO_2. [k] No reaction.

Although α-hydroxy ketones as by-products were also observed in previous researches on the coupling reaction of propargylic alcohols and CO_2 under other catalytic conditions,[13] their formation mechanism and synthetic application have long been ignored. Notably, Yamada and co-workers have recently showed that optically active α-hydroxy ketone could be obtained through the hydrolysis of corresponding cyclic carbonate.[14] To gain more information of the reaction mechanism and develop a facile mercury-free route to access α-hydroxy ketones from readily available propargylic alcohols, we further investigated the reaction with 2-methyl-4-(pyridin-2-yl)but-3-yn-2-ol (**1a**) as a model substrate in the presence of silver salts as catalyst. Gratifyingly, When the reaction of **1a** was conducted in a mixed MeCN/H_2O (10:3) solvent at 90 ^oC in the presence of 10 mol% of AgOAc and 0.5 equiv of DBU, the yield of the desired product **2a** was sharply increased to 91% (Table 1, entry 2). However, raising the temperature to 120 ^oC led to a dramatic decrease in the yield of the product (entry 3). Further optimization revealed that the silver source was critical for the success of this reaction, and other silver catalysts such as AgCl, $AgNO_3$, Ag_2CO_3 and $AgBF_4$ were proved to be less effective than AgOAc (entries 4-7). Screening of different bases showed that the base play an important role in this transformation. Other organic bases, such as N,N-diisopropylethylamine (DIEA), 4-diazabicyclo[2.2.2]octane (DABCO) and triethylamine, were ineffective (entries 8-10). Among various solvents investigated, the mixed solvent MeCN/H_2O (10:3) was found to be the best of choice in the formation of the desired product. Specifically, replacement of MeCN with 1,4-Dioxane or THF made the reaction sluggish, while CH_2Cl_2 and DMF resulted in the formation of a complex mixture of products (entries 11-14). With the use of H_2O as both a reagent and a solvent or under solvent-free conditions, the reaction gave low yield of **2a** along with large amount of unidentified by-products (entries 15-16). Further optimization showed that a decrease in the pressure of CO_2 led to a decrease in the yield of the product (entry 17). Although silver salts have previously been reported to be efficient catalyst for the hydration of terminal alkynes,[7] no reaction occurred when the procedure was performed under N_2 atmosphere instead of CO_2 in our case (entry 18), suggesting that CO_2 was involved in the product-forming step. Two more control experiments showed that both silver salt and organic base are essential for this reaction (entries 19-20).

With the optimized conditions in hand (Table 1, entry 2), we turned our attention to examine the scope and limitation of our synthetic protocol by using a series of structurally and functionally diverse propargylic alcohols (Table 2). Gratifyingly, various internal tertiary propargylic alcohols with a 2-pyridyl substituent at the acetylenic terminus could be efficiently converted into the corresponding α-hydroxy ketones in moderate to excellent yields (**2a-2j**). The data showed that sterically less bulky propargylic alcohols were favourable to the transformation. When the substrate bearing a bulky alkyl group (**1e**) or a phenyl group (**1h**) at the propargylic position was employed, lower yield was observed (62% and 69%, respectively). The reaction of five- or six-membered-ring-substituted propargylic alcohols proceeded smoothly under the optimized conditions to afford the corresponding product in high yields (**2i-2j**). Interestingly, even propargylic alcohols bearing a 2-thiophenyl group at the acetylenic terminus were well tolerated, and afforded the desired products **2k-2m** in reasonable to good yields at an elevated reaction temperature. A series of aryl-substituted propargylic alcohols were also investigated and the results showed that our method was remarkably compatible with a variety of valuable functional groups at the 4-position of phenyl ring of the propargylic alcohols, including halogen, acetyl, ester, nitro, cyano and methoxy groups (**2n$_1$-2n$_8$**). It was found that the electronic effect on phenyl ring of the propargylic alcohols had a significant influence on the formation of the desired α-hydroxy ketones. In general, aryl rings substituted with electron-withdrawing groups furnished the desired products (**2n$_2$-2n$_7$**) in higher yields than those with electron-neutral or electron-donating ones (**2n$_1$** and **2n$_8$**). Importantly, propargylic alcohols with functional groups at the 2- or 3-position of phenyl ring were also successfully transformed into desired product in high yields (**2o-2p**). Gratifyingly, less reactive alkyl-substituted propargylic alcohol **1q** could also afford the desired product **2q** in 46% yield. As expected, terminal tertiary propargylic alcohols could also undergo the reaction smoothly to afford the corresponding products in high yields (**2r-2t**). However, When primary or secondary propargylic alcohols were employed as the substrates, no desired products were observed and the starting materials were recovered,[15] indicating the synthetic protocol is suitable for the synthesis of α-hydroxy ketones arising from tertiary propargylic

Table 2 Synthesis of various α-hydroxy ketones[a, b]

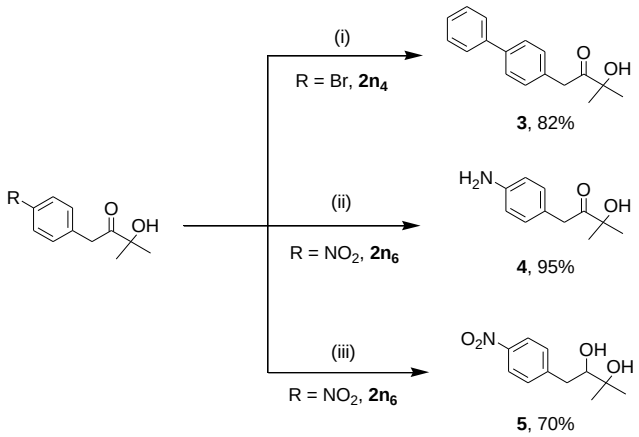




[a] Reaction conditions: **1** (0.5 mmol), AgOAc (10 mol %), DBU (0.25 mmol), MeCN-H_2O (1.3 mL, v/v = 10:3), CO_2 (2 MPa), 90 ^oC, 24 h. [b] Isolated yield. [c] At 120 ^oC.

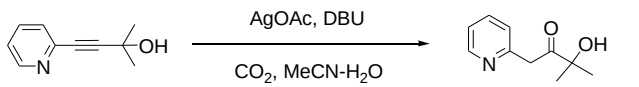
alcohols.

To further demonstrate the synthetic application of this protocol, the newly formed **2n$_4$** and **2n$_6$** were employed for further transformations to prepare a series of functionalized products. As can be seen from Scheme 2, the α-hydroxy ketone **2n$_4$**, which has a -Br group on its phenyl ring, could efficiently undergo Suzuki-Miyaura cross-coupling reactions to afford **3** in high yield. For the α-hydroxy ketone **2n$_6$**, the attached nitro group could be selectively reduced to amino group using our previous developed Zn-H_2O-CO_2 system,[16] affording the product **4** in almost quantitative yield. Moreover, the use of $NaBH_4$ under solvent-free conditions[17] led to exclusive reduction of the carbonyl group of **2n$_6$**, giving 3-methyl-1-(4-nitrophenyl)butane-2,3-diol (**5**) in 70% yield upon isolation.[17]



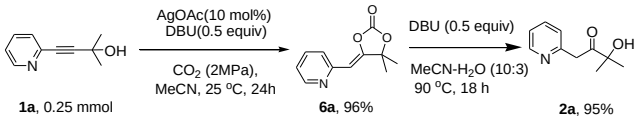
Scheme 2 Further demonstration of the synthetic application of the α-hydroxy ketones. Reaction conditions: (i) **2n$_4$** (0.25 mmol), $PhB(OH)_2$ (1.5 equiv), $Pd(OAc)_2$ (5 mol %), K_3PO_4 (3.0 equiv.), PPh_3 (10 mol %), toluene (5 mL), 110 °C, 9h. (ii) **2n$_6$** (0.25 mmol), zinc dust (6.0 equiv), water (6 mmol), CO_2 (12 MPa), 80 °C, 9h. (iii) A mixture of **2n$_6$** (0.25 mmol), $NaBH_4$ (1.5 equiv) and $PhCO_2H$ (1.0 equiv) was ground in an agate mortar and pestle at room temperature for 30 minutes.

The reaction is practical and scalable since a satisfactory yield (85%) was obtained when the silver-catalyzed and CO_2-promoted hydration reaction of **1a** was performed on 5 mmol scale (Scheme 3).



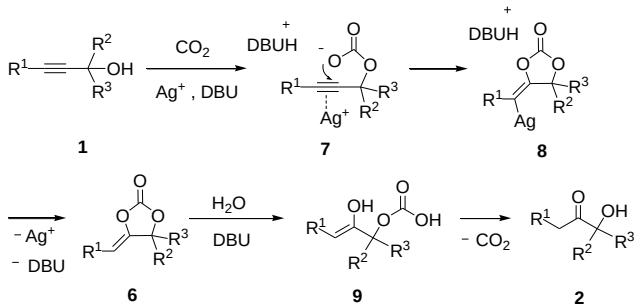
Scheme 3 Synthesis of **2a** on a larger scale. Reaction conditions: AgOAc (10 mol %), DBU (2.5 mmol), MeCN-H_2O (3 mL, v/v = 10:3), CO_2 (2 MPa), 90 °C, 24 h.

In order to clarify the reaction mechanism, a two-step process for the synthesis of **2a** was investigated (Scheme 4). Firstly, treatment of **1a** with 10 mol% AgOAc in the presence of 0.5 equiv. of DBU at 25 °C in MeCN under 2 MPa of CO_2 pressure for 24 h gave cyclic carbonate **6a** in 96% yield. Subsequently, **6a** was heated to 90 °C for 18 h in a MeCN/H_2O (10:3) solvent system in the presence of 0.5 equiv. of DBU, and the desired product **2a** was isolated in excellent yield.



Scheme 4 A two-step process for the synthesis of **2a**

Based on the above-described results and previous reports,[12, 14-15, 18] a plausible mechanism for the reaction is postulated in Scheme 5. Firstly, *Z*-alklidene cyclic carbonate **6** is formed by the incorporation of CO_2 into propargylic alcohol **1** in the presence of the binary catalyst system AgOAc/DBU *via* intermediates **7** and **8**. Then, the nucleophilic attack of a water molecule to such a carbonate **6** occurs at the carbonyl group to give the alkylcarbonic acid intermediate **9**, followed by the keto-enol tautomerization and the release of CO_2 to afford the corresponding α-hydroxy ketone **2**.



Scheme 5 Reaction mechanism of the formation of α-hydroxy ketones

Conclusions

We have established a facile and efficient method to synthesize tertiary α-hydroxy ketones via a tandem incorporation of CO_2 into propargylic alcohols/hydrolysis process. The hydration avoids the use of toxic mercury salts as catalyst and exhibits complete regioselectivity and high functional group tolerance, affording a variety of α-hydroxy ketones in moderate to excellent yields. These features may render this new protocol potentially attractive in synthetic organic chemistry. Now, studies are ongoing in our laboratory to better understand the reaction mechanism and apply this method to the synthesis of other useful heterocyclic compounds.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section and analytical details of the products. See DOI: 10.1039/b000000x/

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