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α-Acyloxy-α'-hydroxy Ketones via Cyclic Carbonate Intermediates Generated in Situ From Tertiary Bromopropargylic Alcohols and Cs_2CO_3

Olesya A. Shemyakina,* Ol'ga G. Volostnykh, Anton V. Stepanov, Igor' A. Ushakov

Abstract: A facile approach to α-acyloxy-α'-hydroxy ketones by reaction of readily available tertiary bromopropargylic alcohols and carboxylic acids in system Cs_2CO_3/H_2O/DMF (50-55 °C, 4 h) was developed. Key intermediates of this synthesis are cyclic carbonates generated in situ from bromopropargylic alcohols and Cs_2CO_3 which have been utilized as both reagent and base promoter.

Introduction

The α-acyloxy carbonyl motifs are the key structural units, which are met in natural products and pharmaceuticals such as cortisone acetate,[1] valrubicin,[1a,2] cortivazol,[1a,3] bendacort,[1a,4] aranidipine,[1a,5] and others that exhibit anti-inflammatory, anticancer, antiallergic, hypotensive properties, etc. (Figure 1). Also, α-acyloxy ketones are used as versatile synthons for further transformations, in particular as precursors of α-hydroxy ketones.[6]

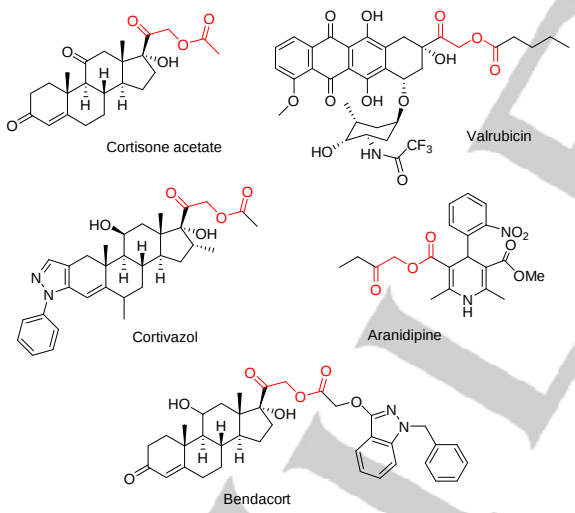

Figure 1. Biologically active compounds incorporating the α-acyloxy carbonyl unit.

The methods for α-acyloxy ketone synthesis are α-acyloxylation of functionalized carbonyl compounds (α-haloketones, α-diazoketones) with an alkaline carboxylates or carboxylic acids,[7] the direct oxidative coupling of ketones with carboxylic acids,[7c,8] oxo-acyloxylation of the alkenes,[7c,9] Ru-catalyzed addition of carboxylic acids to propargylic alcohol.[7c,10] Also, there have been developed alternative methods: NBS/DBU mediated α-acyloxylation of benzylic secondary alcohols with carboxylic acids,[11] the transformation of enamides through an intramolecular oxidative acetyl migration process mediated by hydrogen peroxide and acetic anhydride,[12] $PhI(OAc)_2$-promoted umpolung acetoxylation of enamides,[13] $Yb(OTf)_3$-catalyzed oxidative decarboxylation of β-keto acids mediated by (diacetoxyiodo)benzene and carboxylic acids,[14] self-intermolecular oxidative coupling of aryl ketones using I_2/TBHP[15] and I_2/TBHP-mediated α-benzoyloxylation of ketones,[16] a HI-promoted di-deidoination of α′-acetoxy-α,α-dihaloketones.[17]

Results and Discussion

Herein, we present a new method for the preparation of α-acyloxy-α'-hydroxy ketones by the reaction of tertiary bromopropargylic alcohols **1** with carboxylic acids **2** in system alkali metal carbonate/H_2O/DMF. It is found that α-acyloxy-α'-hydroxy ketones **3** are produced in up to 81% yield along with α,α'-dihydroxy ketones **4** as by-products. Completion of the reaction was monitored by IR and ^{1}H NMR spectroscopy by the disappearance of the bands at 2196–2212 cm^{-1} (–C≡C–Br) and signals of the bromopropargylic alcohols **1**, correspondingly.

To optimize the process conditions we have chosen the reaction of bromopropargylic alcohol **1a** with benzoic acid **2a** as model substrates (Table 1). When the reaction was monitored by ^{1}H NMR, at the initial stages of the reaction two signals were detected at 5.42 and 1.63 ppm. These signals decreased with simultaneous arise and increase of the product signals. This intermediate was isolated and identified as α-bromoethylidene carbonate **5**. In our case, the carbonate **5** was obtained by the reaction of bromopropargylic alcohol **1a** and inorganic carbonate. It was previously reported that Na_2CO_3 can serve as a CO_2 source for the Pd-catalyzed synthesis of cyclic carbonates.[18]

Various alkali metal carbonates (Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3) were studied. Cs_2CO_3 proved to be the most efficient (Table 1, entry 4) ensuring the highest yields (61%) presumably due to a better solubility and dissociation of cesium salts in DMF as compared to the lithium, sodium or potassium salts.[19] Optimal loading of Cs_2CO_3 was 1 equivalent relative to carboxylic acid. Utilizing 1.5 equivalent of the catalyst gave a lower yield of product **3** (Table 1, entry 5), conversion of the bromopropargylic alcohol **1a** with 0.5 equivalent of Cs_2CO_3 after

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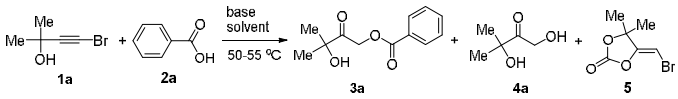
9 h was ~10%. In the presence of other alkali metal carbonates (Li_2CO_3, Na_2CO_3, K_2CO_3), the yields decreased dramatically (Table 1, entries 1-3). With K_2CO_3, the yield raised twice, when **1a**:**2a** molar ratio was increased from 1:1 to 1.5:1, however the reaction time prolonged to 14 h (Table 1, entry 10).

Table 1. Optimization of reaction conditions[a]



Entry	Solvent	Inorganic carbonate	Time, h	Ratio of **3a**:**4a**:**5**,[b] %	Isolated yield of **3a**, %
1	H_2O-DMF, 1:5	Li_2CO_3	4	50/-/50	10
2	H_2O-DMF, 1:5	Na_2CO_3	4	33/-/67	14
3	H_2O-DMF, 1:5	K_2CO_3	4	100/-/-	26
4	**H_2O-DMF, 1:5**	**Cs_2CO_3**	**4**	**88/12/-**	**61**
5	H_2O-DMF, 1:5	Cs_2CO_3[c]	3	73/-/23	33
6[d]	H_2O-DMF, 1:5	Cs_2CO_3	20	100/-/-	52
7	H_2O-DMF, 1:1	Cs_2CO_3	7	18/82/-	9
8	H_2O-DMF, 5:1	Cs_2CO_3	8	-/100/-	-
9	H_2O	Cs_2CO_3	13	-/100/-	-
10[e]	H_2O-DMF, 1:5	K_2CO_3	14	91/-/9	55
11	DMF	Cs_2CO_3	3	17/-/83	11
12	DMF	Cs_2CO_3	9	85/15/-	55
13	MeCN	Cs_2CO_3	10	trace/-/-	-

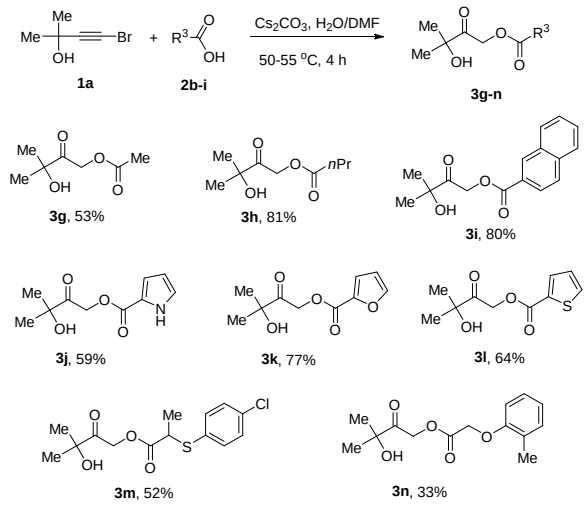
[a] Conditions: bromopropargylic alcohol **1a** (1.0 mmol), acid **2a** (1.0 mmol), inorganic carbonate (1.0 mmol). [b] According to ^{1}H NMR spectra of crude mixture. [c] 1.5 mmol. [d] At rt. [e] 1.5 mmol of alcohol **1a**.

The reaction at room temperature [Cs_2CO_3, H_2O-DMF (1:5)] slowed down and took 20 h (Table 1, entry 6).

The H_2O-DMF (1:5) mixture is an efficient solvent for the hydration/acylation of bromopropargylic alcohols **1** (Table 1, entry 4). Only trace of α-acyloxy-α'-hydroxy ketone **3a** was observed when DMF was replaced by MeCN probably due to the limited solubility of inorganic carbonates in this solvent (Table 1, entry 13). Using water as a solvent or increasing the amount of water in the system H_2O-DMF up to 5:1 ratio did not lead to α-acyloxy-α'-hydroxy ketone **3a** (Table 1, entries 8, 9). The sole product in these cases was α,α'-dihydroxy ketone **4** (up to 38% isolated yields). In DMF (without additional water), after 4 h the crude reaction mixture contained cyclic carbonate **5** as a major product (46% isolated yield, Table 1, entry 11). In this case, complete hydration/acylation of the carbonate **5** occurred for 9 h (Table 1, entry 12).

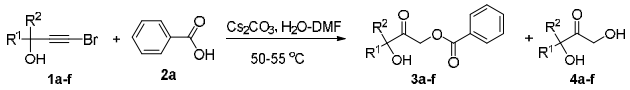
Finally, **1**:**2**:Cs_2CO_3 molar ratio 1.2:1:1, H_2O-DMF (1:5) as a solvent and 50-55 °C were found to be the optimized conditions and used to study the effect of the substituents at the α-position of the hydroxyl group in bromopropargylic alcohols **1a–f** (Table 2). In going from **1a** (R^1 = R^2 = Me) to **1b** (R^1 = Et, R^2 = Me) and **1c** [R^1 - R^2 = $(CH_2)_5$], there was not influence of the substituents on the process (Table 2, entries 1-3), products **3a-c** were formed in satisfactory yields. In contrast, rate of the reaction of alcohols **1d–f** bearing sterically hindered substituents significantly reduced. The reaction time to full conversion for **1e** (R^1 = Ph, R^2 = Me) was 10 h. Increasing temperature up to 75 °C led to a shorter reaction time (3 h) and the yield of the product **3e** arisen from 31 to 57% (Table 2, entries 5, 6). For alcohols **1d** (R^1 = *t*Bu, R^2 = Me) and **1f** (R^1 = R^2 = Ph), the conversions were incomplete after 11 h (Table 2, entry 4, 7). The yield of **3f** was poor even with temperature boost (to 75 °C) and prolonging the process duration to 25 h (Table 2, entry 8). Based on these results, substituents at the hydroxyl moiety generating steric hindrance had a negative impact on the reaction. We tried to involve secondary and primary bromopropargylic alkohols (4-bromobut-3-yn-2-ol and 3-bromoprop-2-yn-1-ol) in the reaction with benzoic acid **2a**. The corresponding α-acyloxy-α'-hydroxy ketones were detectable in the reaction solutions after 3 h by ^{1}H NMR (along with starting compounds), however, the attempts to isolate the products failed. Hence, these reactions require further optimization.

The synthesis was proved to be efficiently extendable over to various carboxylic acids (Scheme 1). Carboxylic acids with alkyl, aryl and hetaryl substituents were successfully involved into the reaction to afford the corresponding products **3g-n** in up to 81% isolated yields under the optimized conditions.

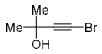
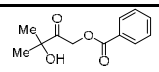
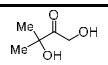
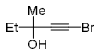
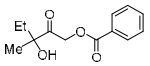
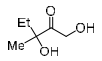
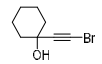
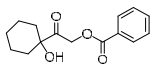
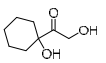
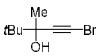
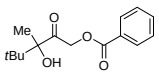
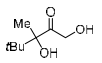
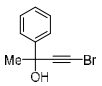
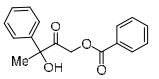
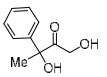
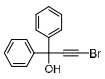
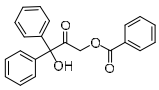
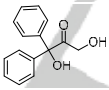


Scheme 1. Scope with respect to carboxylic acids **2b-i**.

Table 2. Scope with respect to bromopropargylic alcohols **1a-f** [a]

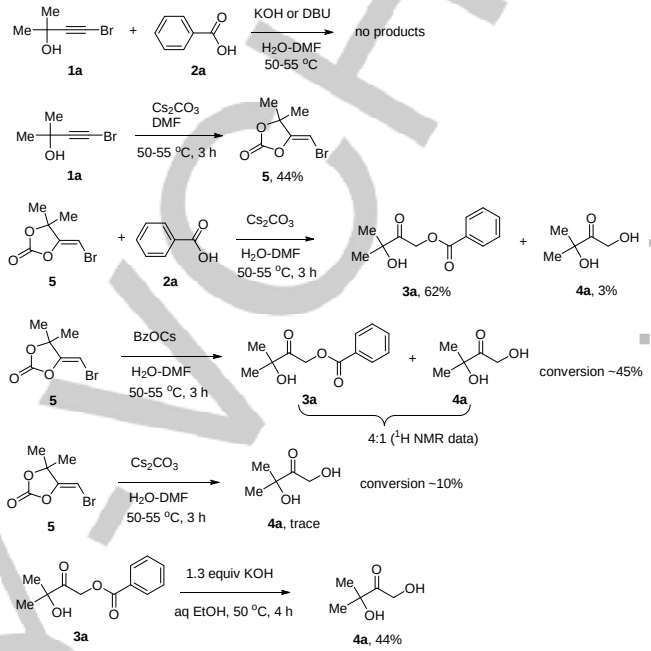


1a-f 2a 3a-f 4a-f

Entry	Propargylic alcohol **1**	Time, h	Product, **3**	Isolated yield, %	Product, **4**	Isolated yield, %
1	 **1a**	4	 **3a**	70	 **4a**	7
2	 **1b**	4	 **3b**	78	 **4b**	14
3	 **1c**	4	 **3c**	76	 **4c**	18
4	 **1d**[b]	19	 **3d**	56	 **4d**	trace
5	 **1e**	10	 **3e**	31	 **4e**	15
6[c]	**1e**	3	**3e**	57	**4e**	26
7	 **1f**[d]	11	 **3f**	34	 **4f**	trace
8[c]	**1f**[e]	25	**3f**	13	**4f**	trace

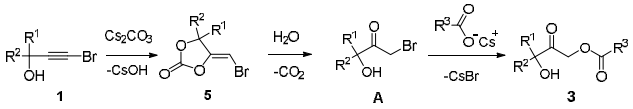
[a] Conditions: bromopropargylic alcohol **1** (1.2 mmol), benzoic acid **2a** (1.0 mmol), Cs_2CO_3 (1.0 mmol), H_2O (1 ml), DMF (5 ml). [b] Conversion was 60%. [c] At 75 °C. [d] Conversion was 30%. [e] Conversion was 75%.

Several control experiments were carried out (Scheme 2). We tested KOH or DBU as base promoter (H_2O-DMF, 1:5, 50-55 °C, 20 h) in the reaction of bromopropargylic alcohol **1a** with benzoic acid **2a**, which failed to provide the desired product. Next, cyclic carbonate **5** was formed from bromopropargylic alcohol **1a** and Cs_2CO_3 in DMF and underwent hydration/acylation to afford the product **3a**. These findings suggest that the carbonate **5** is the key intermediate in the formation of α-acyloxy-α'-hydroxy ketones and Cs_2CO_3 acts as both reagent and base promoter. We evaluated the reaction of **5** with BzOCs and Cs_2CO_3 in DMF/H_2O. When BzOCs was applied, crude product contained α-acyloxy-α'-hydroxy ketone **3a** and α,α'-dihydroxy ketone **4a** along with unreacted carbonate (**5**:**3a**:**4a** ratio is 4:4:1, ^{1}H NMR data). At the same time, Cs_2CO_3 hardly catalyzed hydration of carbonate **5**. These results indicated the participation of the carboxylic acid in the ring opening of the carbonate. α,α'-Dihydroxy ketones **4** are obviously resulted from hydrolysis of products **3**.



Scheme 2. Control experiments.

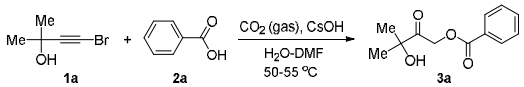
A plausible mechanism has been proposed (Scheme 3). Initially, the formation of cyclic carbonate **5** from bromopropargylic alcohol **1** and Cs_2CO_3 proceeds. Then, the hydration of **5** promoted by cesium carboxylate and the release of CO_2 give the bromoketone **A**, followed by the substitution of bromine with carboxylic acid to deliver the α-acyloxy-α'-hydroxy ketone **3**.



1 5 A 3

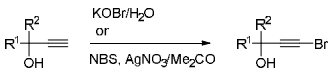
Scheme 3. Proposed mechanism.

We made an experiment using CO_2 gas instead of Cs_2CO_3 (Scheme 4). Reaction of bromopropargylic alcohol **1a** with free CO_2 gas in the presence of 100 mol% of CsOH and benzoic acid in H_2O-DMF after 3 h afforded acyloxy ketone **3a** in 48% yield. However, these results do not clarify the mechanism clearly since Cs_2CO_3 is likely to form in reaction mixture from CO_2 gas and CsOH.



Scheme 4. Control experiment.

The formation of cyclic carbonates from propargylic alcohols are known to proceed with CO_2 in the presence of transition metal catalysts[20] or phosphines,[21] guanidine,[22] K_2CO_3-crown ether,[23] *N*-heterocyclic carbenes[24] and olefins[25] and ionic liquids.[26] Thus, the first stage of the reaction represents a unique example of transition-metal-free synthesis of cyclic carbonates from propargylic alcohols without using CO_2 gas. Taking into account that the starting bromopropargylic alcohols are readily prepared from commercially available propargylic alcohols and hypobromite[27] or *N*-bromosuccinimide [28] (Scheme 5), the method presented here may be considered as one of the most expedient approaches to so far known to α-acyloxy-α'-hydroxy ketones.



Scheme 5. Synthesis of bromopropargylic alcohols **1**.

Conclusions

In conclusion, we have developed a new approach to synthesis of α-acyloxy-α'-hydroxy ketones by hydration/acylation of tertiary bromopropargylic alcohols with carboxylic acids in system Cs_2CO_3/H_2O/DMF. The reaction proceeds via transition-metal-free formation of cyclic carbonate intermediates from bromopropargylic alcohols and Cs_2CO_3. This step-economical process takes place under mild reaction conditions with simple easily available starting materials.

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Keywords: α-acyloxy ketone • cyclic carbonate • propargylic alcohols • hydration • acylation

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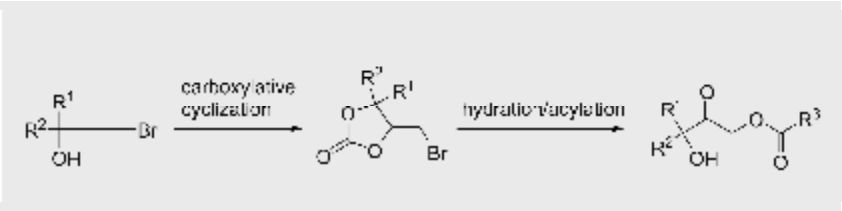

The Cs_2CO_3-catalyzed synthesis of α-acyloxy-α'-hydroxy ketones is reported, in which tertiary bromopropargylic alcohols undergo hydration/acylation with carboxylic acids via in situ formation of cyclic carbonates.

Key Topic: bromopropargylic alcohols hydration/acylation

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α-Acyloxy-α'-hydroxy Ketones via Cyclic Carbonate Intermediates Generated in Situ From Tertiary Bromopropargylic Alcohols and Cs_2CO_3