Tetrahedron 73 (2017) 5813–5819

Contents lists available at ScienceDirect

Tetrahedron

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

α-Alkoxycarbonyl-α-hydroxy secondary amides from a carbamoylsilane and α-ketoesters

Weidong Li, Yuling Han, Jianxin Chen*

College of Chemistry and Materials Science, Shanxi Normal University, Linfen 041004, PR China

A R T I C L E I N F O

Article history:
Received 29 June 2017
Received in revised form
16 August 2017
Accepted 18 August 2017
Available online 19 August 2017

Keywords:
Ketoesters
Carbamoylsilanes
Amides
Addition
Synthetic methods

A B S T R A C T

The addition of *N*-methoxymethyl-*N*-organylcarbamoyl(trimethyl)silane to α-ketoesters in anhydrous toluene at 60 °C afforded α-alkoxycarbonyl-α-siloxy amides in high yields (75–96%). The methoxymethyl was used as an amino protecting group and could be easily converted into hydrogen atom by simple acid hydrolysis leading to α-alkoxycarbonyl-α- hydroxy secondary amides.

1. Introduction

α-Alkoxycarbonyl-α-hydroxy amides have attracted a great deal of attentions, because their moieties are often found in antibiotics,[1] and they serve as useful synthetic intermediates in many natural products and pharmaceuticals such as olmesartan, dihydroimidazoquinoline, vitamin B6, and thrombin-activatable fibrinolysis inhibitor (TAFIa).[2] They also are common structural units in various functional group transformations as they constitute an intriguing class of pronucleophiles providing densely and differently functionalized chemical entities at the tetrasubstituted carbon center.[3] Due to their potential application, a number of methods have been developed to synthesize the α-alkoxycarbonyl-α-hydroxy amides.[4] In recent years, the direct oxidation of the α-alkoxycarbonyl amides with various oxidants or molecular oxygen catalyzed by a transition-metal catalyst is a most frequently used method in organic synthesis.[5] However, the use of organic oxidants or an oxygen atmosphere, the further oxidation of α-alkoxycarbonyl-α-hydroxy amides under oxidative reaction, the restricted scope of substrates, and the need to dispose toxic byproducts restrict their applications. We have recently reported on a new addition reaction of the *N*,*N*-dimethylcarbamoyl(trimethyl)silane onto α-ketoesters leading to the formation of α-alkoxycarbonyl-α-hydroxy amides.[6] The key feature of this reaction is the introduction of an aminocarbonyl group into an organic substrate under mild conditions without the aid of a catalyst. However, this approach only explored the formation of α-alkoxycarbonyl-α-hydroxy-*N*,*N*-dimethyl–substituted amide derivatives (tertiary amides), for efficient application within these areas, synthesizing α-alkoxycarbonyl-α-hydroxy secondary amides are required. We must meanwhile further develop this method towards the preparation of α-alkoxycarbonyl-α-hydroxy secondary amides by using a special carbamoylsilane. Therefore, carbamoylsilane containing an amino protecting group are expected to solve this problem. Considering this, the *N*-methoxymethyl-*N*-organylcarbamoyl(trimethyl)silane was selected as an amide source to synthesize α-alkoxycarbonyl-α-hydroxy secondary amides, wherein methoxymethyl was used as an amino protecting group. The reaction proceeded smoothly, however, we previously found that *N*-methoxymethyl-*N*-methylcarbamoyl(trimethyl)silane could not react with α-ketoamides.[7] We here report on the successful attempt in this regard.

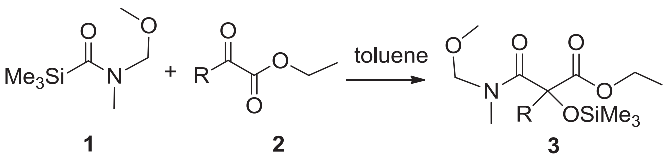
2. Results and discussion

Starting *a*-ketoesters **2** were readily accessible in good yields according to the procedures described in the literature[8] from the corresponding ethyl oxalyl chloride and aryl compounds catalyzed

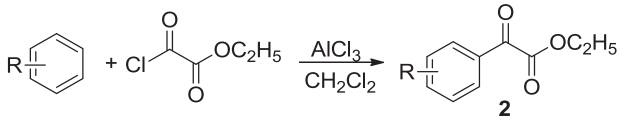
---

* Corresponding author.
E-mail address: jjxxcc2002@yahoo.com (J. Chen).

http://dx.doi.org/10.1016/j.tet.2017.08.035



Scheme 1. Synthesis of α-alkoxycarbonyl-α-siloxy amides **3**.



Scheme 2. Synthesis of α-ketoesters **2**.

by AlCl$_3$ in dichloromethane at 40 °C (Scheme 2), which were allowed to react with 1.2 equiv of carbamoylsilane **1**[9] in toluene under anhydrous conditions, good to excellent yields of α-alkoxycarbonyl-α-siloxy amides **3** were obtained, generally within a matter of a few hours at 60 °C (Scheme 1 and Table 1).

First, the addition of *N*-methoxymethyl-*N*-methylcarbamoyl (trimethyl)silane to ethyl α-ketophenylacetate was chosen as a model reaction to investigate the effects of solvents. When a range of solvents were tested, the reaction proceeded smoothly in tested solvents. As shown in Table 2, when the reaction was carried out in toluene, the highest yields of product was achieved, and the reaction time was short (Table 2, entry 3). Several other tested solvents, including benzene, THF, and acetonitrile, gave inferior results compared to toluene.

Next, we selected aliphatic α-ketoesters, such as ethyl pyruvate to react with 1.2 equiv of carbamoylsilane **1** in toluene at 60 °C. It was found that no desired product was obtained, and carbamoylsilane **1** was completely consumed. We speculate that the competitive protonolysis of the carbamoylsilane **1** has occurred as the ethyl pyruvate contained enolizable β-hydrogens, led to the desilylative protonolysis of **1** into *N*-methoxymethyl-*N*-methylformamide, which had been found in reaction mixture.[10] However, ethyl pyruvate could react with *N*,*N*-dimethylcarbamoyl(trimethyl)silane smoothly.[6] Similar phenomenon was previously observed when *N*-sulfonylimines with enolizable α-hydrogens were reacted with carbamoylsilane.[11]

To explore the scope of the reaction between α-ketoesters and carbamoylsilane **1**, we tested the representative aryl or heteroaryl α-ketoesters. Experimental results were summarized in Table 1. For the aryl, heteroaryl and unsaturated aryl α-ketoesters, all of the reactions gave good to excellent yields. A comparison of the results obtained from **2a**–**2f** indicates that the electronic proper-ties of the substituents in the phenyl influenced both the reaction time and the yields of products **3**. Phenyl α-ketoesters bearing an electron–donating group, such as a methoxy or methyl group, gave slightly lower yields than those possessing electron–with drawing group, such as a fluoro, chloro or bromo group. The α-ketoesters **2a**, **2b**, and **2c** afforded the addition products in good yields (entries 1–3), while **2d**, **2e** and **2f** gave higher yields (entries 4–6). The reaction time of α-ketoesters **2d** was shorter than that of other α-ketoesters. This result may be from the strong electron-withdrawing induction effect of fluoro. α-Ketoesters **2g** possessing two alkyl substituents on aromatic ring, and the meth-yl being at the ortho-position of carbonyl, offered the slightly lower yield of product **3g** (entry 7). It was showed that the steric environment is not an important factor. The α-ketoesters **2h** and **2i** containing an electron–rich heteroaryl group, the furyl and thienyl, reacted with carbamoylsilane **1** to afford excellent yields of desired addition products **3h** and **3i** (entries 8 and 9), and the reaction time was short compared to most of aryl α-ketoesters. β,γ-Unsaturated α-ketoester **2j** was investigated to determine whether 1,2- or 1,4-addition would occur in a conjugated system. It was found that compound **3j** corresponding to 1, 2-addition product was exclusively obtained in higher yield (entry 10).

The α-alkoxycarbonyl-α-siloxy-*N*-methoxymethyl-*N*-methyl amides **3** can be easily hydrolyzed in a mixture of hydrochloric acid and dichloromethane at room temperature, led to the α-alkoxycarbonyl-α-hydroxy secondary amides **4** (Scheme 3). For example, α-ethoxycarbonyl-α-siloxy-*N*-methoxymethyl-*N*-met-hyl amide **3e** could be readily converted into α-ethoxycarbonyl-α-hydroxy-*N*-methyl(4-chloro)phenylacetamide (**4e**) in 96% yields.

To further explore the synthetic potential of developed protocol, carbamoylsilanes possessing different alkyls were selected as amides source, such as *N*-methoxymethyl-*N*-propylcarbamoyl(trimethyl)silane (**5**) and *N*-cyclohexyl-*N*-methoxymethylcarbamoyl(trimethyl)silane (**6**) to react with α-ketoesters **2a**, **2c** and **2e** which have different substituents in the phenyl under same reaction conditions. The results are listed in Table 3. All carbamoylsilanes reacted smoothly to afford the corresponding α-alkoxycarbonyl-α-siloxy-*N*-methoxymethyl amides in good yields. Phenyl α-ketoesters bearing both an electron–withdrawing and electron–donating group were tolerated. The total yields of products are slightly lower than those of Table 1(**3a**, **3c**, **3e**).

A possible route to products **4** is presented in Scheme 4. Carbamoylsilane **1** can rearrange to its nucleophilic carbene form **A**.[12] which attacked the α-carbonyl of α-ketoesters **2** to produce an unstable intermediate **B**, followed by silyl group 1,4-migration to give the α-alkoxycarbonyl-α-siloxy-*N*-methoxymethyl-*N*-me-thyl amides **3**. The latter can be easily hydrolyzed under the acid condition to form α-alkoxycarbonyl-α-hydroxyl secondary amides **4**.

3. Conclusions

We have successfully developed a novel and highly efficient procedure toward the α-alkoxycarbonyl-α-hydroxy secondary amides by the addition of *N*-methoxymethyl-*N*-organylcarbamoyl(trimethyl)silane to α-ketoesters. The simple procedure allows the preparation of a broad variety of α-alkoxycarbonyl-α-hydr-oxy amides in one step, and in general provides good to excellent yields of the products under mild reaction condition. This approach is an efficient synthesis method for secondary amides because of the acid hydrolysis of methoxymethyl of amides **3** was easy at room temperature. This method can be applied to the synthesis of complex compounds, which can introduce an aminocarbonyl group into the molecule directly in the absence of active hydrogen substrate, led to the formation of α-hydroxy secondary amides. So the method provides a choice for the synthesis of complex compounds. We anticipate that our study may draw significant attention of chemists working on the development of synthetic methodologies and will find applications in organic and medicinal chemistry. Further investigations to develop an asymmetric version of this reaction are now in progress.

4. Experimental section

4.1. General

Dry toluene and aromatic compounds were freshly distilled from sodium and benzophenone as a moisture indicator under Ar atmosphere before use. Dichloromethane was distilled from phosphorous pentoxide. Carbamoylsilane**s** was prepared according to our previous reported methods.[9] ^{1}H (600 MHz) and ^{13}C (150.8 MHz) NMR spectra were recorded on Bruker (AV600) NMR