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# Facile Synthesis of Single $\alpha$ -tert-Alkylated Acetaldehydes via Hydroxyalkylation of Enamide in Water Solution.

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Abstract: In this paper, we established the general protocol to synthesize single a-tert-alkylated acetaldehydes via Cu-catalyzed hydroxyalkylation of enamides in water solution. The yields of the products were very high and excellent functional group compatibilities. Our reaction realized easy access to a highly functionalized acetaldehydes that can transform to various useful compounds including spirocycles. The control experiments revealed that this reaction includes hydroxyalkylation process via radical reaction.

Aldehyde compounds are undoubtedly indispensable building blocks in synthetic organic chemistry and many synthetic protocols have been developed. Among them, single  $\alpha$ -tert-alkylated acetaldehydes, which have a 1,4-dicarbonyl skeleton, are extremely useful synthetic intermediate for the synthesis of bioactive compounds, such as (-)-jiadifenolide<sup>[1]</sup>, LY426965<sup>[2]</sup>, and (-)mesembrine<sup>[3]</sup>(Figure 1). Despite their importance, a synthetic methodology for α-tertiary-alkylation of acetaldehyde is limited.



Figure 1. α-Tertiary-alkylated acetaldehyde as a useful building block.

β-Tert-alkylated aldehydes can be prepared from 1,4-addition of enals<sup>[4]</sup>, whereas single  $\alpha$ -alkylation reactions of acetaldehyde are problematic. Generally, direct alkylation of acetaldehyde with an alkyl halide under basic conditions is very difficult due to a rapid formation of aldol adducts<sup>[5]</sup>. Although the use of enamine is effective to obtain primary- and secondary-alkylated aldehyde<sup>[5]</sup>, tertiary-alkylations of enamine or enamide are challenging (Scheme 1, A). On the other hand, substituted acetaldehydes can undergo alpha-alkylation under organocatalyst<sup>[6]</sup> and photoredox<sup>[7]</sup> conditions probably due to slow aldol reaction of substituted acetaldehydes, in which double  $\alpha$ -alkylated acetaldehydes can be

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obtained (Scheme 1. B). It is therefore of great significance to develop facile methodology to synthesize single  $\alpha$ -tert-alkylated acetaldehydes which are important building blocks in organic synthesis<sup>[1-3]</sup>.

We have studied the utility of functionalized tert-alkyl radicals generated from the reaction of a-bromocarbonyl compound and a copper catalyst in olefination, cyclization and fluorination reactions via addition-eliminations or couplings<sup>[8]</sup>. During the course of our research, we found that tert-alkylation of enamide catalyzed by a copper salt in the presence of water directly provides the desired tertalkylated acetaldehydes, in which a radical addition followed by hydroxylation could occur (Scheme 1. C) [9]. Similar to alkylations of enols<sup>[10]</sup> or nitroalkanes<sup>[11]</sup>, alkylations of enamides to produce  $\alpha$ tert-alkylated aldehydes is challenging due to the limited protocol of tert-alkylations. Herein, we would like to report the general protocol to synthesize single  $\alpha$ -tert-alkylated acetaldehydes.









Scheme 1. The synthetic protocols for alkylated acetaldehydes

Initially, we expected that the desired tert-alkyl-substituted acetaldehyde 4a can be synthesized in two steps, in which tertalkylation of enamide 2a followed by hydrolysis is conducted. Therefore, reactions were conducted in anhydrous conditions (Table 1). The reaction without ligands provided 19% of 3a with concomitant formation of 15% of 4a (Run 1). On the other hand, the reaction with a nitrogen ligand dramatically improved the yield of 3a (Runs 2-5). For example, the combination of CuBr<sub>2</sub> and PMDETA provided 86% yield of 3a and 13% yield of 4a, respectively (Run 3). The yields of 3a were not significantly

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improved by changing solvents (Runs 6-8). Under the optimized conditions of run 3, one-pot 4a synthesis was carried out. But tertalkylation of enamide followed by hydrolysis (dil. HCl(aq.) at room temperature) generated 4a in 66% yield probably due to instability of 4a. We tried various hydrolysis conditions but yield was not improved. Surprisingly, the alkylation of enamide in the presence of water directly provided 4a in 93% yield (Run 9). We expected that 4a might be generated from the alkylation reaction followed by hydration reaction (Scheme 1C).

#### Table 1. Optimization[a]



<sup>[a]</sup>All reactions were carried out at 60 °C for 20 h with Cu salt (10 mol%), Ligand (10 mol%), Et<sub>3</sub>N (1.5 equiv.), **1a** (1.0 equiv.) and **2a** (3.0 equiv.). Yields were determined by <sup>1</sup>HNMR.

Enamide **2a** is easily available, cheap and stable compound which could be suitable for the facile synthesis of alkylated acetaldehydes. To obtain more good results, we screened various enamides (**2b-2f**) under the optimal conditions (Table 2). For example, **2b**, which has a secondary amide skeleton, reacted with **1a** in 77% yield. Acetylated enamide **2b** was very effective but p-tosylated (p-Ts) enamide **2c** was not reactive. In the case of **2c**, the starting material was recovered. Cyclic enamides (**2d-2f**) also reacted with **1a** to produce **4a** in the range of 60 to 88% yield. We examined various enamides but **2a** was found to be the best substrate.

#### Table 2. Substrate scope[a]



 $^{[a]}$ All reactions were carried out at 60 °C for 20 h with CuBr<sub>2</sub> (10 mol%), PMDETA (10 mol%), Et<sub>3</sub>N (1.5 equiv.), **1a** (1.0 equiv.) and **2** (3.0 equiv.) in THF/water (10/1). Yields were isolated.

We next tested functional group compatibilities in the reaction of various substituted 1 (Table 3). The scope of substituents in 1 is very

broad. For example, substrate possessing silyl ether (1c), alkyl-Cl bond (1f),  $\alpha$ ,β-unsaturated ester (1g), alcohol (1k), amine (1l, 1p), Ar-Br or -I bond (1h, 1m), alkyne (1o) and malonate (1q) can be applied to this reaction with yields of aldehydes 4 ranging from 61% to 85%. We also checked the reactivities of substrates 1 possessing various degrees of steric bulkiness at the carbonyl α-position. In the case of the reaction of 1j, the isolated yield was moderate because 2a was difficult to separate. Enamides 2 were very stable during the reaction. To obtain good isolated yield, 2b was used and pure 4j was obtained in 84% yield. As a result, various lengths of alkyl chains showed good reactivities and no limitations of the reactivities of 1 for the steric bulkiness were observed (1b-f, 1h-n, 1p). Indications that functional group tolerance is good can be found from products 4b-4q, which probably reflects the mildness of the tert-alkylation event.

Table 3. Optimization[a]



<sup>[a]</sup>All reactions were carried out at 60 °C for 20 h with CuBr<sub>2</sub> (10 mol%), PMDETA (10 mol%), Et<sub>3</sub>N (1.5 equiv.), **1** (1.0 equiv.) and **2a** (3.0 equiv.) in THF/water (10/1). Yields were isolated. <sup>[b]</sup> **2b** was used instead of **2a**.

The rationale behind the attention given to the synthesis of single  $\alpha$ -tert-alkylated acetaldehydes **4** (1,4-dicarbonyl compounds having both aldehyde and esters) has been based, in part, on its potential to streamline routes toward challenging synthetic targets, including various heterocyclic compounds, such as spirocyclic compounds (Scheme 2). For example, the reaction of **4e** in the presence of NaBH4 gave a spirolactone **5** in 67% yield. Similarly, a spirolactone **6** having alcohol was obtained in 75% yield under basic conditions (Scheme 2a). The reductive amination reaction of **4b** gave spirolactam **7** in 59% yield (Scheme 2b). The reaction of hydrazine

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with 4 gave 6-membered rings, dihydropyridazinone derivatives (8 and 9) in 97 and 79% yields, respectively (Scheme 2c). Multicyclic compound 10 can be obtained from the reaction of 4a and ethylendiamine in 76% yield (Scheme 2d).



Scheme 2. Transformations of alkylated acetaldehydes

An outline for a plausible copper-catalyzed hydroxyalkylation mechanism is shown in Figure 2. The reaction starts with the generation of tertiary-alkyl radical species **A** generated from the reaction between Cu(I) and **1**. In this reaction, we used Cu(II) as a catalyst but an active catalyst should be Cu(I)<sup>[12]</sup>. Weiss and co-workers have reported that excess amine can reduce Cu(II) to Cu(I)<sup>[13]</sup>. An evidence of this radical generation step could be confirmed by the reaction in the presence of TEMPO. Indeed, this



reaction in the presence of TEMPO did not occur. After the generation of A, addition of A to 2 takes place to give the radical intermediate B. Then, intermediate B reacts with the Cu(II) species and water to produce hemiaminal intermediate C with concomitant formation of the Cu(I) species to complete the catalytic cycle. We failed to isolate or detect C but control experiments supported the existence of C indirectly (see Scheme 4). Under neutral or basic conditions, both enamide 1a and alkylated enamide 3a were stable with or without a Cu catalyst or a base, whereas aldehyde 4a was smoothly obtained from 3a under acidic conditions (Scheme 3). Our best conditions employed a weak basic conditions, in which the hydrolysis of 3a could be very difficult in this reaction. We next carried out the reaction with EtOH instead of water (Scheme 4)<sup>[14]</sup>. Although we failed to detect unstable C, 11 was obtained under the best conditions using EtOH instead of water. 11 was also not stable and spontaneously generated 4 after the isolation. Therefore, we hypothesized that the hemiaminal intermediate C could be generated during the catalytic cycle and undergoes elimination to give the desired product 4.



Scheme 3. The stability of 3a.

1a + 2a



Scheme 4. The reaction with EtOH.

In conclusion, we have developed tert-alkylation of enamides via hydroxyalkylation in the presence of a copper catalyst and water, which provide the general protocol to synthesize single  $\alpha$ -tert-alkylated acetaldehydes via hydroxyalkylation. The synthesis of 1,4-dicarbonyl compound is rare by using copper catalyst system<sup>[15]</sup>. The resulting aldehydes are very useful building blocks for the synthesis of various cyclic compounds including spirolactones or -lactams.

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Keywords: copper • aldehyde • hydroxyalkylation • addition

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**Get bulky aldehydes**: Sterically bulky 1,4-dicarbonyl compounds having aldehyde ,which are important building blocks, can be synthesized from the reaction of enamides and  $\alpha$ -bromocarbonyls in the presence of Cu catalyst and water via hydroxyalkylations.

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