Novel Synthesis of 4-chloro-3-hydroxy-2-pyrone by using Glyceraldehyde Acetonide

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Summary: Under the condition of free solvent, 2-chloro-3-(2,2-dimethyl-1,3-dioxolan-4-yl) oxirane-2-carboxylate was synthesized by Darzens condensation with cheaper and environment-friendly glyceraldehyde acetonide. Based on this intermediate compound, 4-chloro-3-hydroxy-2-pyrone was obtained by one pot rearrangement- cyclization reaction with the catalysis of zinc chloride. The ultimate yield of 4-chloro-3-hydroxy-2-pyrone achieved 95% after two steps synthesis.

Keywords: 2-Pyrone; Darzens condensation; Dichloroacetate; Cyclization; Zinc chloride.

Introduction

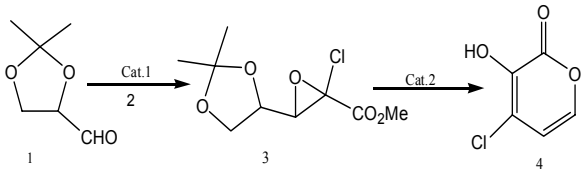
The 2-pyrone moiety is a very important component of natural products and it has been used in the synthesis of many useful compounds [1-4]. 3-hydroxy-2-pyrone was an efficient diene component in base-catalyzed Diels-Alder reactions to synthesize hydroxy substituted 1,4-naphthoqui- none. However, just a few methods have been reported for 3-hydroxy-2-pyrone [5, 6]. As a result, 3-hydroxy-2-pyrone and its derivatives are very costly.

In this paper, we demonstrate an effective synthesis of 4-chloro-3-hydroxy- 2-pyrones (**4**) by the reaction of methyl 2-chloro-3-(2,2-dimethyl-1,3-dioxolan-4-yl) oxirane-2-carboxylate (**3**), which is prepared by the Darzens condensation of 2,2-di-methyl-1,3-dioxolane- 4-carbaldehyde (**1**) with methyl dichloroacetate (**2**), as shown in Scheme 1. The synthesis of substituted 2-pyrones is a kind of rearrangement-cyclization reaction reported by Takuzo komiyma et al in 2004 [6]. Here we focus on the effect of different reaction conditions, especially the solvent and catalyst, on the synthesis of intermediate ester **3** and target product **4**. This procedure can be generalized and a variety of substituted 2-pyrones can be prepared from various glyceraldehydes acetonide derivatives.

Result and Discussion

2.1 Synthesis of methyl 2-chloro-3-(2,2-dimethyl-1,3-dioxolan-4-yl) oxirane-2-carboxylate **(3)**

The classical Darzens reaction has attracted many attentions due to it's widely usage in the synthesis of numerous compounds to construct epoxy structure [7]. But there is no report about synthesis of methyl-2-chloro-3-(2,2-dimethyl-1,3-dioxolan-4-yl)o xirane-2-carboxylate with 2,2-dimethyl-1,3-dioxo-lane-4-carbaldehyde.



Scheme 1:The synthesis of target product **4**.

The solvents played an important influence on the yield of intermediate ester **3** when glyceraldehyde acetonide **1** reacted with same equivalent of **2** by using potassium *tert*-butoxide (KTB) as catalyst (Table-1). When the toluene, CH_2Cl_2 or Et_2O was used as a solvent, the yield of intermediate ester **3** was very low due to poor solubility of the reactants and catalyst (entries 4-6). In contrast, the yield of intermediate ester **3** increased to 84.8% or 73.4% when the solvent of THF or EtOAc was used as recommended by literature [6]. (entries 2-3). However, it was found, in our work, the yield was even higher under solvent-free condiction (entry 1).

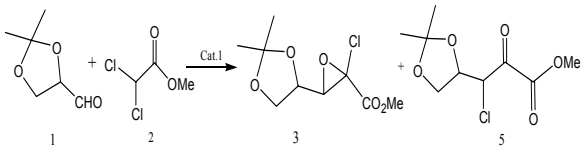
There were many advantages of this solvent-free synthesis. Firstly, perfect mutual solubility was observed in this system. Secondly, it is possible for catalyst KTB to reduce hydrolysis. Besides, this method avoided drying process of the solvents and purification procedure.

Table-1: Effect of solvent on the yield of 3 (20 °C, 24 t, $n_1:n_2:n_{KTB}$ =1:1:0.05).

Entry	1	2	3	4	5	6
Solvent	—	THF	EtOAc	Toluene	CH_2Cl_2	Et_2O
Yield (%)	97.0	84.8	73.4	58.3	30.2	24.5

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The influence of catalyst amount was investigated in terms of the yield of intermediate ester **3** (Fig. 1). The increase of the amount of catalyst KTB led to the increase of the yield. But when the catalyst KTB came up to 0.07 equivalents, the yield decreased instead. The possible reason is that it may give rise to the by-product **5** (Scheme 2). The yield curve over time showed the yield reached 98% in 24h.



Scheme 2: Synthesis of intermediate ester **3**.

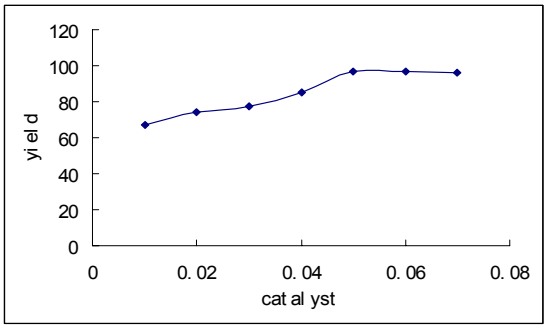


Fig. 1: Effect of the catalyst amount on the synthesis yield of intermediate ester 3 (20 ^{o}C, 24 h, solvent-free).

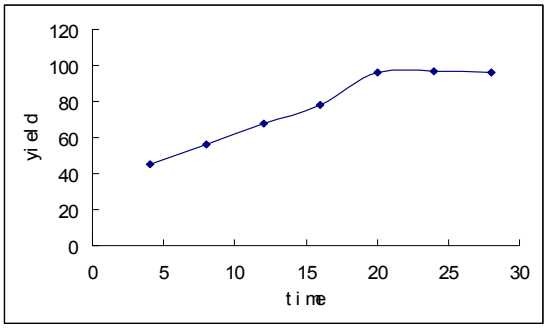


Fig. 2: Effect of the reaction time on the synthesis yield of intermediate ester 3 (20 ^{o}C,n_1:n_2:n_{KTB} =1:1:0.05, solvent-free).

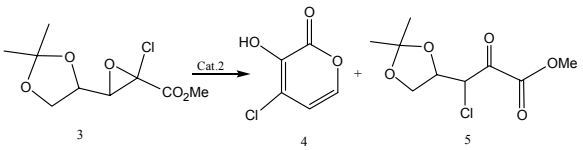
Synthesis of 4-chloro-3-hydroxyl-2-pyrone **(4)**

We firstly investigated the solvent effect on the yield of target product **4** from intermediate ester **3** (Table-2). We found that some solvents were suitable for this reaction. Especially when THF was used as a solvent, good yields of target product 4 were obtained (entries 2-7). In case of EtOAc or Et_2O, the yield of target product 4 became moderate (entries 8-9). Furthermore, when toluene was used, the yield of target product **4** was much lower (entry 10). It may come from the rearrangement by-product **5** (Scheme 3). On the contrary, benzene and CH_2Cl_2 gave no desired product due to poor solubility of reagents (entries 11-12).

Table-2: Effect of $ZnCl_2$, solvent and time on the synthesis of target product 4 (reflux).

	Solvent	$ZnCl_2$ equiv	Temperature ^{o}C	Time h	Yield
1	THF	—	67	2	0.0
2	THF	1.0	67	2	61.7
3	THF	2.0	67	2	67.8
4	THF	4.0	67	2	81.2
5	THF	1.0	67	5	89.3
6	THF	2.0	67	5	95.6
7	THF	4.0	67	5	98.3
8	EtOAc	4.0	78	2	77.9
9	Et_2O	4.0	35	2	70.3
10	Toluene	4.0	110	2	52.4
11	CH_2Cl_2	4.0	41	2	0.0
12	benzene	4.0	80	2	0.0

When the intermediate ester **3** was treated without $ZnCl_2$ in THF under reflux, no desired target product was traced and only starting reagents were retained (entry 1). These results showed that the reaction was heavily dependent of the catalytic amount. Treatment ester **3** with 1.0 equivalent $ZnCl_2$ in THF under reflux for 2 h provided target product **4** in yield of 61.7% after purification by silica gel flash chromatography (entry 2). With the increase of its equivalents to 2.0 and 4.0, respectively (entries 3-4), both reactions gave target product **4** in higher yields. Under the certain amount of $ZnCl_2$, higher yield was accompanied by longer time. For example, when reaction time was up to 5 h, the yield of entry 5 to 7 was almost 20% higher than that of entry 2 to 4, respectively. These results indicated that $ZnCl_2$ played a vital role in the synthesis of 4-chloro-3-hydroxyl-2-pyrone.



Scheme 3: Synthesis of 4-chloro-3-hydroxy-2-pyrone **(4)**.

Experiment

All the Reagents in this work were used as received. Glyceraldehyde acetonide was synthesized in our lab. THF was dryed by refluxing over sodium wire/ benzophenone before use. Melting points were measured in open capillary tubes on melting point B-545. The compounds were detected under UV light (180-400nm) with Perkin-Elmer Lambda 17 UV/vis Spectrophotometer. TLC was performed on

pre-coated silica gel (60G 254, Merck) and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Column chromatography was performed on silica gel G60 (70-230 mesh). IR spectra were taken with a Bruker Equinox 55 Infrared Spectrometer using KBr pellets. NMR spectra were recorded on a Varain Inova-400MHz NMRA spectrometer using DMSO-*d6* as a solvent. Elemental analyses were performed on Perkin-Elmer 2400 series II CHNS/O analyzer.

4.1. Synthesis of methyl 2-chloro-3-(2,2-dimethyl-1,3-dioxolan-4-yl) oxirane-2-carboxylate **(3)**

A solution of 2,2-dimethyl-1,3-dioxo-lane-4-carbaldehyde (1.3 g, 10 mmol) and methyl dichloro- acetate (1.4297 g, 10 mmol) was added with vigorous stirring to a fine suspension of potassium *tert*- butoxide (KTB) (0.0561 g, 0.5 mmol). Slight exothermic reaction was observed. The reaction mixture was stirred for 24 h under 20 ^{o}C. During the reaction, glyceraldehyde acetonide was tracked by TLC and intermediate esters **3** was analyzed with dioxane-HCl solution. After reaction, the mixture was poured into ice water, and acidified with HCl up to pH 4-5. Then EtOAc was added and shaked. The organic layer was separated. The aqueous layer was extracted with Et_2O twice. The organic extracts were combined, washed with water to neutral, and dried over $MgSO_4$. After evaporating in vacuo the residue was distilled. The oil–like crude product was purified by column-chromatography on silica gel (eluent: hexane-EtOAc, 2:1) to give a yellow oil 2.367g (yield 97%).IR (neat): 1765, 1282, 1051, 842 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*)) δ 1.49 (s, 6H),3.58 (m, 1H), 3.73 (m, 1H), 3.83 (s, 3H), 4.01(m, 1H), 4.05 (m, 1H);^{13}C NMR (100MHz): δ 25.4, 26.7, 54.4, 67.5, 68.8, 70.0, 82.2, 165.6; Anal. Calcd for $C_9H_{13}ClO_5$: C, 45.68; H, 5.54. Found: C, 46.2; H, 5.71.

4.2. Synthesis of 4-chloro-3-hydroxyl-2-pyrone **(4)**

$ZnCl_2$ (4.906 g, 36 mmol) was added to a stirred solution of intermediate ester **3** (1.311 g, 9 mmol) in THF (19 mL), and the reaction mixture was heated to reflux for 5 h. Then the reaction mixture was cooled to room temperature. Distilled water (19 mL) was added and the organic layer was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column-chromatography on silica gel (eluent: hexane-EtOAc, 3:1) to a pale yellow crystal 1.296g (yield 98%); m.p. 166–167 ^{o}C; IR (neat):3425, 1644, 1373, 1167, 769 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.317(d, 1H), 6.567 (br,1H), 7.103 (d, 1H); ^{13}C NMR (100MHz): δ 108.0, 115.8, 135.8, 148.4, 158.2.

Conclusion

We have developed an efficient and novel protocol for the synthesis of 4-chloro-3-hydroxy-2-pyrone by the reaction of Darzens condensation and rearrangement-cyclization in excellent yields. This protocol can be generalized and a variety of similar substituted 2-pyrones can be prepared from commercially available or synthesized aldehydes. Further investigation and a more detailed study of this methodology are in progress and will be reported in the future [8-10].

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