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Novel synthesis of 4-chloro-3-hydroxy-2-pyrone by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with magnesium chloride

Takuzo Komiyama, Yutaka Takaguchi and Sadao Tsuboi*

Department of Environmental Chemistry and Materials, Faculty of Environmental Science and Technology, Okayama University, Tsushima, Okayama 700-8530, Japan

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Abstract—Treatment of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with magnesium chloride gave 4-chloro-3-hydroxy-2-pyrone in excellent to good yields.

The 2-pyrone moiety is an important component of large number of natural products, which demonstrate a wide range of biological activity.[1] Recently, it has been discovered that phenyl substituted 2-pyrone has potent activity as HIV-1 protease inhibitors.[2] In addition to biological activity, 2-pyrones have been used for the syntheses of many useful molecules. For example, it is used as a diene component in Diels–Alder reactions[3] and as a precursor to other heterocyclic compounds.[4] One group reported efficient asymmetric base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone.[5] As mentioned above, the 2-pyrone units are very useful and have drawn much attention for its synthesis. There are various reported methods for the synthesis of 2-pyrone.[6] But concerning with the synthesis of 3-hydroxy-2-pyrone, only a few methods are reported.[7] Moreover, there is no report about synthesis of 6-substituted 4-halo-3-hydroxy-2-pyrone so far. Here, in this paper we demonstrate the novel synthesis of 4-chloro-3-hydroxy-2-pyrones by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with magnesium chloride.

The starting material of this pyrone synthesis, 2-chloroglycidic ester **1**, was prepared by the Darzens condensation reaction of aldehyde **4** with dichloroacetate by our original procedure as shown in Scheme 1. Aldehyde, substituted with electron donating aromatic group such as **4c**, is directly converted to 3-chloro-2-keto ester **5c** by Darzens condensation reaction with dichloroacetate.[8] The reaction of aliphatic aldehydes with dichloroacetate gives 2-chloroglycidates, which were transformed to 3-bromo-2-keto esters **5b** by the treatment with $MgBr_2 \cdot Et_2O$.[9] Ester **5** was converted to the corresponding protected diol **6** in three steps via substitution of halogen by hydroxyl group with K_2CO_3 in the H_2O/acetone, followed by $NaBH_4$ reduction and acetonide protection of hydroxyl groups. Dihydroxylation of α,β-unsaturated esters can also be used for the preparation of this protected diols.[10] Treating of the ester **6** with DIBAL-H in ether at −78 °C afforded the corresponding aldehyde, and again Darzens condensation reaction with methyl dichloroacetate furnished glycidic esters **1**. With this procedure, variety of glycidic esters **1** can be prepared from various commercially available or synthesized aldehydes.

In the presence of magnesium chloride, 2-chloroglycidic ester **1a**–**c**[11] was converted to corresponding 4-halo-3-hydroxy-2-pyrones **2a**–**c** in excellent to good yields[12,13] (Table 1). Treatment of glycidic ester **1a** with 4 equiv of magnesium chloride in THF under refluxing condition for 2 h provided 4-chloro-3-hydroxy-2-pyrone (**2a**) in 97% yield after purification by silica gel flash chromatography (Table 1, entry 1). When EtOAc was used as a solvent, the yield became moderate (entry 2) and, the

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* Corresponding author. Tel./fax: +81-86-251-8898; e-mail: stsuboi6@cc.okayama-u.ac.jp

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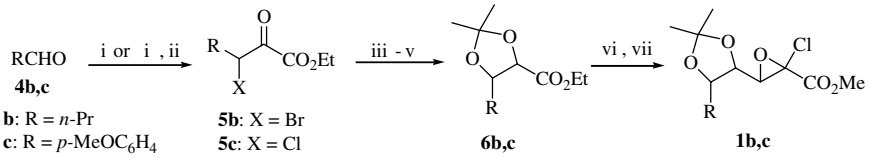
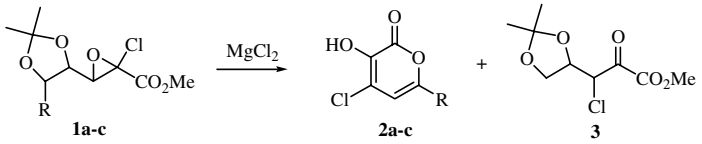


Scheme 1. Reagents and conditions: (i) *t*-BuOK (1.2 equiv), $CHCl_2CO_2Et$ (1.0 equiv), THF, **5c** (72%); (ii) $MgBr_2{\cdot}Et_2O$ (2.0 equiv), Et_2O, reflux, **5b** (80%, two steps); (iii) K_2CO_3, H_2O–acetone; (iv) $NaBH_4$, THF–MeOH, 0 °C; (v) DMP, PTSA (cat.), acetone, rt, **6b** (51%, three steps), **6c** (71%, three steps); (vi) DIBAL-H (1.5 equiv), Et_2O, −78 °C; (vii) *t*-BuOK, $CHCl_2CO_2Me$ (1.0 equiv), THF, **1b** (76%, three steps), **1c** (71%, two steps).

Table 1. Synthesis of 4-chloro-3-hydroxy-2-pyrone **2** by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester **1** with magnesium chloride

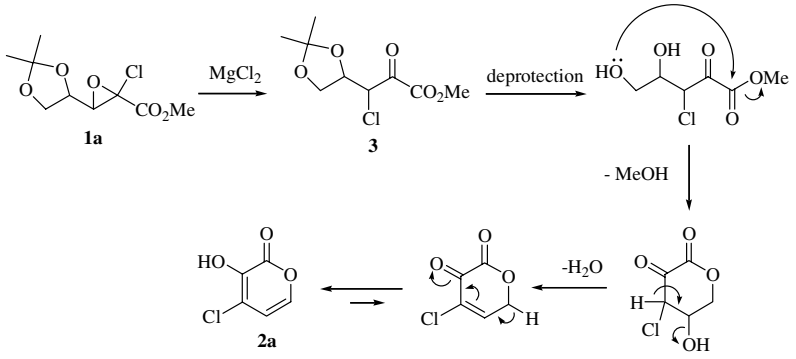


Entry	Substrate[a]	Conditions	Product/yield (%)
1	**1a**	$MgCl_2$ (4.0 equiv), THF, reflux, 2 h	**2a**/97
2	**1a**	$MgCl_2$ (4.0 equiv), EtOAc, 60 °C, 3 h	**2a**/81, **3**/7
3	**1a**	$MgCl_2$ (4.0 equiv), toluene, reflux, 23 h	**2a**/49, **3**/26[b]
4	**1a**	$MgCl_2$ (1.0 equiv), THF, reflux, 5 h	**2a**/97
5	**1a**	$MgCl_2$ (0.2 equiv), THF, reflux, 29 h	**2a**/91
6	**1b**	$MgCl_2$ (4.0 equiv), THF, reflux, 68 h	**2b**/92[b,c]
7	**1c**	$MgCl_2$ (4.0 equiv), THF, reflux, 20 h	**2c**/92

[a] A mixture of two stereoisomers was used as a substrate (ratio is 1.9:1 for entries 1–5). Major isomers, which were obtained from Scheme 1 were used as a substrate (entries 6 and 7).
[b] Starting material was also recovered in 20% and 25% yields, respectively (entries 3 and 6).
[c] Based on consumed **1b**.

reaction was not completed even after 23 h, and the reaction in toluene gave the product in 49% yield (entry 3). In entries 2 and 3, 3-chloro-2-keto ester **3** was also obtained. To optimize the effect of magnesium chloride, its concentration was reduced to 1.0 and 0.2 equiv, respectively (entries 4 and 5). In these cases it was found to take longer reaction time to complete the reaction. But the yield of **2a** was almost same as that of entry 1. These result shows that the reaction proceeds with catalytic amount of magnesium chloride. Furthermore, treatment of 5-substituted glycidic esters **1b**,**c** with magnesium chloride also gave the desired products **2b**,**c** in good yields (entries 6 and 7), but reaction was not completed in case of entry 6. This is because some steric hindrance may prevent magnesium chloride to approach the substrate.

Plausible mechanism for furnishing pyrone **2a** from glycidic ester **1a** is shown in Scheme 2. At first, as reported,[9] 2-chloroglycidic ester **1a** was transformed to 3-chloro-2-keto ester **3** in the presence of magnesium chloride. Then acetonide group was deprotected, followed by nucleophilic addition of hydroxyl group to ester carbonyl carbon. Finally, elimination of water



Scheme 2.

and tautomerization furnished 4-chloro-3-hydroxy-2-pyrone (**2a**).

In conclusion, we have developed an efficient and novel protocol for the synthesis of 4-chloro-3-hydroxy-2-pyrone by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with magnesium chloride in excellent to good yields. And a variety of 6-substituted 4-chloro-3-hydroxy-2-pyrones can also be prepared from commercially available or synthesized aldehydes by this method. Further investigation and a more detailed study of this methodology are in progress and will be reported in the future.

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11. Compound **1a** was prepared from acetonide protected D-glyceraldehyde via Darzens condensation reaction with dichloroacetate. For preparation of acetonide protected D-glyceraldehyde see: Schmid, C. R.; Bryant, J. D.; Dowlatzedah, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. D.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056–4058.
12. Typical procedure (synthesis of **2a** from **1a**): To a stirred solution of α-chloroglycidic ester **1a** (50 mg, 0.21 mmol) in THF (2 mL) was added magnesium chloride (80 mg, 0.84 mmol), and the reaction mixture was heated to reflux for 2 h. Then the reaction mixture was allowed to cool to room temperature. Distilled water (2 mL) was added and the organic layer was extracted three times with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column-chromatography (hexane/EtOAc 5:1 to 2:1) to give 4-chloro-3-hydroxy-2-pyrone (**2a**) in 97% yield.
13. Compound **2a**: pale yellow needle like crystal; mp 166–167 °C (*i*-PrOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (d, J = 5.7 Hz, 1H), 6.56 (br, 1H), 7.11 (d, J = 5.7 Hz, 1H); IR (neat): 3321, 1683, 1349, 1112, 779. Spectral data were identical with those of the authentic sample.[14] Compound **2b**: color less oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 7.5 Hz, 3H), 1.67 (m, 2H), 2.44 (t, 7.5 Hz, 2H), 6.05 (s, 1H), 6.2–6.8 (br, 1H); IR (neat): 3317, 1685, 1648, 1366, 1206 cm^{-1}. Anal. Calcd for $C_8H_9ClO_3$: C, 50.94; H, 4.81. Found: C, 50.98; H, 5.15. Compound **2c**: white powdery crystal; mp 154–156 °C (*i*-PrOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3 H), 6.2–6.4 (br, 1H), 6.59 (s, 1H), 6.95 (d, 2H, J = 9.0 Hz) 7.66 (d, 2H, J = 9.00 Hz); IR (neat): 3282, 1699, 1639, 1512, 1368, 1174 cm^{-1}. Anal. Calcd for $C_{12}H_9ClO_4$: C, 57.05; H, 3.59. Found: C, 56.65; H, 3.90.
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