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NOVEL SYNTHESIS OF 4-ARYLSULFENYL-3-HYDROXY-2-PYRONE: ONE POT SUBSTITUTION-REARRANGEMENT-CYCLIZATION REACTION OF ACETONIDE PROTECTED 4,5-DIHYDROXY-2-CHLOROGLYCIDIC ESTER BY SODIUM ARYLTHIOLATE

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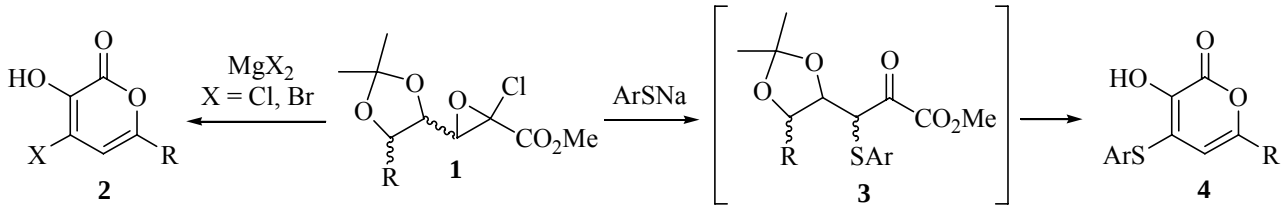
Abstract – Treatment of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with sodium arylthiolate gave 4-arylsulfenyl-3-hydroxy-2-pyrone in excellent to good yields in one pot.

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 their synthesis. There are various reported methods for the synthesis of 2-pyrone.[6] But concerning the synthesis of 3-hydroxy-2-pyrone, only a few methods are reported.[7] Moreover, there is no report about the synthesis of sulfur-substituted 3-hydroxy-2-pyrone so far.

During some other researches in our group, we have unexpectedly discovered that 3-hydroxy-2-pyrone (**2**) could be obtained in one pot by treating acetonide protected 4,5-dihydroxy-2-chloroglycidic ester (**1**) with magnesium halide (Scheme 1).[8] We carried out further investigation in this field and applied sodium arylthiolate for this one pot cyclization reaction. And we found that the treatment of glycidic ester (**1**) with sodium arylthiolate also gave 4-arylsulfenyl-3-hydroxy-2-pyrone (**4**) in good yield. As far as we 2-chloroglycidic ester by sodium thiolate. Furthermore, this reaction proceeds very smoothly under mild

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of Tokyo University.

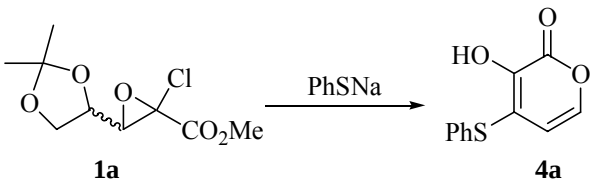
condition and gives desired product in good yield. Therefore, this reaction is not only unique but also very effective protocol for the preparation of 4-arylsulfenyl-3-hydroxy-2-pyrone. In this paper we demonstrate the novel synthesis of 4-arylsulfenyl-3-hydroxy-2-pyrone (**4**) by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester (**1**) with sodium arylthiolate.



Scheme 1

Firstly, we optimized reaction conditions for the synthesis of 3-hydroxy-4-phenylsulfenyl-2-pyrone (**4a**) (Table 1). The starting material, 2-chloroglycidic ester (**1a**) was prepared from acetonide protected glyceraldehyde[9] *via* Darzens condensation reaction with dichloroacetate.[10] When 2-chloroglycidic ester (**1a**) was treated with 1.5 equiv. of PhSNa at room temperature, the reaction proceeded cleanly but became stagnant and the starting material was recovered (entry 1). However, all starting material was consumed under refluxing condition and furnished 2-pyrone (**4a**) in excellent yield (entry 2). When equivalent of PhSNa was reduced to 1.0, starting material was recovered again (entry 3).

Table 1. Optimization of reaction conditions for the synthesis of 3-hydroxy-4-phenylsulfenyl-2-pyrone (**4a**).

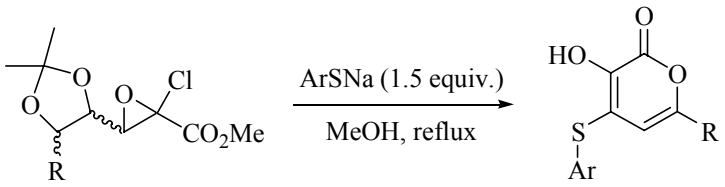


entry	solvent	PhSNa (equiv.)	temp.	time (h)	yield (%)
1	MeOH	1.5	rt	3	75[a)]
2	MeOH	1.5	reflux	0.5	95
3	MeOH	1.0	reflux	3	83[a)]

a) Starting material (**1a**) was recovered: 22%, 16% yields (entries 1, 3), respectively.

Then we also tried to apply this reaction to the synthesis of various 4-arylsulfenyl-3-hydroxy-2-pyrone (**4**) (Table 2). Treatment of glycidic esters (**1a-e**)[8] with sodium arylthiolate in MeOH under refluxing conditions provided 4-arylsulfenyl-3-hydroxy-2-pyrones (**4b-j**) in excellent to good yield after purification by silica gel flash chromatography. On the other hand, treatment of 2-chloroglycidic ester with sodium alkylthiolate gave 4-alkylsulfenyl-3-hydroxy- 2-pyrone in slightly low yield.[11]

Table 2. Synthesis of various 4-arylsulfenyl-3-hydroxy-2-pyrone (**4b-j**).

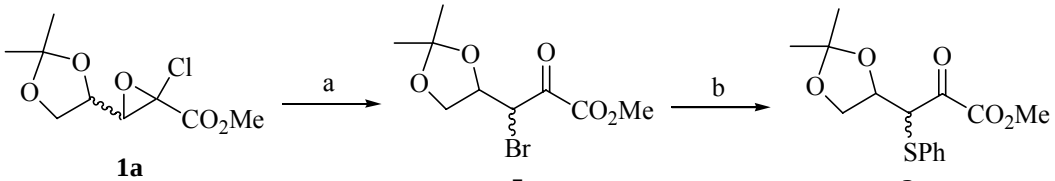


1a-e **4b-j**

entry	substrate	R	Ar	time (h)	product/ yield
1	**1a**	H	4-MePh	0.5	**4b**/ 90
2	**1a**	H	4-ClPh	1	**4c**/ 72 (93)[a)]
3	**1a**	H	4-FPh	1	**4d**/ 84 (93)[a)]
4	**1a**	H	3-MeOPh	1	**4e**/ 96
5	**1a**	H	2-naphtyl	1	**4f**/ 91
6	**1b**	Me	Ph	1	**4g**/ 96
7	**1c**	Ph	Ph	1	**4h**/ 88
8	**1d**	4-MeOPh	Ph	1	**4i**/ 84
9	**1e**	1-naphtyl	Ph	1	**4j**/ 80

a) Based on consumed **1**.

In order to further investigation of this reaction, we also carried out the next reaction concerning the substitution-rearrangement product keto ester (**3a**) (Table 3). (This keto ester (**3a**) was prepared by the procedure as shown in Scheme 2). When the keto ester (**3a**) was treated with 0.5 equiv. of PhSNa in MeOH under refluxing condition, 2-pyrone (**4a**) was furnished smoothly in excellent yield (entry 1). On the other hand, 2-pyrone (**4a**) was also obtained without PhSNa (entry 2). But in this case the starting material remained even after 2 h. These results indicate that PhSNa plays a vital role not only in the rearrangement of glycidic ester (**1a**) to keto ester (**3a**), but also in the conversion of keto ester (**3a**) to 2-pyrone (**4a**). Furthermore, the rearrangement product (**3a**) was converted to 2-pyrone (**4a**) in good yield by our reported $MgCl_2$ treatment method (entry 4).[8]



1a **5** **3a**

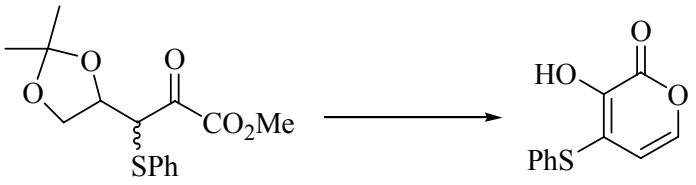
Reagents and conditions: (a) $MgBr_2 \cdot 6H_2O$ (4.0 equiv.), THF, reflux, 4 h, 92%; (b) PhSNa (1.0 equiv.), toluene, rt, 6 h, 40%.

Scheme 2

Plausible mechanism for the furnishing 2-pyrone (**4a**) from glycidic ester (**1a**) is shown in Scheme 3. The first step of the reaction is a conversion of glycidic ester (**1a**) to keto ester (**3a**) resulted from the

regioselective nucleophilic attack of thiophenoxide anion to the epoxide ring. Then, acetone was eliminated *via* base catalyzed keto-enol tautomer (**3a'**), which thereby converted into intermediate compound (**6**). Then the nucleophilic attack toward the ester carbonyl carbon would furnish the 3-hydroxy-4-phenylsulfenyl-2-pyrone (**4a**) after elimination of MeOH and tautomerization.

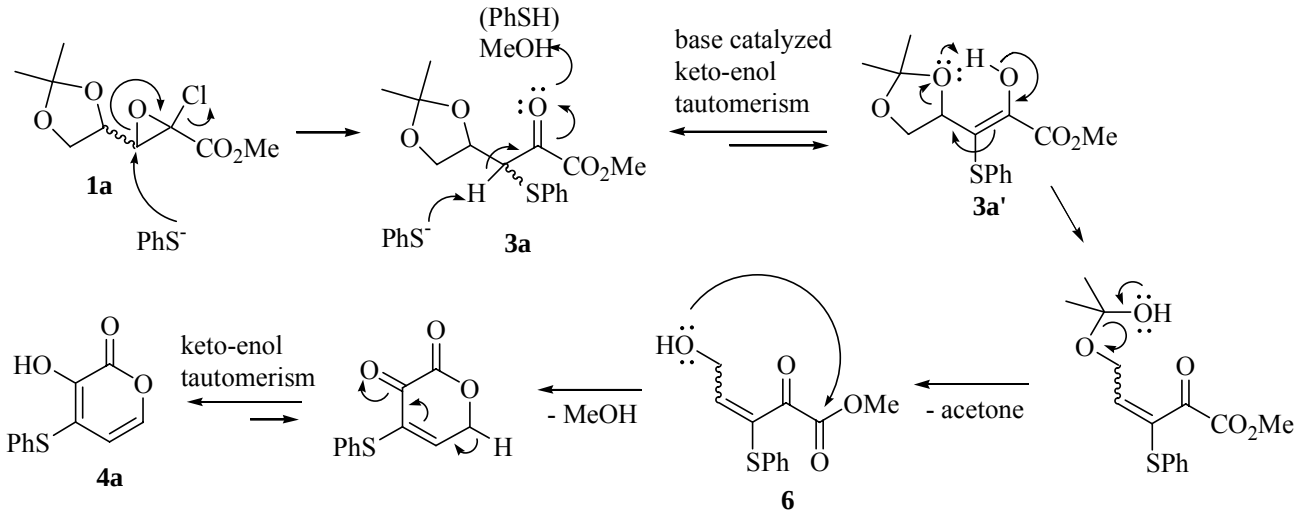
Table 3. Synthesis of 4-phenylsulfenyl-3-hydroxy-2-pyrone (**4a**) from 3-phenylsulfenyl-2-keto ester (**3a**)



3a **4a**

entry	additive (equiv.)	solvent	temp.	time (h)	yield (%)
1	PhSNa (0.5)	MeOH	reflux	0.5	95
2	----	MeOH	reflux	2	70 (93)[a)]
3	----	THF	reflux	3	0[b)]
4	$MgCl_2$ (1.0)	THF	reflux	3	92

a) Based on consumed **3a**
b) Starting material was recovered quantitatively.



Scheme 3

In conclusion, we have developed an efficient and novel protocol for the synthesis of 4-arylsulfenyl-3-hydroxy-2-pyrones by the reaction of acetonide protected 4,5-dihydroxy-2-chloroglycidic ester with sodium arylthiolate in excellent to good yields. And we have found that sodium arylthiolate plays a vital role not only in the rearrangement of glycidic ester, but also in cyclization step in this reaction.

EXPERIMENTAL

NMR spectra were recorded on JEOL JNM-AL300 instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Thermo Nicolet Avatar 360T2 infrared spectrophotometer. Elemental analyses were performed on Perkin-Elmer 2400 series Ⅱ CHNS/O analyzer. For thin layer chromatography aluminum sheets Merk silica gel coated 60 F254 plates were used and the plates were visualized with UV light and phosphomolybdic acid (5% in EtOH). Merck silica gel 60 N (spherical, neutral) (40-50 μm) was used for the flash chromatography. Melting points were obtained in open capillary tubes on a Mel-Temp-II hot stage microscope. THF was distilled from sodium wire/ benzophenone before use. All other chemicals were used as received.

General procedure for the synthesis of 4a-j (synthesis of 4a from 1a): To a stirred solution of 2-chloroglycidic ester (**1a**) (50 mg, 0.21 mmol) in MeOH (5 mL) was added PhSNa (42 mg, 0.32 mmol), and the reaction mixture was stirred at refluxing condition for 30 min. Then the reaction mixture was allowed to cool to rt. After evaporation of MeOH, the resulting solution was diluted with EtOAc and saturated NH_4Cl solution (0.3 mL) was added. Then 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 10:1 to 1: 1) to give 3-hydroxy-4-phenylsulfenyl-2-pyrone (**4a**) (44 mg, 95 %).

3-Hydroxy-4-phenylsulfenyl-2-pyrone (4a). Pale yellow crystal; mp 159-161 ^{o}C (toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (d, *J*=5.7 Hz, 1H), 6.34 (br, 1H), 6.96 (d, *J*=5.7 Hz, 1H), 7.43-7.47 (m, 3H), 7.53-7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.3, 128.4, 129.4, 129.8, 129.9, 135.2, 135.7, 141.2, 158.9; IR (neat): 3295, 1671, 1345, 1176, 1107, 752. Anal. Calcd for $C_{11}H_8O_3S$: C, 59.99; H, 3.66. Found C, 59.74; H, 3.59.

3-Hydroxy-4-(4-tolylsulfenyl)-2-pyrone (4b). Pale yellow crystal; mp 180-183 ^{o}C (Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 5.66 (d, *J*=5.7 Hz, 1H), 6.30 (br, 1H), 6.94 (d, *J*=5.7 Hz, 1H), 7.25 (d, *J*=8.1 Hz, 2H), 7.43 (d, *J*=8.1 Hz, 2H); IR (neat): 3304, 1671, 1344, 1177, 1107, 816. Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30. Found C, 61.89; H, 4.27.

4-(4-Chlorophenylsulfenyl)-3-hydroxy-2-pyrone (4c). White crystal; mp 159-160 ^{o}C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (d, *J*=5.4 Hz, 1H), 6.34 (br, 1H), 6.99 (d, *J*=5.4 Hz, 1H), 7.41 (d, *J*=8.7 Hz, 2H), 7.48 (d, *J*=8.7 Hz, 2H); IR (neat): 3274, 1662, 1345, 1177, 1106, 829. Anal. Calcd for $C_{11}H_7O_3ClS$: C, 51.87; H, 2.77. Found C, 51.75; H, 2.57.

4-(4-Fluorophenylsulfenyl)-3-hydroxy-2-pyrone (4d). White crystal; mp 180-181 ^{o}C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.64 (d, *J*=5.7 Hz, 1H), 6.28 (br, 1H), 6.98 (d, *J*=5.7 Hz, 1H), 7.12-7.18 (m,

2H), 7.52-7.53 (m, 2H); IR (neat): 3293, 1671, 1346, 1180, 1108, 838. Anal. Calcd for $C_{11}H_7O_3FS$: C, 55.46; H, 2.96. Found C, 55.54; H, 2.84.

3-Hydroxy-4-(3-methoxyphenylsulfenyl)-2-pyrone (4e). White crystal; mp 116-117 °C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3H), 5.74 (d, *J*=5.7 Hz, 1H), 6.37 (br, 1H), 6.97 (d, *J*=5.7 Hz, 1H), 6.97-7.14 (m, 3H), 7.33-7.38 (m, 1H); IR (neat): 3303, 1679, 1348, 1180, 1102, 762. Anal. Calcd for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03. Found C, 57.45; H, 3.98.

3-Hydroxy-4-(2-naphthylsulfenyl)-2-pyrone (4f). White crystal; mp 126-129 °C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, *J*=5.7 Hz, 1H), 6.39 (br, 1H), 6.93 (d, *J*=5.7 Hz, 1H), 7.51-7.60 (m, 3H), 7.84-7.91 (m, 3H), 8.11 (s, 1H); IR (neat): 3288, 1663, 1347, 1180, 1103, 817. Anal. Calcd for $C_{15}H_{10}O_3S$: C, 66.65; H, 3.73. Found C, 66.79; H, 3.61.

3-Hydroxy-6-methyl-4-phenylsulfenyl-2-pyrone (4g). White crystal; mp 186-187 °C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 5.40 (s, 1H), 6.11 (br, 1H), 7.26-7.47 (m, 3H), 7.51-7.55 (m, 2H); IR (neat): 3266, 1668, 1392, 1360, 1210, 1153, 859. Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.52; H, 4.30. Found C, 61.46; H, 4.22.

3-Hydroxy-6-phenyl-4-phenylsulfenyl-2-pyrone (4h). Pale yellow crystal; mp 207-208 °C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.11 (s, 1H), 6.42 (br, 1H), 7.33-7.36 (m, 3H), 7.45-7.50 (m, 5H), 7.58-7.61 (m, 2H); IR (neat): 3270, 1672, 1373, 1182, 750. Anal. Calcd for $C_{17}H_{12}O_3S$: C, 68.90; H, 4.08. Found C, 68.66; H, 4.04.

3-Hydroxy-6-(4-methoxyphenyl)-4-phenylsulfenyl-2-pyrone (4i). Pale yellow crystal; mp 145-146 °C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 5.98 (s, 1H), 6.22 (br, 1H), 6.85 (d, *J*=9.0 Hz, 2H), 7.42 (d, *J*=9.0 Hz, 2H), 7.45-7.50 (m, 3H), 7.57-7.61 (m, 2H); IR (neat): 3283, 1676, 1623, 1511, 1372, 1251, 1169. Anal. Calcd for $C_{18}H_{14}O_4S$: C, 66.24; H, 4.32. Found C, 65.94; H, 4.17.

3-Hydroxy-6-(1-naphthyl)-4-phenylsulfenyl-2-pyrone (4j). Yellow crystal; mp 200-202 °C (Hexane/ EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (s, 1H), 6.44 (br, 1H), 7.42-7.53 (m, 7H), 7.60-7.63 (m, 2H), 7.83-7.93 (m, 3H); IR (neat): 3261, 1664, 1367, 1176. Anal. Calcd for $C_{21}H_{14}O_3S$: C, 72.81; H, 4.07. Found C, 72.86; H, 4.09.

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11. The reaction of 2-chloroglycidic ester (**1a**) with sodium 2-propanethiolate furnished 3-hydroxy-4-(2-propylsulfenyl)-2-pyrone in 48% yield.