Synthesis of 2,3,4,4a-Tetrahydroxanthen-1-ones and 3,3a-Dihydro-2*H*-cyclopenta[b]chromen-1-ones from the Reaction of Salicylaldehydes and 2-Cyclohexen-1-one and 2-Cyclopenten-1-one

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Received October 30, 2002

Chromenes (2*H*-1-benzopyrane derivatives) have been widely employed as important intermediates in the synthesis of many natural products and medicinal agents.[1] Thus, various synthetic methods for the formation of these compounds have been reported.[1,2] Among them synthesis from salicylaldehydes is most common.[2] The reaction of activated vinyl compounds and salicylaldehydes gave the chromenes in good to moderate yields. Most frequently used base in the reaction is DABCO[2a-d] and potassium carbonate.[2e-f] Activated vinyls involve acrolein, acrylate esters, acrylonitrile and alkyl vinyl ketones. However, the reaction of cycloalkenones and salicylaldehyde, which could produce xanthene derivatives, has not been reported until now.

Initially, we examined the reaction of salicylaldehyde (**1a**) and 2-cyclohexen-1-one (**2a**) with DABCO or K₂CO₃.[2] However, desired xanthene derivative **3a** was obtained in low yield.[3] As previously reported the corresponding chromene derivatives were obtained in moderate yields in the reaction with other activated vinyl compounds except 2-cyclohexen-1-one and 2-cyclopenten-1-one. As an example, the corresponding chromene derivative was obtained without any problem in the reaction of **1a** and methyl vinyl ketone in 60% yield (aq. CHCl₃, DABCO, 7 days).[2a] Thus, we examined various reaction conditions for the formation of xanthene derivatives **3** from 2-cyclohexen-1-one and finally found that the use of DMAP in aqueous THF suffice the formation of the desired compounds in reasonable yields.[4]

As shown in Scheme 1, the reaction of salicylaldehydes **1** and 2-cyclohexen-1-one (**2a**) in aqueous THF in the presence of DMAP (0.2-1.2 equiv.) at room temperature gave 2,3,4,4a-tetrahydroxanthen-1-ones **3a**-**e** in 39-53%

yields. By using 2-cyclopenten-1-one (**2b**) 3,3a-dihydro-2*H*-cyclopenta[b]chromen-1-ones **4a**-**c** were synthesized in 50-58% yields. The results are summarized in Table 1. The reaction conditions can be applied to other activated vinyls. As an example, the corresponding chromene derivative, 1-(2*H*-chromen-3-yl)ethanone, was obtained in the reaction of **1a** and methyl vinyl ketone with DMAP in 75% yield (rt, 3 days, aq. THF). The result showed that the use of DMAP is superior to the use of DABCO (*vide supra*).

Synthesis of 2,3,4,9-tetrahydroxanthen-1-one (**5a**) from cyclohexane-1,3-dione and *o*-hydroxybenzyl alcohol has been reported (Figure 1).[5] However, synthesis of 2,3,4,4a-tetrahydroxanthen-1-ones **3** and 3,3a-dihydro-2*H*-cyclopenta[b]chromen-1-ones **4** has not been reported yet.[6]

Table 1. Synthesis of 2,3,4, 4a-tetrahydroxanthen-1-ones **3a-e** and 3,3a-dihydro-2*H*-cyclopenta[b]chromen-1-ones **4a-c**

Entry	Salicyl-aldehydes 1	Cyclo-alkenones 2	Conditions	Products (%)[a]
1	1a	2a	THF/H₂O DMAP (0.2 equiv.) rt, 36 h	3a (53) (135-138)
2	1b	2a	THF/H₂O DMAP (0.2 equiv.) rt, 48 h	3b (50) (142-144)
3	1c	2a	THF/H₂O DMAP (0.2 equiv.) rt, 36 h	3c (47) (145-148)
4	1d	2a	THF/H₂O DMAP (0.2 equiv.) rt, 48 h	3d (49) (134-135)
5	1e	2a	THF/H₂O DMAP (1.2 equiv.) rt, 72 h	3e (39) (96-102)[b]
6	1a	2b	THF/H₂O DMAP (0.2 equiv.) rt, 6 h	4a (58) (113-115)
7	1c	2b	THF/H₂O DMAP (0.2 equiv.) rt, 12 h	4b (56) (150-151)
8	1d	2b	THF/H₂O DMAP (0.2 equiv.) rt, 12 h	4c (50) (151-152)
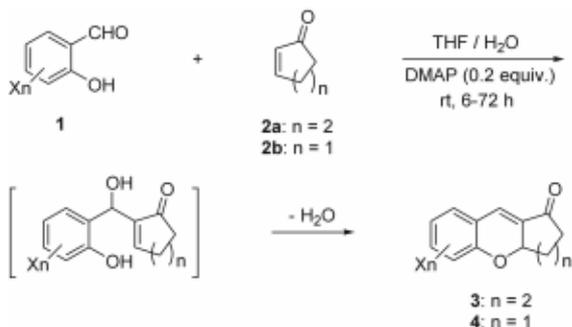
[a]Mp (ºC) was written in parenthesis. [b]Decomposition.

Scheme 1

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2,3,4,4a-tetrahydroxanthen-1-one (3a)   2,3,4,9-tetrahydroxanthen-1-one (5a)

Figure 1

The reaction mechanism could be proposed as follows as shown in Scheme 1. DMAP catalyzed Baylis-Hillman reaction[7] and subsequent intramolecular Michael addition followed by dehydration gave desired **3** and **4**. Under the same reaction conditions, the reaction of **1a** and 4,4-dimethyl-2-cyclohexen-1-one (**2c**) did not proceed at all presumably due to the unfavorable zwitterion formation[7] between DMAP and 4,4-dimethyl-2-cyclohexen-1-one by the steric hindrance of *gem*-dimethyl group.

Experimental procedure is very simple and straight-forward. As shown in Scheme 1, a stirred mixture of **1** and **2** (1.0 equiv.) in aq. THF in the presence of DMAP (0.2 equiv.) was maintained at room temperature for the time given in Table 1. Usual workup and column chromatographic purification (hexane/ether, 5 : 1) gave analytically pure products.[8]

As a conclusion, we disclosed a facile synthesis of novel 2,3,4,4a-tetrahydroxanthen-1-ones and 3,3a-dihydro-2*H*-cyclopenta[b]chromen-1-ones from the reaction of salicyl-aldehydes and 2-cyclohexen-1-one and 2-cyclopenten-1-one for the first time in reasonable yields. Further studies on the transformation of these compounds towards phenolic compounds or 2,3,4,9-tetrahydroxanthen-1-ones are currently underway.

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3. The reaction of **1a** and **2a** in aqueous THF in the presence of DABCO gave maximum 20% yield of **3a** after 21 days at room temperature. The same reaction in the presence of K_2CO_3 in dioxane or in DMF showed similar results.
4. Recently, Aggarwal et al. have reported that the rate of Baylis-Hillman reaction including cycloalkenones can be accelerated dramatically by using 3-quinuclidinol in aqueous solvent. Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510. By applying the conditions, we obtained similar result in our case (49% yield of **3a** from **1a** and **2a** in aqueous THF using 3-quinuclidinol (0.2 equiv.) at room temperature for 48 h).
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6. Conversion of **3a** to the corresponding **5a** was examined. However, we did not succeed until now for the conversion. The xanthene **3a** are unstable in acidic or basic conditions presumably due to the acidic nature of the proton at the 4a-position. The instability of **3a** might be the reason for the low yield of product when we used stronger bases such as DABCO or K_2CO_3 instead of DMAP.
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8. Some selected spectroscopic data of **3a** and **4a** are as follows.
   3a: yellow solid, mp 135-136 °C; IR (KBr) 1671, 1604 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.6-2.7 (m, 6H), 4.9-5.1 (m, 1H), 6.8-7.4 (m, 4H), 7.43 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (DMSO-d$_6$) δ 17.48, 29.29, 38.62, 74.56, 115.89, 122.15, 122.29, 130.03, 130.16, 131.12, 132.24, 155.53, 196.95; Mass (70 eV) *m/z* (rel intensity) 115 (16), 144 (100), 171 (6), 200 (M$^+$, 25).
   4a: yellow solid, mp 113-115 °C; IR (KBr) 1702, 1641 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.08-2.76 (m, 4H), 5.26-5.33 (m, 1H), 6.90-7.31 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 28.09, 37.04, 75.69, 116.55, 121.93, 122.32, 127.64, 130.45, 131.66, 132.42, 155.29, 201.42; Mass (70 eV) *m/z* (rel intensity) 29 (102), 115 (18), 130 (60), 144 (100), 157 (55), 158 (61), 186 (M$^+$, 57).