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Potassium Carbonate-Catalyzed Reactions of Salicylic Aldehydes with Allenic Ketones and Esters: an Effective Way to Synthesize Functionalized 2*H*-Chromenes

Min Shi,[a,*] Lun-Zhi Dai,[a] Yong-Ling Shi,[a] Gui-Ling Zhao[b]

[a] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Reüpublic of China
Fax: (+86)-21-6416-6128, e-mail: mshi@pub.sioc.ac.cn
[b] School of Chemistry & Pharmaceutics, East China University of Science and Technology, 130 MeiLong Road, Shanghai 200237, People's Republic of China

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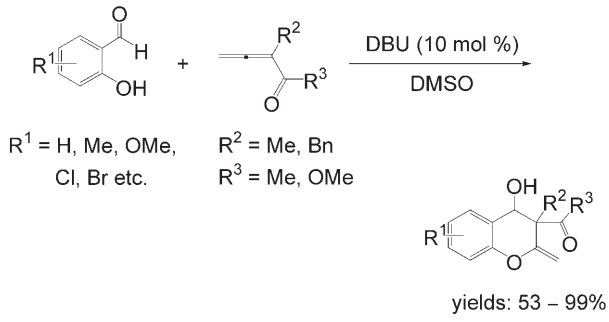
Abstract: Potassium carbonate-catalyzed reactions of salicylic aldehydes with 3-methylpenta-3,4-dien-2-one, 3-benzylpenta-3,4-dien-2-one or ethyl 2-methylbuta-2,3-dienoate gave the corresponding functionalized 2*H*-1-chromenes in good to excellent yields and good stereoselectivities in some cases in DMSO at 120 °C within 1 h, respectively.

Keywords: 3-benzylpenta-3,4-dien-2-one; DMSO; ethyl 2-methylbuta-2,3-dienoate; 3-methylpenta-3,4-dien-2-one; potassium carbonate; salicylic aldehydes

Introduction

2*H*-1-Chromenes are an important class of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity of naturally occurring representatives.[1,2] Recently, the reactions of salicylic aldehydes with various conjugated olefins such as acrylate derivatives or α,β-unsaturated ketones to give different substituted chromenes were reported.[3] In addition, the formation of 2*H*-1-chromene derivatives from the reactions of salicyclic aldehydes with allenic ketones or esters catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature has also been disclosed by our group (Scheme 1).[4] Herein we report the cyclization reactions of salicylic aldehydes with allenic ketones and esters to correspondingly give another type of 2*H*-1-chromene derivatives in good to excellent yields in the presence of potassium carbonate (10 mol %) at 120 °C. On the basis of this facile synthetic protocol, a variety of interesting 2*H*-1-chromene derivatives can be obtained in a simple way.

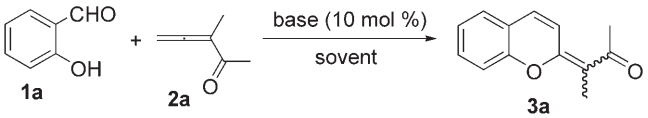


Scheme 1. Reactions of salicylic aldehydes with 3-methylpenta-3,4-dien-2-one in the presence of DBU (10 mol %) in DMSO at room temperature.

Results and Discussion

We first systematically examined the reactions of salicylaldehyde (**1a**) (1.0 equiv.) with 3-methylpenta-3,4-dien-2-one (**2a**) (1.5 equivs.) catalyzed by various bases (10 mol %) including K_2CO_3, KOH, PPh_3, DABCO and DMAP in a variety of solvents at room temperature (25 °C) up to 120 °C. The results are summarized in Table 1. DMSO is the solvent of choice and K_2CO_3 is the best base promoter in this reaction, leading to 3-chromen-2-ylidene-butan-2-one (**3a**) as mixtures of *E*- and *Z*-isomers in good yields at 80–120 °C (Table 1, entries 1–10). When the reaction was carried out at 120 °C, **3a** was obtained in 91% yield within 1 h with a ra-

Table 1. Reactions of salicylaldehyde (**1a**) (0.5 mmol) with 3-methylpenta-3,4-dien-2-one (**2a**) (0.75 mmol) in the presence of various bases and solvents.



Entry	Solvent	Temp. [°C]	Time [h]	Base	Yield [%][a] 3a (*E*/*Z*)
1	DMSO	25	3	K_2CO_3	23[b] (5/1)
2	CH_3CN	25	25	K_2CO_3	disordered
3	DMF	25	25	K_2CO_3	disordered
4	CH_2Cl_2	25	25	K_2CO_3	disordered
5	THF	25	25	K_2CO_3	disordered
6	PhMe	25	25	K_2CO_3	disordered
7	DMSO	40	2	K_2CO_3	35[b] (3/1)
8	DMSO	80	1	K_2CO_3	85 (3/1.7)
9	DMSO	120	1	K_2CO_3	91 (8.3/1)
10	DMSO	120	1	Li_2CO_3	41 (5/1)
11	DMSO	120	1	Na_2CO_3	85 (4.2/1)
12	DMSO	120	1	Cs_2CO_3	80 (3.8/1)
13	DMSO	120	1	KOH	50 (4.1/1)
14	DMSO	120	24	PPh_3	trace
15	DMSO	120	24	DABCO	35
16	DMSO	120	24	DMAP	20

[a] Yields of isolated products.
[b] Including some other products shown in Scheme 5.

tio of *E*/*Z* = 8.3/1 (Table 1, entry 9). Li_2CO_3, Na_2CO_3, Cs_2CO_3, PPh_3, DABCO and DMAP are less effective than K_2CO_3 in DMSO at 120 °C (Table 1, entries 10–16).

Under these optimized conditions, we next examined the reactions of a variety of salicylic aldehydes **1** with **2a**, 3-benzylpenta-3,4-dien-2-one (**2b**) and ethyl 2-methylbuta-2,3-dienoate (**2c**) to explore the scope and limitations of this reaction. The results are shown in Tables 2 and 3, respectively. The corresponding adducts **3** were obtained in good to excellent yields as mixtures of *E*- and *Z*-isomers at 120 °C within 1 h (Table 2, entries 1–11). In some cases, these two isomers can be easily separated on silica gel column chromatography (see Supporting Information).

To our surprise, the reactions of salicylic aldehydes with **2c** exclusively produced the corresponding chromene derivatives **4** in good yields in the *E*-geometric configuration (Table 3, entries 1–7). The substituents on the salicylic aldehydes have significant effects on this reaction. Electron-donating group substituted salicylic aldehydes, probably due to the higher nucleophilicities of the corresponding phenolate anionic intermediates, give higher yields than those bearing electron-withdrawing groups on the aromatic ring under identical conditions.

Their structures were determined by spectroscopic data, microanalyses, HR-MS and X-ray diffraction. The geometric configuration was determined by NOESY spectroscopy (see Supporting Information). The ORTEP drawing of *E*-**3f** is shown in Figure 1 (see also the Supporting Information).[5]

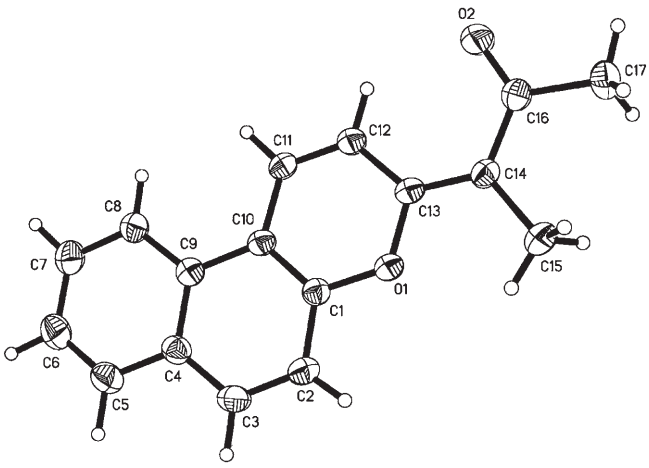
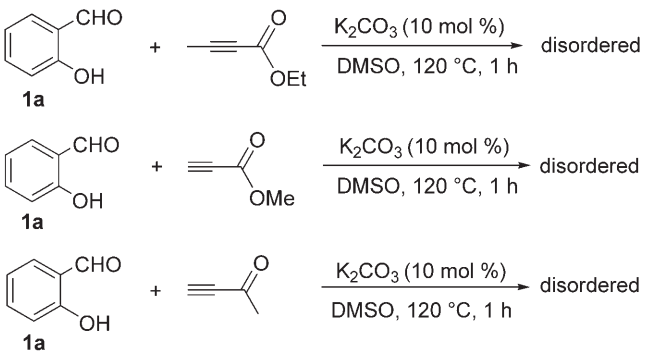


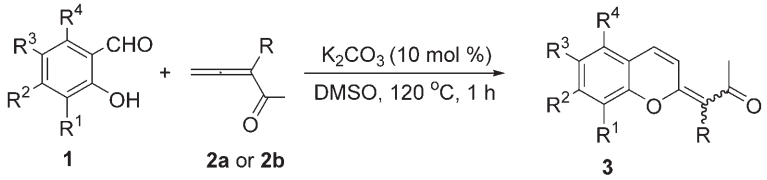
Figure 1. The X-ray crystal structure of *E*-**3f**.

Moreover, the reactions of salicylic aldehyde (**1a**) (0.5 mmol) with ethyl 2-butynoate, methyl propiolate and but-3-yn-2-one (0.75 mmol) were examined under identical conditions (Scheme 2). Disordered reactions were observed. On the other hand, when 2-hydroxyacetophenone (**6a**) in place of salicylic aldehyde (**1a)** was applied to the reaction with **2c**, the desired product **7a** was obtained in 79% yield along with traces of unidentified by-products, although the reaction of **6a** with **2a** afforded complicated products under the standard conditions (Scheme 3).



Scheme 2. Reactions of **1a** with ethyl 2-butynoate, methyl propynoate and but-3-yn-2-one in the presence of potassium carbonate.

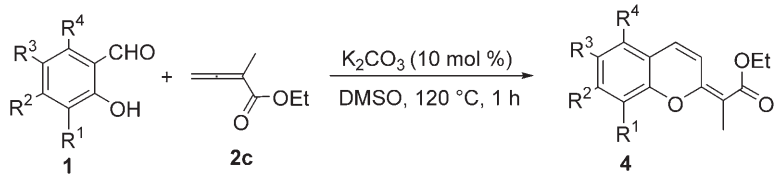
Table 2. Reactions of salicylaldehydes **1** (0.5 mmol) with **2a** (0.75 mmol) or 3-benzylpenta-3,4-dien-2-one (**2b**) in DMSO in the presence of potassium carbonate (10 mol %) at 120 °C.



Entry	R^1	R^2	R^3	R^4	R	Yield [%][a] **3** (*E*/*Z*)
1	H	H	H	H	Me	**3a**, 91 (8.3/1)
2	OMe	H	H	H	Me	**3b**, >99 (2.1/1)
3	H	OMe	H	H	Me	**3c**, 84 (4.2/1)
4	H	H	OMe	H	Me	**3d**, >99 (6/1)
5	H	H	Me	H	Me	**3e**, 99 (4/1)
6	H	H			Me	**3f**, 89 (11.5/1)
7	H	H	Br	H	Me	**3g**, 77[b] (1.7/1)
8	Cl	H	Cl	H	Me	**3h**, 85[b] (4/7)
9	H	H	H	H	Bn	**3i**, 93 (3.6/1)
10	OMe	H	H	H	Bn	**3j**, 67 (1.5/1)
11	H	H	Br	H	Bn	**3k**, 84 (2/1)

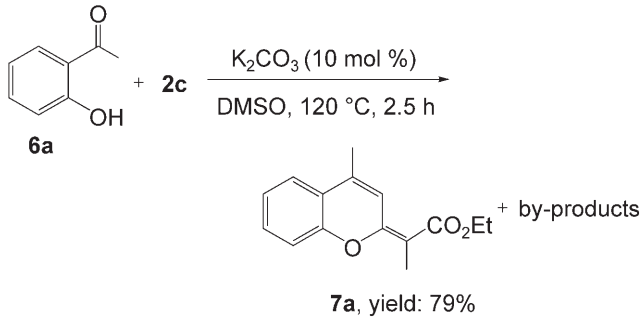
[a] Yields of isolated products.
[b] The *E*- and *Z*-isomers are separable by silica gel chromatography.

Table 3. Reactions of salicylic aldehydes **1** (0.5 mmol) with ethyl 2-methylbuta-2,3-dienoate (**2c**) (0.75 mmol) in the presence of potassium carbonate (10 mol %) in DMSO at 120 °C.



Entry	R^1	R^2	R^3	R^4	Yield [%][a] **4**
1	H	H	H	H	**4a**, 89
2	OMe	H	H	H	**4b**, 93
3	H	OMe	H	H	**4c**, 84
4	H	H	Me	H	**4d**, 79
5	H	H			**4e**, 88
6	H	H	Br	H	**4f**, 88
7	Cl	H	Cl	H	**4g**, 81

[a] Yields of isolated products.

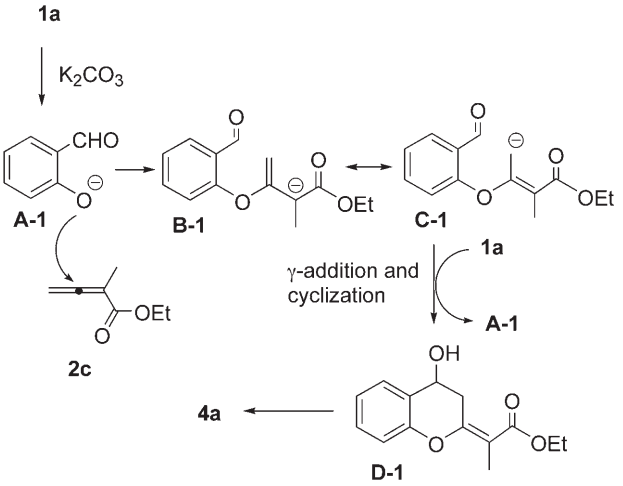


Scheme 3. Reactions of 2-hydroxyacetophenone (**6a**) with **2c** in the presence of potassium carbonate.

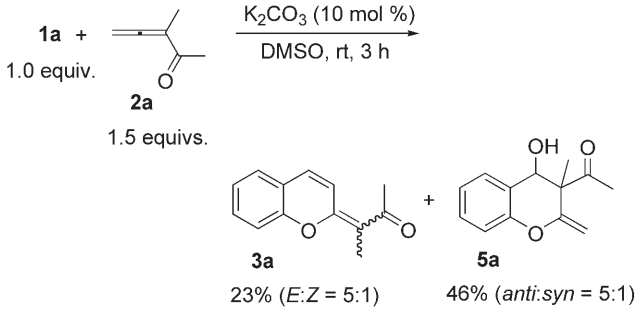
A plausible mechanism for the reaction is shown in Scheme 4 based on the earlier reports[4,6–8] and our investigations. The reaction is most likely to proceed through a domino oxa-Michael/aldol condensation pathway. Initially the non-nucleophilic base potassium carbonate abstracts a proton from salicylaldehyde (**1a**) to produce the oxy-anionic intermediate **A-1**. The subsequent conjugate addition of **A-1** to allenic ester **2c** generates **B-1**, which easily resonates to **C-1** at high temperature (120 °C), because α-addition usually occurs under kinetic control at low temperature while γ-addition is preferred at elevated temperature. The following intramolecular aldol reaction produces the cyclized intermediate, which abstracts a proton from **1a** to afford compound **D-1** and regenerates intermediate **A-1** to accomplish the catalytic cycle. Dehydration of **D-1** under basic condition at high temperature gives the final product **4a**.

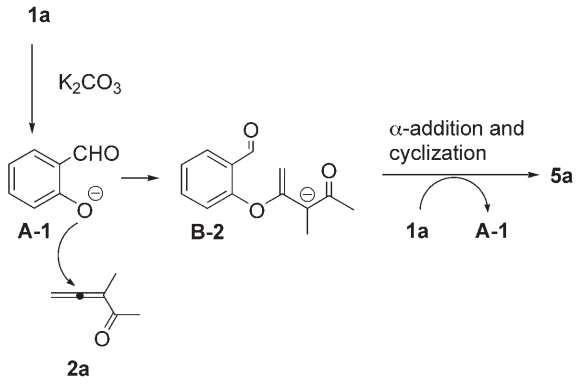
Performing the reaction at room temperature (Table 1, entry 1), the adduct **3a** was obtained in low yield together with another product **5a**,[4] which is produced *via* α-addition and cyclization of intermediate **B-2** (Scheme 5). Moreover, we envisioned that **5a** might be converted to **3a** at a higher temperature. To test this hypothesis, a control experiment was performed (Scheme 6). When **5a** was treated with K_2CO_3 at 120 °C, the corresponding product **3a** was obtained in good yield. One plausible mechanism for the formation of **3a** is shown in Scheme 7. K_2CO_3 first abstracts a proton from **5a** to produce intermediate **A-2**, then a *retro*-aldol reaction occurs to give intermediate **B-2**, which easily resonates to intermediate **C-2**. Subsequently the reaction follows the same pathway as shown in Scheme 4 to yield **3a**. This result also suggests that at a high reaction temperature, the corresponding adducts **3** are preferably formed in the presence of K_2CO_3 *via* γ-addition.

It should be noted that when penta-3,4-dien-2-one was used in the reaction with salicylaldehyde (**1a**) catalyzed by potassium carbonate under the same conditions as those described above, the reaction became disordered, leading to the corresponding chromene derivative in traces only presumably due to the high reactivity of penta-3,4-dien-2-one.

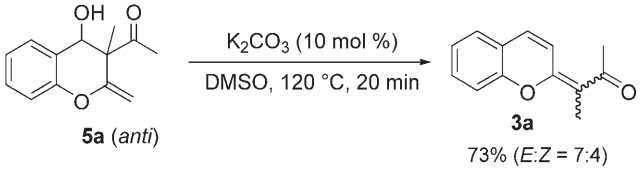


Scheme 4. A plausible mechanism for the reaction of **1a** with **2c** at high temperature.

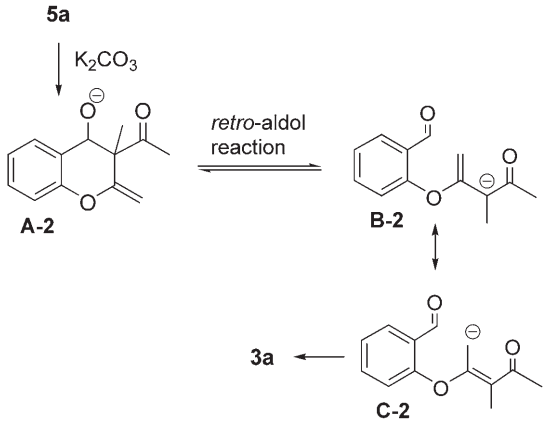




Scheme 5. Reaction of **1a** with **2a** in the presence of potassium carbonate at room temperature.



Scheme 6. Control experiment.



Scheme 7. A plausible reaction mechanism for the formation of **3a**.

Conclusion

In this paper, we have presented an efficient, K_2CO_3-catalyzed reaction of salicylaldehydes with allenic ketones or esters, which provides an easy route for the synthesis of functionalized 2*H*-1-chromenes[9] in DMSO at 120 °C in good to excellent yields. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

Experimental Section

General Methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI, MALDI and ESI methods, and HR-MS was measured by the EI method. Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used without further purification. All reactions were monitored on TLC plates. Flash column chromatography was carried out using silica gel or Al_2O_3 at increased pressure.

Reactions of Salicylic Aldehydes with 3-Methylpenta-3,4-dien-2-one Catalyzed by K_2CO_3. Typical Reaction Procedure of Salicylaldehyde with 3-Methylpenta-3,4-dien-2-one in the Presence of K_2CO_3 in DMSO at 120 °C

To a Schlenk tube containing DMSO (2.0 mL) were added salicylaldehyde (61 mg, 0.5 mmol), 3-methylpenta-3,4-dien-2-one (72 mg, 0.75 mmol) and K_2CO_3 (7.0 mg, 0.05 mmol). The solution was stirred for 1 h at 120 °C. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the mixture of compounds *E*-**3a** and *Z*-**3a** (eluent: EtOAc/petroleum ether = 1/10) as a yellow solid; yield: 91 mg (91%).

Supporting Information Available

^{13}C and ^{1}H NMR spectroscopic and analytical data for compounds **3** and **4** and the ORTEP drawing of *E*-**3f** are presented in the supporting information.

Acknowledgements

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[5] The crystal data of *E*-**3f** has been deposited under CCDC 284282. Empirical formula: $C_{17}H_{14}O_2$, formula weight: 250.28, crystal size: 0.450 × 0.417 × 0.295 mm, crystal color, habit: colorless, prismatic, crystal system: triclinic, lattice type: primitive, lattice parameters: a = 6.6270(8) Å, b = 7.4087(10) Å, c = 13.6216(17) Å, α = 82.876(2)°, β = 76.011(2)°, γ = 80.120(2)°, V = 671.86(15) Å^3, space group: P-1, Z = 2, D_{calc} = 1.305 g/cm^3, F_{000} = 264, R1 = 0.0497, wR2 = 0.1209, diffractometer: Rigaku AFC7R.

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