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Synthesis of Functionalized 2*H*-1-Benzopyrans by DBU-Catalyzed Reactions of Salicylic Aldehydes with Allenic Ketones and Esters

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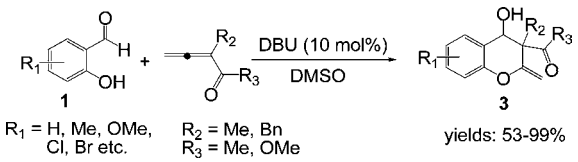
ABSTRACT



DBU-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 diastereoselectivities in some cases in DMSO, respectively.

2*H*-1-Chromenes are important classes of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity of naturally occurring representatives.[1,2] The synthesis of 2*H*-1-chromenes via the cyclization of suitably elaborated phenyl ethers commonly suffers from a lack of regiocontrol in the cyclization step. Recently, the reactions of salicyclic aldehydes with various conjugated olefins such as acrylate derivatives or α,β-unsaturated ketones to give different substituted chromenes were reported.[3] To our surprise, the reactions of salicylaldehydes with allenic ketones or esters[4−6] have never been mentioned so far. Herein, we wish to report the cyclization reactions of salicylic aldehydes with allenic ketones and esters catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the corresponding 2*H*-1-chromene derivatives in excellent yields and good diastereoselectivities.

We first systematically examined the reactions of salicylaldehyde **1a** (1.0 equiv) with 3-methylpenta-3,4-dien-2-one **2a** (4.0 equiv) catalyzed by various phosphine and nitrogen Lewis bases in a variety of solvents at 80 °C. The results are summarized in Table 1. Using PPh_3, PPh_2Me, and

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(2) Hepworth, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp 737−883.

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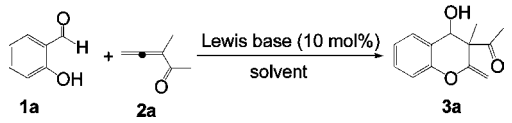
Table 1. Reactions of Salicylaldehyde **1a** (0.5 mmol) with 3-Methylpenta-3,4-dien-2-one **2a** (2.0 mmol) in the Presence of Various Lewis Bases and Solvents



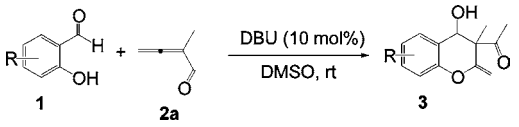
entry	Lewis base	solvent	T/°C	yield[a]/% **3a** (*anti*/*syn*)[b]
1	PPh_3	DMSO	80	trace
2	PPh_2Me	DMSO	80	trace
3	$PPhMe_2$	DMSO	80	72 (*anti*)
4	PBu_3	DMSO	80	68 (*anti*)
5	DABCO	DMSO	80	trace
6	DMAP	DMSO	80	79 (76:3)
7	DBU	DMSO	80	81 (*anti*)
8	DBU	DMF	80	76 (*anti*)
9	DBU	CH_3CN	80	56 (*anti*)
10	DBU	$PhCH_3$	80	59 (28:31)
11	DBU	THF	60	72 (28:44)
12	DBU	DCE	80	53 (*anti*)
13	DBU	DMSO	60	84 (73:11)
14	DBU	DMSO	40	99 (82:17)
15	DBU	DMSO[c]	40	92 (67:25)
16	DBU	DMSO[c]	20	99 (74:25)

[a] Isolated yields and the reaction time are determined by TLC on the basis of consuming the starting materials **1a**. [b] The *anti*- and *syn*-diastereoisomers can be separated by silica gel column chromatography. [c] The reaction was carried out with 1.0 equiv of **1a** and 2.0 equiv of **2a**.

DABCO as the Lewis base promoters, the reactions were sluggish in DMSO (Table 1, entries 1, 2, and 5). When phosphine Lewis base $PPhMe_2$ or PBu_3 was used as a promoter, 2*H*-chromene **3a** was obtained in 72% or 68% yield within 2 h, respectively (Table 1, entries 3 and 4). By use of nitrogen Lewis base DMAP or DBU as a promoter in DMSO, we found that the adduct **3a** was produced in higher yield (Table 1, entries 6 and 7). The solvent effects have also been examined in the presence of DBU (Table 1, entries 8−12). We found that DMSO is the solvent of choice for this reaction. The reaction temperature also played a very important role in this reaction. When this reaction was carried out at 60 or 40 °C in DMSO, **3a** was obtained in 84% or 99% yield as a pair of diastereoisomers, respectively (Table 1, entries 13 and 14). The best reaction conditions were found that when 2.0 equiv of 3-methylpenta-3,4-dien-2-one **2a** was employed, and the reaction was carried out at 20 °C (room temperature), the product **3a** can be obtained in 99% yield after 24 h as a pair of diastereoisomers (Table 1, entry 16).

Next, we examined the reactions of a variety of salicyclic aldehydes **1** with 3-methylpenta-3,4-dien-2-one **2a** under these optimized conditions. The results are shown in Table 2. The corresponding adducts **3** were obtained in good to excellent yields as a pair of diastereoisomers at room temperature (Table 2, entries 1−8). These two isomers can be easily separated on silica gel column chromatography (Supporting Information). For the starting materials **1** having an electron-donating group on the phenyl ring, the reactions

Table 2. Reactions of Salicylic Aldehydes **1** (0.5 mmol) with 3-Methylpenta-3,4-dien-2-one **2a** (1.0 mmol) in the Presence of DBU (10 mol %) in DMSO at Room Temperature



entry	R	time[b]/h	yield[a]/% **3** (*anti*/*syn*)[c]
1	5-Me (**1b**)	24	**3b**, >99 (70:30)
2	3-MeO (**1c**)	48	**3c**, >99 (81:19)
3	4-MeO (**1d**)	48	**3d**, >99 (88:11)
4	5-MeO (**1e**)	48	**3e**, >99 (70:30)
5	3-OH (**1f**)	120	**3f**, 92 (68:24)
6	3,5-Cl_2 (**1g**)	60	**3g**, >99 (76:23)
7	5-Br (**1h**)	60	**3h**, 93 (64:29)
8	1-naphthyl (**1i**)	48	**3i**, >99 (80:20)
9	5-NO_2 (**1j**)	48	0

[a] Isolated yields. [b] The reaction time is determined by TLC on the basis of consuming the starting materials **1**. [c] The *anti*- and *syn*-diastereoisomers can be separated by silica gel column chromatography.

can complete within shorter reaction time to give the adducts **3** in higher yields. On the other hand, for the starting materials **1** having an electron-withdrawing group on the benzene ring, the reaction rate is much slower. For the starting material **1** bearing a strongly electron-withdrawing group such as nitro group on the phenyl ring (starting material **1j**), no reaction occurred (Table 2, entry 9).

Their structures were determined by spectroscopic data, microanalyses, HRMS, and X-ray diffraction. The ORTEP drawing of *anti*-**3h** is shown in Figure 1.[7]

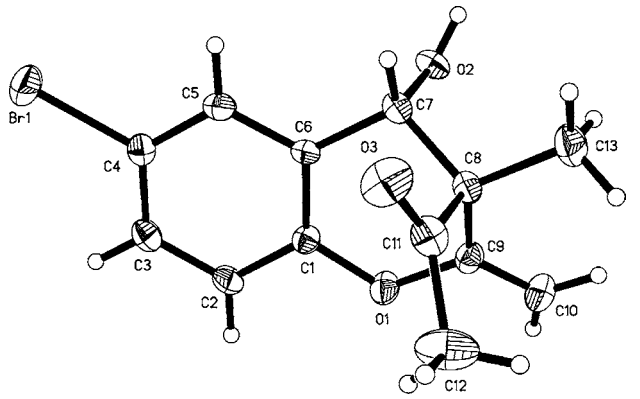
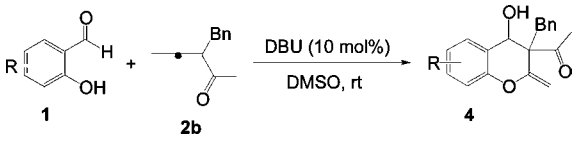


Figure 1. X-ray crystal structure of *anti*-**3h**.

The reactions of salicylic aldehydes with 3-benzylpenta-3,4-dien-2-one **2b** catalyzed by DBU in DMSO at 20 °C were also examined. The results are summarized in Table 3. The corresponding adducts **4** were formed in excellent yields with good to high diastereoselectivities (Table 3, entries 1−5). In some cases, the adducts **4** were formed

Table 3. Reactions of Salicylic Aldehydes **1** (0.5 mmol) with 3-Benzylpenta-3,4-dien-2-one **2b** (1.0 mmol) in the Presence of DBU (10 mol %) in DMSO at Room Temperature



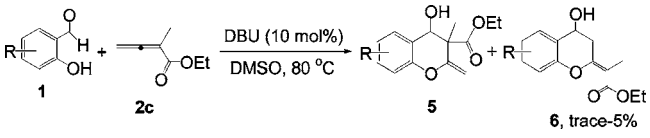
entry	R	time[b]/h	yield[a]/% 4 (*anti*/*syn*)[c]
1	H (**1a**)	48	**4a**, 84 (*anti*)
2	5-Me (**1b**)	60	**4b**, 96 (*anti*)
3	4-MeO (**1d**)	48	**4d**, >99 (>20:1)
4	5-Br (**1h**)	72	**4h**, 93 (86:7)
5	1-naphthyl (**1i**)	48	**4i**, >99 (73:26)

[a] Isolated yields. [b] The reaction time is determined by TLC on the basis of consuming the starting materials **1**. [c] The *anti*- and *syn*-diastereoisomers can be separated by silica gel column chromatography.

exclusively as *anti*-configuration based on comparison of ^{1}H NMR spectroscopic data with those of adducts **3** (Table 3, entries 1 and 2).

Similarly, ethyl 2-methylbuta-2,3-dienoate **2c** can also react with various salicyclic aldehydes in the presence of a Lewis base promoter. The results on the screen of the reaction conditions are summarized in Table SI-1 in the Supporting Information. The best reaction conditions were found to carry out the reaction in DMSO at 80 °C with DBU as a promoter because **2c** is less reactive in this reaction. Under these optimized conditions, we found a variety of salicyclic aldehydes can react with ethyl 2-methylbuta-2,3-dienoate **2c** to give the corresponding adducts **5** in moderate to good yields along with trace or low yields of byproducts **6** (Table 4, entries 1−6). In some cases, the adducts **5** were formed exclusively as the *anti*-configuration based on comparison

Table 4. Reactions of Salicylic Aldehydes **1** (0.5 mmol) with Ethyl 2-Methylbuta-2,3-dienoate **2c** (1.0 mmol) in the Presence of DBU (10 mol %) in DMSO at 80 °C



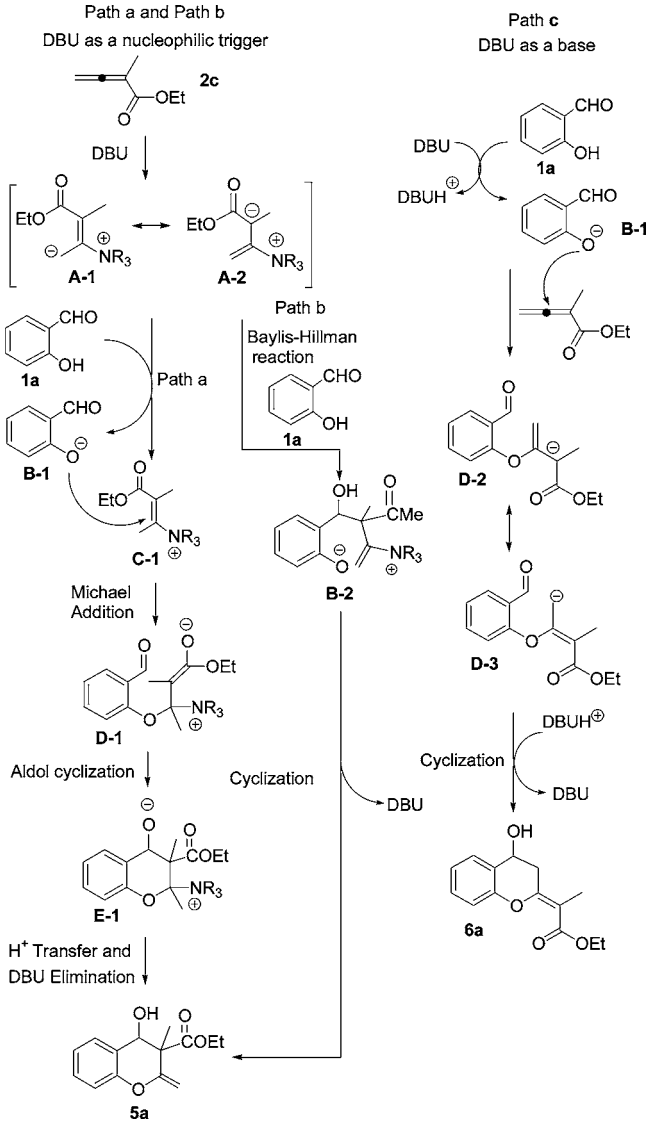
entry	R	time[b]/h	yield[a]/% 5 (*anti*/*syn*)[c]
1	H (**1a**)	6	**5a**, 59 (*anti*)
2	5-Me (**1b**)	5	**5b**, 61 (*anti*)
3	4-MeO (**1d**)	5	**5d**, 64 (*anti*)
4	5-MeO (**1e**)	5	**5e**, 65 (35:30)
5	5-Br (**1h**)	15	**5h**, 53 (*anti*)
6	1-naphthyl (**1i**)	5	**5i**, 72 (37:35)

[a] Isolated yields. [b] The reaction time is determined by TLC on the basis of consuming the starting materials **1**. [c] The *anti*- and *syn*-diastereoisomers can be separated by silica gel column chromatography.

of ^{1}H NMR spectroscopic data with those of adducts **3** (Table 4, entries 1−3 and 5).

The mechanism of this unprecedented reaction has not been unequivocally established, but a plausible explanation is proposed in Scheme 1 using less reactive ethyl 2-meth-

Scheme 1. Plausible Reaction Mechanism



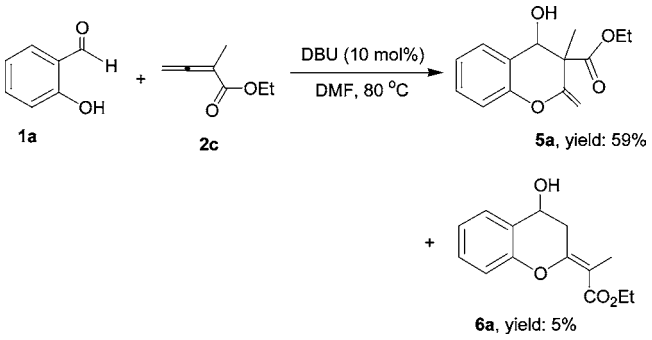
ylbuta-2,3-dienoate **2c** as substrate based on the previous literature and our investigation.[4−6] In path a, initially the Lewis base promoter DBU acts as a nucleophilic trigger[8]

(7) The crystal data of *anti*-**3h** have been deposited with the CCDC with number 273551: empirical formula, $C_{13}H_{13}BrO_3$; formula weight, 297.14; crystal color, habit, colorless, prismatic; crystal dimensions 0.401 × 0.357 × 0.338 mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, a = 13.9423(18) Å, b = 10.7041(14) Å, c = 17.044(2) Å, α = 90°, β = 91.314(2)°, γ = 90°, V = 2542.9(6) Å^3; space group $P2(1)/c$; Z = 8; D_{calc} = 1.552 g/cm^3; F_{000} = 1200; diffractometer: Rigaku AFC7R; residuals, R; R_w, 0.0387, 0.0740.

(8) For reactions in which DBU acts as a nucleophilic trigger: (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311−2312. (b) Kaye, P. T.; Nocanda, X. W. *Synthesis* **2001**, 2389−2392. (c) Ghosh, N. *Synlett* **2004**, 574−575.

and produces the zwitterionic intermediate **A-1** (an allylic anion) or another resonance-stabilized zwitterionic intermediate **A-2** (an enolate), which deprotonates the phenolic group in aldehyde **1a** to give the corresponding intermediates **B-1** and **C-1**. Subsequent Michael addition produces the enolate **D-1**. The aldol cyclization of the resulting enolate **D-1** affords the intermediate **E-1**, which is followed by proton transfer and elimination of DBU to produce 2*H*-1-chromene **3a** and regenerate DBU promoter. The conjugate addition step is assumed to be the rate-determining step, accounting for the longer reaction time required for those salicyclic aldehydes with electron-withdrawing groups on the benzene ring which decrease the nucleophilicity of the oxygen atom. In path b, an initial Baylis−Hillman reaction and proton transfer afford the intermediate **B-2**. The subsequent cyclization and elimination of DBU yield **3a**.[3] This reaction may also proceed via a third pathway based on the previous literature[3] shown as path c. Namely, DBU serves as a Brønsted base which abstracts a proton from salicylaldehyde **1a** to produce nucleophilic intermediate **B-1**. The subsequent conjugate addition of **B-1** to ethyl 2-methylbuta-2,3-dienoate **2c** generates the intermediate **D-2** which exists as a resonance-stabilized anionic intermediate **D-3** (allylic anion). Intramolecular aldol addition of **D-3** and subsequent protonation from $DBUH^+$ afford the compound **6a** and regenerate DBU to complete the catalytic cycle. As a matter of fact, product **6a** was indeed formed as a byproduct in 5% yield in the reaction of salicylaldehyde with ethyl 2-methylbuta-2,3-dienoate in the presence of DBU in DMF (Scheme 2). Thus, we believe

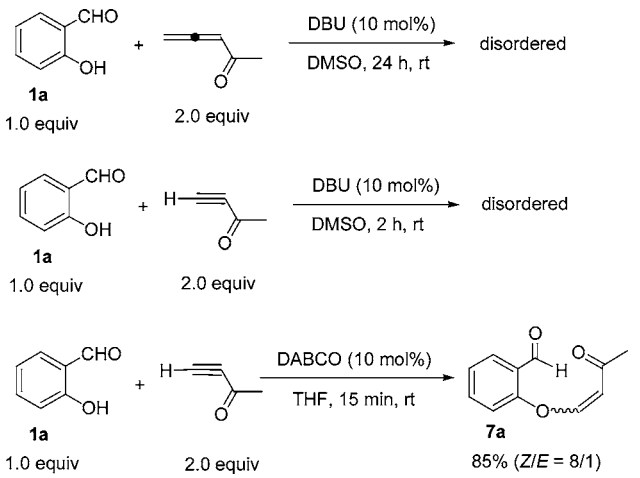
Scheme 2. Formation of Product **6a** in the Reaction of Salicylaldehyde with Ethyl 2-Methylbuta-2,3-dienoate



that path a or path b is the major reaction pathway in above three reaction pathways, and therefore, the adduct **5a** was formed as a major product. For more reactive allenic ketones **2a** and **2b**, the reaction exclusively proceeds via path a or path b to give the corresponding adducts **3** and **4** in excellent yields.

It should be noted that when penta-3,4-dien-2-one was used in the reaction with salicylaldehyde **1a** catalyzed by DBU under the same conditions as those described above, the reaction became disordered presumably due to the high

Scheme 3. Reactions of Penta-3,4-dien-2-one or But-3-yn-2-one with Salicylaldehyde **1a**



reactivity of penta-3,4-dien-2-one (Scheme 3). As for the reaction between salicylaldehyde **1a** and but-3-yn-2-one, DBU as a catalyst also led to disordered reaction, while Michael addition product **7a** was obtained in 85% yield as mixtures of *Z*- and *E*-isomers in THF in the presence of DABCO (Scheme 3) (the NOESY spectrum of *Z*-**7a** is shown in the Supporting Information).

In this paper, we have presented an efficient, DBU-catalyzed reaction of salicylaldehydes with allenic ketones or esters, which provides an easy access to the synthesis of the corresponding functionalized 2*H*-1-chromenes[9] under mild reaction conditions in good to excellent yields as well as good diastereoselectivities. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

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Supporting Information Available: ^{13}C and ^{1}H NMR spectroscopic and analytic data for compounds **3**−**6** and the ORTEP drawing of *anti*-**3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For reactions in which DBU acts as a nucleophilic trigger: (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311−2312. (b) Kaye, P. T.; Nocanda, X. W. *Synthesis* **2001**, 2389−2392. (c) Ghosh, N. *Synlett* **2004**, 574−575.

(10) For other examples of synthesis of chromenes: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 9074−9075. (b) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966−11983. (c) Mondal, M.; Argade, N. P. *Synlett* **2004**, 1243−1246. (d) Sosnovskikh, V. Y.; Usachev, B. I.; Sizov, A. Y.; Kodess, M. I. *Tetrahedron Lett.* **2004**, *45*, 7351−7354. (e) Pettigrew, J. D.; Cadieux, J. A.; So, S. S. S.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 467−470.