Synthesis of novel four-fused-ring chromeno-benzoxepinones from salicylaldehydes and 1-benzoxepin-5-ones *via* the oxa-Michael reaction/aldol condensation

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Abstract

In this study, the synthesis of a series of novel four-fused-ring chromeno-benzoxepinones is described. The reaction of 1-benzoxepin-5-ones with salicylaldehydes mediated by 1,4-diazabicyclo[2,2,2]octane (DABCO) involves domino reactions including an oxa-Michael reaction, an aldol condensation and dehydration in a one-pot sequence to yield the target compounds in fairly good yields.

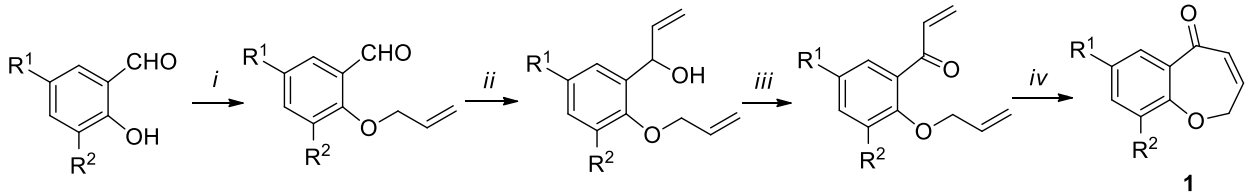
Keywords: Salicylaldehydes, oxa-Michael/aldol condensation, 1-benzoxepin-5-ones, DABCO, fur-fused ring compounds

Introduction

The oxa-Michael reaction has become a useful, concise and efficient tool for the synthesis of oxycyclic compounds, and was recently reviewed by Nising *et al.*[1] Furthermore, the reactions of salicylaldehydes with α,β-unsaturated cyclic carbonyl compounds catalyzed by base to undergo the domino oxa-Michael and aldol condensation to provide an easy access to a variety of chromene derivatives have also been documented in the literature. For instance, the reaction of salicylaldehydes with α,β-unsaturated cyclohexenone yielded three-fused ring compounds with 1-chromene fused to a cyclohexanone ring, providing the key intermediates for various bioactive tetrahydroxanthones,[2] the reaction of salicylaldehydes with chiral substituted α,β-unsaturated cyclohexenone *via* the Morita-Baylis-Hillman reaction or oxa-Michael addition generated the bioactive diversonol,[3] the reaction of salicylaldehydes with α,β-unsaturated aldehydes catalyzed

by prolinol yielded chiral chromenes,[4] the reaction of 2-(2-nitrovinyl)phenol with α,β-unsaturated aldehydes gave tetrahydro-6*H*-benzo[*c*]chromenes,[5] the reaction of salicylaldehyde with α,β-unsaturated aldehydes catalyzed by chiral amine/chiral acid afforded chiral chromenes,[6] as well as others.[7] Although numerous syntheses based on these oxa-Michael addition/aldol condensation have been well developed, the construction of four-fused-ring systems had not been studied. Therefore, to synthesize such four-fused-ring chromene derivatives is an attractive and important topic, not only for synthetic purposes, but also in the search for bioactive compounds. In continuing our studies on benzoheterocyclic compounds,[8] herein we report the synthesis of a series of novel four-ring compounds, specifically 5a,6-dihydro-12*H*-chromeno-[2,3-*c*][1]benzoxepin-12-ones, comprising a 1-benzoxepin-5-one and chromene units.

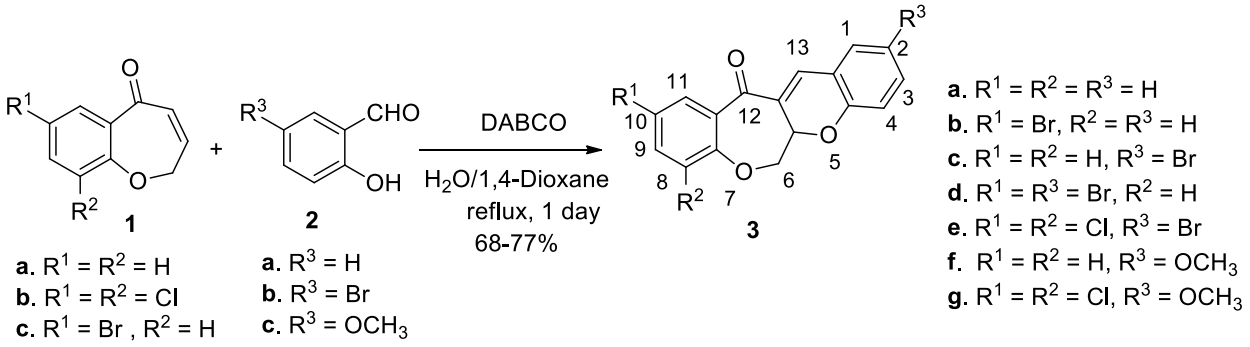
Results and Discussion

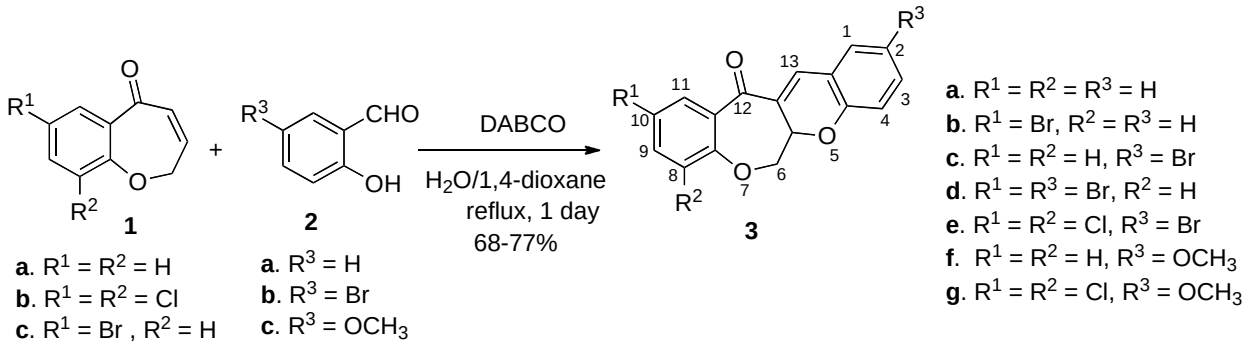


Reagents and conditions: i. allyl bromide, K_2CO_3 , in refluxing CH_3CN, 95-97%; *ii*. vinyl magnesium bromide, in THF, 73-81%; *iii*. MnO_2 in CH_2Cl_2, 71-80%; *iv*. Grubbs catalyst (2nd generation), in CH_2Cl_2, 81-84%

Scheme 1. Preparation of the key intermediate benzoxepin-5-ones (**1a-c**) from salicylaldehydes.[9]

Our synthetic strategy is based on the reaction of the key intermediate 1-benzoxepin-5-ones (prepared from salicylaldehydes in four synthetic steps as outlined in Scheme 1[9]), with further salicylaldehydes, mediated by 1,4-diazabicyclo[2,2,2]octane (DABCO) (Scheme 2). Our synthetic strategy successfully provides a concise one-pot reaction to afford the target compounds in fairly good yields.

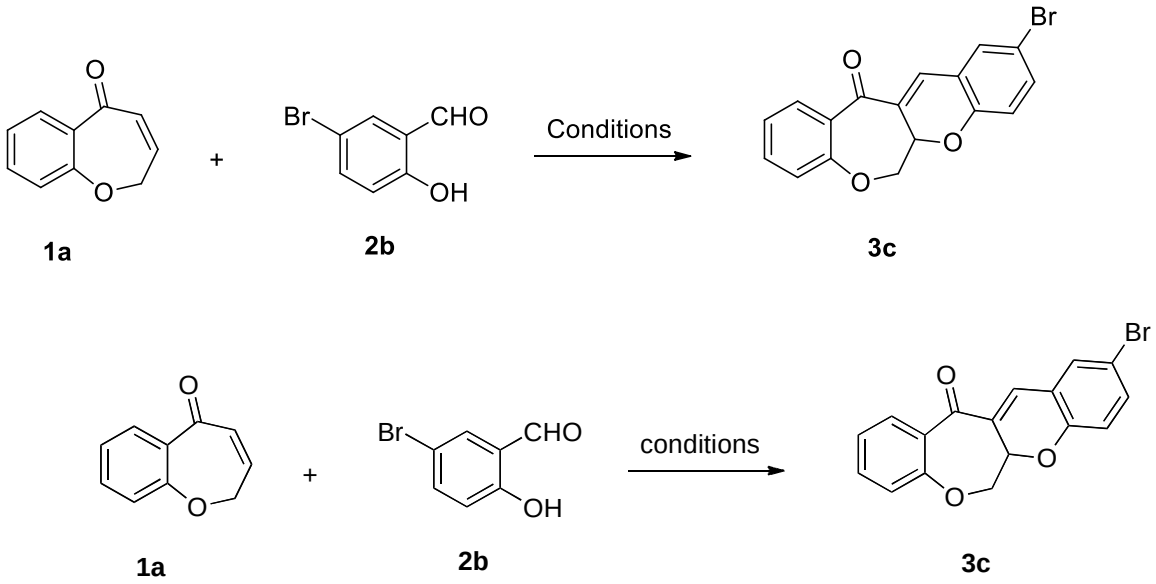




Scheme 2 The reaction of 1-benzoxepin-5-ones (**1**) with salicylaldehydes (**2**) mediated by DABCO to yield the four-ring compounds, chromenobenzoxepinones **3**.

Initially, 1-benzoxepin-5-one (**1a)** was allowed to react with 5-bromosalicylaldehyde (**2b**) as a model reaction. Various solvents and two tertiary amines were investigated to determine appropriate conditions for obtaining the target compound, 2-bromo-5a,6-dihydro-12*H*-chromeno[2,3-c][1]benzoxepin-12-one (**3c**). The results obtained are presented in Table 1.

Table 1. Comparison of various conditions[a] for the synthesis of **3c** from **1a** and **2b**



Entry	Solvent	Tertiary amine	Yield (%)[b]
1	H_2O	DABCO	28[c]
2	1,4-dioxane	DABCO	49[c]
3	CH_3OH	DABCO	42[c]
4	CH_2Cl_2	DABCO	15[c]
5	DMSO	DABCO	55[c]
6	H_2O/DMSO (2:1)	DABCO	60
7	H_2O/1,4-dioxane (2:1)	DABCO[d]	73

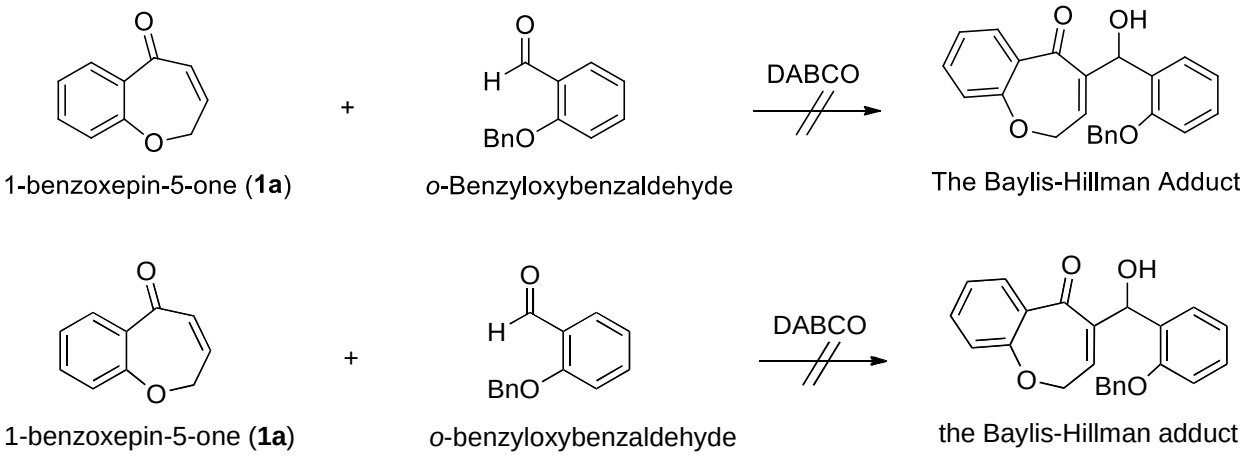
Table 1. Continued

Entry	Solvent	Tertiary amine	Yield (%)b
8	H_2O/1,4-dioxane (2:1)	DBU[d]	46[c]

[a] General procedure: A mixture of 5-bromosalicylaldehyde (**2b**) (5 mmol) and 1-benzoxepin-5-one (**1a)** (5 mmol) in solvent (60 mL) was mixed with amine (11 mmol). The resulting mixture was stirred at reflux for 1 day. [b] Isolated from column chromatography. [c] Accompanied with recovery of starting material. [d]DABCO = 1,4-diazabicyclo[2,2,2]octane ; DBU =1,8-diazabicyclo[5.4.0]undec-7-ene.

As shown in Table 1, in 1,4-dioxane:H_2O = 1:2 as reaction solvent, DABCO as base, and at the reflux temperature (100-102 ^oC), **3c** was produced in the highest yield (73%, entry 7). Comparing those reaction conditions, we found the utilization of H_2O as a sole reaction solvent without any organic solvent and the utilization of DABCO as a reaction base gave a lower yield (28%) (entry 1). Furthermore, other organic solvents such as 1,4-dioxane, CH_3OH, and DMSO used as reaction solvent, and DABCO used as base, did not improve the yields (42-55%) (entries 2, 3 and 5). When CH_2Cl_2 was used as reaction solvent and DABCO as base, the yield of **3c** was lower (15%) than other conditions and starting materials were recovered (entry 4). In order to improve the percentage yields, binary solvent systems were examined. In the mixed solvent system H_2O/DMSO (2:1) and base DABCO, the reaction of **1a** with **2b** under reflux gave **3c** in 60% yield (entry 6). Under the same reaction condition as entry 7 (dioxane:H_2O = 1:2, DABCO, and at reflux) but DABCO was replaced by DBU as a reaction base, the yield of compound **3c** was 46% (entry 8). Finally, the reaction of **1a** with **2b** in the mixed solvents 1,4-dioxane/H_2O (1:2) and the use of DABCO base under reflux gave **3c** in 73% yield (entry 7), the highest yield. Thus, the reaction trend of solvent systems we found in this reaction is H_2O/1,4-dioxane > H_2O/DMSO > DMSO > 1,4-dioxane > CH_3OH > H_2O > CH_2Cl_2. For the tertiary amine used in the reaction, we found that DABCO is superior to DBU in giving the final product.

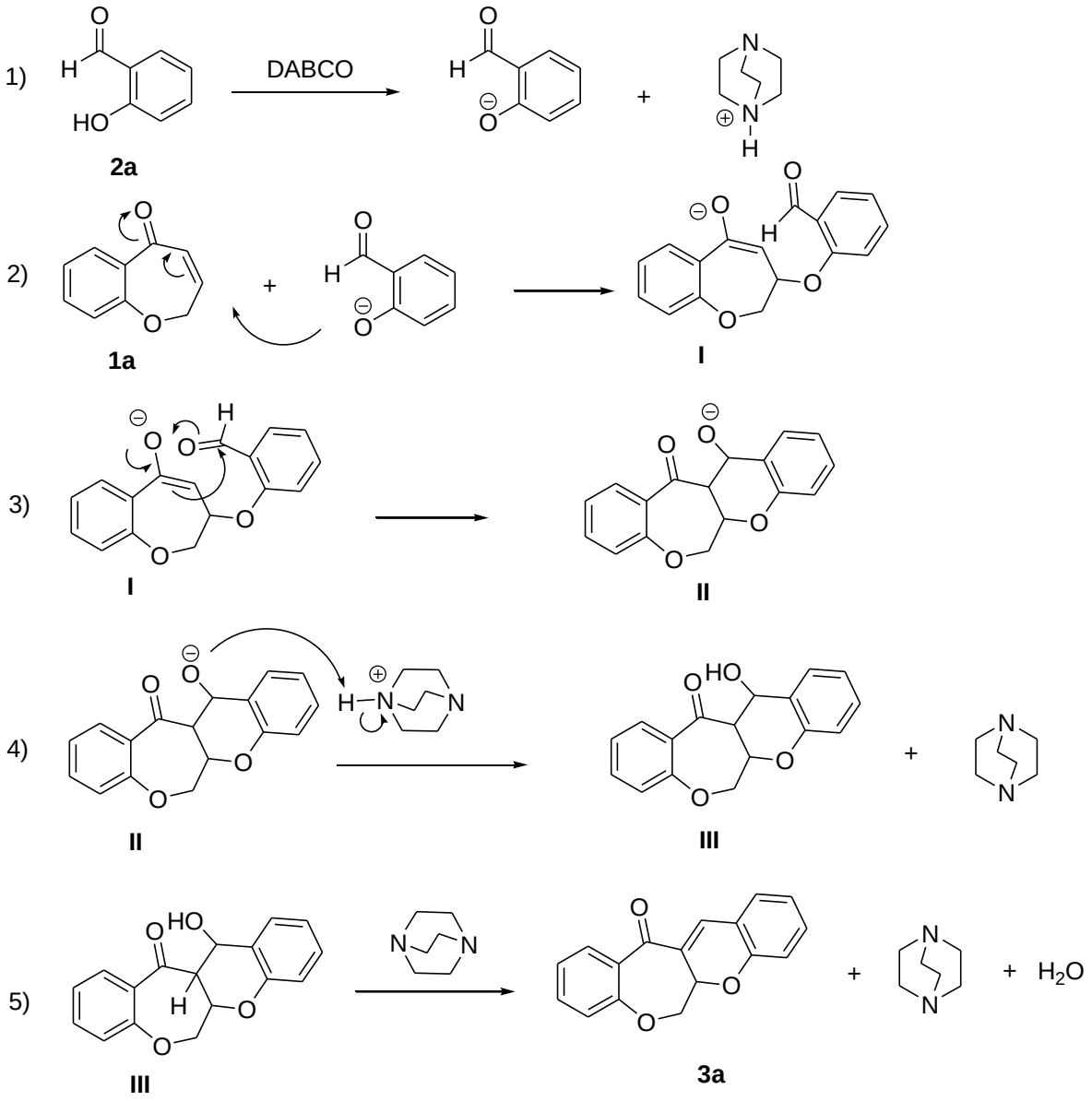
In our synthetic strategy, two possible reaction pathways may occur to yield the same target products. One pathway could go initially through the oxa-Michael reaction and the other one may start with a Baylis-Hillman reaction. In order to understand which reaction pathway is more possible, 1-benzoxepin-5-one (**1a**) was reacted with *o*-benzyloxybenzaldehyde in which the phenolic OH is protected, under the conditions which gave a high yield, described above i.e., solvent, H_2O/1,4-dioxane = 2:1; base, DABCO, at reflux. After 24 h, we found that no Baylis-Hillman adduct was obtained, just the recovery of both starting materials (Scheme 3). This result strongly suggests that the reaction of 1-benzoxepin-5-one (**1a**) with *o*-hydroxybenzaldehyde mediated by DABCO may predominantly be via a domino sequence of reactions involving an oxa-Michael reaction, aldol condensation, and dehydration.



Scheme 3. The reaction of 1-benzoxepin-5-one (**1a**) with *o*-benzyloxybenzaldehyde mediated by DABCO in H_2O / 1,4-dioxane (2:1) at reflux.

Therefore, the formation of **3a** from the reaction of **1a** and **2a**, as an example, could be rationally illustrated by the mechanism shown in Scheme 4. Initially, the phenolic proton of salicylaldehyde (**2a**) is abstracted by DABCO to generate a phenolate anion (step 1). The anion then attacks 1-benzoxepin-5-one (**1a**) in a Michael addition and yields the intermediate **I** (step 2), which then undergoes an intramolecular crossed aldol reaction to afford the intermediate **II** (step 3). This then picks up a proton from protonated DABCO to generate the intermediate **III** and regenerate free DABCO (step 4). Finally, the intermediate **III** is dehydrated by initial deprotonation by DABCO and hydroxide ion elimination to yield the final product, compound **3a** (step 5).

According to the best reaction conditions we found, the reactions of **1a-c** with **2a-c** were carried out mediated by DABCO in 1,4-dioxane:H_2O = 1:2 at reflux, to afford compounds **3a-g** in 68-77% yields.



Scheme 4. The proposed mechanism of formation of **3a** from the reaction of **1a** and **2a**.

The structural elucidation of compounds **3a-g** is mainly based on their ^{1}H-NMR spectra, ^{13}C-NMR, EI-MS and HRMS or EA. For instance, the ^{1}H-NMR spectrum of 2,10-dibromo-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (**3d**) was assigned as follows. Two double doublet sp^{3}-protons, one at δ 4.38 and the other at δ 4.79, indicate the signals of H-6a and H-6b which are coupled to each other and commonly coupled with H-5a, respectively. The signal at δ 5.14 with multiplet splitting (ddd), coupled with H-13, H-6a and H-6b, was assigned to H-5a. An aromatic proton with a doublet (*J* 8.8 Hz) signal at δ 6.86 was assigned to H-4. The proton with a doublet signal at δ 7.02, which has a typical *ortho* coupling constant (*J* 8.8 Hz), was assigned to H-8. The doublet signal at δ 7.28 that has an allylic coupling (*J* 1.6 Hz) with H-5a, was assigned to H-13. The proton with a doublet (*J* 2.4 Hz) signal at δ 7.36 was assigned to H-1, the proton

with a double doublet (*J* 9.2, 2.4 Hz) signal at δ 7.38 was assigned to H-3, The correlation of H-1 linked with H-3, and H-3 linked with H-4 was also proved by the COSY technique. The proton with a double doublet signal at δ 7.56 which has a typical *ortho* and *meta* coupling constant *J* 8.8, 2.8 Hz was assigned to H-9. Similarly, the proton with a doublet signal at δ 8.24 which has a *meta* coupling constant *J* 2.8 Hz was assigned to H-11. The other spectral data of compound **3d** such as ^{13}C-NMR, EI-MS and HRMS are all consistent with the proposed structure.

For further structural confirmation, an X-ray analysis of 2,10-dibromo-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (**3d**) was undertaken. The resulting ORTEP, which is consistent with the structure of compound **3d**, is depicted in Figure 1.

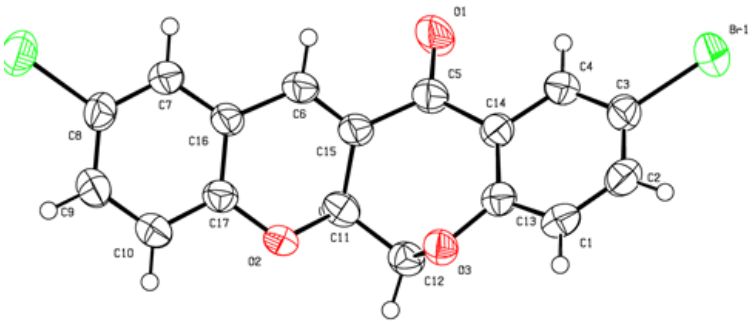
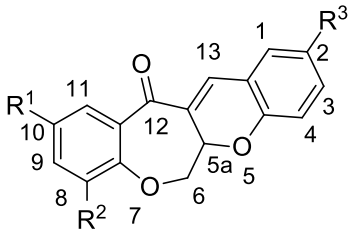


Figure 1. The ORTEP diagram of 2,10-dibromo-5a,6-dihydro-12*H*-chromeno[2,3-*c*]-[1]benzoxepin-12-one [or 3,8-dibromo-11a,12-dihydro-11,13-dioxabenzo[4,5]cyclohepta[1,2-*b*]-naphthalen-5-one] (**3d**).[10]

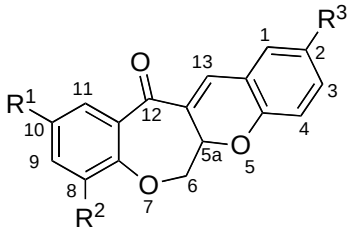
All structures of these novel four-fused ring benzooxycyclic compounds **3a-g** obtained from the oxa-Michael reaction/aldol condensation of **1a-c** and **2a-c**, were confirmed by physical and spectral data, and HRMS. Their physical and selected spectral data were compiled in Table 2.

Table 2. The physical and selected spectral data of compounds **3a-g**



3

a. $R^1 = R^2 = R^3 = H$
b. $R^1 = Br$, $R^2 = R^3 = H$
c. $R^1 = R^2 = H$, $R^3 = Br$
d. $R^1 = R^3 = Br$, $R^2 = H$
e. $R^1 = R^2 = Cl$, $R^3 = Br$
f. $R^1 = R^2 = H$, $R^3 = OCH_3$
g. $R^1 = R^2 = Cl$, $R^3 = OCH_3$



3

a. $R^1 = R^2 = R^3 = H$
b. $R^1 = Br$, $R^2 = R^3 = H$
c. $R^1 = R^2 = H$, $R^3 = Br$
d. $R^1 = R^3 = Br$, $R^2 = H$
e. $R^1 = R^2 = Cl$, $R^3 = Br$
f. $R^1 = R^2 = H$, $R^3 = OCH_3$
g. $R^1 = R^2 = Cl$, $R^3 = OCH_3$

Compd	Yield[a] (%)	IR (cm^{-1}) (C=O)	H-13 [b] d (*J*)	H-5a [b] ddd (*J*)	H-6a [b] dd(J)	H-6b [b] dd (*J*)	HRMS Formula Calcd	Found
3a	68	1643	7.37 (2.0)	5.13 (4.0, 2.8, 2.0)	4.39 (12.8, 2.8)	4.79 (12.8, 4.0)	$C_{17}H_{12}O_3$ 264.0786	264.0788
3b	72	1644	7.40 (2.0)	5.14 (4.0, 2.8, 2.0)	4.39 (12.8, 2.8)	4.79 (12.8, 4.0)	$C_{17}H_{11}BrO_3$ 341.9892	341.9889
3c	73	1639	7.47 (2.0)	5.14 (4.0, 2.8, 2.0)	4.38 (12.8, 2.8)	4.79 (12.8, 4.0)	$C_{17}H_{11}BrO_3$ 341.9892	341.9895
3d	75	1649	7.28 (2.0)	5.14 (4.0, 2.4, 2.0)	4.38 (13.2, 2.4)	4.79 (13.2, 4.0)	$C_{17}H_{10}Br_2O_3$ 419.8997	419.8993
3e	74	1644	7.46 (1.6)	5.18 (4.8, 3.2, 1.6)	4.42 (12.4, 3.2)	4.85 (12.4, 4.8)	$C_{17}H_9BrCl_2O_3$ 409.9112	409.9113
3f	77	1646	7.34 (2.0)	5.08 (4.0, 2.8, 2.0)	4.38 (12.4, 2.8)	4.79 (12.4, 4.0)	$C_{18}H_{14}O_4$ 294.0892	294.0893
3g	76	1640	7.42 (1.6)	5.11 (4.8, 3.2, 1.6)	4.40 (12.4, 3.2)	4.85 (12.4, 4.8)	$C_{18}H_{12}Cl_2O_4$ 362.0113	362.0110

[a] Isolated yield from column chromatography; [b]Measured using 400 MHz ^{1}H-NMR in $CDCl_3$

Conclusions

In this study we have established an efficient synthesis of various substituted 5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-ones, novel four-fused-ring heterocyclic compounds, *via*

sequential reactions including an oxa-Michael addition/aldol condensation/dehydration in one pot. This study also demonstrated that in this reaction participation of the Baylis-Hillman reaction can be excluded. All title compounds have been fully characterized by spectral data such as ^{1}H-NMR, ^{13}C-NMR and HRMS. The structure of compound **3d** was further confirmed by X-ray diffraction.

Experimental Section

General. Melting points were measured with Yanaco micro melting-point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Unity Plus 400 spectrometer. Chemical shifts are indicated in parts per million with respect to TMS. IR spectra were measured on a Perkin Elmer system 2000 FT-IR spectrometer. Elemental analyses were recorded on a Heraeus CHN-O Rapid analyzer. Mass spectra were recorded on a Chem/hp/middle spectrometer connected to a Hewlett Packard series II model gas-liquid chromatography. HRMS spectra were performed on a JEOL JMS SX/SX 102A instrument. Silica gel (230-400 mesh) for column chromatography and precoated silica gel plates (60 F-254) for TLC was purchased from E. Merck Co. UV light (254 nm) was used to detect spots on TLC plates after development.
Salicylaldehydes (**1a-c**) were purchased from Aldrich Chemical Co. 2-Allyloxybenzaldehyde (97%), 2-allyloxy-3,5-dichlorobenzaldehyde (95%), 2-allyloxy-5-bromobenzaldehyde (96%); 1-(2-allyloxyphenyl)-2-propen-1-ol (81%), 1-(2-allyloxy-3,5-dichlorophenyl)prop-2-en-1-ol (75%), 1-(2-allyloxy-5-bromophenyl)- prop-2-en-1-ol (73%); 1-(2-allyloxyphenyl)-2-propen-1-one (80%), 1-(2-allyloxy-3,5-dichlorophenyl)-2-propen-1-one (73%), 1-(2-allyloxy-5-bromophenyl)-2-propen-1-one (71%); 2*H*-1-benzoxepin-5-one (**2a**) (81%), 7,9-dichloro-2*H*-1-benzoxepin-5-one (**2b**) (84%), and 7-bromo-2*H*-1-benzoxepin-5-one (**2c**) (82 %) were prepared by known procedures described in our previous report.[9]

General procedure for the preparation of compounds (3a-g). To a mixture of salicylaldehyde (**1a-c**) (5 mmol) and 1-benzoxepin-5-one (**2a-c**) (5 mmol) was added DABCO (1.23 g, 11 mmol) in a mixture of 1,4-dioxane (20 mL) and water (40 mL). The resulting mixture was stirred at reflux for 1 day. Then, the reaction mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layer was washed with brine, and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated *in vacuo* to give crude **3a-g**, which was purified by column chromatography (ethyl acetate:*n*-hexane: 1:20).
5a,6-Dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3a). Compound **3a** (0.90 g, 68%) was obtained as yellow liquid, R_f = 0.54 (ethyl acetate: *n*-hexane = 1: 6); IR (KBr) cm^{-1}: 1643 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.39 (dd, *J* 12.8, 2.8 Hz, 1H, H-6a), 4.79 (dd, *J* 12.8, 4.0 Hz, 1H, H-6b), 5.14 (ddd, *J* 4.0, 2.8, 2.0 Hz, 1H, H-5a), 7.21 (m, 5H, ArH), 7.37 (d, *J* 2.0 Hz, 1H, H-13), 7.48 (td, *J* 8.0, 1.8 Hz, 1H, ArH), 8.13 (dd, *J* 8.4, 1.8 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 73.9, 75.3, 116.2, 121.2, 121.4, 122.3, 123.2, 126.8, 129.3, 131.3, 131.8, 132.8, 133.7, 134.6, 154.5, 161.2, 180.2; EI-MS (70eV) *m/z* (rel. intensity, %) 264 (M^+, 55), 205

(15), 176 (11), 146 (37), 144 (100), 117 (24), 115 (19); HRMS calcd for $C_{17}H_{12}O_3$: 264.0786. Found: 264.0788.

2-Bromo-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3b). Compound **3b** (1.23 g, 72%) was obtained as yellow crystals, mp = 155-156 ^oC; R_f = 0.55 (ethyl acetate: *n*-hexane = 1: 6); IR (KBr) cm^{-1}: 1644 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.39 (dd, *J* 12.8, 2.8 Hz, 1H, H-6a), 4.79 (dd, *J* 12.8, 4.0 Hz, 1H, H-6b), 5.13 (ddd, *J* 4.0, 2.8, 2.0 Hz, 1H, H-5a), 6.97 (d, *J* 8.4 Hz, 1H, ArH), 7.01 (d, *J* 8.4 Hz, 2H, ArH), 7.30 (dd, *J* 8.0, 1.6 Hz, 2H, ArH), 7.40 (d, *J* 2.0 Hz, 1H, H-13), 8.25 (d, *J* 2.8 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 74.1, 75.1, 116.1, 116.3, 121.3, 122.5, 123.2, 127.9, 129.5, 132.2, 133.0, 133.7, 133.8, 137.3, 154.6, 160.3, 186.3; EI-MS (70eV) *m/z* (rel. intensity, %) 341 (M^+, 1), 205 (10), 176 (12), 145 (13), 144 (100), 116 (11), 115 (11); HRMS calcd for $C_{17}H_{11}BrO_3$: 341.9892. Found: 341.9889; Anal. Calcd for $C_{17}H_{11}BrO_3$: C, 59.50; H, 3.23. Found: C, 59.32; H, 3.51.

10-Bromo-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3c). Compound **3c** (1.24 g, 73%) was obtained as colorless liquid, R_f = 0.56 (ethyl acetate : *n*-hexane = 1: 6); IR (KBr)cm^{-1}: 1639 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.38 (dd, *J* 12.8, 2.8 Hz, 1H, H-6a), 4.79 (dd, *J* 12.8, 4.0 Hz, 1H, H-6b), 5.14 (ddd, *J* 4.0, 2.8, 2.0 Hz, 1H, H-5a), 6.86 (d, *J* 8.8 Hz, 1H, ArH), 7.13 (td, *J* 8.4, 1.2 Hz, 1H, ArH), 7.17 (td, *J* 8.4, 1.2 Hz, 1H, ArH), 7.36 (m, 2H, ArH), 7.47 (d, *J* 2.0 Hz, 1H, H-13), 7.50 (dd, *J* 8.4, 2.0 Hz, 1H, ArH), 8.12 (dd, *J* 8.4, 2.0 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 73.8, 75.6, 114.4, 118.0, 121.2, 123.2, 123.4, 126.4, 128.5, 129.4, 131.3, 131.4, 134.3, 134.9, 153.4, 161.4, 187.7; EI-MS (70eV) *m/z* (rel. intensity, %) 341 (M^+, 20) 224 (98), 222 (100), 176 (17), 116 (16), 115 (43), 89 (14); HRMS calcd for $C_{17}H_{11}BrO_3$: 341.9892. Found: 341.9895.

2,10-Dibromo-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3d). Compound **3d** (1.57 g, 75%) was obtained as colorless liquid, R_f = 0.53 (ethyl acetate : *n*-hexane = 1: 6); IR (KBr)cm^{-1}: 1649 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.37 (dd, *J* 13.2, 2.4 Hz, 1H, H-6a), 4.79 (dd, *J* 13.2, 4.0 Hz, 1H, H-6b), 5.12 (ddd, *J* 4.0, 2.4, 2.0 Hz, 1H, H-5a), 6.86 (d, *J* 8.8 Hz, 1H, ArH), 7.02 (d, *J* 8.8 Hz, 1H, ArH), 7.28 (d, *J* =2.0 Hz, 1H, H-13), 7.36 (dd, *J* 9.2, 2.4 Hz, 2H, ArH)**,** 7.56 (dd, *J* 8.8, 2.8 Hz, 1H, ArH), 8.24 (d, *J* 2.8 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ74.0, 75.4, 114.6, 116.1, 118.1, 123.0, 123.2, 127.7, 131.5, 132.3, 134.7, 134.1, 134.6, 137.6, 153.5, 160.5, 186.2; EI-MS (70eV) *m/z* (rel. intensity, %) 420 (M^+, 5), 225 (12), 224 (99), 223 (14), 222 (100), 176 (12), 115 (26); HRMS calcd for $C_{17}H_{10}Br_2O_3$: 419.8997. Found: 419.8993.

2-Bromo-8,10-dichloro-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3e). Compound **3e** (1.51 g, 74%) was obtained as colorless liquid, R_f = 0.55 (ethyl acetate : *n*-hexane = 1: 6); IR (KBr)cm^{-1}: 1644 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 4.42 (dd, *J* 12.4, 3.2 Hz, 1H, H-6a), 4.85 (dd, *J* 12.4, 4.8 Hz, 1H, H-6b), 5.18 (ddd, *J* 4.8, 3.2, 1.6 Hz, 1H, H-5a), 6.96 (d, *J* 8.4 Hz, 1H, ArH), 7.02 (dd, *J* 8.8, 1.2 Hz, 1H, ArH), 7.30 (m, 1H, ArH), 7.46 (d, *J* 1.6 Hz, 1H, H-13), 7.58 (d, *J* 2.4 Hz, 1H, ArH), 7.97 (d, *J* 2.8 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 74.1, 74.7, 114.6, 118.2, 119.0, 122.6, 127.7, 129.0, 129.3, 131.7, 132.7, 133.3, 134.6, 134.9,

153.2, 155.1, 185.6; EI-MS (70eV) *m/z* (rel. intensity, %) 410 (M^+, 6), 225 (13), 224 (100), 223 (17), 223 (100), 222 (97), 115 (26); HRMS calcd for $C_{17}H_9BrCl_2O_3$: 409.9112. Found: 409.9113.

2-Methoxy-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3f). Compound **3f** (1.13 g, 77%) was obtained as colorless liquid, R_f = 0.56 (ethyl acetate : *n*-hexane = 1: 6); IR (KBr)cm^{-1}: 1646 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H, $ArOCH_3$), 4.38 (dd, *J* 12.4, 2.8 Hz, 1H, H-6a), 4.79 (dd, *J* 12.4, 4.0 Hz, 1H, H-6b), 5.08 (ddd, *J* 4.0, 2.8, 2.0 Hz, 1H, H-5a), 6.78 (d, *J* 2.8 Hz, 1H, ArH), 6.85(dd, *J* 8.8, 3.2 Hz, 1H, ArH), 6.91 (d, *J* 8.8 Hz, 1H, ArH), 7.13 (dd, *J* 8.4, 1.6 Hz, 1H, ArH), 7.17 (dd, *J* 8.0, 2.0 Hz, 1H, ArH), 7.34 (d, *J* 2.0 Hz, 1H, H-13), 7.48 (td, *J* 8.4, 2.0 Hz, 1H, ArH), 8.14 (dd, *J* 8.0, 1.6 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.8, 73.9, 75.5, 113.0, 117.0, 118.1, 121.2, 121.9, 123.2, 126.6, 131.4, 133.0, 134.5, 134.7, 148.6, 154.7, 161.4, 187.8; EI-MS (70eV) *m/z* (rel. intensity, %) 294 (M^+, 25), 175 (12), 174 (100), 159 (8), 146 (6), 131 (6), 103 (6); HRMS calcd for $C_{18}H_{14}O_4$: 294.0892. Found: 294.0893.

8,9-Dichloro-2-methoxy-5a,6-dihydro-12*H*-chromeno[2,3-*c*][1]benzoxepin-12-one (3g). Compound **3g** (1.38 g, 76%) was obtained as yellow crystals, mp = 142-143 ºC; R_f = 0.55 (ethyl acetate: *n*-hexane = 1: 6); IR (KBr)cm^{-1}: 1640 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H, $ArOCH_3$), 4.40 (dd, *J* 12.4, 3.2 Hz, 1H, H-6a), 4.85 (dd, *J* 12.4, 4.8 Hz, 1H, H-6b), 5.11 (ddd, *J* 4.8, 3.2, 1.6 Hz, 1H, H-5a), 6.79 (d, *J* 2.4 Hz, 1H, ArH), 6.88 (dd, *J* 8.8, 2.8 Hz, 1H, ArH), 6.91 (d, *J* 8.8 Hz, 1H, ArH), 7.42 (d, *J* 1.6 Hz, 1H, H-13), 7.58 (d, *J* 2.4 Hz, 1H, ArH), 7.98 (d, *J* 2.4 Hz, 1H, ArH); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.8, 74.2, 74.6, 113.1, 117.2, 118.8, 121.4, 119.4, 120.4, 124.8, 121.4, 127.7, 128.8, 132.9, 134.4, 148.4, 154.8, 186.7; EI-MS (70eV) *m/z* (rel. intensity, %) 362 (M^+, 30), 333 (9), 319 (7), 175 (8), 174 (100), 159 (7), 103 (6); HRMS calcd for $C_{18}H_{12}Cl_2O_4$: 362.0113. Found: 362.0110; Anal. Calcd for $C_{18}H_{12}Cl_2O_4$: C, 59.53; H, 3.33. Found: C, 59.42; H, 3.31.

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10. The CIF file of crystal **3d** has been deposited at the Cambridge Crystallographic Centre (CCDC), UK, and received the CCDC no. 862431. The X-ray crystallographic study of **3d** is summarized as follows. Crystal data: $C_{17}H_{10}Br_2O_3$, M = 422.07, monoclinic system, space group P 1 21/c 1, *a* = 4.28210(10) Å, *b* = 13.1164(3) Å, c = 26.6831(6) Å, *V* =1498.65(6) $Å^3$, *Z* = 4, d = 1.871 Mg/m^3. A crystal of dimensions 0.23 x 0.02 x 0.02 mm^3 was used for measurements on a RIGAKU AFC7S diffractometer with a graphite monochromator (ω scans, $2\theta_{max}$ = 45.0°), Mo Kα radiation (λ=0.71073 Å). The total number of independent reflections measured was 3066 [R(int) = 0.0386], of which 23771 were observed. The crystal structure was solved by the direct method and expanded using difference Fourier techniques, further refined by the program SHELXTL 97 and full-matrix least-squares calculations. Final indices: R_f = 0.0701, R_w = 0.0819 ($w = 1/[\sigma^2(F_o^2)+(0.1692P)^2]$ where $P = (F_o^2+2F_c^2)/3$). The CIF file is also available in supplementary data. [Please note the carbon numbering in ORTEP is different from that of carbon numbering in its chemical nomenclature].

