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Abstract: An organocatalytic [4 + 2] cascade annulation of salicylaldehydes and 1,3-bisarylsulfonylpropenes has been developed. This protocol enables the efficient and straightforward synthesis of a new series of 3-sulfonyl-2-sulfonylmethyl-2H-chromenes that are useful for exploring pharmacologically valued compounds. Further reductive modifications result in 3-desulfonylated chromene or chromane derivatives. This protocol can be expanded to the synthesis of 3-sulfonyl-2-sulfonylmethyl 1,2-dihydroquinoline.

Keywords: 2H-chromene; [4 + 2] annulation; salicylaldehyde; 1,3-bisarylsulfonylpropene; organocatalysis

1. Introduction

2H-chromene constitutes an important class of unsaturated 1-benzopyrans. Particularly, 2-substituted 2H-chromene is a privileged structural motif of numerous biologically active natural products and synthetic compounds [1–3]. Figure 1 lists some representative molecules incorporating this structural motif. Iclaprim is well known for its selective inhibitory activity against microbial dihydrofolate reductase and has been used to cure complicated skin or respiratory infections [4]. Naturally occurring Daurichromenic acid, isolated from the leaves of Rhododendron dauricum, exhibits promising anti-HIV activity [5]. EM-800 is a highly effective nonsteroidal antiestrogen for the treatment of breast cancer [6]. Cordiachromone possesses antibacterial properties and inhibitive effects against cyclooxygenase [7]. Gaudichaudianic acid is described as a potential anti-trypanocidal agent [8]. Anthyllisone is a suitable candidate nonsteroidal anti-inflammatory agent by decreasing NO release without cytotoxicity [9]. In addition to these, 2H-chromene derivatives also find interesting applications in the fields of photochromic materials and laser dyes [10,11].

Due to their diverse applications, synthetic chemists have invested persistent efforts to assemble various 2H-chromene skeletons. Transition-metal promoted synthesis has made great progress in recent years [12–14]. However, metal-free synthetic methods deserve particular consideration from the viewpoint of environmental friendliness and sustainability [15–20]. Since the pioneering work of Kawase about the K2CO3-mediated one-step synthesis of 2,2-dimethyl-2H-chromenes in 1982 [21], salicylaldehydes have become popular reaction partners in 2H-chromenes synthesis. The key steps of ring-closing strategies involve Petasis reaction [22], Wittig reaction [23], Morita-Baylis-Hillman reaction [24], Knoevenagel condensation [25,26], oxa-Michael addition [27] and Diels–Alder cycloaddition [28], etc.
Vinyl sulfones have long been regarded as powerful building blocks in organic synthesis owing to the strong inductive effect of the sulfone group [29,30]. On the other hand, some vinyl sulfones behave as potent inhibitors of various enzymatic processes [31]. For these reasons, the use of readily available starting materials to synthesize molecules in which vinyl sulfone moiety is embedded in the 2H-chromene core should be appealing in medicinal and pharmaceutical chemistry based on the combination principle. Until now, only β-ketosulfones [32] and bromoallyl sulfones [33] have been independently reported to react with salicylaldehydes to construct 2-functionalized 3-sulfonyl-2H-chromenes. 1,3-Bisarylsulfonylpropenes are usually applied in all kinds of benzannulation reactions as binucleophilic C3 building blocks [34–37]. In contrast, the co-existing electrophilic property of this kind of alkenes is seldom explored. So far, only in two [3 + 2] annulation examples have they been applied as electron-deficient C2 synthons [38,39]. Herein, we would like to report a convenient and straightforward synthetic approach toward structurally novel 3-sulfonyl-2-sulfonylmethyl-2H-chromenes through organocatalytic [4 + 2] cyclization of salicylaldehydes and 1,3-bisarylsulfonylpropenes (Scheme 1).

2. Results and Discussion

2.1. Optimization of Reaction Conditions

We initiated our study by exploring the reaction between salicylaldehyde and 1,3-bis(p-tolylsulfonyl)propene 2a in toluene under the catalysis of 0.3 equivalent of DBU at 90 °C for 8 h. Although 2a could be completely converted, 3-tosyl-2-((tosylmethyl)-2H-chromene 3a was obtained with a very poor yield (Table 1, Entry 1). Replacing Cs2CO3 still provided a low yield. Even though using a stoichiometric amount of Cs2CO3, the yield remained unsatisfactory (Entry 2). Next, we turned our attention to nucleophilic amine catalysts. Although no yield enhancement was observed by treating the reaction with 30 mol% of piperidine, we were delighted to observe that when an equal equivalent of AcOH was added, the yield was drastically increased to 77% within a shorter period of
reaction time (Entries 3 and 4). For comparison, AcOH showed no catalytic activity in the absence of any bases (Entry 5). Having identified the synergistic catalytic effect of a Brønsted acid, a quick survey including benzoic acid, trifluoroacetic acid (TFA), and p-toluenesulfonic acid (p-TsOH) was conducted, and p-TsOH was revealed to be a better choice (Entries 6–8). As expected, p-TsOH alone showed no catalytic activity (Entry 9). Next, the screening was on the cooperation between different amine bases and p-TsOH. It was found that pyrrolidine provided a slightly lower yield, whereas other bases such as 1,4-Diazabicyclo [2.2.2]octane (DABCO), NH$_4$OAc, and pyridine were less effective or ineffective (Entries 10–13). Other reaction parameters, including the catalytic amount of both the p-TsOH and piperidine, solvent, reaction temperature, mole ratio, substrate concentration, and effect of water scavenger, were then screened (for details, see Table S1 in Supplementary Materials). When the reaction was conducted with 0.24 mmol of salicylaldehyde and 0.20 mmol of 2a in 2 mL of toluene at 60 ºC, the product yield could be improved to 92% (Entry 14). In contrast, just reversing the mole ratio of starting materials caused a 12% loss in yield (Entry 15 vs. 14). Considering both the product yield and reaction time, the optimal reaction conditions were finally affirmed, as illustrated in Table 1, Entry 14.

### Table 1. Optimization studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (Mol%)</th>
<th>Brønsted Acid (Mol%)</th>
<th>Solvent</th>
<th>Temp. (ºC)</th>
<th>Time (h)</th>
<th>Yield of 3a (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU (30)</td>
<td>/</td>
<td>toluene</td>
<td>90</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>Cs$_2$CO$_3$</td>
<td>/</td>
<td>toluene</td>
<td>90</td>
<td>12</td>
<td>40 (45) c</td>
</tr>
<tr>
<td>3</td>
<td>piperidine (30)</td>
<td>/</td>
<td>toluene</td>
<td>90</td>
<td>7</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>piperidine (30)</td>
<td>AcOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>6</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>/</td>
<td>AcOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>24</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>piperidine (30)</td>
<td>PhCOOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>6</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>piperidine (30)</td>
<td>TFA (30)</td>
<td>toluene</td>
<td>90</td>
<td>8</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>piperidine (30)</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>/</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>24</td>
<td>N.R.</td>
</tr>
<tr>
<td>10</td>
<td>pyrrolidine</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>3</td>
<td>81</td>
</tr>
<tr>
<td>11</td>
<td>DABCO</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>12</td>
<td>NH$_4$OAc (30)</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>13</td>
<td>Pyridine (30)</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>90</td>
<td>24</td>
<td>N.R.</td>
</tr>
<tr>
<td>14 d</td>
<td>piperidine (30)</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>60</td>
<td>10</td>
<td>92</td>
</tr>
<tr>
<td>15 e</td>
<td>piperidine (30)</td>
<td>p-TsOH (30)</td>
<td>toluene</td>
<td>60</td>
<td>10</td>
<td>80</td>
</tr>
</tbody>
</table>

a Reaction conditions: unless otherwise noted, reactions were conducted with salicylaldehyde 1 (0.22 mmol), 1,3-bis(p-Tolylsulfonyl)propene 2a (0.2 mmol), indicated amount of base and Brønsted acid in toluene (2 mL) at indicated temperature. b Yields of isolated products. c 1.0 equiv. of Cs$_2$CO$_3$. d Using 0.24 mmol of 1 and 0.20 mmol of 2a. e Using 0.20 mmol of 1 and 0.24 mmol of 2a. N.R. = no reaction.

#### 2.2. Substrate Scope of the [4 + 2] Annulation Reaction

We then explored the scope and limitations of this [4 + 2] annulation reaction under the optimized reaction conditions (Scheme 2). As far as 1,3-bisarylsulfonylpropenes 2 were concerned, aryl groups (Ar = Tol, phenyl or 4-chlorophenyl, 2a–2c) had no obvious influence on the reaction outcomes, giving rise to products 3a–3c in similarly high yields. A variety of salicylaldehydes decorated with different substituents at any available position of phenyl moiety were all readily accommodated, enabling access to 3d–3v in 70%–90% yields. In general, salicylaldehydes possessing a halo-substituent (F, Cl, Br) were able to be fully converted into target molecules (3e, 3f, 3h–3j, 3o, 3p, 3s, and 3t) in 73%–89% yields. The reaction of electronically more deficient salicylaldehyde bearing
either a 5-nitro group or 3,5-dichloro groups could successfully proceed to generate 3k or 3w in parallel yield. An electron-donating group such as methyl, methoxy, or $N,N'$-diethylamino group attached salicylaldehydes also proved to be suitable reactants by delivering corresponding products (3d, 3g, 3l–3n, and 3q) in 70%–90% yields. Notably, the sterically hindered tert-butyl group(s) attached salicylaldehydes were well tolerated, giving 3r and 3u in 88% and 77% yields, respectively. It is worth mentioning that no desired product appeared when 4,6-dimethoxy-substituted salicylaldehyde was examined. The strong electron-donating property of two methoxy groups might account for the too low reactivity of the formyl group. Furthermore, as related congeners of salicylaldehyde, the 2-hydroxy-1-naphthaldehyde and 1-hydroxy-2-naphthaldehyde exhibited favorable chemical compatibility to give rise to naphthochromenes 3w and 3x, albeit in somewhat lower yields as well as at higher reaction temperature.

Scheme 2. Substrate scope of the [4 + 2] annihilation reaction.

The resulting 2H-chromene products could be readily isolated by column chromatography. In the $^1$H NMR spectrum of representative compound 3h, signal at $\delta$ 5.48 (dd, $J = 12.0$ Hz, 4.0 Hz, 1H) can be tentatively assigned to a methine proton, and signals at $\delta$ 3.63 (dd, $J = 12.0$ Hz, 12.0 Hz, 1H) and 3.38 (dd, $J = 12.0$ Hz, 4.0 Hz, 1H) to two methylene protons attached to the same carbon atom based on their large coupling constant ($J = 12.0$ Hz). Thus, the adjacent position of these two types of protons can be rationalized by the observation of another two mutual coupling relationships ($J = 12.0$ Hz and 4.0 Hz, respectively). In the H-H COSY spectrum of 3h, a suitable correlation between the methine proton ($\delta$ 5.48) and one of the two methylene protons ($\delta$ 3.63) can be observed. The correlation effect of
the two characteristic protons also agrees with the regiochemical assignment as set in 3h. Moreover, the signal at δ 7.55 (s, 1H) can be assigned to the vinyl proton on the 2H-pyrany ring. Similarly, according to the analysis of 13C NMR and HSQC spectra of 3h, signals at δ 68.4 and 57.2 can be assumed to methine carbon and methylene carbon, respectively. Since it is the methine carbon rather than methylene carbon that displays correlation with a vinyl proton in the HMBC spectrum, the chemical structure of 3h can be further proved. The structure of 3h was detailedly identified by 1H NMR, 13C NMR, HRMS, and 2D NMR analysis (for detailed analysis, see Table S2 and related discussion in Supplementary Materials).

2.3. Study on Reaction Mechanism

Since the reaction intermediates could not be isolated during the reaction process, control experiments were performed to help better understand the sequence in which Knoevenagel condensation and oxa-Michael addition take place (Scheme 3). We first conduct the reaction of 1 with phenyl vinyl sulfone 4 under the current reaction conditions. Phenyl vinyl sulfone 4 can be viewed as an analog of 2a yet with a more reactive and less hindered β site for the Michael addition of phenolic OH. However, no generation of oxa-Michael adduct 5 or annulation product 6 was observed (Scheme 3, Equation (1)). Then, salicylaldehyde dimethyl acetal 7, which can be viewed as salicylaldehyde bearing a masked formyl group and an exposed phenolic hydroxyl group with stronger nucleophilicity, was subjected to the reaction with 2a. Likewise, oxa-Michael adduct in the form of compound 8 was failed to produce (Scheme 3, Equation (2)). This outcome shows that the cascade process would unlikely be triggered by oxa-Michael addition. The very poor nucleophilicity of salicylaldehyde in conjugated addition has also been mentioned in literature before [27]. Moreover, we have also prepared Knoevenagel condensation intermediate 9 by condensation of 2a with tert-butyldimethylsilyl (TBDMS) group-protected salicylaldehyde followed by deprotection. This phenol derivative could be smoothly converted into 3a in excellent yield (Scheme 3, Equation (3)), which indicates in another way that Knoevenagel condensation would occur first.

Scheme 3. Reaction mechanistic investigation.

On the basis of this fact, a plausible reaction mechanism is proposed in Scheme 4. Salicylaldehyde is first condensed into iminium ion pair I by interaction with piperidine and p-TsOH. Intermediate I suffers a nucleophilic attack by 2a to generate II and p-TsOH. Then, intermediate II gives Knoevenagel-type intermediate III upon Hofmann-like elimination of piperidine. Finally, an intramolecular oxa-Michael addition occurs to deliver 3a [24].
Alternatively, the reduction in the C = C bond of preparation of functionalized 1,2-dihydroquinoline products, studies on selective reduction in the functional groups were carried out. As shown in Scheme 4, treatment of 3a or 3q with magnesium powder and a buffer solution of AcOH/NaAcO in DMF could smoothly remove the conjugated sulfone group, whereas the methylene sulfone group survived intact. Then, desulfonylated product 10a or 10q could be hydrogenated using Pd-C/H₂ to afford chromane derivative 11a or 11q in high yield. Alternatively, the reduction in the C = C bond of 3a was achieved by using NaBH₄ with LiCl as an additive, furnishing chromanes (±)-12a and (±)-12a' in roughly equal yields.


2.4. Derivation of 2H-Chromene Products

To obtain more insight into the synthetic utility of the obtained annulation products, studies on selective reduction in the functional groups were carried out. As shown in Scheme 5, treatment of 3a or 3q with magnesium powder and a buffer solution of AcOH/NaAcO in DMF could smoothly remove the conjugated sulfone group, whereas the methylene sulfone group survived intact. Then, desulfonylated product 10a or 10q could be hydrogenated using Pd-C/H₂ to afford chromane derivative 11a or 11q in high yield. Alternatively, the reduction in the C = C bond of 3a was achieved by using NaBH₄ with LiCl as an additive, furnishing chromanes (±)-12a and (±)-12a' in roughly equal yields.

Scheme 5. Reductive applications of 2H-chromene products.

The practicality of this methodology is outlined in Scheme 6. First, gram-scale preparation of 3a was carried out. When 4.3 mmol of 2a was conducted under standard reaction conditions, 3a was produced in a 90% yield (Scheme 6a). This catalytic protocol was further expanded to the reaction of 2-aminobenzaldehyde 13 and 2a by generating functionalized 1,2-dihydroquinoline 14 in a 78% yield (Scheme 6b).

a) Gram-scale reaction

Scheme 6. Gram-scale synthesis and reactivity of 2-aminobenzaldehyde.
3. Materials and Methods

3.1. Instruments and Reagents

Melting points were determined in open glass capillaries using a Buchi melting point M-565 apparatus. NMR (\(^1\)H, \(^{13}\)C, DEPT, \(^1\)H-\(^1\)H COSY, HSQC, HMBC) spectra were recorded on Bruker Advance III 400 MHz spectrometers with tetramethylsilane (TMS) as an internal reference, and CDCl\(_3\) or DMSO-\(d_6\) as a solvent. Chemical shifts (\(\delta\)) were given in parts per million (ppm) as values relative to the internal chloroform (7.26 ppm for \(^1\)H and 77.16 ppm for \(^{13}\)C) or dimethyl sulfoxide (2.50 ppm for \(^1\)H and 39.53 ppm for \(^{13}\)C). High-resolution electrospray ionization mass spectrometry (ESI HRMS) was recorded on a Waters SYNAPT G2. Reactions were monitored by thin-layer chromatography (TLC) on aluminum-backed plates with pre-coated G254 silica gel. In experiments requiring dry solvents, THF was distilled from sodium using benzophenone as an indicator. DCE and PhCF\(_3\) were distilled from CaH\(_2\). All chemicals were reagent grade and used without purification as commercially available from Aldrich, Sigma, or Merck. 1,3-Bisarylsulfonylpropenes were prepared according to the literature procedure [37].

3.2. Experimental Method


To a solution of salicylaldehyde derivative 1 (0.24 mmol) and 1,3-bisarylsulfonylpropene 2 (0.2 mmol) in dry toluene (2 mL) was added piperidine (6.0 \(\mu\)L, 0.06 mmol) and \(p\)-TsOH (10.3 mg, 0.06 mmol). The reaction mixture was stirred at 60 \(^\circ\)C. After completion (monitored by TLC), the reaction mixture was purified by flash chromatography over silica gel (eluent: petroleum ether/ethyl acetate = 8:1) to provide product 3. The 2H-chromene 3 resulting from this procedure is sufficiently pure for most characterization; otherwise, it may be recrystallized from ethanol.

3.2.2. Synthesis of 2-(sulfonylmethyl)-2H-chromene 10

Taking 10a as an example: To a solution of compound 3a (100.0 mg, 0.22 mmol) in DMF (3 mL) under \(N_2\) atmosphere was added Mg powder (74.8 mg, 3.08 mmol) and 8 mol/L of AcOH/AcONa solution (1.5 mL). The reaction mixture was stirred at room temperature for 3 h and then filtered through celite. Water (10 mL) was added to the filtrate, and the organic layer was extracted with ethyl acetate (20 mL \(\times\) 3). The combined organic phases were washed successively with water and brine, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (eluent: petroleum ether/ethyl acetate = 8:1) to provide product 10a.

3.2.3. Synthesis of 2-(sulfonylmethyl)chromane 11

Taking 11a as an example: To a solution of compound 10a (40.0 mg, 0.13 mmol) in THF (10 mL) was added 5% Pd/C (4.0 mg, 10 wt%). The reaction mixture was stirred for 3 h at room temperature under a \(H_2\) atmosphere (1 atm), then filtered through celite and the filtrate was concentrated under reduced pressure. Purification by flash chromatography over silica gel (eluent: petroleum ether/ethyl acetate = 10:1) provided 11a.

3.2.4. Synthesis of Chromane (\(\pm\)−12a and (\(\pm\)−12a′)

To a solution of 3a (100.0 mg, 0.22 mmol) and LiCl (18.7 mg, 0.44 mmol) in MeOH/THF (10 mL, v:v = 1:1) was added NaBH\(_4\) (16.6 mg, 0.44 mmol) at 0 \(^\circ\)C. The reaction mixture was stirred for 24 h at room temperature, then quenched with water (1 mL) and partitioned between CH\(_2\)Cl\(_2\) (30 mL) and brine (10 mL). The organic layer was separated, and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 \(\times\) 20 mL). The combined organic layers were washed successively with water and brine, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford compounds (\(\pm\)−12a and (\(\pm\)−12a′).
3.2.5. Synthesis of 1,2-Dihydroquinoline 14

According to general procedure for synthesis of 3-sulfonyl-2\textsubscript{H}-chromenes 3, piperidine (6.0 µL, 0.06 mmol) and \textit{p}-TsOH (10.3 mg, 0.06 mmol) were added to a solution of 2-aminobenzaldehyde (29.1 mg, 0.24 mmol) and 1,3-bis(\textit{p}-Tolylsulfonyl)propene 2a (70.1 mg, 0.2 mmol) in dry toluene (2 mL). The reaction mixture were stirred at 60 °C for 6 h. Flash chromatography over silica gel (eluent: petroleum ether/ethyl acetate = 5:1) provided 1,2-dihydroquinoline 14.

4. Conclusions

In conclusion, an organocatalytic [4 + 2] annulation reaction for the synthesis of 3-sulfonyl-2-sulfonylmethyl-2\textsubscript{H}-chromenes from salicylaldehydes and 1,3-bisarylsulfonylpropenes has been developed. A series of new 2\textsubscript{H}-chromenes were assembled in generally high yields through the Knoevenagel condensation/oxa-Michael reaction cascade approach. Moreover, the advantages such as mild reaction conditions, broad substrate scope, and selective reductive transformations of target products make this protocol promising, from structural diversity to applications of the 2\textsubscript{H}-chromene family. Further investigation regarding synthetic applications of 1,3-bisarylsulfonylpropenes in cyclization reactions will be conducted and published in due course.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12050491/s1. Compound characterization data, details of the structure analysis of product 3h, and copies of NMR spectra for new compounds. Table S1. Further optimization of reaction conditions. Table S2. \textsuperscript{1}H and \textsuperscript{13}C NMR (400 and 100 MHz, CDCl\textsubscript{3}) spectroscopic data of 3h.

Author Contributions: L.J. and M.Y. (Minglong Yuan) conceived and designed the research; P.P. and M.L. performed the experiments; L.L. and M.Z. analyzed the data; M.Y. (Mingwei Yuan) supervised the project; L.J. wrote the original draft and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: More data can be obtained by request from authors.

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Conflicts of Interest: The authors declare no conflict of interest.

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