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Tertiary Amine-Catalyzed (4 + 2) Annulations of δ-Acetoxy Allenoates: Synthesis of Multisubstituted 4*H*-Pyran and 4*H*-Chromene

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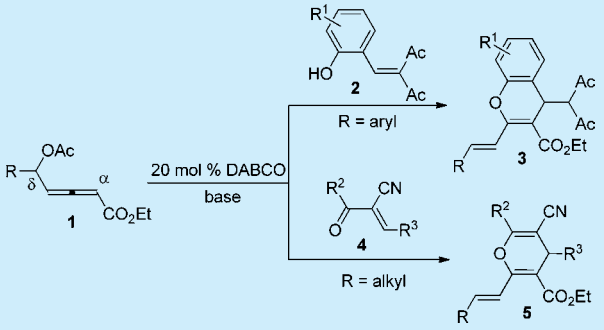
Supporting Information

ABSTRACT: The DABCO-catalyzed divergent (4 + 2) annulations of δ-acetoxy allenoates **1** are reported. The chemical behavior of **1** under DABCO catalyst was found to be substrate dependent. Allenoate **1** with an aromatic group at δC preferentially reacted with salicylaldehyde derivative **2**, delivering 4*H*-chromenes **3**. On the other hand, allenoates **1** with an alkyl group at δC readily underwent (4 + 2) annulations with oxo diene **4** to afford 4*H*-pyrans **5**.



4*H*-Pyrans and 4*H*-chromenes represent important classes of heterocycles that have a wide range of remarkable biological activities and are prevalent in natural products. Several compounds containing these privileged molecular skeletons are associated with interesting biological and pharmacological activities, such as anti-HIV,[1] antiviral,[2] highly anticancer,[3] and anticonvulsant.[4] However, most approaches toward these extensively studied compounds employ the Knoevenagel−Michael process. Therefore, the development of efficient and mild alternatives for the divergent synthesis of these compounds is an active research area.[5]

Over the past decades, significant progress in allenoate chemistry has been made.[6] In particular, the transformations of allenoate under nucleophilic Lewis base catalysis have received considerable interest due to their potential for facile and efficient increasing of molecular complexity.[7,8] In this context, the amine-catalyzed (4 + 2) annulations of simple allenoates have been well developed and found to strongly rely on the key zwitterionic intermediate **A2**, which serves either as a base to react with salicylal derivatives or as a nucleophile to react with oxo dienes, furnishing (4 + 2) annulations (Scheme 1a).[9] As part of our ongoing project on the Lewis base catalyzed reactions of allenoates,[10] we became interested in δ-acetoxy allenaotes **1** (Scheme 1b). We envisioned that, for the case of allenoate **1** under the amine catalysis, the reactivity of carboanion of the zwitterionic intermediate **B2** might be reduced due to increased steric hindrance. Alternatively, intermediate **B2** would undergo 1,2-elimination of the acetoxy group, leading to the formation of electrophilic intermediate **C**, which might provide some opportunities for the development of new reaction scenarios (Scheme 1b). It was indeed interesting to find that the DABCO-catalyzed reaction of **1** was substrate dependent. Allenoates **1** with an aromatic group at δC preferentially reacted with salicylaldehyde derivatives **2**, delivering 4*H*-chromenes, while the ones with an alkyl group at δC readily underwent (4 + 2) annulations with oxo dienes **4** to afford 4*H*-pyrans (Scheme 1b). Herein, we report our preliminary results.

We initially explored the reaction of allenoate **1a** with a phenyl group at δC and **2a** in the presence of 20 mol % of DABCO catalyst and 1.2 equiv of K_2CO_3 additive. A (4 + 2) annulation was found to occur smoothly in toluene at room temperature, affording product **3aa** in 62% yield. Subsequently, various solvents and base additives were examined (Table S1, Supporting Information), which revealed that the combination of $CHCl_3$ and K_2CO_3 was the optimal choice, giving product **3aa** in 85% yield.

With the optimal conditions in hand, we then turned our attention to investigate the substrate scope of the (4 + 2) annulations between **1** and **2**. The results are summarized in Scheme 2. Various allenaotes **1** with different electron properties of Ar group (e.g., electron-neutral, -rich, or -deficient) reacted well with substrate **2a**, affording the corresponding 4*H*-chromene products **3aa**−**fa** in excellent yields. The reaction of styryl-functionalized allenoate **1g** with **2a** smoothly occurred, delivering conjugated triene product **3ga** in 76% isolated yield. In contrast, the electron properties of phenyl group in substrates **2** strongly affected the reaction performance in term of isolated yield. Substrates **2b** and **2c** with chloro and bromo substituents *para*-orientated to hydroxyl group gave products **3ab** and **3ac** in somewhat lower yields.

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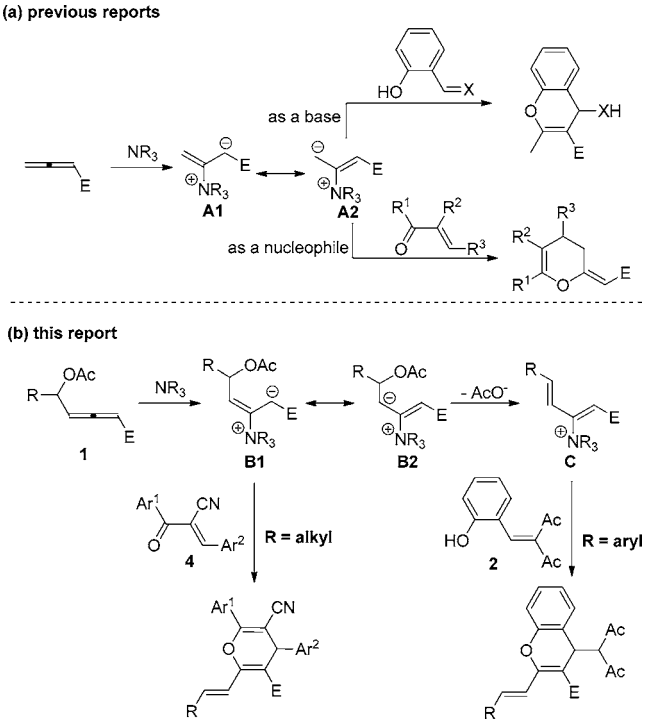
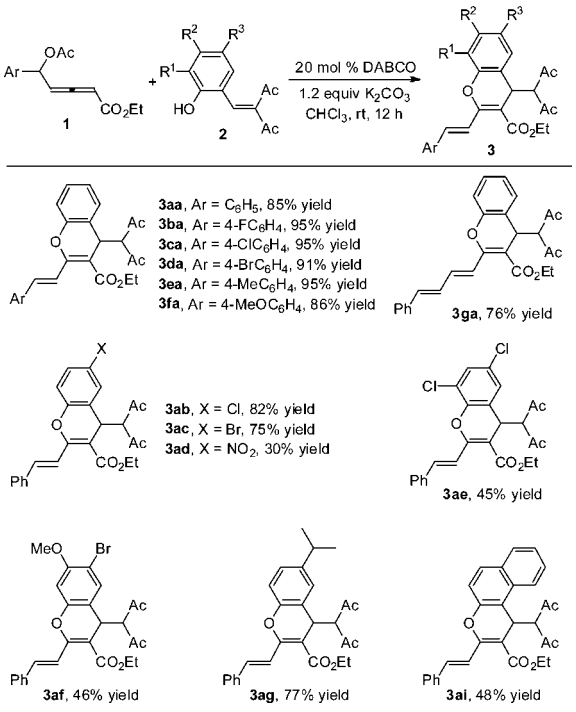
Scheme 1. Amine-Catalyzed (4 + 2) Annulations of Allenoates

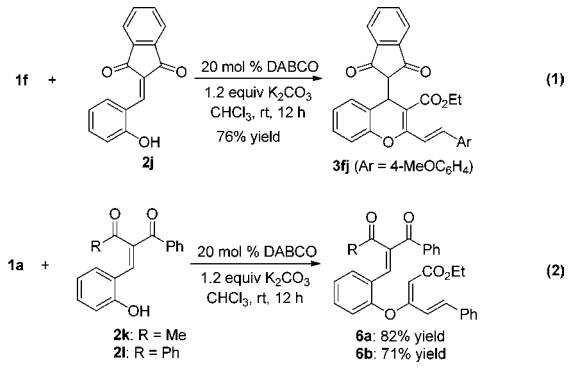


Scheme 2. Scope of DABCO-Catalyzed (4 + 2) Annulations of 1 and 2



The yields dramatically dropped to ca. 40% for the cases of substrates **2d** and **2c** with more electron-deficient phenyl groups. However, substrates **2f** and **2g** with electron-rich phenyl group also gave the corresponding products in relatively lower yields. Although 2-hydroxy-1-naphthaldehyde-derived substrate **2i** was workable under these conditions, the yield of product **2ai** was only 48%.

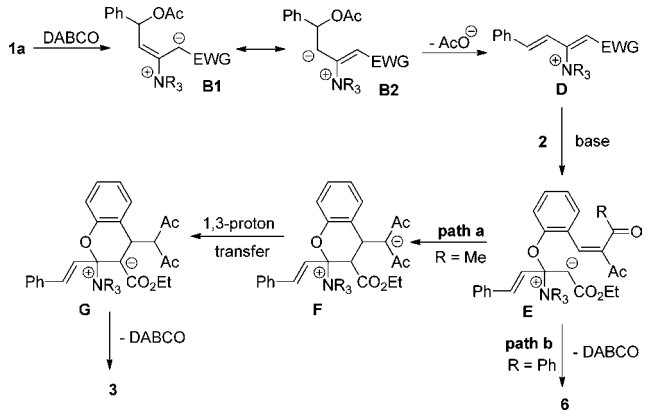
It was found that the property of alkene in substrate **2** also played an important role in the reaction. In addition to **2a**–**i**, substrate **2j** reacted well with **1f** to give product **3fj** in 76% yield (eq 1). However, substrates **2k** and **2l**, which were prepared via



the condensation of salicylaldehyde with 1-phenylbutane-1,3-dione and 1,3-diphenylpropane-1,3-dione, respectively, reacted with **1a** to afford formal addition–elimination products **6** (eq 2).[11]

On the basis of these observations and the related amine-catalyzed reactions of allenoate,[8,10] a plausible reaction mechanism of the DABCO-catalyzed annulations of **1a** and **2** is depicted in Scheme 3. First, addition of DABCO to allenoate

Scheme 3. Plausible Mechanism of the Reaction of 1a and 2



1a generates zwitterionic intermediates **B1** and **B2**. The latter undergoes 1,2-elimination of acetate group to form intermediate **D**. The fact that no deuterium atom was incorporated into γC implied that the 1,2-elimination process might be a fast step. With the help of a base, addition of **2** to intermediate **D** yields intermediate **E**. For the cases of **2a**–**j**, intermediate **E** undergoes intramolecular Michael addition to form intermediate **F** (Scheme 3, path a), which is converted to intermediate **G** via a 1,3-proton-transfer process. Finally, 1,2-elimination of DABCO catalyst leads to product **3**. In contrast to **2a**–**i**, compound **2k** has a less activated alkene, presumably due to both the steric hindrance and the effect of delocalization imposed by phenyl group. Thus, the corresponding intermediate **E** would not undergo a similar Michael addition, while 1,2-elimination of DABCO alternatively occurs to generate product **6** (Scheme 3, path b).

We were surprised to find that allenoate **1m** with a methyl group at δC did not react with **2a** under these conditions (Scheme 4a). Although we could not unequivocally elucidate

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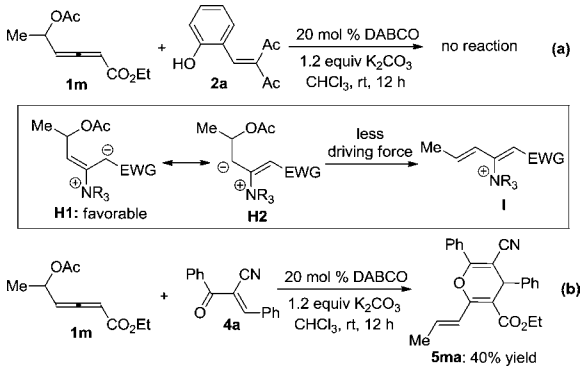
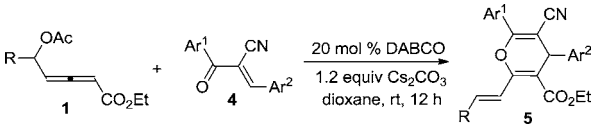
Scheme 4. Possible Explanation of the Reactivity of 1m



the difference in reactivity between **1a** and **1m** at this stage, one reasonable explanation is shown in Scheme 4. Compared to intermediate **D**, the methyl-substituted analogue **I** might be unfavorable to formation via the interaction of **1m** with DABCO, likely due to the lack of conjugation effect imposed by aryl substituent. Alternatively, zwitterionic intermediate **H1** would be dominant (Scheme 4). Thus, we envisioned that an electrophile would be required to match the reactivity of intermediate **H1**. To our delight, we finally found that oxo diene **4a** was able to trap this zwitterionice intermediate, furnishing a (4 + 2) annulation to afford 4*H*-pyran product **5ma** in 40% yield under the otherwise identical conditions (Scheme 4b).

We were pleased to find that the yield of **5ma** could be improved to 80% when the reaction was conducted in dioxane with the use of Cs_2CO_3 as base (Table 1, entry 1). Under these conditions, a variety of oxo dienes **4a**−**l** were found to be suitable substrates, and the products **5ma**−**5ml** were isolated in good yields (Table 1, entries 2−12). Furthermore, both allenoates **1n** and **1o** smoothly underwent (4 + 2) annulations

Table 1. Scope of DABCO-Catalyzed (4 + 2) Annulations of 1 and 4[a]



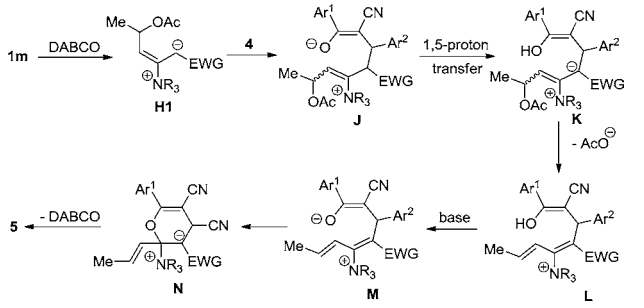
entry	1 (R)	4 (Ar^1, Ar^2)	5, yield[b] (%)
1	**1m** (Me)	**4a** (C_6H_5, C_6H_5)	**5ma**, 80
2	**1m**	**4b** (4-$MeOC_6H_4$, C_6H_5)	**5mb**, 81
3	**1m**	**4c** (4-$MeOC_6H_4$, 4-FC_6H_4)	**5mc**, 86
4	**1m**	**4d** (4-$MeOC_6H_4$, 4-ClC_6H_4)	**5md**, 75
5	**1m**	**4e** (4-$MeOC_6H_4$, 4-BrC_6H_4)	**5me**, 85
6	**1m**	**4f** (4-$MeOC_6H_4$, 4-$NO_2C_6H_4$)	**5mf**, 45
7	**1m**	**4g** (4-$MeOC_6H_4$, 2-BrC_6H_4)	**5 mg**, 76
8	**1m**	**4h** (4-$MeOC_6H_4$, 4-MeC_6H_4)	**5mh**, 78
9	**1m**	**4i** (4-$MeOC_6H_4$, 2-furan)	**5 mi**, 75
10	**1m**	**4j** (4-ClC_6H_4, 4-BrC_6H_4)	**5mj**, 71
11	**1m**	**4k** (4-BrC_6H_4, 4-BrC_6H_4)	**5mk**, 71
12	**1m**	**4l** (2-furan, 4-BrC_6H_4)	**5ml**, 70
13	**1n** (Pr)	**4e** (4-$MeOC_6H_4$, 4-BrC_6H_4)	**5ne**, 88
14	**1o** (H)	**4e** (4-$MeOC_6H_4$, 4-BrC_6H_4)	**5oe**, 58
15	**1a** (Ph)	**4a** (C_6H_5, C_6H_5)	**5aa**, NR[c]

[a]Reaction conditions: **1** (0.24 mmol), **4** (0.2 mmol), DABCO (0.04 mmol), Cs_2CO_3 (0.24 mmol), dioxane (4 mL). [b]Isolated yield. [c]NR = no reaction.

with **4e**, giving products **5ne** and **5oe** in 88% and 58% yields, respectively (Table 1, entries 13 and 14). Again, no reaction of **1a** with **4a** was observed (Table 1, entry 15), which is consistent with the possible explanation shown in Scheme 4.

A proposed mechanism of the (4 + 2) annulations of **1m** and oxo dienes **4** is depicted in Scheme 5. For zwitterionic

Scheme 5. Plausible Mechanism of the Reaction of 1m and 4



intermediate **H1**, the nucleoplilicity of carboanion may be dominant among its reactivity, thus enabling addition with **4** to form intermediate **J**. Through a 1,5-proton transfer process, **J** is converted into intermediate **I**, which is followed by elimination of acetoxy group to deliver intermediate **L**. With the help of base, the intramolecular addition of enolate results in the formation of intermediate **N**. At last, **L** undergoes 1,2-elimination to release catalyst and 4*H*-pyran product **5** (Scheme 5).

In summary, we have developed two different types of (4 + 2) annulations of *δ*-acetoxy allenoates **1** in the presence of DABCO catalyst under mild conditions. Allenoates **1** with an aromatic group at *δ*C were favorable toward reaction with salicylaldehyde derivatives **2**, delivering 4*H*-chromenes **3**, while the compound with an alkyl group at *δ*C readily underwent (4 + 2) annulations with oxo dienes **4** to afford 4*H*-pyrans **5**. Although there is no further evidence, we believe that the substrate-dependent reactivity of **1** might stem from different chemical behaviors of the involved zwitterionic intermediates. Efforts are underway to elucidate the mechanistic details and to realize asymmetric variants.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) It should be noted that no reaction of **1a** with **2k** was observed without DABCO catalyst. When $(^{i}Pr)_2NEt$ or DBU was instead used, no reaction was observed. These results implied that DABCO might work as catalyst rather than a base.

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