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# One-pot facile conversion of Baylis–Hillman adduct into *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-dione. Formal synthesis of tacamonine

Chung-Yi Chen,[a] Meng-Yang Chang,[b,*] Ru-Ting Hsu,[a] Shui-Tein Chen[c] and Nein-Chen Chang[a,*]

[a]*Department of Chemistry, National Sun Yat-Sen University, Kaohsiung 804, Taiwan, ROC*
[b]*Department of Applied Chemistry, National University of Kaohsiung, Kaohsiung 811, Taiwan, ROC*
[c]*Institute of Biological Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan, ROC*

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**Abstract**—A stepwise [3+3] strategy to *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-dione **1** used various *N*-alkyl α-substituted sulfonylacetamides **2** and α,β-unsaturated esters **3** as starting materials. α,β-Unsaturated esters **3** were generated by Baylis–Hillman reaction. A ring closure mechanism was proposed for the reactions. This method provides a convenient formal synthesis of tacamonine.
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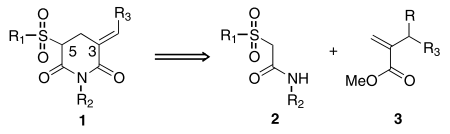
## 1. Introduction

Cyclic imides possess various potential biological activities,[1] therefore, the synthesis of these cyclic imides such as piperidine-2,6-diones (glutarimides) has attracted considerable attention.[2,3] Piperidine-2,6-diones are in most cases obtained via cyclization of δ-dinitriles in an acidic solution[2g] or via monoamides with acid in the presence of thionyl chloride[2e] or BOP.[2f] Owing to the harsh classical conditions, some milder methods have been reported,[2b,c,h,i] such as the condensation of a diacidic compound with amine. Recently, we developed a facile synthesis for an unsymmetrical glutarimide with the sulfonyl group at α-position, and proposed a mechanism of reaction.[3] We investigated this reaction strategy using different α-substituted sulfonylacetamides with various α,β-unsaturated esters to yield diverse substituents on the skeleton.

The alkylidene group of C-3 position on the skeleton of piperidine,[4] piperidinone[5] and glutarimide[6] exhibits potential biological activities. Therefore, α,β-unsaturated ester for providing the alkylidene group is produced via Baylis–Hillman reaction of carbon–carbon bond in a controlled manner to match stepwise [3+3] annulation route. In recent years, the Baylis–Hillman reaction has become a powerful tool for construction of carbon–carbon bonds in organic chemistry because it is completely atom economical and provides densely functionalized structural units, which have been successfully employed in a variety of interesting organic transformations.[7–9] The method is a convenient approach for α-functionalized acrylate that can be used for the subsequent elaboration of a variety of useful compounds. Continuing our investigation on the application of this methodology to the synthesis of alkaloids, we herein describe a one-pot stepwise [3+3] annulation synthesis of *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-dione **1** via the treatment of the α-substituted sulfonylacetamides **2** with Baylis–Hillman adducts **3** and investigate the reaction mechanism (see Scheme 1).




**Scheme 1.** Retrosynthetic synthesis of *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-dione **1**.

*Keywords*: stepwise [3+3] strategy; Baylis–Hillman reaction; glutarimide; tacamonine.

* Corresponding authors. Tel.: +(886)-7-5252000 ext. 3914; Fax: +(886)-7-5253913 (M.-Y.C.); Tel.: +(886)-7-5252000, ext. 3913; fax: +(886)-7-5253913 (N.-C.C.); e-mail: season_6386@yahoo.com.tw; ncchang@mail.nsysu.edu.tw1

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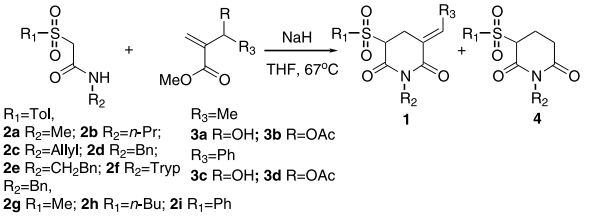
## 2. Results and discussion

### 2.1. Reaction of different acetamides 2 with esters 3

In the course of our study toward the synthesis of 3-(*E*)-ethylidene or benzylidene glutarimide, **2** and **3** serve as starting materials for the addition reaction. Compounds **2** and **3** were prepared as follows. Sequential treatment of chloroacetyl chloride with various amines and different sulfinic acid sodium salt furnished different compounds **2**. Compounds **3** were carried out via Baylis–Hillman reaction of methyl acrylate with acetaldehyde and benzaldehyde.[9] Reactions of **2** having various *N*-substituents ($R_2$) α-substituents ($R_1$) with Michael acceptors **3** yielded **1** and **4** (see Eq. (1)). After deprotonation of **2** with sodium hydride in tetrahydrofuran at room temperature, the resulting dianion reacted with four α,β-unsaturated esters **3a–d** to yield the corresponding **1** and **4** at reflux temperature in different ratios (see Table 1). The unexpected isolation of **4** promoted us to investigate the mechanism based on the previous report.[3] Presumably, the hydroxy group on **3a** is an important factor affecting the ratio of products. To block the hydroxy group, **3a** or **3c** were acetylated with acetic anhydride in pyridine to form **3b** or **3d**.



(1)

**Table 1.** Reaction of different compounds **2** with **3**

| No. | **2** ($R_1$, $R_2$) | **3** ($R_3$, R) | Ratio[a] (**1**:**4**) | Yield[b] (**1**+**4**) |
|---|---|---|---|---|
| 1 | **2c** Tol, Allyl | **3a** Me, OH | 1:1 | 68% |
| 2 | **2d** Tol, Bn | **3a** Me, OH | 1:1 | 57% |
| 3 | **2f** Tol, Allyl | **3a** Me, OAc | 1:0 | 64% |
| 4 | **2d** Tol, Bn | **3b** Me, OAc | 1:0 | 61% |
| 5 | **2f** Tol, Tryp | **3b** Me, OAc | 1:0 | 72% |
| 6 | **2d** Tol, Bn | **3c** Ph, OH | 1:3 | 53% |
| 7 | **2f** Tol, Tryp | **3c** Ph, OH | 1:4 | 59% |
| 8 | **2g** Me, Bn | **3c** Ph, OH | 1:3 | 48% |
| 9 | **2h** *n*-Bu, Bn | **3c** Ph, OH | 1:4 | 55% |
| 10 | **2i** Ph, Bn | **3c** Ph, OH | 1:4 | 41% |
| 11 | **2a** Tol, Me | **3d** Ph, OAc | 1:0 | 75% |
| 12 | **2b** Tol, *n*-Pr | **3d** Ph, OAc | 1:0 | 68% |
| 13 | **2c** Tol, Allyl | **3d** Ph, OAc | 1:0 | 66% |
| 14 | **2d** Tol, Bn | **3d** Ph, OAc | 1:0 | 67% |
| 15 | **2e** Tol, $CH_2Bn$ | **3d** Ph, OAc | 1:0 | 59% |
| 16 | **2f** Tol, Tryp | **3d** Ph, OAc | 1:0 | 71% |
| 17 | **2g** Me, Bn | **3d** Ph, OAc | 1:0 | 55% |
| 18 | **2h** *n*-Bu, Bn | **3d** Ph, OAc | 1:0 | 51% |
| 19 | **2i** Ph, Bn | **3d** Ph, OAc | 1:0 | 71% |

[a] The product ratio was adjusted based on isolated products.
[b] All yields were based on **2** confirmed.

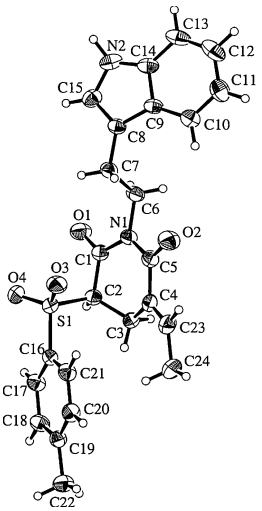


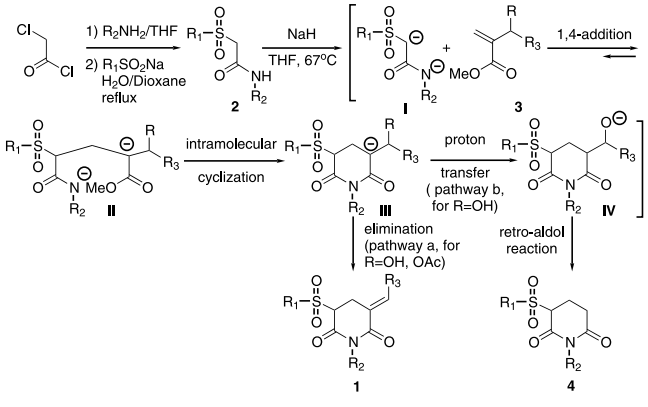

**Figure 1.** X-Ray crystallography of **1fb**

When **3b** is the Michael acceptor, the sole products **1** were produced in modest yield. The reaction possesses specificity for (*E*)-form isomer, similar to reports from literature.[5b,10] Elimination of acetate group of the initial adduct occurred in situ and afforded the new enone as a single geometric isomer. Furthermore, the chemical shift of vinylic hydrogen of (*E*)-form isomer showed a more downfield value than (*Z*)-form isomer in the skeleton of piperidine,[4a,e] piperidinone[5b] and glutarimide.[10a] The structure of **1fb** was determined by single-crystal X-ray analysis. These results provided another pathway for the addition reaction and expanded on the original proposed mechanism (Fig. 1).

### 2.2. Proposed mechanism of different 2 with 3

The proposed reaction mechanism of different **2** with **3** is shown in Scheme 2.

First, the formed dianion **I** attacks esters **3** to produce dianion **II** by Michael addition reaction. The less stable dianion **II** using intramolecular cyclization forms **III**. The **III** is a key intermediate in the mechanism. However, when the substrate has hydroxy group (R = OH) on **3a** or **3c**, we detected two kinds of **1** and **4** under



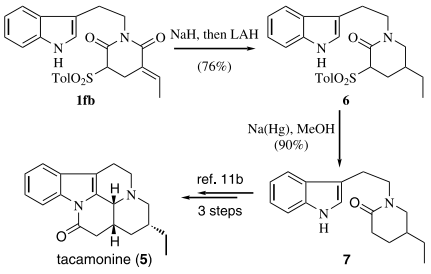

**Scheme 2.** Proposed mechanism of different α-sulfonylacetamides **2** with **3**.

proper condition of **III**. The **III** eliminates the hydroxy group (pathway a) to produce **1**. Furthermore, when **III** goes forward to the **IV** via a proton transfer with acidic hydrogen (OH) reaction (pathway b), compounds **4** were produced via retro-aldol reaction. From the view of products ratio on the reaction with **3a** or **3c**, we believe that the reaction preferred pathway b than pathway a. When we reacted **2** with another **3b** or **3d**, the only (*E*)-form products **1** via elimination of **III** (pathway a) was produced. Using this protocol, various compounds **1** on the reaction with **3b** or **3d** were produced in moderate yields via acetate elimination of **III**.

### 2.3. Formal synthesis of tacamonine (5)

Tacamonine (**5**), one of the few indole alkaloids of the tacamane type, was isolated in 1984[11a] from *Tabernaemontana eglandulosa*; it possesses vasodilator and hypotensive activities. Lactam **7**[11] has been converted to **7** in three steps via Bischler–Napieralski cyclization.[11b] The family possesses a wide range of biological activities and has served as an important pharmacological tool. The interesting biological functions of this family have induced many attempts to synthesize these compounds. The alkaloid has a common characteristic pentacyclic ring framework comprised indole ring. Here we report the synthesis of tacamonine (**5**) via above method.

We describe the stepwise reduction leading to the intermediate **7** of tacamonine (**5**) as illustrated in Scheme 3. There are two remarkable steps for the formal synthesis of **5**. One is the rapid access to produce a wide variety of piperidin-2,6-dione **1fb** by stepwise [3+3] annulation reaction. The other is the regioselective transformation from α-sulfonylpiperidin-2,6-dione **1fb** to piperidinone **6** using the reduction. We discovered that treatment of **1fb** with sodium hydride at room temperature followed by addition of lithium aluminum hydride, the resulting mixture was further refluxed; δ-lactam **6** was obtained in good yield. Reductive desulfonation of **6** with sodium amalgam in methanol solution furnished **7** in good yield, which had been readily converted into tacamonine **5**.[11b]




**Scheme 3.** Formal synthesis of tacamonine (**5**).

## 3. Conclusion

In conclusion, we have explored an efficient formal [3+3] reaction strategy that is synthetically useful for constructing *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-diones. Formal synthesis of tacamonine is also described by the above method. We are currently studying the scope of this process as well as additional application of the methodology to the synthesis of pyrrolizidines and indolizidines.

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