Synthesis of Bicyclic Pyridones via Cyclocondensation of Heterocyclic Ketene Aminals with β-Ketoester Enol Tosylates

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Abstract: A series of novel bicyclic pyridones were easily prepared by cyclic condensation of heterocyclic ketene aminals with β-keto ester enol tosylates in the presence of a base to give products in excellent yields (80–95%).

Key words: pyridones, cyclocondensation, heterocyclic ketene aminals, β-keto ester enol tosylates

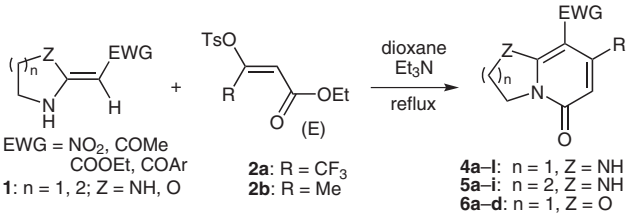
Heterocyclic ketene aminals (HKA) are versatile intermediates for the synthesis of a wide variety of fused heterocyclic compounds.[1] Reactions of HKA with 1,2- and 1,3-bifunctional substrates leading to five- and six-membered fused heterocycles have been reported. Five-membered-ring systems belonging to aminopyrrolone derivatives[2] have been synthesized. Six-membered-ring systems such as 2-aminotetrahydropyridines,[3] 6-aminodihydropyridinones,[4] dihydropyridine-2-amines,[5] 6-aminopyridinones,[4a–c,6] 6-iminodihydropyridine-2-amines[7], and 2-aminodihydropyridine[8] have also been obtained. Furthermore, seven-membered 3-amino-2*H*-benzo[*c*]azepin-1(5*H*)-one could also be obtained with ethyl 2-bromobenzoate.[9]

These fused heterocyclic structures are frequently found in pharmacophores and play important roles in the drug industry and have found uses as herbicides, pesticides,[10] anti-anxious agents,[11] antileishmanial agents,[12] antibacterial and antitherapeutic drugs.[13] Of these compounds, bicyclic pyridones **3** are of general interest within medicinal chemistry, and a series of substituted variants of **3** (n = 1, 2) have been reported as a basis for analgesics and anti-inflammatory agents (Figure 1).[14] Published methods for the synthesis of bicyclic pyridones **3** (n = 1, 2) are based on the following approaches: cyclocondensation of ketenaminals,[4a–c,6] addition of diamines to cyanobutenoic esters,[14a,b] addition of diamines to halo-[14] or thiomethylpyridones,[15] nucleophilic substitution and intramolecular condensation of 2,6-dihalopyridine,[16] and other methods.[17] The first method is the most used procedure. However, only propiolic ester[4a,b,6a–f] or diethyl but-2-ynedioate[6g] can be used as the starting materials to undergo cyclocondensation with ketene aminals. This, in turn, places limitations on the flexibility and subsequent applications of this chemistry.

In order to develop an efficient method for the rapid generation of libraries of bicyclic pyridones (Figure 1), we are focusing on the reaction of HKA **1** with β-keto ester enol tosylates **2**. They are recognized as useful cross-coupling reagents which have been widely employed in C–C bond formation in organic synthesis.[18] In addition, β-keto ester enol tosylates are considerably less expensive and more readily accessible than other reagents, such as triflating agents.[18a] However, they are only useful as single-site nucleophiles, and do not function as bisnucleophiles when forming cyclic compounds. In this communication, we report herein an efficient method for the rapid generation of libraries of the 5,6- and 6,6-ring bicyclic pyridones **4a–l**, **5a–i**, and **6a–d** based upon the results of cyclocondensation of HKA **1** with β-ketoester enol tosylates **2** under basic conditions.

Figure 1 Bicyclic pyridones derived from HKA

Firstly, an easily available starting material 2-(nitromethylene)imidazolidine **1a** was reacted with β-keto ester enol tosylates **2a** in 1,4-dioxane in the presence of Et_3N under refluxing temperature for 14 hours. The bicyclic pyridone **4a** was successfully obtained in 80% yield (Scheme 1, Table 1, entry 1). All new compounds **4–6** were fully characterized on the basis of their ^1H NMR, ^{13}C NMR spectra and high resolution mass spectra.[19] The structure



Scheme 1 Synthesis of bicyclic pyridones

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of product **4d** was further confirmed by X-ray crystallographic analysis (Figure 2).[20]

Encouraged by this result, we explored the scope and limitations of the cyclocondensation reactions involving various HKA **1a–l** with two β-keto ester enol tosylates **2a**,**b** (Table 1, entries 1–21). The results demonstrated that HKA, with various substituents and different ring sizes, were all good substrates for the cyclocondensation reaction. The reactions usually took 3–14 hours at refluxing temperature in 1,4-dioxane under basic conditions for completion, and the yields were generally good.

The structures of the HKA **1** have an obvious influence on the reactivity and product yield. For example, the reactivity of **1** was increased by the electron-rich properties of the group on the aromatic ring (Table 1, entries 1–7, 8–12, 13–17, 18–21). Under the experimental conditions, the reactivity order of five-membered HKA is **1g** > **1f** > **1d** >

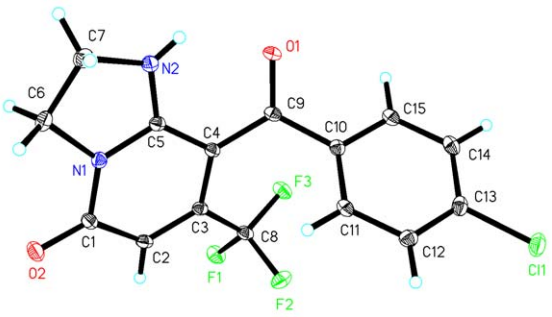
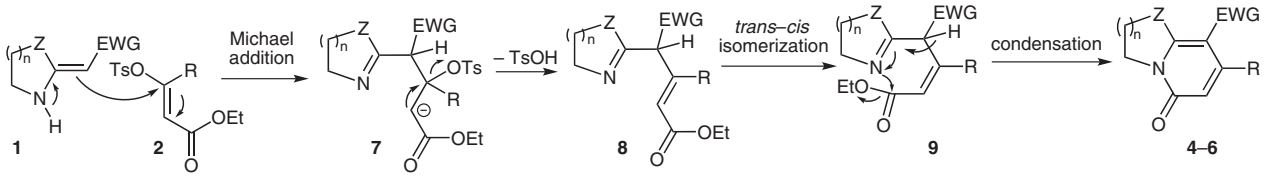


Figure 2 X-ray crystal structure of **4d**

Table 1 Synthesis of Bicyclic Pyridones

Entry	HKA	Enol tosylates	Product	n	Z	EWG	R	Yield (%)[a]
1	**1a**	**2a**	**4a**	1	NH	NO_2	CF_3	80
2	**1b**	**2a**	**4b**	1	NH	COMe	CF_3	82
3	**1c**	**2a**	**4c**	1	NH	COOEt	CF_3	83
4	**1d**	**2a**	**4d**	1	NH	4-ClC_6H_3CO	CF_3	95
5	**1e**	**2a**	**4e**	1	NH	C_6H_4CO	CF_3	90
6	**1f**	**2a**	**4f**	1	NH	4-MeC_6H_3CO	CF_3	94
7	**1g**	**2a**	**4g**	1	NH	4-$MeOC_6H_3CO$	CF_3	95
8	**1b**	**2b**	**4h**	1	NH	COMe	Me	82
9	**1d**	**2b**	**4i**	1	NH	4-ClC_6H_3CO	Me	88
10	**1e**	**2b**	**4j**	1	NH	C_6H_4CO	Me	90
11	**1f**	**2b**	**4k**	1	NH	4-MeC_6H_3CO	Me	78
12	**1g**	**2b**	**4l**	1	NH	4-$MeOC_6H_3CO$	Me	84
13	**1h**	**2a**	**5a**	2	NH	4-FC_6H_3CO	CF_3	83
14	**1i**	**2a**	**5b**	2	NH	4-ClC_6H_3CO	CF_3	89
15	**1j**	**2a**	**5c**	2	NH	C_6H_4CO	CF_3	85
16	**1k**	**2a**	**5d**	2	NH	4-MeC_6H_3CO	CF_3	90
17	**1l**	**2a**	**5e**	2	NH	4-$MeOC_6H_3CO$	CF_3	91
18	**1i**	**2b**	**5f**	2	NH	4-ClC_6H_3CO	Me	94
19	**1j**	**2b**	**5g**	2	NH	C_6H_4CO	Me	90
20	**1k**	**2b**	**5h**	2	NH	4-MeC_6H_3CO	Me	92
21	**1l**	**2b**	**5i**	2	NH	4-$MeOC_6H_3CO$	Me	93
22	**1m**	**2a**	**6a**	1	O	C_6H_4CO	CF_3	85
23	**1n**	**2a**	**6b**	1	O	4-MeC_6H_3CO	CF_3	87
24	**1o**	**2a**	**6c**	1	O	4-$MeOC_6H_3CO$	CF_3	89
25	**1m**	**2b**	**6d**	1	O	C_6H_4CO	Me	83

[a] Isolated yields.



Scheme 2 Proposed mechanism for the formation of bicyclic pyridones

1e > 1c > 1b >1a. The reactivity order of six-membered HKA also showed the same tendency, i.e., **1l > 1k > 1i > 1j**.

In order to expand the scope of the cyclocondensation reaction, HKA were replaced by *N*,*O*-acetal (Table 1, entries 22–25). The reaction proceeded smoothly under the same conditions, and the reactivity of *N*,*O*-acetal **1m–o** was found to be similar to that of the HKA.

The mechanism of the cyclocondensation reaction is depicted in Scheme 2. HKA **1** reacted via Michael addition with compound **2** to give the adduct **7** followed by elimination of tosylate to form compound **8**. The *trans–cis* isomerization then provided **9**, subsequent imine–enamine tautomerization and condensation afforded the target product **4–6**.

In conclusion, we have developed a procedure for the facile synthesis of the bicyclic pyridones by simply refluxing a reaction mixture of HKA and β-ketoe ster enol tosylates catalyzed by Et_3N. As a result, a library of novel bicyclic pyridones was rapidly constructed in good yields. Preliminary biological activity screening using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay showed some of the title compounds **4–6** possessed moderate anticancer activities against the K562, HL60, A431, HepG2, and Skov-3 cell lines (see Supporting Information for details).

Consequently, this simple process presented herein has great potentials for application to parallel synthesis in drug discovery.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(19) **General Procedure for the Cyclocondensation Reaction**
A 50 mL round-bottom flask was charged with β-keto ester enol tosylates **2** (1 mmol), 1,4-dioxane (10 mL), and Et_3N (3 mL), then the solution was added to HKA **1** (1 mmol), and the solution was refluxed. The resulting solution was stirred for 3–14 h until the β-keto ester enol toslates **2** were completely consumed. The mixture was quenched by the addition of H_2O (50 mL). The reaction mixture was filtered off, and the residue was washed with H_2O to give a crude product that was recrystallized by EtOH or acetone to form the final products **4**–**6**.
Compound **4d**: yellow solid; mp 184–187.5 °C. IR (KBr): 3366 (NH), 3079 (C=CH), 1679 (C=O), 1602 (C=O), 1558 (C=C), 1324 (CN), 1165 (CF) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 3.68 (t, *J* = 9.2 Hz, 2 H, CH_2), 4.11 (t, *J* = 9.1 Hz, 2 H, CH_2), 6.00 (s, 1 H, CH=), 7.56–7.79 (m, 5 H, ArH, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 42.6 (NCH_2), 43.7 (NCH_2), 91.8 (*C*COAr), 104.3 (*C*HCO), 122.5 (q, *J* = 211.3 Hz, CF_3), 128.5 ($2 \times CH_{ar}$), 131.1 ($2 \times CH_{ar}$), 137.0 (C_{ar}), 137.8 (C_{ar}), 140.0 (q, *J* = 30 Hz, *C*CF_3), 154.4 (*C*=CCOAr), 159.0 (C=O), 190.2 (COAr). HRMS (TOF ES^-): *m/z* calcd for $C_{15}H_9ClF_3N_2O_2$ [M – H^+]: 341.0310; found: 341.0308.

(20) CCDC 738457 contains the supplementary crystallographic data for compound **4d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.