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Efficient Synthesis of Highly Functionalized Dihydropyrido[2,3-*d*]pyrimidines by a Double Annulation Strategy from α-Alkenoyl-α-carbamoyl Ketene-(*S*,*S*)-acetals

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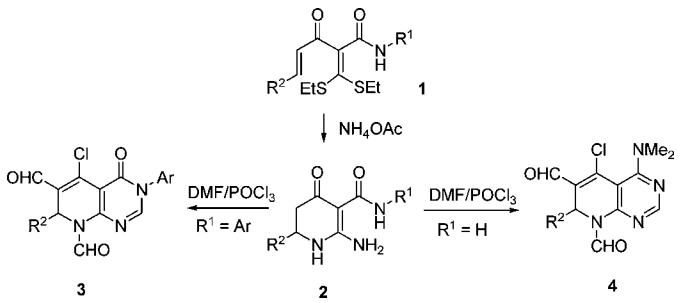

A convenient and efficient synthesis of highly functionalized dihydropyrido[2,3-*d*]pyrimidines via a double [5 + 1] annulation strategy starting from easily available α-alkenoyl-α-carbamoyl ketene-(*S*,*S*)-acetals **1** and cheap reagents (NH_4OAc, DMF, and $POCl_3$) has been developed. In the first step of the double annulation route, 2-amino-3-carbamoyl-5,6-dihydro-4-pyridones **2** were created in high to excellent yields by a formal [5C + 1N] annulation reaction of ketene-(S,S)-acetals **1** with ammonia (from ammonium acetate). In the second step of the double annulation strategy, the highly functionalized dihydropyrido-[2,3-*d*]pyrimidine derivatives, 7,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **3** (when R^1 = aryl) and 7,8-dihydropyrido[2,3-*d*]pyrimidines **4** (when R^1 = H), were constructed, respectively, in fair to good yields by reacting **2** with excessive Vilsmeier reagent (DMF/$POCl_3$). A mechanism involved in the second [5 + 1] annulation step, including a formal [5 + 1] annulation and accompanied chlorovinylation, chloroformylation, amination, and aromatization reactions, is proposed.

Introduction

Pyrido[2,3-*d*]pyrimidines, as a kind of annulated uracils, have received considerable attention due to their wide range of biological activities.[1] General methods for their synthesis involve the annulation reactions starting from either suitably substituted 6-aminouracils[2] or 2-amino-3-cyanopyridines[3] and related substrates.[4] However, many of these methods suffer from drastic reaction conditions and complex procedures, and use expensive or not readily available starting materials.[2−4] During the course of our studies on the chemistry of functionalized ketene-(*S*,*S*)-acetals,[5] we found that the easily available α-alkenoyl ketene-(*S*,*S*)-acetals,[6] for example, α-alkenoyl-α-carbamoyl ketene-(*S*,*S*)-acetals **1**, showed promising structural features as novel organic intermediates in annulation reactions[7a] and a series of *N*-alkylated 2-alkylamino-3-carbamoyl-5,6-dihydro-4-pyridones

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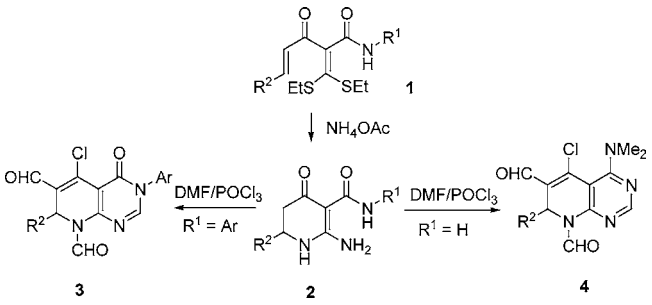
SCHEME 1



were prepared via a formal [5C + 1N] annulation reaction under mild conditions by reacting **1** with aliphatic primary amines.[7b] To explore the synthetic potential of ketene-(*S*,*S*)-acetals **1**, on our ongoing research, a facile synthetic route to dihydropyrido-[2,3-*d*]pyrimidines by a double [5 + 1] annulation strategy[8] was designed and succeeded. The double [5 + 1] annulation strategy includes the following: (1) a formal [5C + 1N] annulation of ketene-(*S*,*S*)-acetals **1** with ammonia to give 2-amino-3-carbamoyl-5,6-dihydro-4-pyridones **2** and (2) a second [5 + 1] annulation of dihydro-4-pyridones **2** with the Vilsmeier reagent ($DMF/POCl_3$, as a one-carbon electrophile[9]) to provide the pyrimidine framework of dihydropyrido[2,3-*d*]pyrimidines.

In the present research, it was found that, accompanying the construction of the dihydropyrido[2,3-*d*]pyrimidines in the second [5 + 1] annulation step, a series of reactions including chlorovinylation, chloroformylation, amination, and aromatization reactions occurred in the presence of excessive Vilsmeier reagent, and as a result, the highly functionalized 7,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **3** (when R^1 = aryl) and 7,8-dihydropyrido[2,3-*d*]pyrimidines **4** (when R^1 = H) were created in fair to good yields (Scheme 1). Herein, we wish to describe our results for the short and efficient synthesis of dihydropyrido-[2,3-*d*]pyrimidines **3** and **4** and present the proposed mechanism involved.

Results and Discussion

Synthesis of α-Alkenoyl-α-carbamoyl Ketene-(*S*,*S*)-acetals 1. The substrates, α-alkenoyl-α-carbamoyl ketene-(*S*,*S*)-acetals **1**, as shown in Scheme 1, were prepared in excellent yields by the Claisen−Schmidt condensation reactions of the corresponding α-acetyl ketene-(*S*,*S*)-acetals with aldehydes as described in our previous reports.[7]

TABLE 1. Reaction of 1a with NH_4OAc under Different Conditions

entry	**1a**, equiv	NH_4OAc, equiv	*T*, °C	solvent (mL)	time, h	yield, % (**2a**)
1	1.0	10.0	40	CH_2Cl_2 (5)	20	no reaction
2	1.0	10.0	65	THF (5)	20	no reaction
3	1.0	10.0	100	DMF (5)	10	63
4	1.0	5.0	100	DMSO (5)	5	80
5	1.0	10.0	100	DMSO (5)	4	92
6	1.0	10.0	75	DMSO (5)	6	84

TABLE 2. Synthesis of Dihydro-4-pyridones 2

entry	substrates **1**	R^1	R^2	products **2**	time, h	yield, %
1	**1a**	4-ClC_6H_4	4-MeC_6H_4	**2a**	4.0	92
2	**1b**	4-ClC_6H_4	4-ClC_6H_4	**2b**	5.0	89
3	**1c**	4-ClC_6H_4	C_6H_5	**2c**	4.5	79
4	**1d**	4-ClC_6H_4	3,4-$O_2CH_2C_6H_3$	**2d**	3.5	87
5	**1e**	4-ClC_6H_4	4-FC_6H_4	**2e**	3.0	96
6	**1f**	4-ClC_6H_4	3-pyridyl	**2f**	4.5	80
7	**1g**	4-ClC_6H_4	2-thienyl	**2g**	3.5	84
8	**1h**	4-ClC_6H_4	2-furyl	**2h**	5.0	79
9	**1i**	4-ClC_6H_4	*t*-C_4H_9	**2i**	2.5	86
10	**1j**	H	4-MeC_6H_4	**2j**	4.5	92
11	**1k**	H	4-ClC_6H_4	**2k**	6.0	95
12	**1l**	H	C_6H_5	**2l**	5.0	85
13	**1m**	H	4-$CH_3OC_6H_4$	**2m**	3.5	81

Synthesis of 2-Amino-3-carbamoyl-5,6-dihydro-4-pyridones 2. In the preparation of dihydro-4-pyridones **2**, the initial experiments were carried out between **1a** (R^1 = 4-ClC_6H_4, R^2 = 4-MeC_6H_4) and NH_4OAc (10.0 equiv) exploring different solvents. In the experiments with CH_2Cl_2 or THF as the solvent, however, no reaction was observed (monitored by TLC) either at room temperature or under reflux conditions (Table 1, entries 1 and 2), whereas with DMF as the solvent and stirring at 100 °C for 10 h, a white solid was obtained in pure form in 63% yield after pouring the reaction mixture into aqueous saturated sodium chloride and collecting the filtrate (Table 1, entry 3). The exclusive product was characterized as 2-amino-3-carbamoyl-5,6-dihydro-4-pyridone **2a** on the basis of its spectra and analytical data. The optimization of the reaction conditions, including reaction temperature, solvents, and the feed ratio of **1a** and NH_4OAc, was investigated. After a series of optimization experiments, DMSO was proved to be the best solvent and the yield of pyridone **2a** reached 92% when the reaction of **1a** with NH_4OAc (10.0 equiv) was performed in DMSO at 100 °C for 4 h (Table 1, entry 5).

Under the optimized conditions, a range of reactions between α-alkenoyl ketene-(*S*,*S*)-acetals **1** and NH_4OAc (10.0 equiv) were carried out by varying the substituents R^1 and R^2 of **1** (Table 2). It should be noted that in both cases for substituents R^1 = aryl and hydrogen, the [5C + 1N] annulation reactions of **1** with NH_4OAc proceeded smoothly and the corresponding pyridones **2** were formed in good to excellent yields (Table 2). To our delight, the synthetic procedure of pyridones **2** was very simple. In all the above experiments, pure pyridones **2** could be obtained simply by recrystallization in diethyl ether without using chromatographic separation.

Synthesis of Highly Functionalized Dihydropyrido[2,3-*d*]-pyrimidines 3 and 4. With the readily available 2,3-dihydro-6-amino-4-pyridones **2** at hand, our attention was then turned to its reaction with the Vilsmeier reagent. As a result, a second [5 + 1] annulation took place, in which 6-amino and carbamoyl nitrogen groups of **2** acted as the 1,5-*N*,*N*-dinucleophiles and

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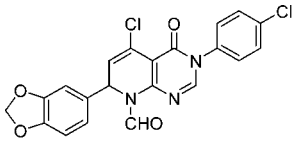
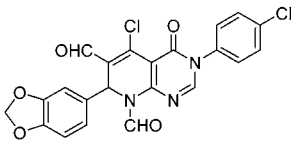
the Vilsmeier reagent served as a one-carbon dielectrophile.[9] It was found in the initial experiment that complex products were produced by reacting **2a** with 1 equiv of $POCl_3$ in DMF at ambient temperature for 48 h. With the consideration that the complex products in the above reaction may result from insufficient amounts of Vilsmeier reagent toward a wide variety of reactive sites in pyridones **2**, large excessive amounts of Vilsmeier reagent were then used to drive the reaction to completion. To our delight, dihydropyrido[2,3-*d*]pyrimidines **3a** was successfully prepared in 42% isolated yield when the reaction of pyridone **2a** with excessive $POCl_3$ (10.0 equiv) was carried out in DMF at room temperature for 48 h. Meanwhile, it was observed that prolonged reaction time, for example 72 h, would increase the yield of **3a** up to 65%. As a result, dihydropyrido[2,3-*d*]pyrimidines **3** (where R^1 = Ar, Table 3, entries 1−9) and **4** (where R^1 = H, Table 3, entries 10−13) were prepared in 43−73% isolated yields under the optimized conditions as described above.

In an effort to understand the mechanism of the formation of dihydropyrido[2,3-*d*]pyrimidines **3** and **4**, in an isolated experiment, the reaction of **2a** with Vilsmeier reagent (10.0 equiv) was quenched with aqueous NaOH after proceeding for 3 h. As a result, compound **5a** was isolated in 30% yield. Under the identical conditions, compound **5d** was obtained from the reaction of **2d** with Vilsmeier reagent (10 equiv) in 22% yield and its structure was established by the X-ray single-crystal analysis (see the Supporting Information, Figure S1).

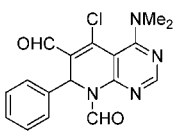
The comparison of ^{1}H NMR, ^{13}C NMR, and mass spectra between **5d** and **3d** leads us to confirm the structure of product **3d** without difficulty. In the ^{1}H NMR spectrum of compound **5d**, 6-H and 7-H display an AB coupling at δ 6.04 and 6.22, respectively. As for **3d**, the corresponding two peaks turn into a singlet at δ 6.84 for 7-H and a new singlet at δ 10.26 for 6-formyl hydrogen. In mass spectroscopy, the mass difference of the molecular ion peaks between **3d** (470) and **5d** (442) is consistent with that of the formylation reaction. All the above information indicated a formyl group was included to the 6-carbon atom of **3d**. Similarly, it could be concluded that the formyl group was oriented at the 6-carbon atom of **4** by comparing their ^{1}H NMR and ^{13}C NMR spectra with those of dihydropyrido[2,3-*d*]pyrimidines **3**. However, for the products **4**, for example **4*l***, the two single peaks at 3.17 and 3.28 ppm in the ^{1}H NMR spectrum (and also the two single peaks at 36.0 and 42.1 ppm in ^{13}C NMR spectrum) clearly indicated that a dimethylamino group exists on the pyrimidine core and should be located at the 4-position.



5d



3d



4l

The Vilsmeier reagent (halomethyleneiminium salt) formed from the interaction of dialkyl formamides such as DMF with

TABLE 3. Synthesis of Dihydropyrido[2,3-*d*]pyrimidines 3 and 4

entry	substrates **2**	products (**3** or **4**)	time, h	yield, %
1	**2a**	**3a**	72	65
2	**2b**	**3b**	80	63
3	**2c**	**3c**	65	61
4	**2d**	**3d**	70	73
5	**2e**	**3e**	76	70
6	**2f**	**3f**	83	63
7	**2g**	**3g**	90	69
8	**2h**	**3h**	90	43
9	**2i**	**3i**	48	64
10	**2j**	**4j**	84	52
11	**2k**	**4k**	96	54
12	**2l**	**4l**	90	49
13	**2m**	**4m**	72	62

$POCl_3$ is one of the most commonly used reagents and its application in some types of reactions such as acylation, halogenation, haloalkylation, haloformylation, dehydration, aromatization, and annulation has been reported.[10−12] In the present research, a similar mechanism for the formal [5C + 1N] annulation related to the transformations from ketene-(*S*,*S*)-acetals **1** to pyridones **2** has been previously discussed.[7b] On the basis of the above experimental results, possible processes for the formation of **3a**−**i** and **4j**−**m** are proposed, and depicted in Schemes 2 and 3, respectively. For the formation of **3a**−**i** (corresponding to the starting materials **2a**−**i**), the formylation may occur first at the ring nitrogen of **2a**−**i** to give intermediate **A** in the presence of Vilsmeier reagent.[13] Next, the amine group at the 2-position of the *N*-formylated intermediate **A** reacts with the Vilsmeier reagent to afford the aminomethylene ammonium salt **B**.[14] Followed by this, a nucleophilic attack of the amide nitrogen at the positive carbon of the methylene moiety leads to an intramolecular cyclization of **B** into **C** with elimination of HCl. Then, **3a**−**i** are constructed through a series of transformations, including acid-catalyzed elimination of dimethylamine (**C** to **D**), chlorovinylation (**D** to **5**),[10,14a] and the final formylation of **5**.

As to the formation of products **4j**−**m** (Scheme 3), initially **2j**−**m** undergo *N*-formylation to give intermediate **E**. Subsequently, the dehydration of the amide group of **E** gives rise to corresponding carbonitrile **F**[15] and the formation of aminomethylene amonnium salt **G** is followed as described above. Then, the nucleophilic attack of a dimethylamine at the carbon atom of the protoned cyano group and subsequent nucleophilic addition of the resulting imine nitrogen onto the positive carbon

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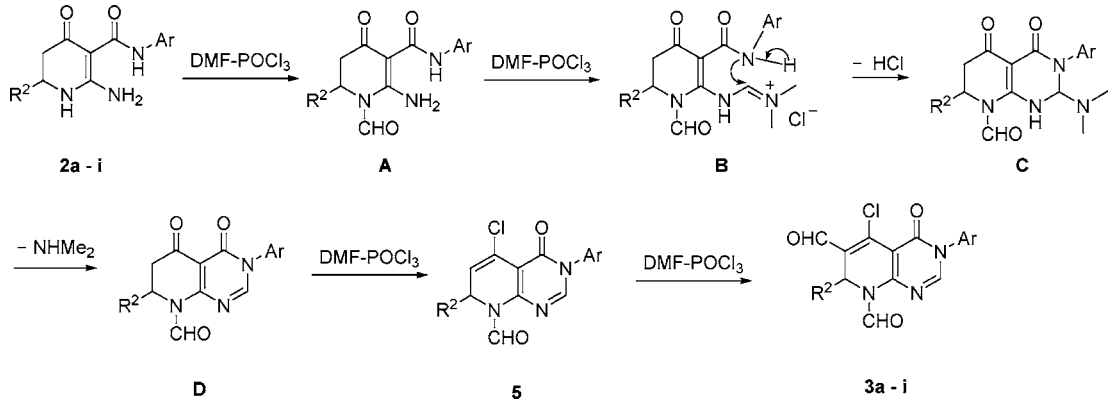
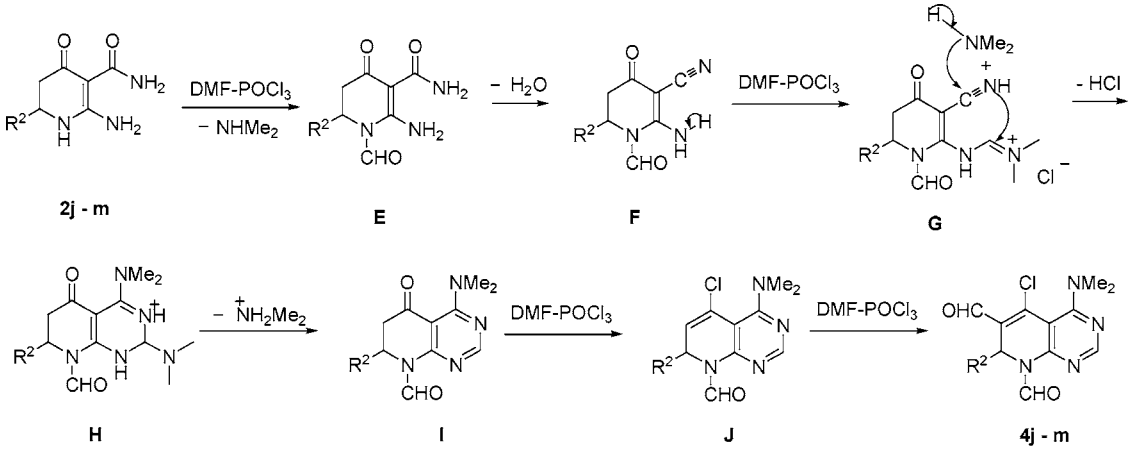
SCHEME 2. Proposed Mechanism for the Formation of 3



SCHEME 3. Proposed Mechanism for the Formation of 4



of the methylene take place. Thus, the annulation product **H** is achieved. Intermediate **H** undergoes elimination of dimethylamine, leading to aromatization. Finally, **4j**−**m** are formed by the reaction of **I** with excessive Vilsmeier reagent.

Conclusion

The synthetic potential of α-alkenoyl ketene-(*S*,*S*)-acetals has been further proven by the synthesis of highly functionalized dihydropyrido[2,3-*d*]pyrimidines **3** and **4** via the double [5 + 1] annulation strategy. Some advantages, such as the readily available substrates, cheap reagents, short steps, and mild reaction conditions, make this novel double [5 + 1] annulation strategy attractive and practical. Further study is currently underway in our laboratory.

Experimental Section

Synthesis of 2a−**m.** General procedure for the preparation of **2a**−**m** (with **2a** as an example): To a solution of α-alkenoyl ketene-(*S*,*S*)-acetal **1a** (890 mg, 2.0 mmol) in DMSO (5 mL) was added NH_4OAc (1.54 g, 20.0 mmol) in one portion at room temperature. The reaction mixture was stirred for 4 h at 100 °C and then poured into saturated aqueous sodium chloride (50 mL). The precipitated solid was collected by filtration, washed with water (3 × 30 mL), and dried in vacuo to afford a white solid, which was purified by recrystalization in diethyl ether solution to afford **2a** (652 mg, 92%): mp 202−204 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.29 (s, 3H), 2.65 (m, 2H), 4.69 (m, 1H), 7.01 (s, 1H), 7.21 (s, 2H), 7.29 (m, 4H), 7.55 (d, J = 8.0, 2H), 7.81 (s,1H), 9.77 (s, 1H), 12.6 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 188.3, 167.4, 164.4, 138.9, 138.2, 137.6, 129.6 (2C), 129.11 (2C), 126.8 (2C), 126.1, 121.3 (2C), 88.5, 52.1, 43.8, 21.2. IR (KBr, cm^{-1}) 3392, 1636, 1520, 490, 416. MS calcd *m*/*z* 355.1, found 356.3 [(M + 1)$^+$]. Anal. Calcd for $C_{19}H_{18}ClN_3O_2$: C, 64.13; H, 5.10; N, 11.81. Found: C, 64.24; H, 5.06; N, 11.72.

Synthesis of 3a−**i and 4j**−**m.** General procedure for the preparation of **3** and **4** (with **3a** as an example): The vilsmeier reagent was prepared by adding $POCl_3$ (10.0 mmol) dropwise to ice cold dry DMF (5 mL) under stirring. The mixture was then stirred for 10−15 min at 0 °C. To the above Vilsmeier reagent was added **2a** (1 mmol) as a solution in DMF (5 mL). Then the mixture was allowed to warm to room temperature and then stirred for 72 h. After the staring material was consumed (monitored by TLC), the reaction mixture was poured into saturated sodium chloride aqueous (50 mL). The mixture was extracted with dichloromethane (3 × 20 mL), the combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether:diethyl ether = 2:1) to give **3a** (286 mg, 65%) as a yellow solid: mp 227−229 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.21(s, 3H), 6.57 (s, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.61 (d, J = 7.5 Hz, 2H), 8.56 (s, 1H), 9.51(s, 1H), 10.14 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1, 160.5, 156.3, 155.3, 151.4, 140.7, 138.8, 136.2, 134.0, 129.9 (2C), 129.5 (2C), 128.0 (2C), 127.6, 126.9 (2C), 102.2, 50.1, 21.1 (one of the signals was not observed). IR (KBr, cm^{-1}) 3446, 1359, 2341, 1684, 1489, 1601, 1443. MS calcd *m*/*z* 439.1, found 440.2 [(M + 1)$^+$]. Anal. Calcd

for $C_{22}H_{15}Cl_2N_3O_3$: C, 60.02; H, 3.43; N, 9.54. Found: C, 60.08; H, 3.46; N, 9.40.

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Supporting Information Available: Experimental details and spectral data for compounds **1j**−**m**, **2a**−**m**, **3a**−**i**, **4j**−**m**, **5a**, and **5d**; CIF data for **5d**. T This material is available free of charge via the Internet at http://pubs.acs.org.

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