[5C + 1N] Annulation: a novel synthetic strategy for functionalized 2,3-dihydro-4-pyridones†

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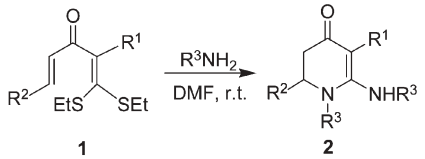
A novel and facile route to functionalized mono/bicyclic 2,3-dihydro-4-pyridones has been developed *via* formal [5C + 1N] annulation of readily available α-alkenoyl ketene-(*S*,*S*)-acetals with various aliphatic primary amines.

Six-membered nitrogen heterocycles are key units in medicinal chemistry and versatile intermediates in organic synthesis.[1] As representatives of these compounds, substituted 2,3-dihydro-4-pyridones have been extensively investigated as valuable building blocks for the construction of piperidines, perhydroquinolones, indolizidines, quinolizidines and other alkaloid ring systems, with a wide range of biological and pharmacological activities.[2] Therefore, development of simple and convenient synthetic procedures for such nitrogen-containing heterocycles represents an attractive and interesting area of research in synthetic organic and medicinal chemistry. A variety of synthetic procedures are already available, based on either the modification of the pre-constructed nitrogen heterocyclic ring system *via* pyridium salt chemistry[3] or through the construction of the nitrogen heterocyclic ring from appropriately substituted open chain precursors. These procedures include the condensation of a Schiff base with β-diketones,[4] aza Diels–Alder reactions of electron-rich dienes with aldimine,[5] and the condensation of β-amino acids/esters with β-keto esters.[6] Nevertheless, to match the increasingly scientific and practical demands for functionalized dihydro-4-pyridones, it is still of continued interest and great importance to explore novel and efficient synthetic approaches for such heterocycles.

Over the past decades, the utility of α-oxo ketene-(*S*,*S*)-acetals as versatile intermediates in organic synthesis has been recognized.[7] As three carbon 1,3-bielectrophilic synthons, α-oxo ketene-(*S*,*S*)-acetals have been widely applied in the synthesis of substituted and fused aromatic structural frameworks by reaction with Grignard reagents, Reformatsky reagents and 3-(trimethylsilyl)allyllithium.[8] On the other hand, they have been extensively exploited for the construction of five- and six-membered heterocycles, relying on the reactions with bifunctional heteronucleophiles such as hydrazine, amidines, guanidines, enamines and diamines.[7a,9] During the course of our studies on the chemistry of α-oxo ketene-(*S*,*S*)-acetals,[10] we found that α-alkenoyl ketene-(*S*,*S*)-acetals **1** showed promising structural features as novel organic intermediates, including: (1) double Michael acceptors serving as five carbon 1,5-bielectrophilic species, (2) dense and flexible substitution patterns, and (3) good leaving alkylthio groups when subjected to a nucleophilic vinyl substitution (S_NV) reaction.[11] Most recently we developed a new synthetic strategy for the construction of highly substituted phenolic rings, relying upon the utilization of **1** as a five carbon 1,5-bielectrophilic species in [5C + 1C] annulations with nitroalkanes.[12] These studies and our continued interest in the development of new general methods for biologically important heterocycles[10b,13] promoted us to explore the feasibility of a [5C + 1N] annulation of **1** with primary amines for the synthesis of functionalized and substituted 2,3-dihydro-4-pyridones. In the present communication, we wish to show our preliminary findings in this area.

Initially, the reaction of α-alkenoyl ketene-(*S*,*S*)-acetal **1a** (R^1 = 4-ClC_6H_4NHCO, R^2 = 4-MeC_6H_4) with methylamine (aq. 30%) was performed in DMF at ambient temperature for three days (Scheme 1). A pure white solid was produced after work-up and column chromatography of the resulting mixture.‡ The only product was characterized as substituted 2,3-dihydro-4-pyridone **2a1** on the basis of its spectra and analytical data.§ The reaction was then carried out under various conditions to optimize the yield. The results revealed that the reaction could proceed in polar solvents such as DMF, EtOH, THF and CH_3CN. Among those examined, DMF proved to be the most efficient medium for the reaction. In addition, the appropriate addition of an excess of amine resulted in a slightly faster transformation to **2a1** along with a good yield.

Subsequently, a range of reactions of α-alkenoyl ketene-(*S*,*S*)-acetals **1** with various primary monoamines were carried out in DMF, and some of the results are summarized in Table 1. All the reactions between methylamine and α-alkenoyl ketene-(*S*,*S*)-acetals **1a–f**, with systemic variation of R^1 and R^2, proceeded smoothly to afford the corresponding substituted 2,3-dihydro-4-pyridones **2a1–2f1** under the optimized conditions in good yields (up to 85%, entries 1–6). Similarly, **1a** reacted with various primary amines to yield the corresponding products **2a2–2a5** (entries 7–10). In comparison to the reactions with amines containing linear alkyl chains (entries 1, 7 and 8), the reactions with amines bearing bulky groups (entries 9 and 10) afforded the corresponding substituted



1 **2**

Scheme 1

† Electronic supplementary information (ESI) available: Experimental section. See http://dx.doi.org/10.1039/b505569e

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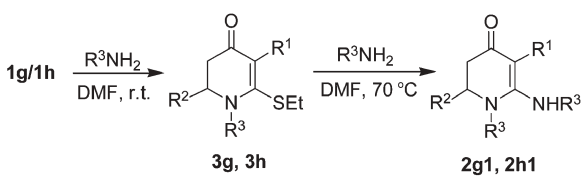
Table 1 The reactions of α-alkenoyl ketene-(*S*,*S*)-acetals **1** with selected primary monoamines

Entry	Substrate **1**	R^1	R^2	Amine R^3	Amount[a]	Time (h)	Product **2**	Yield (%)[b]
1	**1a**	4-ClC_6H_4NHCO	4-MeC_6H_4	Me[c]	3.0	36	**2a1**	81
2	**1b**	4-ClC_6H_4NHCO	4-FC_6H_4	Me	3.0	20	**2b1**	80
3	**1c**	4-ClC_6H_4NHCO	2-Thienyl	Me	3.0	48	**2c1**	68
4	**1d**	4-ClC_6H_4NHCO	3-Pyridyl	Me	3.0	12	**2d1**	85
5	**1e**	4-ClC_6H_4NHCO	PhCH=CH	Me	3.0	60	**2e1**	70
6	**1f**	2-MeC_6H_4NHCO	4-MeC_6H_4	Me	3.0	60	**2f1**	77
7	**1a**	4-ClC_6H_4NHCO	4-MeC_6H_4	Et	2.5	15	**2a2**	82
8	**1a**	4-ClC_6H_4NHCO	4-MeC_6H_4	*n*-Bu	2.5	15	**2a3**	85
9	**1a**	4-ClC_6H_4NHCO	4-MeC_6H_4	$PhCH_2$	4.0	72	**2a4**	43
10	**1a**	4-ClC_6H_4NHCO	4-MeC_6H_4	$(MeO)_2CHCH_2$	3.5	68	**2a5**	60
11[d]	**1g**	C_6H_5CO	4-MeC_6H_4	Me	5.0	36	**2g1**	76
12[d]	**1h**	C_6H_5CO	4-ClC_6H_4	Me	5.0	36	**2h1**	84

[a] Molar equivalents. [b] Isolated yields based on compounds **1**. [c] Methylamine (aq. 30%) was used. [d] The reaction mixture was heated to 60 ~ 70 °C after the consumption of substrates **1g** and **1h**, as monitored by TLC.

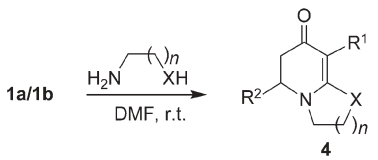
2,3-dihydro-4-pyridones in slightly lower yields, even with prolonged reaction times. It is noteworthy that when **1g** and **1h** were subjected to the identical conditions mentioned previously, following work-up, analysis of the reaction mixtures by thin layer chromatography (TLC) showed the formation of a single product, characterized as ethylthio substituted 2,3-dihydro-4-pyridones **3g** and **3h** in 91% and 92% yields, respectively (Scheme 2). Upon treatment with excess methylamine at 70 °C for 5–6 h, the resulting heterocycles **3g** and **3h** underwent the intermolecular addition–elimination sequence to yield the corresponding 2,3-dihydro-4-pyridones **2g1** and **2h1**, respectively (Table 1, entries 11 and 12). The reactions of α-alkenoyl-α-benzoyl ketene-(*S*,*S*)-acetals **1g-h** need an excess amount of amine and a high reaction temperature for a complete conversion to the corresponding dihydro-4-pyridones **2** in comparison to α-alkenoyl-α-carbamoyl ketene-(*S*,*S*)-acetals **1a-f**. The results shown above demonstrate the wide scope and synthetic interest of the cyclization reaction with respect to different monoamines and α-alkenoyl ketene-(*S*,*S*)-acetals **1** with variable R^1 and R^2 groups. It is worth mentioning that monoadducts **3** could be cleanly obtained in very high yields, which might be reacted with a second (different) amine to generate compounds of type **2** with different R^3 groups. This would be very useful in library synthesis.

The validity of this new 4-pyridone synthesis was further evaluated by performing the reaction on α-alkenoyl ketene-(*S*,*S*)-acetals **1** with *N*,*N*- and *N*,*O*-bielectrophilic substrates, with the aim of synthesizing bicyclic heterocycles. Thus, when **1a** was treated with 1.2 equimolar ethane-1,2-diamine, the product isolated was characterized as bicyclic dihydro-4-pyridone **4a** on the basis of its spectral and analytical data. In the same fashion **1a** and **1b**, as representatives of compounds **1**, underwent tandem annulation reactions with various diamines to afford bicyclic dihydro-4-pyridones **4** in moderate to high yields, and some of the results are summarized in Table 2 (entries 1–4). It appears that the



Scheme 2

Table 2 The reactions of α-alkenoyl-α-carbamoyl ketene-(*S*,*S*)-acetals **1** with selected diamines or 2-aminoethanol



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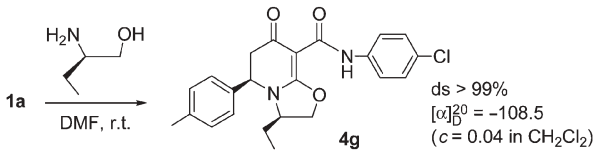
Entry	Substrate **1**	Amines X	*n*	Amount[a]	Time (h)	Product **4**	Yield (%)[b]
1	**1a**	NH	1	1.2	15	**4a**	85
2	**1a**	NH	2	1.2	12	**4b**	90
3	**1a**	NH	3	2.5	48	**4c**	69
4	**1b**	NH	1	1.2	20	**4d**	83
6	**1a**	O	1	2.0	24	**4e**	77
7	**1b**	O	1	2.0	24	**4f**	85

[a] Molar equivalents. [b] Isolated yields.

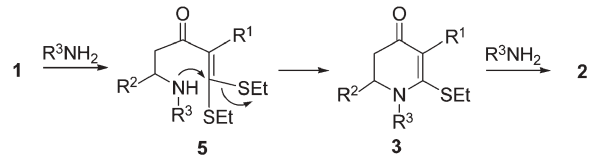
formation of seven-membered heterocycles is more difficult compared to six- or five-membered heterocycles, based on the reaction time, the amount of diamine required and the reaction yield. When unsymmetric 2-aminoethanol was subjected to the identical conditions, the substituted bicyclic 4-pyridones **4e** and **4f** were exclusively formed in good yields (Table 2, entries 6 and 7). Indeed, nitrogen bridgehead heterocycles are present in numerous natural products, and exhibit wide bio- and pharmacological activities.[14] Therefore, the present protocol provides a straightforward and general pathway to construct substituted nitrogen bridgehead heterocycles of type **4**.[15]

The protocol was then utilized in the synthesis of a chirally non-racemic bicyclic 4-pyridone. Thus the reaction of **1a** with L-(−)-2-amino-1-butanol (4.0 eq.) was carried out in DMF at room temperature. The reaction furnished a white solid after work-up and column chromatography of the resulting mixture. To our delight, the product isolated (41%) was characterized as enantiopure bicyclic 4-pyridone **4g**. It is noteworthy that the diastereoselectivity (ds) of the reaction is more than 99% according to the NMR spectra of the crude product. Indeed, the relative configuration of **4g**, as shown in Scheme 3, was proved by an NOE experiment.

On the basis of all the above results, together with our previous work,[12] a reaction mechanism for the [5C + 1N] annulation of **1** with primary amines is proposed as depicted in Scheme 4. Firstly



Scheme 3



Scheme 4 Proposed mechanism for the [5C + 1N] annulation.

the amine adds to the double bond bearing an aryl group, followed by an intramolecular addition–elimination reaction to afford an ethylthio substituted 2,3-dihydro-4-pyridone **3**, which undergoes an intermolecular addition–elimination reaction to furnish the final product of type **2**.

In summary, a new [5C + 1N] annulation strategy relying upon the utilization of α-alkenoyl ketene-(*S*,*S*)-acetal **1** as the five carbon 1,5-bielectrophilic species has been developed for the synthesis of highly substituted mono/bicyclic dihydro-4-pyridones **2–4**. The scope and synthetic application of this [5C + 1N] strategy are under investigation in our laboratory.

Notes and references

‡ *General procedure for the cyclization of α-alkenoyl ketene-(S,S)-acetals **1** with primary amines (preparation of **2a1** as an example):* To a solution of α-alkenoyl ketene-(*S*,*S*)-acetal **1a** (900 mg, 2.0 mmol) in DMF (5 mL) was added methylamine (aq. 30%) (0.63 mL, 6.0 mmol) in one portion at room temperature. The reaction mixture was stirred for 36 h at room temperature and then poured into saturated aqueous sodium chloride (50 mL), which was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with water (3 × 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, diethyl ether : acetone = 6 : 1) to give **2a1** as a white solid (620 mg, 81%).

§ Selected data for **2al**: m.p. 181–183 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 2.80 (dd, 1H, J = 5.5, 16.0 Hz), 2.94–3.10 (m, 7H), 4.46 (dd, 1H, J = 5.5, 11.5 Hz), 7.16 (s, 4H), 7.22 (d, 2H, J = 7.5 Hz), 7.51 (d, 2H, J = 7.5 Hz), 11.32 (br s, 1H), 12.48 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.98, 167.76, 137.91, 137.88, 135.71, 129.63, 128.60, 127.65, 126.29, 121.84, 92.75, 61.14, 41.41, 40.76, 32.95, 21.05. IR (KBr, cm^{-1}) 2973, 1636, 1568, 1521, 1490, 1401, 1090, 825. ES-MS: (*m*/*z*): 384.3 $[(M + 1)]^+$. Anal. Calcd for $C_{21}H_{22}ClN_3O_2$: C, 65.71; H, 5.78; N, 10.95%; Found C, 65.89; H, 5.72; N, 11.15%.

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