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Synthesis of Multi Ring-Fused 2-Pyridones via an Acyl-Ketene Imine Cyclocondensation

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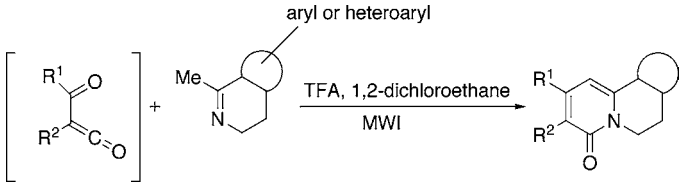
ABSTRACT



Polycyclic ring-fused 2-pyridones (5a–e and 9a–e) have been prepared via a microwave-assisted acyl-ketene imine cyclocondensation. Starting from 3,4-dihydroisoquinolines (4a–b) or 3,4-dihydroharman (8), fused 2-pyridones could be prepared in a one-step procedure. By using either Meldrum's acid derivatives (1a–d) or 1,3-dioxine-4-ones (7a–b) as acyl-ketene sources, mono- or disubstitution of the fused 2-pyridone ring could be accomplished. As an application of the method, a formal synthesis of the indole alkaloid sempervilam was performed.

The 2-pyridone core structure is an important heterocyclic framework that can be found in numerous biologically active compounds. It is also a versatile synthon that can be further transformed to pyridine, piperidine, quinolizidine, and indolizidine alkaloids.[1] The broad range of applications of the 2-pyridone structural motif has resulted in several synthetic methods.[2] The most common and general approaches rely not only on conversion of suitably functionalized pyridines[3] but also on different variations of the Guareschi−Thorpe condensation, where condensations between 1,3-dicarbonyls and amides yield functionalized 2-pyridones.[4] Previously, we have shown that bicyclic 2-pyridones, **3**, possess novel antibacterial properties, as they target periplasmic chaperones,[5] essential for bacterial pathogenesis in uropathogenic *Escherichia coli*. An effective synthesis of these bicyclic systems was developed, and the key step in this route is an acyl-ketene imine cyclocondensation (Figure 1). Thus, by reacting acyl-ketenes generated from Meldrum's acid derivatives **1** with Δ^2-thiazolines **2** under acidic conditions, 2-pyridones **3** were synthesized in excellent yields.[6] This reaction has been further developed using solid-phase techniques[7] and microwave irradiation[8] (MWI), allowing the bicyclic 2-pyridones to be prepared in a fast and parallel manner. However, many biologically interesting 2-pyridones are natural products that contain multi ring-fused systems. Recently reported examples include the yohimbane alkaloid sempervilam[9] (Figure 2) and the antineoplastic agent camp-

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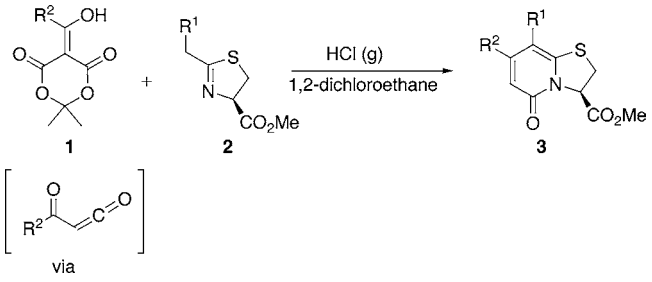


Figure 1. Synthesis of bicyclic sulfur containing 2-pyridones via an acyl-ketene imine cyclocondensation.

tothecin (Figure 2), the latter of which has attracted great interest from synthetic chemists resulting in a large number of synthetic routes.[10]

The benzo[*a*]quinolizine ring system constitutes the structural framework of many naturally occurring alkaloids, e.g., berberine (Figure 2), and can also be found in compounds targeting sleep disorder.[11] Several methods to prepare this structural framework have been developed,[12] and recently, Roy et al. demonstrated an elegant procedure to benzo[*a*]-quinolizine-4-ones **5**.[13] Hence, by reacting 3,4-dihydroisoquinoline **4a** with different β-oxodithioesters, benzo[*a*]-quinolizine-4-thiones were obtained. These could be further converted to benzo[*a*]quinolizine-4-ones **5** via methylation of the sulfur followed by hydrolysis with NaOH (aqueous), resulting in overall yields of 54−64% over three steps.

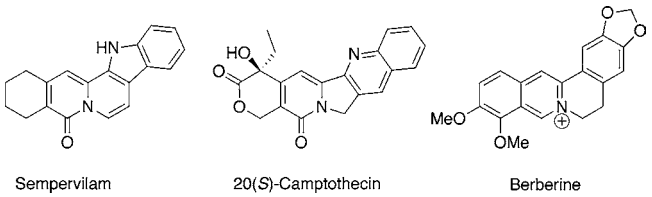
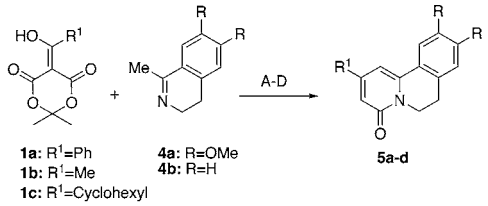


Figure 2. Examples of 2-pyridone containing natural products and the alkaloid berberine containing the tricyclic benzo[*a*]quinolizine ring system.

Provided that we could find conditions to use other imines than thiazolines, we envisioned that our earlier developed acyl-ketene imine cyclocondensation would be ideal to construct multi ring-fused 2-pyridones and still allow variability in the substitution pattern. Indeed, the easy access to different Meldrum's acid derivatives **1a**−**d**[14] in combination with the simple preparation of 3,4-dihydroisoquinolines **4** (via the Bischler−Napieralski reaction) would provide a direct and simple procedure to a variety of different 2-substituted benzo[*a*]quinolizine-4-ones **5**.

Thus, the commercially available 3,4-dihydroisoquinolines **4a** and **4b** were reacted with acyl Meldrum's acid derivatives **1a** and **1b** using the previously developed conditions (64 °C in 1/2-saturated HCl(g) solution of 1,2-dichloroethane or irradiated at 140 °C in 1/8-saturated HCl(g) solution of 1,2-dichloroethane) as a starting point. This resulted in moderate to excellent yields of the 2-substituted benzo[*a*]quinolizine-4-ones **5a**−**c** (Table 1, entries 1−6). To further improve this

Table 1. Synthesis of Benzo[*a*]quinolizine-4-ones **5a**−**d**



A: Δ 64 °C, 1,2-dichloroethane 1/2 sat with HCl (g). B: MWI 140 °C, 1,2-dichloroethane 1/8 sat with HCl (g). C: toluene, 1.5% (v/v) TFA, reflux. D: MWI 160 °C, 1,2-dichloroethane, 1.5% (v/v) TFA

entry	R^1	R	method	equiv of **1**	time	product	yield (%)[a]
1	Ph	OMe	A	3	14 h	**5a**	65
2[b]	Ph	H	A	3[c]	19 h	**5b**	64
3	Ph	OMe	B	3	120 s	**5a**	91
4	Ph	OMe	B	3.5	240 s	**5a**	98
5	Me	OMe	B	3.5	240 s	**5c**	54
6	Me	OMe	B	3.5[d]	360 s	**5c**	55
7	Me	OMe	C	3	4 h	**5c**	86
8	C_6H_{11}	OMe	C	3	2 h	**5d**	49
9	C_6H_{11}	OMe	D	3	120 s	**5d**	69

[a] Isolated yield. [b] Imine **4b** was used as the commercially available hydrochloride salt. [c] **1a** was added portionwise 2 + 1 equiv over 14 h. [d] **1b** was added portionwise 3 + 0.5 equiv over 240 s.

method, it was desirable to avoid the cumbersome use of HCl(g). Thus, by using trifluoroacetic acid (TFA) instead of HCl(g), a more practical procedure with better control of the amount of acid would be obtained. Rewardingly, compound **5c** could be isolated in 86% yield by using 1.5% (v/v) of TFA (3 equiv) in refluxing toluene (Table 1, entry 7), which corresponds to an increased isolated yield of 31% (Table 1, entries 6 and 7). In addition, by exchanging 1,2-dichloroethane for toluene and applying MWI, it was possible to shorten the reaction time substantially and compound **5d** could be prepared in 69% yield after irradiating for only 120 s.

In a recent study, it was shown that acyl Meldrum's acid derivatives react with nucleophiles via the α-oxoketene intermediate (Figure 3) and not via a protonated species as

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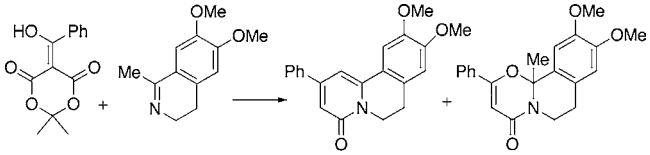
Table 2. Reaction of Dihydroisoquinoline **4a** with Meldrum's Acid Derivative **1a** under Different Reaction Conditions



entry	method	solvent	ratio[a] 5a/6
1	TFA	toluene (Δ)	100:0
2		toluene (Δ)	3:14
3	TEA	toluene (Δ)	1:19[b]
4	TFA	DCE (MWI)	100:0
5		DCE (MWI)	5:8
6	TEA	DCE (MWI)	3:7

[a] Ratio determined by analysis of the crude mixture with ^{1}H NMR. [b] Isolated in 87% yield.

previously suggested.[15] It was also shown that the 2-pyridone could be prepared without addition of acid. From a practical point of view, it would be ideal if neutral conditions could be used. Therefore, to study this further, imine **4a** was reacted with acyl Meldrum's acid **1a** under acidic, neutral, and basic conditions (Table 2, entries 1−6). This study showed that

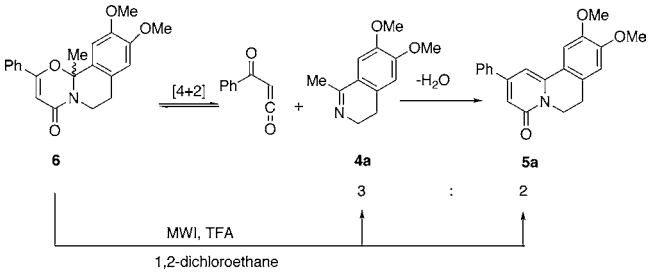


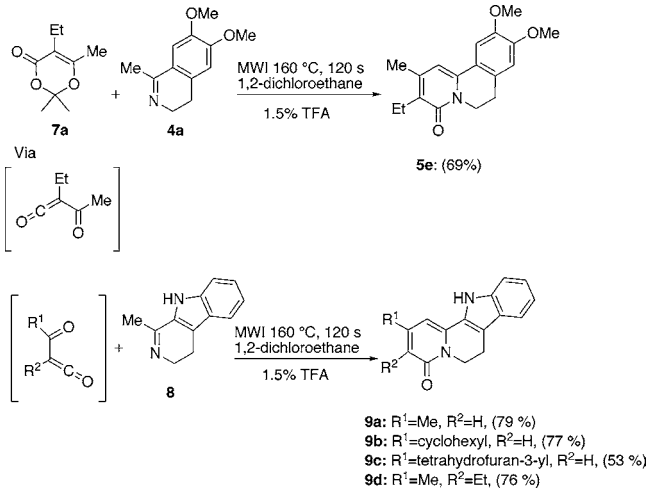
Figure 3. Conversion of isolated 1,3-oxazine-4-one **6** to 2-pyridone **5a** and the 3,4-dihydroisoquinoline **4a**.

the formation of 2-pyridone was clearly favored by acidic conditions (Table 2, entries 1 and 4). Neutral conditions resulted in more complex product mixtures, but both 2-pyridone **5a** and 1,3-oxazine-4-one **6** were observed by NMR analysis of the crude mixtures (Table 1, entries 2 and 5). 1,3-Oxazine-4-ones are known products in the reaction between imines and acyl-ketenes[16] and are believed to be formed via a [4+2] cycloaddition.[17] Basic conditions favored the formation of the 1,3-oxazine-4-one **6**, and by using conventional heating, it was formed almost exclusively resulting in an isolated yield of 87% (Table 2, entry 3).

We theorized that one role of the acid could be to convert preformed 1,3-oxazine-4-one **6** to the more acid-stable dehydrated 2-pyridone **5**. This was confirmed when pure **6** was subjected to MWI at 160 °C for 120 s with 1.5% (v/v) TFA in 1,2-dichloroethane. 1,3-Oxazine-4-one **6** was thus converted to a mixture of the 2-pyridone **5a** and the 3,4-dihydroisoquinoline **4a** in a 2:3 ratio (Figure 3). In summary, the role of the acid is not only to facilitate the dehydration step in the formation of the 2-pyridone framework, but also to provide a possibility to convert formed 1,3-oxazine-4-one **6** to 2-pyridone **5a**.

So far, acyl Meldrum's acids **1** have been used as an acyl-ketene source, but there are several other ways to generate acyl-ketenes.[18] We were now interested in exploring the possibility to further widen the scope of the reaction by using disubstituted acyl-ketenes and thereby obtaining 2-pyridones with a different substitution pattern. 5,6-Disubstituted-1,3-dioxine-4-ones **7** are a well-known acyl-ketene source that can be used to generate disubstituted acyl-ketenes, and they are readily available from β-ketoacids.[19] Thus, 5,6-disubstituted-1,3-dioxine-4-one **7a** was prepared from methyl 2-ethylacetoacetate and then reacted with 3,4-dihydroisoquinoline **4a**. This resulted in 69% yield of the 2,3-substituted benzo[*a*]quinolizine-4-one **5e** (Scheme 1). To challenge the reaction further, unprotected 3,4-dihydroharmane **8**[20] was reacted with acyl-ketenes generated from both Meldrum's acid derivatives **1b**−**d** and 5,6-disubstituted-1,3-dioxine-4-one **7a.** This resulted in good to moderate yields of the fused tetracyclic 2-pyridones **9a**−**d** (Scheme 1).

Scheme 1



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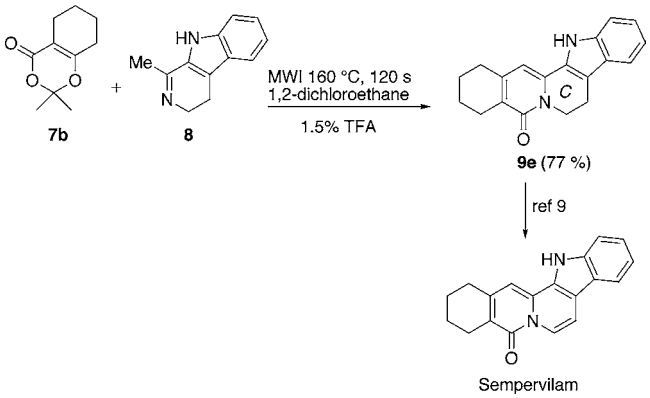
(20) Compound **8** was prepared via a Bischler−Napieralski reaction; see Supporting Information.

This tetracyclic ring system is also the basic structural core of several different indole alkaloids. Recently, Kogure et al. isolated a new indole alkaloid named sempervilam (Figure 2).[9] They also described a synthetic route starting from 3,4-dihydroharman, which was converted to dihydrosempervilam **9e** in 23% over three steps. Aromatization of the C-ring then yielded the desired alkaloid. Knowing that 3,4-dihydroharman **8** worked well in the acyl-ketene imine cyclocondensation for the preparation of the tetracyclic compounds **9a**−**d**, we aimed for a direct approach to the analogous pentacyclic dihydrosempervilam **9e**. The precursor to the desired cyclic α-oxoketene, 5,6-disubstituted-1,3-dioxine-4-one **7b**, was easily prepared according to a published procedure.[19] Dihydrosempervilam **9e** was then obtained in 56% yield by reacting **7b** with 3,4-dihydroharman **8** under MWI for 5 min. By simply increasing the reaction time to 23 min and adding the acyl-ketene source **7b** portionwise, this could be improved to 77% (Scheme 2). This simple short procedure to dihydrosempervilam clearly demonstrates the efficiency of this method as a route to multi ring-fused 2-pyridones.

In conclusion, we have reported a short, fast, and simple pathway to substituted multi ring-fused 2-pyridones **5a**−**e** and **9a**−**e**, via an acyl-ketene imine cyclocondensation. Different conditions were investigated, and the use of TFA instead of solutions containing dry HCl(g) proved to be more efficient and practical. The methodology worked well with different sources of acyl-ketenes and with different types of ring-fused imines, thus providing an excellent platform for future library synthesis of various 2-pyridone-containing heterocycles. In addition, by switching to basic conditions, the 1,3-oxazine-4-one **6** was selectively obtained in a high yield. Further investigations regarding the scope and limitations of the synthesis of 2-pyridones and 1,3-oxazinones via acyl-ketenes and imines are ongoing in our research group.

Scheme 2



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Supporting Information Available: Experimental procedures and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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