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Stereoselctive Formation of β-Lactams with Acyl Ketenes Generated from 5-Acyl-Meldrum's Acids.

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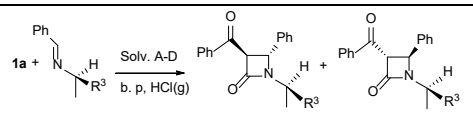
ACYL KETENES FORMED DURING THERMAL DECOMPOSITIONS OF 5-ACYL-2,2-DIMETHYL-1,3-DIOXA-4,6-DIONES UNDERGO STEREOSELECTIVE [2+2] CYCLOADDITION TO CHIRAL ALDIMINES. WE REPORT THE FIRST EXAMPLE OF OPTICALLY ACTIVE 3-ACYL-B-LACTAMS FORMATION FROM MELDRUM'S ACID DERIVATIVES.

The formation of the 2-azetidone system is an ongoing task in organic synthesis. Since the first preparation of β-lactam by Staudinger in 1903 based on [2+2] cycloaddition, many new methods for the formation of these valuable target molecules have been developed. These methods are based on various approaches such as: radical cyclization,[1] dehydration of β-amino acids,[2] Rh-catalyzed insertion of carbene into a C-H bond,[3] ester enolate-imine cyclocondensation[4] or malonate activated cyclization.[5] Nevertheless, the classical [2+2] cycloaddition of ketenes to imines is still the method of choice in many cases.[6] Usually these methods need an activation of carboxylic acids for ketenes generation; the most popular are acid chlorides,[7] Mukaiyama reagent[8] and carbonyldiimidazole.[9]
In 1980 Watanabe[10] and his co-workers proposed an alternative method for the generation of ketenes in the synthesis of 2-azetidones. This approach was based on the thermal decomposition of 5-acyl-2,2-dimethyl-1,3-dioxa-4,6-diones as a convenient source of ketenes[11]. In 2010 we successfully adopted this approach for the preparation of 3-carbamoyl-2-azetidones.[12] In both cases, the azetidones were obtained as a racemic mixture of two trans diastereoisomers. To the best of our knowledge, there have been no reports of any successfully stereocontrolled preparation of 2-azetidones using derivative of Meldrum's acid as a source of ketenes[113], in contrast to a situation where classical methods have been used to generate the ketenes. However, in 2005 Almqvist and his co-workers published a paper describing the stereoselective reaction of 5-acyl Meldrum's acid with 2-thiazolines, which according to the authors should lead to the synthesis of optically active β-lactams. Nevertheless, later insightful structure elucidation revealed incorrect structure assignment: the obtained product turned out a six-membered ring instead of a four-membered ring.[16]
In this paper, we would like to present the first example of stereoselective formation of 2-azetidone from 5-acyl Meldrum's acid as a ketene source and chiral imines. As a source of asymmetric induction we have used chiral imines, which were easily formed from commercially available optically pure amines: (R)-(+)-1-phenylethylamine, (R)-(+)1-(1-naphthyl)ethylamine, (R)-(+)1-(2-naphthyl)ethylamine or racemic sec-butylamine.
The first experiment was performed between 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-dione **1a** and (*R*)-*N*-benzylidene-1-phenylethylamine **2aa** in boiling DCE saturated with gaseous HCl (entry 2, Table 1). After the reaction workup, we isolated a mixture of two diastereoisomers.

Table 1. Acylketenes [2+2] cycloaddition to chiral imines - optimization of reaction variables.



2aa, ab 3aaa, aab 4aaa, aab

Entry	R^3	Solv.[a]	Time (min)	Temp (°C)	Ratio **1a**:**2**	Yield **3**+**4**
1	Ph	A	45	110	1:1	17
2	Ph	B	105	84	2:3	15
3	Ph	A	30	110	1:1	18
4	Ph	A	30	110	3:2	19
5	Ph	A	30	110	2:3	22[b]
6	Ph	C	15	131	2:3	25
7	Et	C	15	131	2:3	32
8	Et	A	30	110	2:3	25
9	Et	C	15	131	2:1	29
10	Et	C	15	131	1:1	28
11	Et	C	15	131	1:5	29
12	Et	C	24h	60	1:2	26
13	Et	D	120	100	1:2	12

a) Solvent: A = toluene, B = DCE, C = chlorobenzene, D = nitromethane, b) 22% of 2,6-diphenyl-3-(1-phenylethyl)-2H-1,3-oxazin-4(3H)-one was isolated.

(3S,4S)-3-benzoyl-1-((R)-1-phenylethyl)-4-(p-tolyl)azetidin-2-one and (3R,4R)-3-benzoyl-1-((R)-1-phenylethyl)-4-(p-tolyl)azetidin-2-one **3aaa** and **4aaa** with only 15% isolated yields. The most important variable in the case of our reaction is the type of solvent and its boiling range, which has a direct influence on the rate and reactivity of generated ketenes. We have observed that increasing the temperature of the process resulted in slightly higher yields of 2-azetidones with the maximum at 131°C for chlorobenzene as a

solvent (Table 1). Chlorobenzene has one advantage over hydrocarbons with a similar boiling point: a higher dipole moment, which allows iminium salt to remain dissolved during thermolysis. The second variable we tested was the reagents ratio. Experiments with (*R*)-*N*-benzylidene-1-phenylethylamine as well as with racemic *N*-benzylidenebutan-2-amine demonstrated that higher yields of 2-azetidones are obtained when 1.5 eq of imine is used in boiling chlorobenzene.

Despite optimization, yields for 2-azetidones formed from 5-[hydroxy(phenyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-dione did not exceed 32%. It has to be added that during the reaction, we observed the formation of a significant amount of polar tar, which was separated during flash chromatography. Additionally, in all reactions the formation of 2H-1,3-oxazin-4(3H)-ones **5** (a six-membered products of competitive [4+2] cycloaddition reaction) was observed (Figure 1).

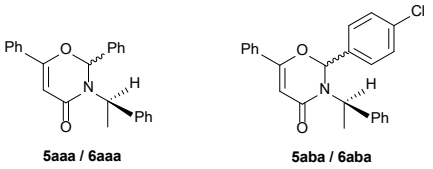
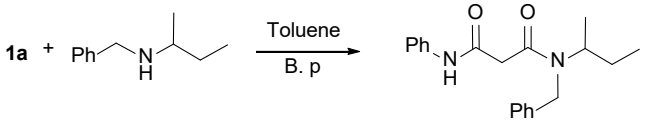


Figure 1

These undesired diastareoisomeric side products, **5aaa/6aaa** and **5aba/6aba,** were isolated and characterized in two experiments (entry 5, Table 1 and entry 4, Table 2). The competitive formation of [4+2] products during the reaction of ketenes formed from 5-acyl Meldrum's acid and imines had already been observed in similar models.[10, 17]

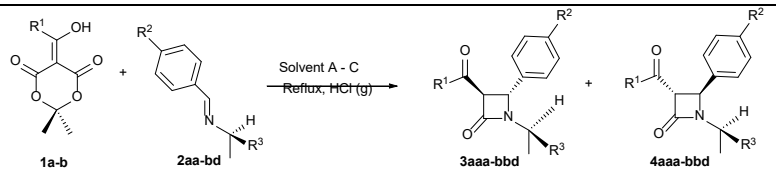
Our experiments were carried out with chiral imines, which typically contain benzyl moiety. However, this type of imines causes the largest problems during [2+2] cycloaddition to acylketenes and usually leads to low yields of β-lactams, as has previously been reported on achiral models.[10, 12]

To confirm our suppositions, we performed the reaction of **1a** with a reduced form of nucleophile containing the same substituents. In the reaction of racemic N-benzyl-sec-butylamine with **1a** in boiling toluene, we obtain N^1-benzyl-N^1-(sec-butyl)-N^3-phenylmalonamide with 82% yield and a visibly lower amount of tar (Scheme 1).



Scheme 1

Table 2. Stereoselective synthesis of 3-acyl-β-lactams with use of 5-[Hydroxy(phenyl/1-naphthylmethyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-diones



1a-b 2aa-bd 3aaa-bbd 4aaa-bbd

Entry	R^1	1	R^2	R^3	2	**3**, **4**	Solvent[a]	Ratio[b] **3**[c]:**4**[c]	Yield **3**+**4**
1	Ph	a	H	Ph	aa	aaa	A	77:23	20
2	Ph	a	H	Ph	aa	aaa	C	65:35	25
3	Ph	a	Cl	Ph	ba	aba	A	74:26	28
4[d]	Ph	a	Cl	Ph	ba	aba	C	64:36	28
5	Ph	a	H	1-naphthyl	ac	aac	A	58:42	24
6	Ph	a	H	1-naphthyl	ac	aac	C	63:37	26
7	Ph	a	H	2-naphthyl	ad	aad	A	68:32	18
8	Ph	a	H	2-naphthyl	ad	aad	C	53:47	25
9	1-Naphthylmethyl	b	H	Ph	aa	baa	C	52:48	42
10	1-Naphthylmethyl	b	H	Ph	aa	baa	A	67:33	44
11	1-Naphthylmethyl	b	H	Ph	aa	baa	B	67:33	35
12	1-Naphthylmethyl	b	Cl	Ph	ba	bba	A	66:34	49
13	1-Naphthylmethyl	b	H	1-naphthyl	ac	bac	A	61:39	37
14	1-Naphthylmethyl	b	H	2-naphthyl	ad	bad	A	62:38	48

[a] Solvent A = toluene, B = DCE, C = chlorobenzene, [b] diasteroisomeric ratio estimated based on the integration of the ^{1}H spectra [c] arbitrarily assigned configuration [d] 28% of 2-(4-chlorophenyl)-6-phenyl-3-(1-phenylethyl)-2H-1,3-oxazin-4(3H)-ones **5aba** and **6aba** were isolated

Based on the following, the reason for the low yield of 2-azetidones mainly seems to be the weak nucleophilicity of chiral hindered imines.

Applying optimal reaction conditions, we performed a series of experiments between 5-[hydroxy(phenyl/1-naphthylmethyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-diones **1a**,**b** and imines **2aa**, **2ad**.

The results are presented in Table 2. The achieved enantiomeric excesses may seem to be modest; but they, were obtained in processes running at 84°C or even higher temperatures. While similar processes described in the literature involving ketenes generation in the conventional manner, were carried out at temperatures as low as -78 °C, giving comparable enantiomeric excesses[18, 19, 20,21].

As one can see from the presented data, there is a noticeable difference in the reactivity of **1a** and **1b**. Naphthylacetyl **1b** derivative gave better yields of β-lactams but with worse diastereoisomeric ratio (entries 3 and 7, Table 2) whereas **1a** gave lower yields but with higher diastereoisomeric ratio (entries 1, 2 4-8, Table 1). These facts strongly suggest kinetic control of product distribution. In the case of less electrophilic benzoyl ketene the activation barrier for addition to imine is effectively overcome only for one distetreoisomer, whereas for more electrophilic 1-naphthylacetyl ketene energy barrier is significantly lower and feasible for both ways of the reaction, causing significantly lower stereoselectivity. Surprisingly, neither the presence of the more bulky naphthyl group in ketene components nor aldimine molecules led to higher diastereisomeric excess.

In the Staudinger ketene-imine [2+2] cycloaddition, cis and trans β-lactams could be formed, leading to the formation of four diasteroisomers in our case. NMR spectra of all prepared β-lactams showed coupling constants for H3, H4 in the range 2-2.5 Hz, which indicates the exclusive formation of only one pair of distereoisomers.

In summary, we have developed a new process for the stereoselective formation of 3-acyl-β-lactams using 5-[hydroxy(phenyl/1-naphthylmethyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-diones and chiral aldimines in pyrolytic condition. To the best of our knowledge, this study represents the first successful example of use acyl ketenes generated from Meldrum's acid derivatives in stereoselective [2+2] cycloaddition.

Experimental

‡ A typical procedure for the stereoselective preparation of 3-((Naphthalen-1-yl)acetyl)-4-phenyl-1-(1-phenylethyl)azetidin-2-one (**3baa**), (**4baa**): to a stirred mixture of 5-[hydroxy(1-naphthylmethyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-dione **1b** (1 mmol, 0.312 g) in dry toluene (10 ml), (*R*)-N-benzylidene-1-phenylethanamine **2aa** (1.5 mmol, 0.313 g) was added. The reaction mixture was cooled to 0°C and saturated with dry HCl over 20 min. The resulting mixture was stirred and heated to reflux for 0.5 h. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified with flash chromatography R_f 0.30 (EtOAc:Hex 1:3, SiO_2) gave one fraction, mixture of two diasteroisomers (0.44 mmol 0. 185 g, 44%, ratio **3baa** : **4baa** 67:33, yellow oil). Overall *de* = 34%. ^{1}H-NMR

(500 MHz, $CDCl_3$) δ: 7.93-7.83 (m, 2.33H, ArH), 7.78-7.75 (m, 1H, ArH), 7.56-7.46 (m, 2.67H, ArH), 7.45-7.38 (m, 1.67H, ArH), 7.34-7.22 (m, 6.66H, ArH), 7.17-7.14 (m, 2H, ArH), 7.06-7.04 (m, 0.67H, ArH), 4.94 (q, J = 7.3 Hz, 0.67H, CH_3*CH*), 4.79 (d, J = 2.0 Hz, 0.67H, H-4), 4.78 (d, J = 2.0 Hz, 0.33H, H-4), 4.48 (d, J = 16.1 Hz, 0.33H, CH_2), 4.33 (d, J = 16.1 Hz, 0.67H, CH_2), 4.36 (q, J = 7.3 Hz, 0.33H, CH_3*CH*), 4.28 (d, J = 16.1 Hz, 0.33H, CH_2), 4.25 (d, J = 16.1 Hz, 0.67H, CH_2), 4.19 (d, J = 2.0 Hz, 0.67H, H-3), 4.17 (d, J = 2.0 Hz, 0.33H, H-3), 1.80 (d, J = 7.3 Hz, 0.99H, CH_3), 1.37 (d, J = 7.3 Hz, 2.01H, CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 199.8 (maj), 199.5 (min), 163.6, 140.8 (maj), 139.7 (min), 137.9 (min), 136.7 (maj) 134.1, 132.5 (maj), 132.4 (min), 129.9, 129.1, 129.0 (min), 128.9 (maj), 128.9 (maj), 128.8 (min), 128.5, 128.1 (min), 127.9 (maj), 127.4, 127.2, 127.1, 126.9, 126.8 (maj), 126.8 (min), 126.1 (maj), 126.1 (min), 125.8 (maj), 125.8 (min), 124.2, 69.5 (min), 69.4 (maj), 55.9 (min), 55.5 (maj), 55.1 (maj), 53.5 (min), 48.1 (maj), 48.0 (min), 20.4 (maj), 19.4 (min); HRMS (ESI+): m/z calcd for $C_{29}H_{25}NO_2Na$ $[M+Na]^+$ 442.1783, found. 442.1786.

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