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Base-switched annuloselectivity in the reactions of ethyl malonyl chloride and imines

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The base-switched annuloselectivity, namely [2+2] and [2+2+2] selectivitiy, in the reactions of ethyl malonyl chloride and imines is successfully realized. In the presence of the weak nucleophilic base 2-chloropyridine, the reactions deliver ethyl *trans*-β-lactam-3-carboxylates as the exclusive [2+2] products in up to 93% yields; while with the strong nucleophilic *N*-methylimidazole as base, the reactions give rise to 2,3-dihydro-1,3-oxazin-4-one derivatives as the sole products in up to 99% yields via the formal [2+2+2] cycloaddition involving one molecule of imines and two molecules of the ketene generated from malonyl chloride. Notably, ethyl *trans*-β-lactam-3-carboxylates were first synthesized directly from the reactions of ethyl malonyl chloride and imines. Mechanistic discussions reveal that the annuloselectivity is controlled by the nucleophilicity of organic bases.

Introduction

The Staudinger reaction, namely [2+2] cycloaddition between ketenes and imines, has proven to be one of the most powerful strategies in constructing the β-lactam backbone, which acts as a key structural motif in a variety of antibiotics.[1] Since first discovered by Staudinger in 1907,[2] extensive and intensive studies have been directed to this useful reaction.[3] However, experimental results revealed that the reactions between ketenes and imines do not always give β-lactams. For example, when using alkanoyl chlorides as substrates, Maujean's,[4] Sohar's,[5] Arjona's,[6] and our groups[7] independently encountered the formation of 2,3-dihydro-1,3-oxazin-4-one derivatives, the formal [2+2+2] products incorporating two molecules of ketenes and one molecule of imines, as byproducts. In other cases with diazomethylketones as ketene precursors, both Podlech's [8] and our groups [9] discovered the existence of another formal [2+2+2]-type cycloaddition involving one molecule of ketenes and two molecules of cyclic imines. Our recent DFT studies on the annuloselectivity in the cycloaddition of ketenes and imines conclude that ketenes with weak electron-donor and conjugated monosubstituents prefer the former formal [2+2+2] cycloaddition of two molecules of ketenes and one molecule of imines, while less sterically bulky imines prefer the later formal [2+2+2] cycloaddition of one molecule of ketenes and two molecules of imines.[10] Although the computational studies theoretically revealed the nature of the annuloselectivity, the experimental control of the annuloselectivity still remains unsolved, and becomes one of the most topical issues in this field.

In our continuing interest on the Staudinger reaction,[9,11,12] we hope to experimentally control the annuloselectivity. Based on the conclusion of our DFT studies on the ketenes with conjugated monosubstituents (vide supra), we decided to choose alkyl malonyl chlorides as our model ketene precursors to react with different imines. Inspired by our recent work on the reactions of alkanesulfonyl chlorides with imines,[13] we envisage that the bases used in the reaction system might play a vital role in governing the fates of the reactions. Thus, we set off to explore the base effect on the reactions of ethyl malonyl chloride with imines, and surprisingly found out that the annuloselectivity, namely [2+2] annulation involving one molecule of the ketene and one molecule of imines and the [2+2+2] annulation involving two molecules of the ketene and one molecule of imines, can be successfully switched by using different bases. The base-switched annuloselectivity provides convenient and efficient methods to specificially synthesize two classes of important compounds, namely ethyl *trans*-β-lactam-3-carboxylates and 2,3-dihydron-1,3-oxazin-4-one derivatives as well.

β-Lactams with 3-electron-withdrawing substituents, especially alkyl β-lactam-3-carboxylates, which are crucial precursors for synthesis of bi/tricyclic β-lactam antibiotics, are important intermediates in organic and medicinal synthesis. Before this report, synthesis of β-lactams with 3-electron-withdrawing substituents from the corresponding acyl halides and imines was generally regarded unpractical.[14] Therefore, in previous reports, these β-lactams were generally accessed by the transition-metal-catalyzed carbene C-H insertion of 2-diazocarboxamides,[15] the Mn(III)-promoted radical 4-*exo*-*trig* cyclization of enamides due to narrow substrate scope,[16] and the acidic thermal rearrangement of spiro[cyclopropane-1,5'-isoxazolidine] derivatives.[17] The carbene-based protocol was plagued by the multi-step syntheses, poor regioselectivity, and low tolerance of the carbene-sensitive functionalities. The radical- and rearrangement-based protocols also suffer from multi-step synthesis, as well as low to moderate yields and limited applications. Recently, our group developed a sequence of Staudinger cycloaddition and desulfurization to

synthesize ethyl β-lactam-3-carboxylates in high yields, based on the Rh-catalyzed Wolff rearrangement of diazoacetate thioesters.[12] In the desulfurization step, the stereochemical outcome seemed to be not so satisfactory. Later Melman and coworkers reported that ethyl malonyl imidazole, generated *in situ* from monoethyl malonate and carbonyldiimidazole (CDI), reacted with *N*-benzylideneaniline to give the corresponding ethyl *trans*-β-lactam-3-carboxylates in good yields.[18a] However, this method is only limited to *N*-aryl imines. Very recently, Ungvary and coworkers reported the one-pot synthesis of ethyl *trans*-β-lactam-3-carboxylates, applying the $Co_2(CO)_8$-catalyzed carbonylation of ethyl diazoacetate to generate ketenes.[18b] Requiring harsh conditions, high CO pressure, and toxic and explosive ethyl diazoacetate, the method seems not a convenient one. Compared with the reported methods above, our control of the annuloselectivity provides a convenient and efficient route for the synthesis of ethyl *trans*-β-lactam-3-carboxylates, especially for the *N*-alkyl derivatives, from readily available ethyl malonyl chloride and imines under very mild conditions, with the yields comparable to, or even better than those reported.

The 2,3-dihydro-1,3-oxazin-4-one heterocycles are prevalent subunits in natural products.[19] Although these structures were frequently encountered in published reports,[20] they always emerged as undesired and unexpected byproducts. Only limited accesses targeted to their synthesis were developed, for example, the α-formylation of amides followed by cyclization of aldehydes,[21] and the Norrish-Yang reaction of α-mesyloxy-β-keto amides.[22] In addition, they have been synthesized *via* cycloadditions of imines and α-acylketenes generated from α-dizao-β-diketones.[23] We can easily prepare this kind of heterocycles from readily available ethyl malonyl chloride and imines with *N*-methylimidazole as base. Herein, by control of the annuloselectivity we can easily prepare these two classes of compounds in only one step by simply mixing readily available ethyl malonyl chloride and imines with different bases.

Results and Discussion

Provided that most of the syntheses of β-sultams from sulfonyl chlorides and imines share such a feature that one equivalent of sulfonyl chlorides are reacted with two equivalents of imines without any other bases,[24] we started our optimization by simply mixing ethyl malonyl chloride (**1**) and *N*-benzylidenebenzylamine (**2a**). After stirring at room temperature for 48 h, the crude mixture was directly submitted to ^{1}H NMR analysis. Gratifyingly, the desired β-lactam product ethyl *trans*-1,4-diphenylazetidin-2-one-3-carboxylate (**3a**) was detected in 30% yield (Table 1, entry 1). The *trans*-configuration was decided by the coupling constants of the protons on the C3 and C4 positions (J = 4-6 Hz for *cis*-isomers, J = 0-3 Hz for *trans*-isomers, generally). This encouraging result promoted us to further optimize the reaction conditions. Shortening the time to 24 h or 12 h had slight influence on the yield of **3a** (Table 1, entries 2 and 3). Solvent screening revealed that THF was the best choice (Table 1, entries 4-7). Increasing the amount of **1** to 1.2 equivalents and **2a** to 2.2 equivalents gave better yield of 36% (Table 1, entry 8). In these optimization reactions, the imine **2a** acted as not only nucleophile but also weak base. Thus, we wondered whether the reaction could still take place if we use other weak bases instead of the imine **2a**. As expected, the β-lactam **3a** was obtained in better 43% yield in the presence of pyridine (Table 1, entry 9). Decreasing the reaction temperature to 0 ^{o}C and shortening the time to less than 6 h resulted in low yields (Table 1, entries 10-12). Other bases were also screened. In the presence of imidazole, pyrrole, K_2CO_3, P. S. [proton sponge, 1,8-bis(dimethylamino)naphthalene], and 2-fluoropyridine, **3a** was obtained exclusively in 17%, 35%, 27%, 28%, and 45% yields, respectively (Table 1, entries 13-17). The best yield of **3a** was obtained in 50% when 2-chloropyridine was employed (Table 1, entry 18). Further optimization by doubling the amount of the acyl chloride **1** and 2-chloropyridine and changing the addition sequence gave rise to satisfactory 70% yield (Table 1, entries 19-21). With stronger bases such as 2,6-lutidine, quinoline, DMAP, DABCO, and *N*-methylimidazole, the β-lactam **3a** was obtained in low yields. However, beyond our expectation, the formal [2+2+2] product **4a** involving two molecules of ethoxycarbonyl ketene and one molecule of the imine **2a** was detected in 9%, 7%, 35%, 38%, and 44% yields, respectively (Table 1, entries 22-26). By adjusting the equivalent of the acyl chloride **1** and *N*-methylimidazole, the best yield of **4a** was obtained in 95% yield (Table 1, entrie 27-28). We also repeated our previous work using Et_3N as a base, and obtained **3a** and **4a** in 12% and 9% yields, respectively. Finally, we used 3 equivalents of 2-chloropyridine and the acyl chloride **1** to react with one equivalent of imine **2a**, and the yield of [2+2] product was increased slightly to 74%, while no formal [2+2+2] product was detected by ^{1}H NMR analyses. The results in Table 1 indicate that the annuloselectivity is not dependent on the ratios of the acyl chloride to imine, but on the basicity or nucleophilicity of bases.

In Table 1, the yields range from a low of 9% to a high of 95%. What are the fates of the other starting materials in the reactions? In most cases, large amount of imine **2a** was not reacted. It was hydrolyzed into benzaldehyde and benzylamine during the workup process. As for the acyl chloride **1**, we supposed it was converted into ethoxycarbonylketene completely in the presence of bases because the α-proton of ethyl malonyl chloride is more acidic than that of other acyl chlorides, such as alkanoyl chlorides, arylacetyl chlorides, and haloacetyl chlorides, which can be converted to the corresponding ketenes in the presence of pyridine or triethylamine. The remaining unreacted ketene or its dimer was hydrolyzed during the workup process.

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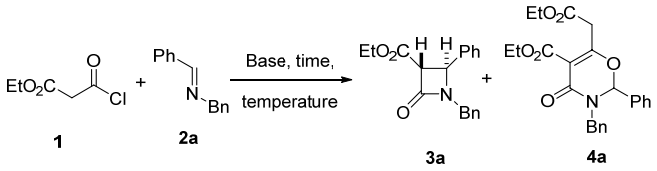
Table 1 Optimization of Reaction Conditions.[a]



1 2a 3a 4a

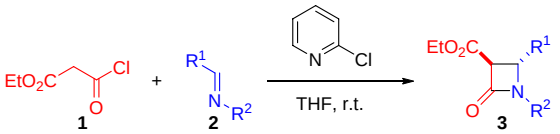
Entry	**1** (equiv)	**2a** (equiv)	Base (equiv)	Solvent	Temp.(°C)	Time (h)	Yields (%)[b]	
							3a	**4a**
1	1.0	1.0	**2a** (1.0)	THF	r.t.	48	30	0
2	1.0	1.0	**2a** (1.0)	THF	r.t.	24	24	0
3	1.0	1.0	**2a** (1.0)	THF	r.t.	12	28	0
4	1.0	1.0	**2a** (1.0)	$PhCH_3$	r.t.	12	27	0
5	1.0	1.0	**2a** (1.0)	CH_2Cl_2	r.t.	12	9	0
6	1.0	1.0	**2a** (1.0)	MeCN	r.t.	12	12	0
7	1.0	1.0	**2a** (1.0)	Et_2O	r.t.	12	12	0
8	1.2	1.0	**2a** (1.2)	THF	r.t.	12	36	0
9	1.2	1.0	Pyridine (1.2)	THF	r.t.	12	43	0
10	1.2	1.0	Py. (1.2)	THF	0	1	20	0
11	1.2	1.0	Py.(1.2)	THF	0	3	24	0
12	1.2	1.0	Py.(1.2)	THF	0	6	18	0
13	1.2	1.0	Imidazole (1.2)	THF	r.t.	12	17	0
14	1.2	1.0	Pyrrole (1.2)	THF	r.t.	12	35	0
15	1.2	1.0	K_2CO_3	THF	r.t.	12	27	0
16	1.2	1.0	P.S. (1.2)	THF	r.t.	12	28	0
17	1.2	1.0	2-FPy.(1.2)	THF	r.t.	12	45	0
18	1.2	1.0	2-ClPy. (1.2)	THF	r.t.	12	50	0
19	**2.4**	**1.0**	**2-ClPy. (2.4)**	**THF**	r.t.	**12**	**70**	**0**
20[c]	**2.4**	**1.0**	**2-ClPy. (2.4)**	**THF**	r.t.	**12**	**68**	**0**
21[d]	2.4	1.0	2-ClPy. (2.4)	THF	r.t.	12	59	0
22	1.2	1.0	2,6-lutidine (1.2)	THF	r.t.	12	10	9
23	1.2	1.0	quinoline (1.2)	THF	r.t.	12	7	7
24	1.2	1.0	DMAP (1.2)	THF	r.t.	12	3	35
25	1.2	1.0	DABCO (1.2)	THF	r.t.	12	2	38
26	1.2	1.0	*N*-methyl imi. (1.2)	THF	r.t.	12	2	44
27	2.4	1.0	*N*-methyl imi. (2.4)	THF	r.t.	12	2	66
28	**3.6**	**1.0**	***N*-methyl imi. (3.6)**	**THF**	**r.t.**	**12**	**0**	**95**
29	1.2	1.0	Et_3N (1.2)	THF	r.t.	12	12	9
30[e]	**3.6**	**1.0**	**2-ClPy. (3.6)**	**THF**	**r.t.**	**12**	**74**	**0**

[a]All the reactions, except for those otherwise noted, were conducted in the following addition sequence: to a solution of imine **2a** (91 mg, 0.5 mmol) and base in a solvent was added a solution of ethyl malonyl chloride (**1**) in the same solvent. [b]Yields were determined by ^{1}H NMR with dimethyl malonate as an internal standard. [c]A solution of imine **2a** (91 mg, 0.5 mmol) and base in THF was added to a solution of the acyl chloride **1** in THF. [d]To a solution of imine **2a** (91 mg, 0.5 mmol) in THF was added a solution of the acyl chloride **1** in THF. After 2 h, a solution of 2-chloropyridine in THF was added. [e]Mesitylene was used as an internal standard.

With the optimal conditions for the synthesis of ethyl *trans*-β-lactam-3-carboxylate (**3a**), we decided to test this method to

prepare such an important class of compounds. The results are presented in Table 2. In order to get more precise results to analyze the substituent effect on the [2+2] cycloaddition, the yields were obtained from ^{1}H NMR analysis of the crude reaction mixtures. With the more sterically bulky *tert*-butyl and less sterically bulky allyl groups attached at the nitrogen atom of imines **2b** and **2c**, the desired [2+2] cycloadducts **3b** and **3c** can still be obtained in 74% and 58% yields, respectively (Table 2, entries 2 and 3). However, the presence of the methyl group at the *N*-position of imine **2d** sharply decreased the yield of **3d** to 24% (Table 1, entry 4). This result is in accordance with our previous DFT calculations that the less sterically bulky imines prefer the formal [2+2+2] cycloaddition to the [2+2] cycloaddition (vide supra).[10] Further studies on the *C*-substituent effect on this reaction were conducted with *N*-cyclohexyl imines **2e** and **2f**, and the corresponding desired β-lactams **3e** and **3f** were obtained in low 28% and excellent 93% yields, respectively, indicating that the *C*-electron-withdrawing group facilitate the [2+2] cycloadditions (Table 1, entries 5 and 6). This had been further demonstrated by the reactions with imines **2g-i** (Table 2, entries 7-9). Comparison between the reactions of the acyl chloride **1** with imines **2h** and **2i** additionally indicated that the more steric the *N*-substituents are, the higher yields can be obtained (Table 2, Entries 1-4, 8, and 9). However, when the electron-donating *N*-alkyl group was replaced with the electron-accepting *N*-aryl group, the yield of product **3j** decreased sharply to 26% (Table 2, entry 10). The reaction of α,β-unsaturated *N*-aryl imine **2k** did not give any β-lactam product possibly because the substituent styryl group can stabilize the zwitterionic intermediate generated from the acyl chloride **1** and imine **2k** due to the existence of the conjugative effect (see intermediate B in scheme 1) (Table 2, entry 11).

Table 2 2-Chloropyridine-induced [2+2] cycloaddition for synthesis of ethyl *trans*-β-lactam-3-carboxylates

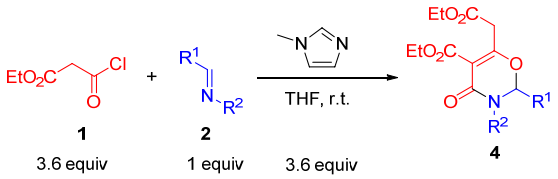


Entry	R^1	R^2	Imine	Product	Yield[a]
1	Ph	Bn	**2a**	**3a**	70 (60)
2	Ph	*t*-Bu	**2b**	**3b**	74 (69)
3	Ph	Allyl	**2c**	**3c**	58 (49)
4	Ph	Me	**2d**	**3d**	24 (10)
5	4-$MeOC_6H_4$	Cy	**2e**	**3e**	28 (20)
6	4-$O_2NC_6H_4$	Cy	**2f**	**3f**	93 (86)
7	4-$O_2NC_6H_4$	Bn	**2g**	**3g**	93 (80)
8	4-$O_2NC_6H_4$	*n*-Pr	**2h**	**3h**	59 (58)
9	4-$O_2NC_6H_4$	*i*-Pr	**2i**	**3i**	88 (81)
10	Ph	Ph	**2j**	**3j**	26 (18)
11	PhCH=CH	4-$MeOC_6H_4$	**2k**	**3k**	0

[a] The yields outside the parenthesis were determined by ^{1}H NMR with dimethyl malonate as an internal standard, while those in the parenthesis were isolated yields.

The *N*-methylimidazole-induced formal [2+2+2] cycloadditions were also intensively studied, and 2,3-dihydro-1,3-oxazin-4-one heterocycles were conveniently obtained. The results are presented in Table 3. In the separation process, we found that these products were inclined to decompose in the silica gel chromotography; thus, the accurate yields were obtained from the ^{1}H NMR analysis of the crude reaction mixtures with dimethyl malonate as an internal standard. In most cases for *N*-alkyl imines **2a,c,m,n,p**, the desired products **4a,c,m,n,p** were obtained in excellent yields varying from 95% to 99% (Table 3, entries 1, 3, 7-8, and 10). However, for the imines **2b** and **2o** with sterically bulky *N*-substituent *tert*-butyl group or strong electron-withdrawing *C*-substituent 4-nitrophenyl group, the yields decreased sharply to 7% (Table 3, entries 2) and 49% (Table 3, entry 9), respectively, mainly because of the decreased nucleophilicity of the imines **2b** and **2o**. For imines **2d** and **2q**, the desired products **4d** and **4q** were obtained in moderate to good yields of 61% and 79%, respectively (Table 3, entries 4 and 11). We also found that the *N*-aryl imines **2j** and **2l** were resistant to the formal [2+2+2] cycloadditions, giving no desired products at all, as determined by ^{1}H NMR analysis of the crude reaction mixture (Table 3, entries 5 and 6). We assumed that the failure was blamed on the weak nucleophilicity of the imines **2j** and **2l**.

Table 3 *N*-Methylimidazole-induced formal [2+2+2] cycloaddition



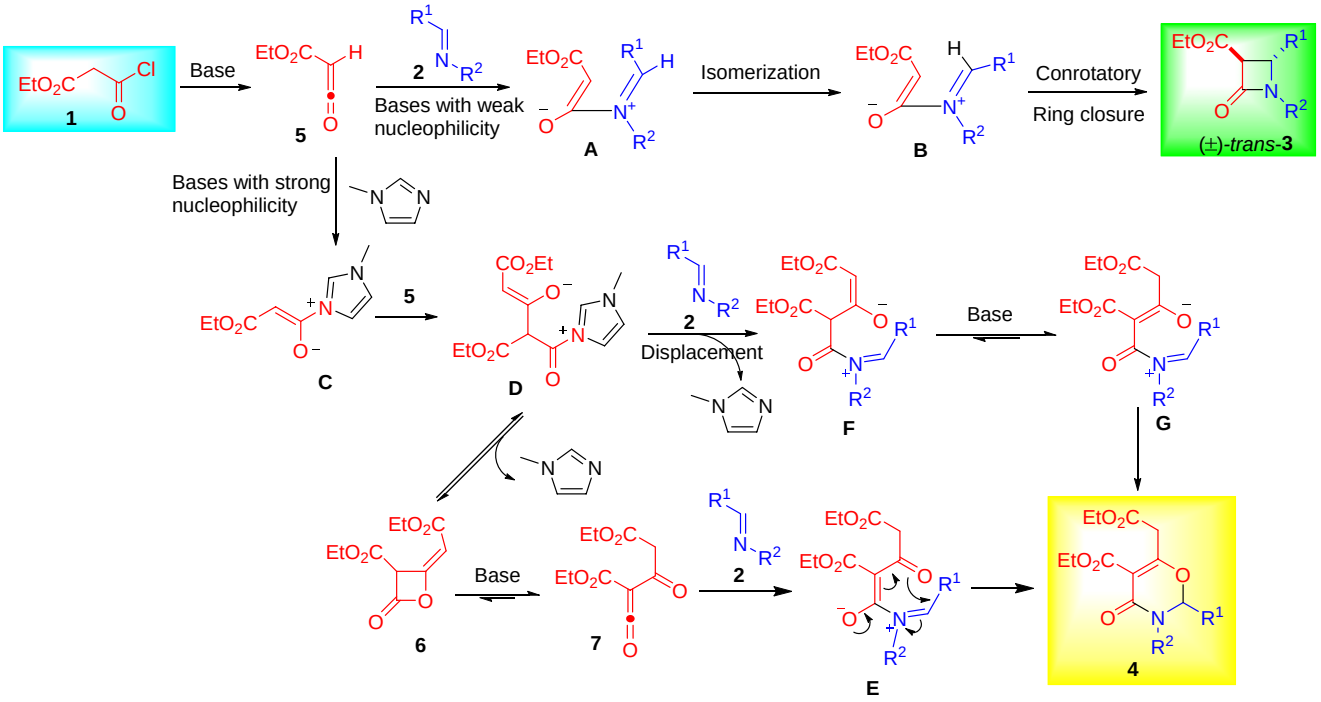
Entry	R^1	R^2	Imine **2**	Product **4**	Yield (%)[a]
1	Ph	Bn	**2a**	**4a**	95 (63)
2	Ph	*t*-Bu	**2b**	**4b**	7 (5)
3	Ph	Allyl	**2c**	**4c**	96 (60)
4	Ph	Me	**2d**	**4d**	61 (50)
5	Ph	Ph	**2j**	**4j**	0
6	Ph	Nathaphen-1-yl	**2l**	**4l**	0
7	4-$MeOC_6H_4$	Bn	**2m**	**4m**	99 (52)
8	4-$MeOC_6H_4$	*n*-Pr	**2n**	**4n**	99 (55)
9	4-$O_2NC_6H_4$	Me	**2o**	**4o**	49 (24)
10	4-$MeOC_6H_4$	Me	**2p**	**4p**	98 (67)
11	4-$MeSC_6H_4$	*i*-Pr	**2q**	**4q**	79 (50)

[a] The yields outside the parenthesis were determined by ^{1}H NMR with dimethyl malonate as internal standard, while those in the parenthesis were isolated yields.

To explain the base-switched annuloselectivity, we proposed the mechanism shown in Scheme 1. In the presence of each of bases, ethyl malonyl chloride (**1**) generates ethoxycarbonylketene (**5**). When weak nucleophilic bases, such as 2-chloropyridine, pyridine, and so on, are applied, the ketene **5** reacts with imines **2** to form intermediates **A**, which isomerize over their iminium

moiety to generate more stable intermediates **B** due to the existence of the electron-withdrawing ester group on the ketene moiety. The ester group decreases the ring closure rate of intermediates **A**.[9b,11a] The intermediates **B** subsequently undergo conrotatory ring closure to afford *trans*-β-lactams **3**.[11,12,25] While the strong nucleophilic bases, for example *N*-methylimidazole, are used. The strong nucleophilic bases catalyze the ketene **5** to dimerize to β-lactone **6**[26] via intermediates **C**[27] and **D**. The resultant β-lactone **6** subsequently isomerizes into α-oxoketene **7** by the treatment with base *N*-methylimidazole. The nucleophilic attack of the imines **2** to α-oxoketene **7** gives rise to zwitterionic intermediates **E**, which readily evolve into the desired products **4** through an intramolecular nucleophilic addition or nucleophilic ring closure.[28] Alternatively, another catalytic mechanism is also plausible. Displacement of active intermediates **D** with imines **2** produces zwitterionic intermediates **F**, which then isomerize to zwitterionic intermediates **G** in the presence of bases. The intermediates **G** undergo an intramolecular addition to deliver the final products **4** as well.

The above methanistic discusions reveal that it is not the basicity of the bases in Table 1 but the nucleophilicity of the bases that controls the annuloselectivity. The control of annuloselectivity is in fact the control of the fates of ketene **5**. For the bases with weak nucleophilicity, the ketene directly reacts with imines **2** to give [2+2] products. However, for the bases with strong nucleophilicity, the ketene first dimerizes under the catalysis of strong nucleophilic bases, and then reacts with imines **2** to yield [2+2+2] products. The pKa values of 2-chloropyridine and *N*-methylimidazole are 0.49[29a] (or 6.3)[29b] and 7.45,[29c] while the MCA (Methyl Cation Affinity) values of 2-chloropyridine and *N*-methylimidazole are less than 518.7[30] and 550.0 kJ/mol,[29d] respectively. Comparison of the pKa values and MCA values draw such a conclusion that *N*-methylimidazole is more basic and nucleophilic than 2-chloropyridine. The data support our rationale on the base nucleophilicity controlled annuloseletivity.



Scheme 1. Base-nucleophilicity-switched annuloseletivity in the reactions of ethyl malnonyl chloride and imines.

Conclusion

In conclusion, we successfully achieved the base-switched annuloselectivity of the reactions of ethyl malonyl chloride and imines, providing convenient and practical synthetic approaches to ethyl *trans*-β-lactam-3-carboxylates and 2,3-dihydro-1,3-oxazin-4-one heterocycles with annulospecificity from readily available substrates under very mild conditions. In the presence of the weak nucleophilic base 2-chloropyridine, the reactions deliver β-lactams as the exclusive [2+2] products in up to 93% yield, while in the presence of the strong nucleophilic base *N*-methylimidazole, the formal [2+2+2] cycloaddition involving two molecules of the ketene and one molecule of imines predominates, giving 2,3-dihydro-1,3-oxazin-4-one derivatives as the sole products in up to 99% yields. Additionally, the detailed mechanisms for the two different annulospecific pathways are also discussed, indicating that the annuloselectivity is actually contolled by the nucleophilicity of the organic bases. Another key conclusion from our work is that, contrary to previous reports,[12,15] acyl chlorides with electron withdrawing groups are in fact viable precursors for the synthesis of β-lactams when a suitable base is applied.

Experimental Section

General Information: Melting points (m.p.) were determined on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 400 NMR spectrometer at 400 MHz and 100 MHz, respectively, in $CDCl_3$ with TMS as the internal standard and chemical shifts were reported in ppm. IR spectra were taken on a Nicolet AVATAR 330 FT-IR spectrometer in dichloromethane (DCM). HRMS spectra were performed on a Brucker LC/MSD TOF mass spectrometer. Column chromatography was carried out on silica gel (200-300 mesh) with petroleum ether (PE, 60-90 ^{o}C) and ethyl acetate (EA) as eluent. All reactions were followed by thin-layer chromatography (TLC) where practical, using silica gel 60 F_{254} fluorescent treated silica gel plates, which were visualizedunder UV light (250 nm).

Preparation of Ethyl Malonyl Chloride (1):
To a 250 mL one-necked flask was added monoethyl malonate (14.67 g, 100 mmol, 90% content) and dry dichloromethane (150 mL). The flask was immersed into an ice-water bath, and oxally chloride (17.2 mL, 200 mmol) was added dropwise through a pressure-equalized addition funnel. Upon addition, the mixture was allowed to reflux for 3 h. Removal of the solvent and distillation at vacuum (42-44 ^{o}C, 2 mmHg) afforded ethyl malonyl chloride as a yellowish oil (10.43 g, 69%).

General Procedure for the Synthesis of β-Lactams 3: To a solution of imine **2** (0.5 mmol) and 2-chloropyridine (113 μL, 1.2 mmol) in dry THF (3 mL) was dropwise added a solution of ethyl malonyl chloride (**1**) (0.181 g, 1.2 mmol) in dry THF (2 mL) *via* a syringe during 3 min. Upon addition, the resultant mixture was allowed to stir at room temperature for 12 h. Then ether (15 mL) and brine (10 mL) was added sequentially. After washing, the organic phase was dried over Na_2SO_4. Removal of the solvent and purification on silica gel chromotography afforded the desired product **3**.

Ethyl *trans*-1-benzyl-4-phenylazetidin-2-one-3-carboxylate (3a)[12]
Colorless oil. 93 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.17 (m, 10H, ArH), 4.87 (d, J = 15.3 Hz, 1H in CH_2), 4.70 (d, J = 2.1 Hz, 1H, C*H*), 4.242 (q, J = 7.1, 1H in CH_2), 4.236 (q, J = 7.1, 1H in CH_2), 3.91 (d, J = 2.1 Hz, 1H, C*H*CO), 3.82 (d, J = 15.3 Hz, 1H in CH_2), 1.29 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 162.4, 136.0, 134.7, 129.1, 129.0, 128.7, 128.2, 127.8, 126.7, 63.5, 61.8, 57.0, 44.8, 14.1.

Ethyl *trans*-1-(*tert*-butyl)-4-phenylazetidin-2-one-3-carboxylate (3b)[12]
Colorless crystals，m.p. 91-94 °C; 95 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.32 (m, 5H, ArH), 4.85 (d, J = 2.0 Hz, 1H, CH), 4.234 (q, J = 7.2, 1H in CH_2), 4.225 (q, J = 7.2, 1H in CH_2), 3.69 (d, J = 2.0 Hz, 1H, CH), 1.29 (t, J = 7.2 Hz, 3H, CH_3), 1.27 (s, 9H, 3CH_3).

Ethyl *trans*-1-allyl-4-phenylazetidin-2-one-3-carboxylate (3c)
Colorless oil, 69 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.38 (m, 3H, ArH), 7.35–7.33 (m, 2H, ArH), 5.81–5.68 (m, 1H, CH), 5.25–5.20 (m, 1H, CH), 5.19 (s, 1H, CH), 4.89 (d, J = 2.2 Hz, 1H, CH), 4.28 (dq, J = 14.2, 7.2 Hz, 1H in CH_2), 4.28 (dq, J = 14.2, 7.2 Hz, 1H in CH_2), 3.90 (d, J = 2.2 Hz, 1H, CH), 3.45–3.36 (m, 2H, CH_2), 1.33 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 162.3, 136.2, 130.7, 129.1, 129.0, 126.7, 118.7, 63.4, 61.8, 57.2, 43.3, 14.1. IR (film) ν cm^{-1} 2984, 2927, 1773, 1731, 1457, 1369, 1327, 1276, 1223, 1196, 1018, 913, 871, 748, 700, 637. HRMS (ESI) calcd for $C_{15}H_{17}NNaO_3$ [M + Na^+] *m/z* 282.1101, found 282.1106.

Ethyl *trans*-1-methyl-4-phenylazetidin-2-one-3-carboxylate (3d)[19]
Colorless oil. 12 mg (10%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.33 (m, 5 H, ArH), 4.82 (d, J = 2.2 Hz, 1H, CH), 4.264 (q, J = 7.2, 1H in CH_2), 4.257 (q, J = 7.2, 1H in CH_2), 3.89 (d, J = 2.2 Hz, 1H, CH), 3.45 (s, 3H, NCH_3), 1.27 (t, J = 7.2 Hz, 3H, CH_3).

Ethyl *trans*-1-cyclohexyl-4-(4-methoxyphenyl)azetidin-2-one-3-carboxylate (3e)
Colorless oil. 35 mg (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2H, ArH), 6.91 (d, J = 8.7 Hz, 2H, ArH), 4.80 (d, J = 2.2 Hz, 1H, CH), 4.28–4.20 (m, 1H), 4.26–4.20 (m, 1H), 3.82 (s, 3H), 3.75 (d, J = 2.2 Hz, 1H), 1.77–1.70 (m, 2H), 1.65–1.51 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H, CH_3), 1.18–1.01 (m, 4H), 0.91–0.82 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 162.1, 160.0, 129.8, 128.0, 114.3, 62.9, 61.6, 56.0, 55.3, 53.1, 31.2, 30.5, 25.1, 25.0, 24.9, 14.1. IR (film) ν cm^{-1} 2931, 2857, 1761, 1737, 1700, 1670, 1683, 1651, 1613, 1515, 1456, 1367, 1306, 1249, 1195, 1180, 1035, 836. HRMS (ESI) calcd for $C_{19}H_{25}NNaO_4$ [M + H^+] *m/z* 354.1676, found 354.1679.

Ethyl *trans*-1-cyclohexyl-4-(4-nitrophenyl)azetidin-2-one-3-carboxylate (3f)
Colorless oil. 159 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 4.98 (d, J = 2.3 Hz, 1H), 4.262 (q, J = 7.1, 1H in CH_2), 4.259 (q, J = 7.1, 1H in CH_2), 3.77 (d, J = 2.3 Hz, 1H), 3.50 – 3.40 (m, 1H), 2.03 – 2.00 (m, 1H), 1.82 – 1.71 (m, 2H), 1.71 – 1.62 (m, 1H), 1.60 – 1.53 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.27 – 1.19 (m, 2H), 1.18 – 1.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 161.6, 148.3, 145.6, 127.6, 124.3, 62.9, 62.1, 55.3, 53.6, 31.3, 30.6, 25.0, 24.9, 24.8, 14.1. IR (film) ν cm^{-1} 2928, 2854, 1768, 1734, 1697, 1686, 1663, 1648, 1636, 1618, 1523, 1491, 1453, 1384, 1348, 1258, 1194, 1181, 1107, 1022, 854, 835. HRMS (ESI) calcd for $C_{18}H_{22}N_2NaO_5$ [M + Na^+] *m/z* 369.1421, found 369.1422.

Ethyl *trans*-1-benzyl-4-(4-nitrophenyl)azetidin-2-one-3-carboxylate (3g)
Yellowish oil, 151 mg (80%). ^{1}H NMR (400 MHz, CDCl3) δ 8.21 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.30 – 7.28 (m, 3H), 7.19 – 7.11 (m, 2H), 4.85 (d, J = 15.2 Hz, 1H), 4.82 (d, J = 1.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.95 (d, J = 15.2 Hz, 1H), 3.91 (d, J = 1.9 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 161.9, 148.2, 143.5, 134.0, 128.9, 128.4, 128.2, 127.6, 124.3, 63.5, 62.2, 56.2, 45.5, 14.1. IR (film) ν cm^{-1} 2984, 1772, 1731, 1607, 1523, 1497, 1348, 1223, 1193, 1015, 855, 748, 729, 699. HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_5$ [M + Na^+] *m/z* 377.1108, found 377.1109.

Ethyl *trans*-4-(4-nitrophenyl)-1-propylazetidin-2-one-3-carboxylate (3h)

Colorless crystals, m.p. 84-85 °C. 95 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.6 Hz, 2H, ArH), 7.54 (d, J = 8.6 Hz, 2H, ArH), 4.98 (d, J = 2.1 Hz, 1H, CH), 4.28 (q, J = 7.1 Hz, 2H, CH_2), 3.84 (d, J = 2.1 Hz, 1H, CH), 3.53–3.43 (m, 1H in CH_2), 2.91–2.84 (m, 1H in CH_2), 1.62–1.49 (m, 2H, CH_2), 1.32 (t, J = 7.1 Hz, 3H, CH_3), 0.94 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 161.9, 148.3, 144.0, 127.5, 124.4, 63.4, 62.1, 56.4, 43.1, 20.9, 14.0, 11.3. IR (film) ν cm^{-1} 2966, 2931, 2876, 1770, 1732, 1606, 1524, 1495, 1463, 1348, 1279, 1223, 1196, 1039, 1013, 854, 749, 670. HRMS (ESI) calcd for $C_{15}H_{18}N_2NaO_5$ [M + Na$^+$] m/z 329.1108, found 329.1110.

Ethyl *trans*-1-isopropyl-4-(4-nitrophenyl)azetidin-2-one-3-carboxylate (3i)

Colorless crystals, m.p. 102-104 °C. 124 mg (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.6 Hz, 2H, ArH), 7.60 (d, J = 8.6 Hz, 2H, ArH), 4.98 (d, J = 2.2 Hz, 1H, CH), 4.26 (q, J = 7.2 Hz, 2H, CH_2), 3.81 (heptet, J = 6.7 Hz, 1H, CH), 3.78 (d, J = 2.2 Hz, 1H, CH), 1.32 (d, J = 6.7 Hz, 3H, CH_3), 1.31 (t, J = 7.2 Hz, 3H, CH_3), 1.07 (d, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.6, 148.3, 145.5, 127.6, 124.3, 62.8, 62.1, 55.2, 46.1, 21.1, 20.3, 14.1. IR (film) ν cm^{-1} 2977, 2925, 1767, 1729, 1601, 1524, 1466, 1348, 1311, 1228, 1196, 1109, 1039, 1013, 856, 842, 700. HRMS (ESI) calcd for $C_{15}H_{19}N_2O_5$ [M + H$^+$] m/z 307.1288, found 307.1288.

Ethyl *trans*-1,4-diphenylazetidin-2-one-3-carboxylate (3j) [12]

Colorless oil. 27 mg (18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.27 (m, 10H, ArH), 5.33 (d, J = 2.4 Hz, 1H), 4.29 (q, J = 7.0 Hz, 2H), 3.97 (d, J = 2.4 Hz, 1H), 1.33 (t, J = 7.0 Hz, 3H).

General Procedure for the Synthesis of 2,3-Dihydro-1,3-oxazin-4-one Derivatives 4: To a solution of imine **2** (0.5 mmol) and *N*-methyl imidazole (193 mg, 1.8 mmol) in dry THF (3 mL) was dropwise added a solution of ethyl malonyl chloride (**1**) (271 mg, 1.8 mmol) in dry THF (2 mL) via a syringe during 3 min. Upon addition, the resultant mixture was allowed to stir at room temperature for 12 h. Then ether (15 mL) and brine (10 mL) was added sequentially. After washing, the organic phase was dried over Na_2SO_4. Removal of the solvent and purification on silica gel chromotography afforded the desired product **4**.

Ethyl 3-benzyl-6-(2-ethoxy-2-oxoethyl)-2-phenyl-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4a)

Colorless oil, yield 141 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40-7.10 (m, 10H), 6.17 (s, 1H), 5.26 (d, J = 15.4 Hz, 1H), 4.33 – 4.28 (m, 2H), 4.04 (dq, J = 10.8, 7.2 Hz, 1H), 3.92 (dq, J = 10.8, 7.2 Hz, 1H), 3.92 (d, J = 15.4 Hz, 1H), 3.65 (d, J = 16.0 Hz, 1H), 3.62 (d, J = 16.0 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.7, 164.2, 160.1, 136.3, 133.9, 130.0, 128.58, 128.57, 127.8, 127.63, 127.58, 108.9, 88.3, 61.3, 61.2, 46.5, 38.9, 14.2, 13.9. IR (film) ν cm^{-1} 2934, 1740, 1667, 1561, 1459, 1367, 1300, 1250, 1199, 1098, 1020, 750, 699. HRMS (ESI) calcd for $C_{24}H_{25}NNaO_6$ [M + Na$^+$] m/z 446.1574, found 446.1572.

Ethyl 3-*tert*-butyl-6-(2-ethoxy-2-oxoethyl)- 2-phenyl-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4b)

Colorless oil, yield 10 mg (5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 5H), 6.62 (s, 1H), 4.224 (q, J = 7.1, 1H in CH_2), 4.220 (q, J = 7.1, 1H in CH_2), 4.00 – 3.92 (m, 1H), 3.78 – 3.71 (m, 1H), 3.69 (d, J = 15.6 Hz, 1H), 3.30 (d, J = 15.6 Hz, 1H), 1.52 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.2, 163.7, 159.7, 141.0, 129.9, 128.5, 124.0, 109.3, 111.7, 88.8, 61.5, 61.4, 38.5, 31.3, 14.1, 13.9. IR (film) ν cm^{-1} 2978, 2934, 1742, 1667, 1563, 1457, 1420, 1367, 1306, 1248, 1201, 1098, 1027, 753, 700. HRMS (ESI) calcd for $C_{21}H_{27}NNaO_6$ [M + Na$^+$] m/z 412.1731, found 412.1727.

Ethyl 3-allyl-6-(2-ethoxy-2-oxoethyl)-2-phenyl-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4c)

Colorless oil, 119 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.41 (m, 5H), 6.24 (s, 1H), 5.78 – 5.69 (m, 1H), 5.14 (dd, J = 10.0, 0.4 Hz, 1H), 5.08 (dd, J = 16.8, 0.8 Hz, 1H), 4.32 – 4.23 (m, 2H), 4.09 – 4.01 (m, 1H), 3.97 – 3.89 (m, 1H), 3.72 (d, J = 17.3 Hz, 1H), 3.64 (s, 2H), 3.47 (dd, J = 15.8, 6.7 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.6, 164.1, 159.6, 134.1, 132.1, 130.0, 128.6, 127.5, 117.9, 108.9, 111.7, 88.4, 61.2, 61.1, 45.7, 38.8, 14.1, 13.8. IR (film) ν cm^{-1} 2983, 2937, 1740, 1713, 1670, 1597, 1465, 1445, 1412, 1369, 1280, 1248, 1180, 1127, 1057, 1030, 995, 927, 739, 699. HRMS (ESI) calcd for $C_{20}H_{23}NNaO_6$ [M + Na$^+$] m/z 396.1418, found 396.1418.

Ethyl 6-(2-ethoxy-2-oxoethyl)-3-methyl-2-phenyl-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4d)

Colorless oil, 87 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 5H), 6.19 (s, 1H), 4.292 (q, J = 7.1, 1H in CH_2), 4.287 (q, J = 7.1, 1H in CH_2), 4.13 – 4.04 (m, 1H), 4.03 – 3.94 (m, 1H), 3.72 (d, J = 16.2 Hz, 1H), 3.58 (d, J = 16.2 Hz, 1H), 2.82 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.7, 164.1, 160.4, 134.0, 130.1, 128.8, 127.4, 108.8, 90.3, 61.2, 61.0, 38.6, 30.6, 14.0, 13.8. IR (film) ν cm^{-1} 2982, 2938, 1738, 1720, 1668, 1614, 1460, 1425, 1398, 1381, 1298, 1280, 1254, 1180, 1127, 1068, 1029, 740, 700. HRMS (ESI) calcd for $C_{18}H_{22}NO_6$ [M + H$^+$] m/z 348.1442, found 348.1442.

Ethyl 3-benzyl-6-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4m)

Colorless oil, 118 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H), 7.13 – 7.07 (m, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.12 (s, 1H), 5.20 (d, J = 15.4 Hz, 1H), 4.303 (q, J = 7.1, 1H in CH_2), 4.296 (q, J = 7.1, 1H in CH_2), 4.06 (dq, J = 10.8, 7.2 Hz, 1H), 3.95 (dq, J = 10.8, 7.2 Hz, 1H), 3.92 (d, J = 15.4 Hz, 1H), 3.81 (s, 3H), 3.65 (d, J = 16.4 Hz, 1H), 3.61 (d, J = 16.4 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.8, 164.2, 160.8, 160.2, 136.3, 129.1, 128.4, 127.7, 127.4, 125.8, 113.8, 108.6, 88.4, 61.2, 61.1, 55.2, 46.3, 38.8, 14.1, 13.8. IR (film) ν cm^{-1} 2980, 2937, 2839, 1738, 1716, 1667, 1612, 1513, 1452, 1414, 1368, 1254, 1176, 1111, 1056, 833, 733, 700. HRMS (ESI) calcd for $C_{25}H_{28}NO_7$ [M + H$^+$] m/z 454.1860, found 454.1861.

Ethyl 6-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-3-propyl-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4n)

Colorless oil, 118 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.20 (s, 1H), 4.272 (q, J = 7.1, 1H in CH_2), 4.269 (q, J = 7.1, 1H in CH_2), 4.06 (dq, J = 10.8, 7.1 Hz, 1H), 3.95 (dq, J = 10.8, 7.1 Hz, 1H), 3.83 (s, 3H), 3.68 – 3.62 (m, 1H), 3.61 (s, 2H), 2.99 – 2.85 (m, 1H), 1.60 – 1.44 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.1, 164.3, 160.7, 159.9, 128.9, 126.5, 113.8, 109.0, 89.0, 61.2, 61.0, 55.2, 45.5, 38.7, 21.3, 14.0, 13.8, 11.1. IR (film) ν cm^{-1} 2966, 1739, 1718, 1666, 1612, 1514, 1464, 1416, 1370, 1253, 1175, 1126, 1094, 1054, 1031, 743, 699. HRMS (ESI) calcd for $C_{21}H_{27}NNaO_7$ [M + Na$^+$] *m/z* 428.1680, found 428.1680.

Ethyl 6-(2-ethoxy-2-oxoethyl)-3-methyl-2-(4-nitrophenyl)-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4o)

Colorless oil, 47 mg (24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 6.31 (s, 1H), 4.277 (q, J = 7.1 Hz, 1H), 4.274 (q, J = 7.1 Hz, 1H), 4.10 (dq, J = 10.8, 7.2 Hz, 1H), 4.01 (dq, J = 10.8, 7.2 Hz, 1H), 3.67 (d, J = 16.6 Hz, 1H), 3.63 (d, J = 16.6 Hz, 1H), 2.95 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 165.2, 163.7, 159.7, 141.0, 129.9, 128.5, 124.0, 109.3, 88.8, 61.5, 61.4, 38.5, 31.3, 14.1, 13.9. IR (film) ν cm^{-1} 2983, 2939, 1737, 1670, 1606, 1526, 1466, 1399, 1350, 1300, 1253, 1184, 1127, 1069, 1027, 941, 828. HRMS (ESI) calcd for $C_{18}H_{21}N_2O_8$ [M + H$^+$] *m/z* 393.1292, found 393.1289.

Ethyl 6-(2-ethoxy-2-oxoethyl)-2-(4-methoxyphenyl)-3-methyl-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4p)

Colorless oil, 127 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.12 (s, 1H), 4.292 (q, J = 7.1 Hz, 1H), 4.288 (q, J = 7.1 Hz, 1H), 4.14 – 4.06 (m, 1H), 4.06 – 3.98 (m, 1H), 3.84 (s, 3H), 3.75 (d, J = 16.2 Hz, 1H), 3.54 (d, J = 16.2 Hz, 1H), 2.79 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.0, 164.3, 161.0, 160.7, 129.0, 126.1, 114.2, 108.7, 90.3, 61.4, 61.2, 55.4, 38.7, 30.5, 14.2, 13.9. IR (film) ν cm^{-1} 2962, 1738, 1733, 1699, 1695, 1652, 1615, 1516, 1464, 1398, 1257, 1175, 1069, 1030, 800. HRMS (ESI) calcd for $C_{19}H_{24}NO_7$ [M + H$^+$] *m/z* 378.1547, found 378.1552.

Ethyl 6-(2-ethoxy-2-oxoethyl)-3-isopropyl-2-(4-methylthiophenyl)-2,3-dihydro-1,3-oxazin-4-one-5-carboxylate (4q)

Colorless oil, 105 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 6.32 (s, 1H), 4.85 (hept, J = 6.9 Hz, 1H), 4.32 – 4.17 (m, 2H), 3.98 (dq, J = 10.7, 7.1 Hz, 1H), 3.76 (dq, J = 10.7, 7.1 Hz, 1H), 3.73 (d, J = 15.7 Hz, 1H), 3.36 (d, J = 15.7 Hz, 1H), 2.48 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.29 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164.1, 163.4, 159.0, 140.7, 132.8, 127.8, 125.5, 110.1, 83.9, 61.2, 60.9, 44.6, 38.7, 20.7, 20.1, 15.0, 14.1, 13.7. IR (film) ν cm^{-1} 2979, 2933, 1741, 1720, 1660, 1598, 1441, 1403, 1370, 1274, 1219, 1180, 1107, 1048, 1029, 975, 850. HRMS (ESI) calcd for $C_{21}H_{28}NO_6S$ [M + H$^+$] *m/z* 422.1632, found 422.1634.

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Notes and references

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