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Et_3N-Catalyzed Tandem Formal [4 + 3] Annulation/Decarboxylation/Isomerization of Methyl Coumalate with Imine Esters: Access to Functionalized Azepine Derivatives

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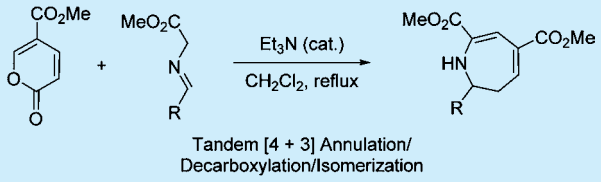
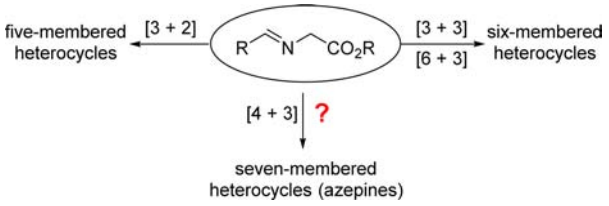
Supporting Information

ABSTRACT: An unprecedented catalytic tandem formal [4 + 3] cycloaddition/decarboxylation/isomerization of methyl coumalate and imine esters is successfully developed. This tandem reaction only requires Et_3N as the mild base affording a series of highly functionalized seven-membered heterocyclic azepine derivatives in good yields with excellent regioselectivities.



Intermolecular cycloaddition reactions are one of the most fundamental and powerful methods used for the facile construction of various complex cyclic compounds in organic synthesis.[1] In this research area, the 1,3-dipolar cycloaddition reaction of *in situ* formed azomethine ylides from simple and readily available imine esters is an efficient and versatile transformation for the convergent construction of N-containing heterocycles.[2] Normally, five-membered heterocyclic compounds such as pyrrolidines are generated via a [3 + 2] reaction with electron-deficient alkenes employed as the two-atom dipolarophiles (Scheme 1). Most recently, fulvenes,[3] tropone,[4] and 2-acyl cycloheptatrienes[5] were successfully employed as diversified 6-π dipolarophiles with azomethine ylides in [6 + 3]-cycloaddition reactions, which offered direct approaches to fused and bridged six-membered piperidines. Alternatively, six-membered heterocyclic frameworks can be facilely accessed through expedient cross 1,3-dipolar [3 + 3] cycloaddition between pyrazolidinium ylides and azomethine ylides.[6]

Scheme 1. Imine Esters as Three-Atom Units in [3 + 2], [3 + 3], and [6 + 3] (Previous Work) and [4 + 3] Cycloaddition (Initial Design of This Work)



To the best of our knowledge, however, methods utilizing the 1,3-dipolar cycloaddition reaction for the direct construction of seven-membered azepine derivatives, in which certain 4-π component must be employed as the four-atom dipolarophile, has yet to be investigated. Along with our ongoing research interest in the transition-metal-catalyzed 1,3-dipolar cycloaddition reaction,[3−7] we wonder whether seven-membered N-containing heterocycles could be synthesized via [4 + 3] cycloaddition.[8] The difficulties of such a transformation are presumably caused by the competition between the [3 + 2] and [4 + 3] reaction pathway, and the former benefits from the transition state in both a stepwise and concerted mechanism because it is consistent with the kinetically more viable [$\pi 4_s$ + $\pi 2_s$] model.[2] Due to the significant bioactive properties of the azepine moiety exhibited in many pharmaceuticals and natural products,[9] many methods for the preparation of azepine-containing heterocycles have been developed, for example, intramolecular Claisen−Schmidt cyclization,[10] radical additions,[11] Heck coupling,[12] ring-closing metathesis,[13] ring-expansion through nitrogen transfer,[14] and some related cycloprocesses.[15] However, most of those methods require multiple-step synthesis. Therefore, the development of a general and facile [4 + 3] cycloaddition using common amine acid derived imine esters to access azepine frameworks remains highly desired.[16] According to the theoretical retrosynthetic analysis of azepine skeleton, 1,3-dipolar cycloaddition reaction of azomethine ylides provides a potential approach to such compounds; nevertheless, selecting the appropriate diene partner as the component is the key factor for realizing this novel transformation.

Methyl coumalate containing a conjugated dienone moiety has been recognized as a very useful synthon in organic synthesis. The typical behavior of coumalate is demonstrated by serving as a dienophile[17] or diene partner[18] in a Diels−Alder cycloaddition in accordance with the classical [4 + 2] cycloaddition reaction model. To date, only a few examples of nonclassical cycloaddition employing coumalate had been reported. For example, a Pd-catalyzed [4 + 3] cycloaddition of trimethylenemethane with methyl coumalate has been reported by Trost.[19] Later, Lu et al.

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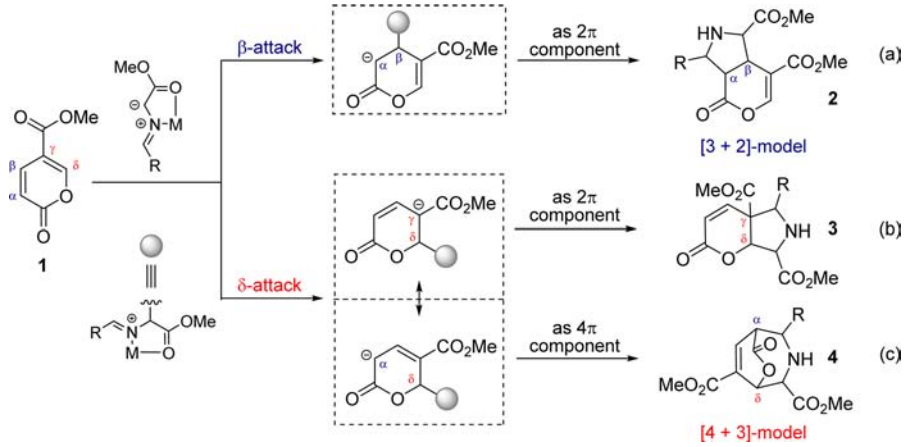
Scheme 2. Possible [3 + 2] and [4 + 3]-Cycloaddition Pathways for the Designed Annulation of Azomethine Ylides with Methyl Coumalate 1

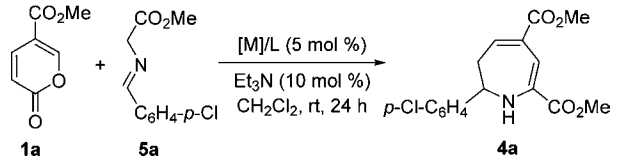


reported an efficient phosphine-catalyzed [4 + 3] annulation of modified allylic carbonates with methyl coumalate.[20] Encouraged by our experience in the construction of five-[7] and six-membered N-containing heterocycles[3−6] via metal-catalyzed 1,3-dipolar cycloaddition, we envisioned that the conjugated dienone moiety in methyl coumalate might serve as a potential 4-π or 2-π component in a 1,3-dipolar cycloaddition with an azomethine ylide as shown in Scheme 2.

In consideration of the reactivity and regioselectivity of coumalate illustrated in the literatures, the δ-position of coumalate could be initially attacked by the nucleophilic site of the *in situ* formed azomethine ylide giving rise to the zwitterionic intermediate which has two possible resonance forms stabilized by the delocalization effect of the contiguous carbonyl group and conjugated alkene moiety. Subsequent intramolecular cyclization of the formed zwitterionic intermediate is believed to prefer undergoing the [4 + 3] reaction pathway (Scheme 2c) to avoid the disfavored steric congestion of the γ-position existing in the [3 + 2] pathway (Scheme 2b), affording the bridged heterocycle **4** as the cycloadduct. Alternatively, the [3 + 2] reaction pathway could take place between the azomethine ylide with an α,β-unsaturated C═C bond in coumalate (Scheme 2a), which is initiated by the nucleophilic attack to the β-position of coumalate. Stimulated by the challenging synthetic difficulties associated with the complex regioselectivity control, we decided to investigate the cycloaddition of imine esters and coumalate. Here, we report an unprecedented Et_3N-catalyzed tandem [4 + 3] annulation/decarboxylation/isomerization of methyl coumalate and imine esters to afford the biologically important azepine derivatives in good yields with exclusive regioselectivity.

To test our hypothesis, we initially chose methyl coumalate **1a** and glycine derived imine ester **5a** as the model substrates, with 5 mol % of $AgOAc/PPh_3$ complex as the catalyst in the presence of 10 mol % of Et_3N as the base in CH_2Cl_2 at rt. To our surprise, the reaction proceeded smoothly giving the unexpected seven-membered azepine **4a** with excellent regioselectivity albeit in a low yield through a tandem annulation followed by decarboxylation and isomerization (Table 1, entry 1). Neither of the [3 + 2] cycloadducts was observed. The structure of **4a** was supported by the analytical and spectral data and was further confirmed by X-ray diffraction analysis (Figure 1).[21] Encouraged by the above results, different metal salts were first tested, and the results are summarized in Table 1. Only a trace amount of the desired cycloadduct was detected when the Cu(I) or $Cu(II)/PPh_3$ complex was used (entries 2 and 3). No reaction occurred with $Ni(ClO_4)_2{\cdot}6H_2O$ and $Zn(OTf)_2$ as the metal precursor (entries 4 and 5). Other commercially available silver metal salts afforded similar results to AgOAc (entries 6 and 7). Subsequently, a chiral bisphosphine ligand was screened in the hope of developing an asymmetric version of this novel transformation; however, only a racemic adduct was obtained with no further improvement of the yield (see entry 8). Intriguingly, in the absence of ligand, cycloaddition catalyzed by AgOAc and Et_3N occurred with a similar yield (entry 9). Furthermore, to our delight, an improved yield was obtained when only a catalytic amount of Et_3N was

Table 1. Initial Investigations of the Cycloaddition of Methyl Coumalate 1a and Imine Ester 5a[a]



entry	[M]	L	Et_3N	yield (%)[b]
1	AgOAc	PPh_3	+	47
2	$Cu(MeCN)_4BF_4$	PPh_3	+	trace
3	$Cu(OTf)_2$	PPh_3	+	trace
4	$Ni(ClO_4)_2$	PPh_3	+	–
5	$Zn(OTf)_2$	PPh_3	+	–
6	$AgSbF_6$	PPh_3	+	40
7	$AgClO_4$	PPh_3	+	45
8[c]	AgOAc	(*R*)-BINAP	+	35
9	AgOAc	–	+	45
10	–	–	+	50

[a]All reactions were carried out with 0.40 mmol of **1a** and 0.50 mmol of **5a** in 2 mL of CH_2Cl_2. [b]Isolated yield. [c]Racemic **4a** was obtained.

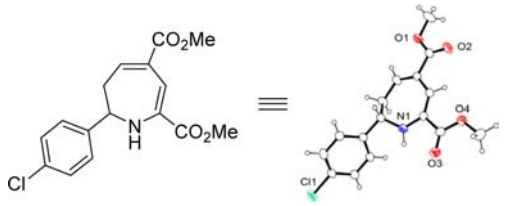


Figure 1. ORTEP representation of **4a** at 30% probability for the drawing of thermal ellipsoids.

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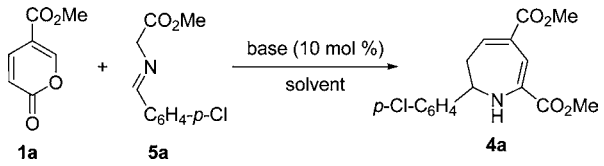
employed without AgOAc (entry 10), which reveals that imine ester acted as a carboanion precursor instead of 1,3-dipole in this annulation.[22]

Inspired by these promising results, we abandoned transition-metal mediation and turned our attention to investigating different bases as the catalysts. Many experimental tests were carried out on the optimization of organic bases and inorganic base (Table 2, entries 1−6), however, no further improvement in

Table 2. Screening Studies of Base-Catalyzed Tandem [4 + 3] Annulation/Decarboxylation/Isomerization of 1a and 5a[a]



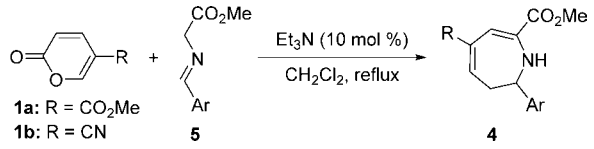
entry	base	solvent	temp (°C)	time (h)	yield (%)[b]
1	Et_3N	CH_2Cl_2	rt	24	50
2	DIPEA	CH_2Cl_2	rt	24	45
3	DABCO	CH_2Cl_2	rt	24	41
4[c]	quinine	CH_2Cl_2	rt	24	45
5	DBU	CH_2Cl_2	rt	24	trace
6	Cs_2CO_3	CH_2Cl_2	rt	24	trace
7	Et_3N	CH_2Cl_2	reflux	12	78
8	Et_3N	$CHCl_3$	reflux	12	69
9	Et_3N	$(CHCl)_2$	reflux	12	68
10	Et_3N	THF	reflux	12	45
11	Et_3N	PhMe	reflux	12	trace
12	Et_3N	MeCN	reflux	12	trace
13	Et_3N	MeOH	reflux	12	trace

[a]All reactions were carried out with 0.40 mmol of **1a** and 0.50 mmol of **5a** in 2 mL of solvent. [b]Isolated yield. [c]Racemic **4a** was obtained.

the yield was achieved.[23] The ratios of the substrates **1a** and **5a** made no contribution to the improvement of the yield. Fortunately, full conversion and an up to 78% yield was obtained when the cycloaddition reaction was carried out at reflux with Et_3N as the base (entry 7). During a subsequent survey of solvent effects, it was found dichloromethane seemed to be the best choice (entries 7−13). It is worth mentioning that an inert atmosphere was not required for this annulation process.

Under the optimal reaction conditions, the substrate scope of this tandem annulation/decarboxylation/isomerization reaction was then explored, and the results are summarized in Table 3. In general, the reactions performed well with a wide range of imine esters derived from various aromatic aldehydes leading to the desired azepine derivatives in moderate to good yields. Imine esters **5** derived from aromatic aldehydes bearing electron-deficient substituents on the benzene ring exhibited higher reactivity with methyl coumalate **1a**, providing the 6,7-dihydro-1*H*-azepine derivatives in good yield (Table 3, entries 1−7). Aryl imine esters bearing electron-rich and -neutral substituents were also tolerated in this catalytic system albeit delivering the corresponding adducts in a moderate yield (entries 8−11). It appears that different substitution patterns on the phenyl ring of imine esters had no obvious effect on this annulation, and the sterically hindered *ortho*-substituted imine ester also performed well (entry 2). Imine ester **5k** containing a fused 1-naphthyl group also worked well affording the desired azepine **3k** in 70% yield (entry 11). Notably, heteroaryl imine ester **5l** also proved to be a viable substrate in this reaction, and the corresponding

Table 3. Substrate Scope of Tandem [4 + 3] Annulation/Decarboxylation/Isomerization of Pyrones 1 with Imine Esters 5[a]



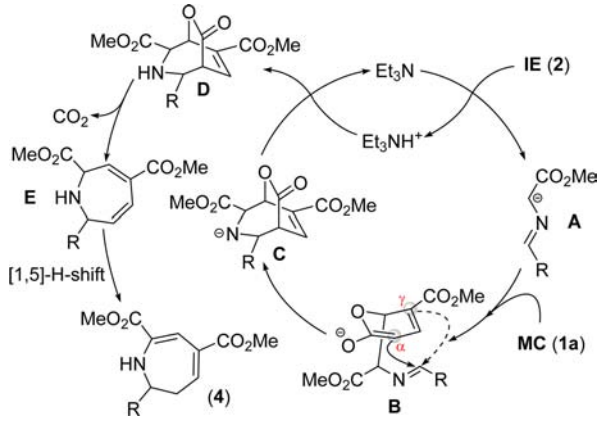
entry	Ar	product	time (h)	yield (%)[b]
1	*p*-Cl-C_6H_4 (**5a**)	**4a**	12	78
2	*o*-Cl-C_6H_4 (**5b**)	**4b**	18	76
3	*m*-Cl-C_6H_4 (**5c**)	**4c**	15	74
4	*p*-Br-C_6H_4 (**5d**)	**4d**	12	72
5	*m*-Br-C_6H_4 (**5e**)	**4e**	15	68
6	*p*-CN-C_6H_4 (**5f**)	**4f**	10	74
7	*p*-NO_2-C_6H_4 (**5g**)	**4g**	10	75
8	Ph (**5h**)	**4h**	16	67
9	*m*-Me-C_6H_4 (**5i**)	**4i**	24	63
10	*m*-MeO-C_6H_4 (**5j**)	**4j**	40	60
11	1-naphthyl (**5k**)	**4k**	28	62
12	2-furyl (**5l**)	**4l**	40	55
13[c]	*p*-Cl-C_6H_4 (**5a**)	**4m**	12	65

[a]All reactions were carried out with 0.40 mmol of **1** and 0.50 mmol of **5** in 2 mL of CH_2Cl_2. [b]Isolated yield. [c]Pyrone **1b** was used.

product was achieved in moderate yield (entry 12). However, no reaction was detected with the less reactive alkyl substituted imine ester or *non*-glycinate derived imine ester under the optimized reaction conditions. Moreover, cyano-substituted pyrone **1b** can be tolerated in the current tandem annulation reaction as well as giving rise to the expected product in an acceptable yield (entry 13). An electron-withdrawing group at the 5-position is very important for this transformation. No reaction occurred when unsubstituted 2-pyrone was tested.

A plausible catalytic cycle of the tandem transformation of methyl coumalate into azepine derivatives was proposed, as shown in Scheme 3. The initial nucleophilic attack of the *in situ*

Scheme 3. Proposed Catalytic Cycle for Et_3N-Catalyzed [4 + 3] Annulation Followed by Decarboxylation/1,5-H-Shift



formed anion **A** from imine ester to the δ-position of coumalate generates the dienolate intermediate **B**, in which the negative charge is delocalized by the contiguous carbonyl group and conjugated alkene moiety. Subsequent intramolecular cyclization of the dienolate **B** is believed to prefer reaction at the α-position of the dienolate and gives rise to the intermediate **C**, followed by

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protonation to afford the bridged species **D** along with regeneration of the catalyst. Extrusion of CO_2 from **D** followed by a [1,5]-H-shift provides the thermodynamically stable product azepine.

In summary, we have successfully developed an unprecedented Et_3N-catalyzed tandem formal [4 + 3] annulation/decarboxylation/isomerization of methyl coumalate with imine esters. This novel transformation provides facile and straightforward access to the biologically important azepine derivatives with excellent regioselectivity control. Further investigations on the detailed mechanism and applications of this tandem reaction in organic synthesis are underway in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(21) CCDC 1013529 (**4a**) contains the supplementary crystallographic data for this paper.

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(23) The initial test on the asymmetric version of this novel tandem reaction was performed with some commonly used organocatalysts; unfortunately, only a racemic product was obtained.