Design of a New Cascade Reaction for the Construction of Complex Acyclic Architecture: The Tandem Acyl-Claisen Rearrangement

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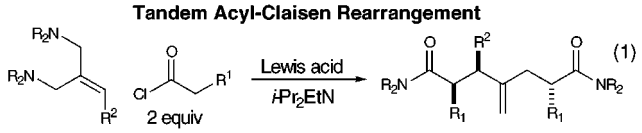
Tandem or domino reactions have long been established as powerful chemical tools for the rapid formation of complex cyclic and polycyclic architecture.[1] Surprisingly, however, relatively few tandem strategies have been directed toward the production of acyclic structural motifs despite significant advances in the area of acyclic stereocontrol. In our recent study, we reported the development of the acyl-Claisen rearrangement, a catalytic [3,3]-bond reorganization that allows the stereoselective synthesis of α,β-disubstituted-γ,δ-unsaturated carbonyls.[2,3] In this communication, we outline the development of the tandem acyl-Claisen reaction, a highly stereoselective three-component coupling that enables the rapid construction of complex *acyclic* systems in the context of 2,3,6-trisubstituted-1,7-dioxoheptane architecture (eq 1). This versatile cascade sequence is conducted by using simple

Tandem Acyl-Claisen Rearrangement



(1)

rapid construction of stereochemically complex acyclic frameworks

allyl diamines and acid chlorides, chemicals that are widely available in a diverse range of structural formats. As such, we expect this tandem reaction to be of broad utility to a number of chemical fields that employ molecule construction including natural product and parallel medicinal agent synthesis.

Design Plan. In accord with our acyl-Claisen studies, we envisioned that a variety of ketenes **2**, generated in situ from acid chloride **3** and *i*-Pr_2NEt, would undergo Lewis acid-catalyzed addition to either the (*Z*)- or (*E*)-amine component of allyl diamine **1** to provide the regioisomeric allyl vinylammonium complexes **4** and **5** (Scheme 1). Given that (i) the (*Z*)-amine derived conformation **5** would be destabilized on the basis of 1,3-diaxial interactions and (ii) the ketene-addition step is likely reversible,[4] the primary Claisen event was expected to proceed selectively by way of the (*E*)-ammonium topography **4**. As a central design element, this regioselective addition-rearrangement would provide the 2,3-disubstituted intermediate **6** with high levels of *syn* selectivity while revealing an allylamine component that can participate in a second acyl-Claisen transform. In this context, the addition of a further equivalent of ketene **2** to intermediate **6** would result in an ammonium enolate that can adopt two chair rearrangement topographies **7** and **8**. Minimization of A(1,2) strain[5] about the C(5)−C(5a) bond of conformer **7** was expected

Scheme 1

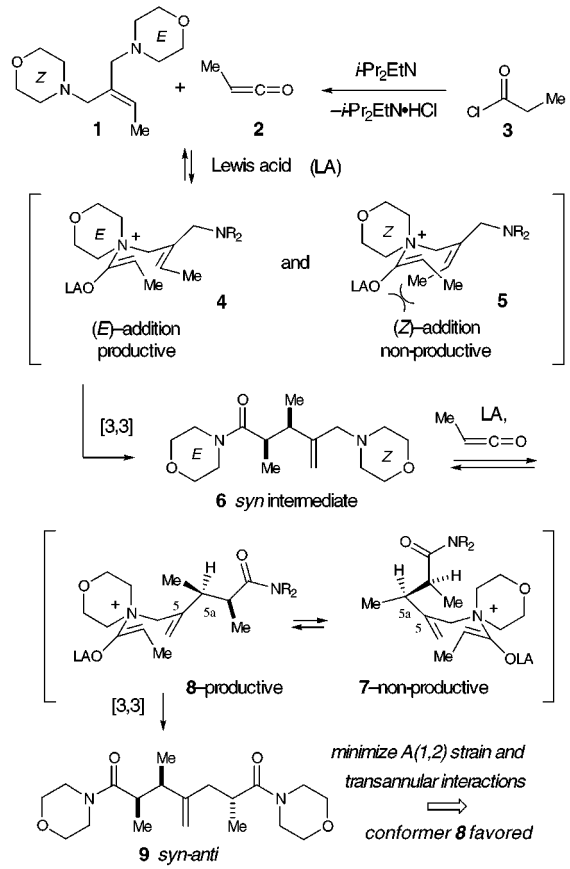


Table 1. Lewis Acid Promoted Tandem Acyl-Claisen Rearrangement between Propionyl Chloride and Allyl Dimorpholine **1** (Scheme 1)[a]

entry	Lewis acid	equiv of LA	% yield of **9**	*syn-anti*/ *anti-anti*[b,c]
1	$Yb(OTf)_3$	2.0	97	98:2
2	$TiCl_4$·THF_2	2.0	93	98:2[d]
3	MgI_2	4.0	70	98:2
4	$AlCl_3$	2.0	93	64:36

[a] Reactions performed in CH_2Cl_2 at 23 °C. [b] Ratios determined by GLC. [c] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [d] Reaction performed at −20 °C.

to enforce transannular interactions between the C(5a)-amide moiety and the axial methylene group, while the same torsional constraints in topography **8** positions the bulky C(5a)-amide chain away from the [3,3]-isomerization event. As such, the second Claisen step was anticipated to proceed via conformer **8** to furnish the complex 2,3,6-trisubstituted-1,7-diamidoheptane **9** with high levels of 2,3-*syn*-3,6-*anti* diastereocontrol.

Scope Studies. Our tandem acyl-Claisen strategy was first evaluated by using allyl dimorpholine **1** with propionyl chloride in the presence of *i*-Pr_2EtN and a series of metal salts. As revealed in Table 1, this tandem sequence was successful with a variety of Lewis acids including $Yb(OTf)_3$, $TiCl_4$·THF_2, and MgI_2 to provide the tandem adduct **9** in excellent yield and diastereoselectivity (entries 1−3, 70−97% yield, ≥98:2 dr). In all cases, the major constituent of **9** was confirmed by X-ray analysis to be the 2,3-*syn*-3,6-*anti* isomer in complete accord with our

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(1) Ho, T.-L. *Tandem Organic Reactions*; Wiley-Interscience: New York, 1992.

(2) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

(3) This reaction is based upon the Bellus ketene−Claisen reaction: (a) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. (b) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860.

(4) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995.

(5) For examples of A(1,2) strain directed reactions see: (a) Johnson, F. *Chem. Rev.* **1968,** *68*, 375. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

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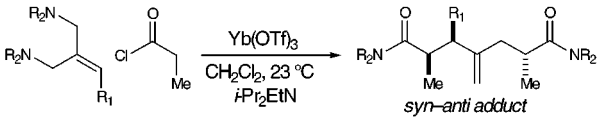
Table 2. Tandem Acyl-Claisen Rearrangement between Propionyl Chloride and Representative Allyl Diamines



entry	allyl diamine		% yield	*syn–anti/ anti–anti*[a,b]
	NR_2	olefin–R_1		
1	morpholine	Me (**1**)	97	98:2[c]
2	pyrrolidine	Me (**10**)	90	95:5
3	piperidine	Me (**11**)	99	96:4
4	morpholine	Cl (**12**)	98	99:1
5	morpholine	OBz (**13**)	86	91:9[c]
6	morpholine	CN (**14**)	78	97:3[c,d]
7	morpholine	SPh (**15**)	70	93:7[d]

[a] Ratios determined by GLC, HPLC, or ^{1}H NMR. [b] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [c] Relative configurations assigned by X-ray analysis. [d] Using $TiCl_4$·THF_2.

mechanistic plan (Scheme 1). The superior levels of diastereoselectivity (98:2 dr) and reaction efficiency (97% yield) exhibited by $Yb(OTf)_3$ (Table 1, entry 3) defined this Lewis acid as the optimal catalyst for further exploration.

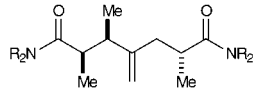
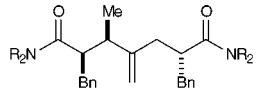
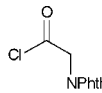
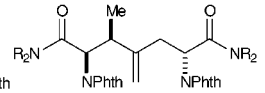
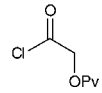
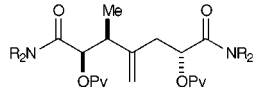
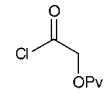
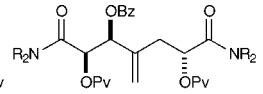
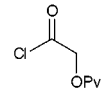
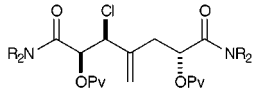
Experiments that probe the scope of the allyl dimorpholine substrate are summarized in Table 2. The reaction appears quite general with respect to the nature of the tertiary amine component (entries 1−3, 90−99% yield, ≥95:5 dr). Considerable variation in the olefin substituent can also be tolerated to afford acyclic arrays that incorporate alkyl, halo, cyano, alkoxy, and sulfanyl substituents in excellent yield and diastereoselectivity (entries 4−7, 70−98% yield, 91:9 to 99:1 *syn-anti*:*anti-syn*). As revealed with the cyano- and phenylthio-substituted amines (entries 6 and 7), the reaction exhibits broad latitude with respect to the electronic contribution of the olefin substituent (≥70% yield, ≥93:7 dr).

The effect of the acid chloride component on the tandem acyl-Claisen rearrangement has also been examined (Table 3). Significant structural variation in the ketene surrogate (R_2 = Me, Bn, NPhth, or OPv) is possible without loss in yield or diastereoselectivity (71−99% yield, 92:8 to 98:2 *syn-anti*:*anti-syn*, entries 1−6). A powerful feature of this cascade reaction is the capacity to build functional and stereochemical arrays that are not readily available using conventional chemical methods. As demonstrated in entry 3, implementation of α-phthalylglycyl chloride allows the rapid construction of carbon-tethered α-amino carbonyls. This tandem strategy also provides an attractive alternative to iterative aldol processes. Indeed, the synthesis of a variety of substitutionally divergent polyol systems can be achieved by using α-pivaloyloxy chloride with alkyl-, halo-, or alkoxy-substituted diamines (entries 4−6, 71−97% yield, ≥92:8 dr).

A demonstration of the synthetic utility of the tandem acyl-Claisen rearrangement and the accompanying 1,7-diamidoheptane products is presented (eq 2). A stereochemical motif commonly found throughout the architecture of macrolide antibiotics is represented by 2,3-*syn*-3,6-*anti*-2,6-dimethyl-1,7-dioxo-3-hydroxyheptane.[6] As revealed in eq 2, this acyclic stereochemical array can be accessed in *one step* from allyl diamine **13** and propionyl chloride by using our tandem Claisen protocol. Moreover, the incorporation of an olefin moiety at C(4) renders these Claisen adducts versatile substrates for oxidative or reductive elaboration (cf. C(4)-erythronolide B, C(4)-neomethynolide). It also important

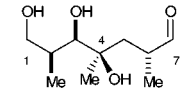
(6) *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando FL, 1984.

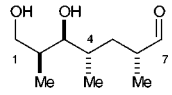
Table 3. Tandem Acyl-Claisen Rearrangement between Representative Allyl Dimorpholines and Acid Chlorides[a]

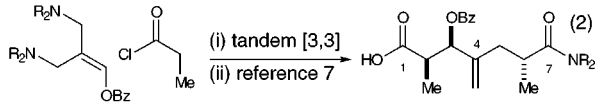
entry	diamine	acid-Cl	product[b]	% yield	*syn–anti/ anti–anti*[c,d]
1	**1**			97	98:2[e]
2	**1**			99	92:8
3	**1**			98	95:5[e]
4	**1**			97	97:3[f]
5	**13**			71	92:8[f,g]
6	**12**			84	95:5[f]

[a] With 2 equiv of $Yb(OTf)_3$ and *i*-Pr_2NEt at 23 °C in CH_2Cl_2. [b] NR_2 = *N*-morpholine. [c] Ratios determined by GLC, HPLC, or ^{1}H NMR. [d] The *syn-syn* and *anti-syn* isomers were isolated in <1% yield. [e] Relative configurations assigned by X-ray analysis. [f] Using $TiCl_4$·THF_2. [g] The *syn-syn* isomer was isolated in 2% yield.

to note that regioselective hydrolysis of the α,β-disubstituted amide of these dicarbonyl Claisen adducts is possible with use of an iodolactonization−ring opening sequence.[7]







NR_2 = morpholine 72% yield (2 steps) 91:9 *syn–anti:syn–*syn

Last, preliminary studies have been completed that outline the utility of the tandem acyl-Claisen reaction as a powerful tool for natural product synthesis. Details of this work along with a full account of this survey will be forthcoming.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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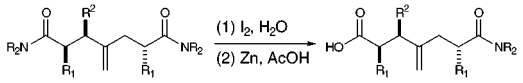
(7) This regioselective hydrolysis protocol appears quite general for a number of tandem Claisen adducts.



NR_2 = morpholine, R_1 = R_2 = Me 83% yield, 92:8 regioselectivity
NR_2 = morpholine, R_1 = Me, R_2 = OBz 88% yield, 83:17 regioselectivity
NR_2 = morpholine, R_1 = Bn, R_2 = Me 82% yield, 92:8 regioselectivity