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Ireland–Claisen rearrangement of ynamides: stereocontrolled synthesis of 2-amidodienes

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ABSTRACT

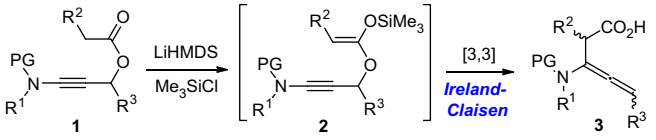
The Ireland–Claisen rearrangement of propargyl ynamido ester substrates is reported. The expected allenamide carboxylic acid products from [3,3]-sigmatropic rearrangement are not isolated, with 2-amidodienes alternatively formed in good yield with high levels of stereocontrol after decarboxylation.

Ynamides have developed a mature and varied area of organic synthesis in recent years.[1] These compounds have been used in a raft of transition metal catalyzed reactions, such as cycloadditions and couplings.[2] While a strongly electron-donating nitrogen is tempered by a nitrogen electron-withdrawing protecting group, the reactivity of ynamides is still pronounced. One area of synthetic chemistry where ynamides are arguably under-developed is in the sigmatropic rearrangement chemistry. Reactions such as the Ireland–Claisen [3,3]-sigmatropic rearrangement[3] offer synthetic versatility, allowing for excellent stereocontrol and the formation of congested stereocenters.

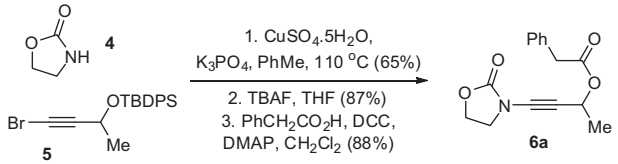
We have recently reported the use of enamides in the Ireland–Claisen [3,3]-sigmatropic rearrangement.[4] As part of this area of research within our group,[5] we have utilized ynamides as synthetic intermediates to the requisite enamide substrates. The availability of ynamido propargyl alcohols has allowed us to ponder the possibility of conducting an Ireland–Claisen rearrangement of these ynamido propargyl systems.[6,7] If successful, this [3,3]-sigmatropic rearrangement would offer a novel stereocontrolled entry to allenamide carboxylic acid fragments (Scheme 1). As allenamides are important synthetic building blocks,[8–10] we felt this rearrangement was worthy of investigation.

To examine this proposal, ester **6a** was synthesized, incorporating the phenyl acetate unit which had been shown to be important for the smooth rearrangement of the analogous enamide[4b] system (Scheme 2). Accordingly, bromopropargylsilyl ether **5** [11] was coupled to 2-oxazolidinone (**4**), promoted by Cu-catalysis.[12] Desilylation mediated by TBAF and subsequent carbodiimide-mediated esterification formed ynamido substrate **6a** in 50% yield over three steps.

Initial attempts to form an allenamide **3** centered upon utilizing the protocol developed for the rearrangement of enamides (Table 1).[4b] However, we were presented with a particularly complex reaction mixture, with attempted diazomethane-mediated carboxylic acid methylation observed to be non-productive, suggesting the absence of a carboxylic acid group. After careful chromatography, oxazolidinone substituted diene **7a**, with the major isomer



Scheme 1. Proposed Ireland–Claisen rearrangement of ynamides to allenamides.



Scheme 2. Model substrate synthesis.

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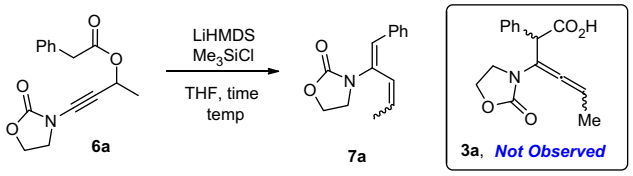
Table 1
Rearrangement optimization



Entry	LiHMDS (equiv)	Me_3SiCl (equiv)	Temp (°C)	Time (h)	Yield (%)	*Z*/*E*
1	1.3	1.3	−78 → rt	24	40	>95:5
2	1.3	1.3	−78 → rt	48	41	>95:5
3	1.3	0	−78 → rt	24	0	—
4[a]	1.3	1.3	−78 → rt	24	13	>95:5
5	1.3[b]	1.3	−78 → rt	24	25	>95:5
6	1.3	1.3	−95 → rt	1.5	21	>99:5
7	1.3	1.05	−78 → rt	1.5	10	>99:5
8	1.3	1.3	−40 → rt	1.5	0[c]	—
9	1.3	1.3	−20 → rt	1.5	0[c]	—
10	1.3	1.3	0 → rt	1.5	0[c]	—
11	5.2	5.2	−95 → rt	24	0	—
12	2.6	2.6	−95 → rt	24	31	1:1
13	2.3	2.3	−95 → rt	24	40	3:1
14	2	2	−95 → rt	24	42	5:1
15	1.8	1.8	−95 → rt	24	83	8:1
16	1.3	1.3	−95 → rt	24	61	>95:5
17	1.05	1.05	−95 → rt	24	19	6:1

[a] Reaction conducted in PhMe.
[b] NaHMDS used as base.
[c] Full mass recovery of **6a**.

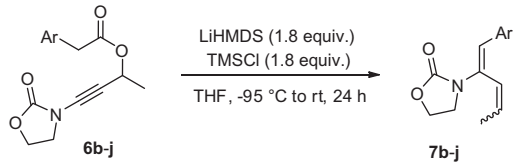
characterized as the *Z,E*-isomer as displayed was obtained. As discussed by Hsung, there appears to be no general synthesis of aminodienes presently available to the synthesis community, and therefore new methodologies that offer a controlled entry to such systems can be viewed as valuable.[13] Thus, we sought to optimize the formation of this amidodiene product (Table 1).

The rearrangement was particularly sensitive to the initial conditions employed (Table 1). For example, low loadings of base and Me_3SiCl resulted in excellent stereocontrol (entries 1–4). The reaction requires the presence of silyl chloride and therefore supports a traditional Ireland–Claisen process occurring (entry 3). The initiating temperature is crucial to any rearrangement occurring, with −95 °C offering the best results (entries 6–10). We feel it is noteworthy that **6a** is re-isolated, with full mass balance, when this reaction is initiated at −40 °C or higher (entries 8–10). Furthermore, the addition of higher loadings of base and silyl chloride is also deleterious to the final isolated yield (entries 11–17).

Previous work in our group has demonstrated that the stereocontrolled formation of aryl-substituted silylketene acetals is a more complex problem than currently is appreciated where the *E*/*Z* ratios are highly dependent on the loadings of base and silyl chloride, as well temperature.[14] Accordingly, we feel the presently reported rearrangement is also sensitive to the complications of forming silylketene acetals from aryl acetate esters.

This diene is presumably the result of a post-rearrangement decarboxylation. Baldwin has reported the decarboxylation of allenyl carboxylic acids, formed from the Ireland–Claisen rearrangement of propargylic esters.[6b,15] However, the decarboxylation step required forcing thermal conditions (140–250 °C) to accomplish the loss of CO_2. Therefore, the presence of N-substitution has a profound effect on this decarboxylation event. With an optimized rearrangement developed on phenyl acetate **6a**, we sought to examine the scope of the aryl acetate moiety (Table 2). The conditions chosen, and in particular the loading of base and silyl chloride, represents striking a balance between optimized yield and *Z*/*E* selectivity, as highlighted in Table 1. Accordingly, the substrate scope was studied with 1.8 equiv of LHMDS and Me_3SiCl.

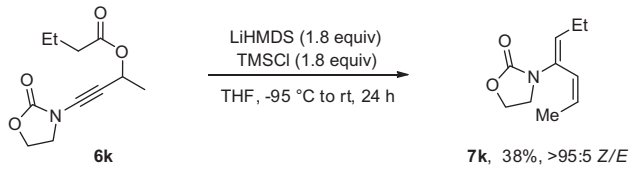
Table 2
Scope of ester functionality[16]



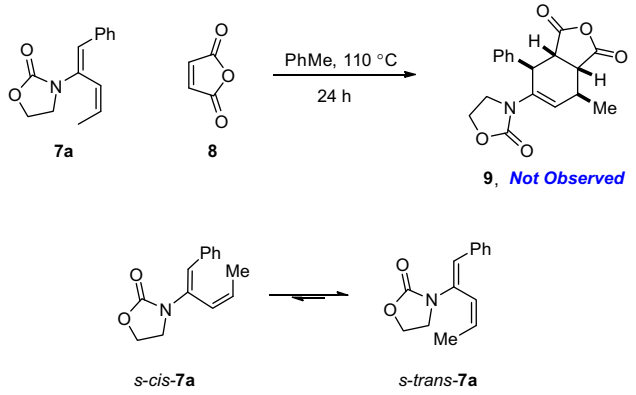
Entry	Ar	Diene	Yield (%)	*Z*/*E*
1	4-$Me_2NC_6H_4$ (**6b**)	**7b**	53	>95:5
2	4-$MeOC_6H_4$ (**6c**)	**7c**	62	9:1
3	3,4-$(OCH_2O)C_6H_3$ (**6d**)	**7d**	69	2:1
4	4-FC_6H_4 (**6e**)	**7e**	67	3:1
5	4-ClC_6H_4 (**6f**)	**7f**	65	4:1
6	4-$O_2NC_6H_4$ (**6g**)	**7g**	54	2:1
7	4-MeC_6H_4 (**6h**)	**7h**	73	3:1
8	3-MeC_6H_4 (**6i**)	**7i**	42	6:1
9	2-MeC_6H_4 (**6j**)	**7j**	43	2:1

This decarboxylative rearrangement can accommodate electron-rich aryl groups (entries 1–3) and electron-poor aryl groups (entries 4–6), with reasonable yields obtained in each instance. The aryl moiety can also cope with *ortho*, *meta*, and *para*-substitution in a range of tolyl acetates (entries 7–9). We would like to point out that the final *Z*/*E* ratio was highly sensitive to the initial conditions, as gauged by the extensive optimization of **6a**. Therefore, it may be reasonable to judge that each individual substrate may in turn have its *Z*/*E* selectivity improved through a local optimization process.

This decarboxylative rearrangement has been demonstrated on alkyl ester **6k** (Scheme 3). While, the rearrangement in this instance is non-optimized, we feel that the excellent levels of *Z*/*E* control are noteworthy and suggest good substrate scope in future studies.



Scheme 3. Incorporation of alkyl functionality.



Scheme 4. Attempted Diels–Alder reaction and diene conformation.

Finally, we briefly examined the feasibility of **7a** acting as a diene component in a Diels–Alder reaction (Scheme 4).[17] To assess this point, diene **7a** was refluxed in toluene for 24 h with the reactive dienophile, maleic anhydride (**8**). Surprisingly, even though an electron-rich diene is present with an electron-deficient dienophile, no reaction was observed, with **7a** recovered with full mass balance. To account for this interesting observation, we suggest that the requisite *s-cis* conformation of **7a** cannot be accessed, even under forcing conditions, from *s-trans*-**7a.**

In conclusion, the first Ireland–Claisen [3,3]-sigmatropic rearrangement of an ynamido ester is reported. A range of trisubstituted amidodienes has been accessed in good to excellent levels of *E/Z* selectivity and good yields. We are currently examining the synthetic utility of these amidodiene products further and investigating the observed *E/Z* stereoselectivity. Details will be reported in due course.

Acknowledgements

We acknowledge the support of the University of Bath and EPSRC for studentship funding (S.J.H.).

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16. Representative example; synthesis of **7b**. To a flask was added LiHMDS (1 M in THF, 0.57 mL, 0.57 mmol, 1.8 equiv) and Me_3SiCl (73 μL, 0.57 mmol, 1.8 equiv). The mixture was stirred at −95 °C for 0.25 h before the dropwise addition of **6b** (100 mg, 0.32 mmol, 1 equiv) in THF (2 mL). After 0.5 h at −95 °C, the reaction mixture was allowed to warm to room temperature after which time it was stirred for an additional 24 h. The reaction was then quenched with 1:1 1 M HCl/brine solution (5 mL) and extracted with EtOAc (3 × 10 mL), with the combined organic extracts being dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification via flash chromatography, eluting with 2:1 petroleum ether/EtOAc, gave *Z*/*E*-**7b** (46 mg, 53%). FTIR (film/cm^{-1}) υ_{max}: 2903, 2798, 1741, 1604, 1519. ^1H NMR (500 MHz, $CDCl_3$) δH: 7.29 (2H, app. d, J = 8.5 Hz), 6.65 (2H, app. d, J = 8.5 Hz), 6.48 (1H, s), 6.17–6.08 (1H, m), 5.79 (1H, dqd, J = 11.4, 7.2, 0.8 Hz), 4.39 (1H, d, J = 7.7 Hz), 4.36 (1H, d, J = 6.7 Hz), 3.80 (1H, d, J = 6.7 Hz), 3.77 (1H, d, J = 7.7 Hz), 2.96 (6H, s), 1.66 (3H, dd, J = 7.2, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δC: 156.1, 149.5, 146.8, 130.3, 130.2, 128.5, 125.2, 123.8, 111.9, 61.6, 46.2, 40.4, 14.7; MS (ESI:+ve) m/z: calcd for $C_{16}H_{20}N_2O_2Na$: 295.1422, found: 295.1417, $[M+Na]^+$.
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