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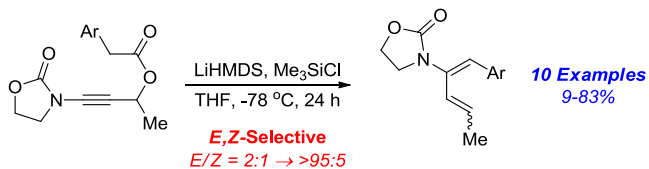
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### Ireland-Claisen rearrangement of ynamides: stereocontrolled synthesis of 2-amidodienes

Stephen J. Heffernan, David R. Carbery\*

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

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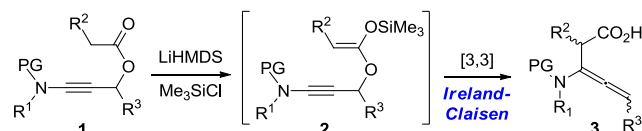
### ABSTRACT

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.

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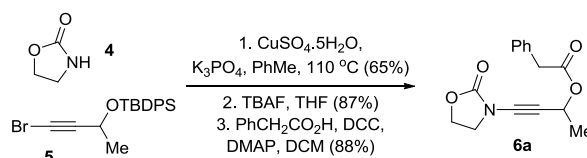
Ynamides have developed a mature and varied area of organic synthesis in recent years.<sup>1</sup> These compounds have been used in a raft of transition metal catalyzed reactions, such as cycloadditions and couplings.<sup>2</sup> Whilst a strongly electron-donating nitrogen is tempered by a nitrogen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

We have recently reported the use of enamides in the Ireland-Claisen [3,3]-sigmatropic rearrangement.<sup>4</sup> As part of this area of research within our group,<sup>5</sup> 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.<sup>6,7</sup> 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,<sup>8-10</sup> we felt this rearrangement was worthy of investigation.



**Scheme 1.** Proposed Ireland-Claisen rearrangement of ynamides to allenamides.

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



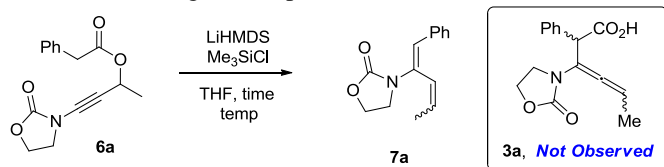
**Scheme 2.** Model Substrate Synthesis.

Initial attempts to form allenamide **3** centered upon utilizing the protocol developed for the rearrangement of enamides (Table 1).<sup>4b</sup> However, we were presented with a particularly complex reaction mixture, with attempted diazomethane-mediated carboxylic acid methylation observed to be non-productive,

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suggesting the absence of a carboxylic acid group. After careful chromatography, oxazolidinone substituted diene **7a**, with the major isomer 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.<sup>13</sup> Therefore, we sought to optimize the formation of this amidodiene product (Table 1).

**Table 1.** Rearrangement optimization



Entry	LiHMDS (equiv)	Me <sub>3</sub> SiCl (equiv)	Temp (°C)	Time (h)	Yield (%)	<i>Z/E</i>
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 <sup>a</sup>	1.3	1.3	-78→rt	24	13	>95:5
5	1.3 <sup>b</sup>	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 <sup>c</sup>	-
9	1.3	1.3	-20→rt	1.5	0 <sup>c</sup>	-
10	1.3	1.3	0→rt	1.5	0 <sup>c</sup>	-
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

<sup>a</sup>Reaction conducted in PhMe. <sup>b</sup>NaHMDS used as base. <sup>c</sup>Full mass recovery of **6a**.

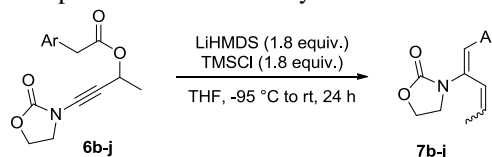
The rearrangement is particularly sensitive to the initial conditions employed (Table 1). For example, low loadings of base and Me<sub>3</sub>SiCl resulted in excellent stereocontrol (entries 1-4). The reaction requires the presence of silyl chloride and therefore supports a traditional Ireland-Claisen 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.<sup>14</sup> 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.<sup>15,16</sup> However, the decarboxylation step required forcing thermal conditions (140-250 °C) to accomplish the loss of CO<sub>2</sub>. Therefore, the presence of the *N*-substitution has a profound effect on this decarboxylation event. With an optimized rearrangement developed on phenyl acetate **6a**, we have sought to examine the scope of the arylacetate 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 has been studied with 1.8 equivalents of LHMDS and Me<sub>3</sub>SiCl.

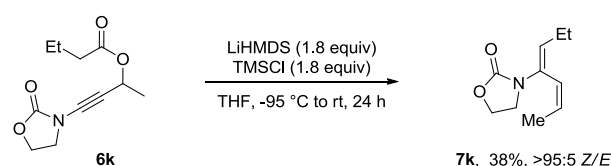
**Table 2.** Scope of ester functionality<sup>17</sup>



Entry	Ar	Diene	Yield (%)	<i>Z/E</i>
1	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> ( <b>6b</b> )	<b>7b</b>	53	>95:5
2	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>6c</b> )	<b>7c</b>	62	9:1
3	3,4-(OCH <sub>2</sub> O)C <sub>6</sub> H <sub>3</sub> ( <b>6d</b> )	<b>7d</b>	69	2:1
4	4-FC <sub>6</sub> H <sub>4</sub> ( <b>6e</b> )	<b>7e</b>	67	3:1
5	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>6f</b> )	<b>7f</b>	65	4:1
6	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>6g</b> )	<b>7g</b>	54	2:1
7	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>6h</b> )	<b>7h</b>	73	3:1
8	3-MeC <sub>6</sub> H <sub>4</sub> ( <b>6i</b> )	<b>7i</b>	42	6:1
9	2-MeC <sub>6</sub> H <sub>4</sub> ( <b>6j</b> )	<b>7j</b>	43	2:1

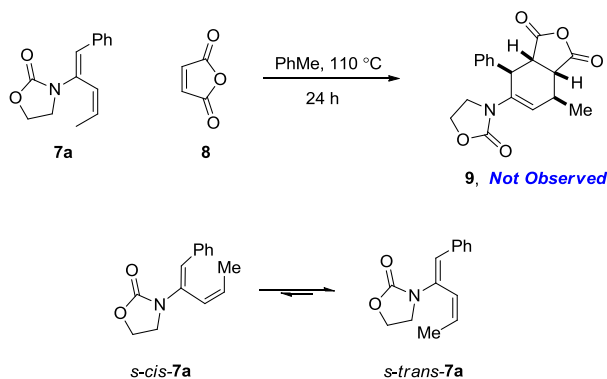
This decarboxylative rearrangement can accommodate electron-rich aryl groups (entries 1-3) and electron-poor aryl groups (entries 4-6), with reasonable yields in each instance. The aryl moiety can also cope with *ortho*, *meta* and *para*-substitution in a range of tolylacetates (entries 7-9). We would 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). Whilst, the rearrangement in this instance is non-optimized, we feel the excellent levels of *Z/E* control are noteworthy and suggest good substrate scope in future studies.



**Scheme 3.** Incorporation of alkyl functionality.

Finally, we have briefly examined the feasibility of **7a** acting as a diene component in a Diels-Alder reaction (Scheme 4).<sup>18</sup> To assess this point, diene **7a** was refluxed in toluene for 24 hours 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*.



**Scheme 4.** Attempted Diels-Alder reaction and diene conformation.

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

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- 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<sub>3</sub>SiCl (73  $\mu$ L, 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 M HCl/brine solution (5 mL) and extracted with EtOAc (3 x 10 mL), with the combined organic extracts being dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification via flash chromatography, eluting with 2:1 petroleum ether/EtOAc, gave **7b** (46 mg, 53%). FTIR (film/cm<sup>-1</sup>)  $\nu_{\max}$ : 2903, 2798, 1741, 1604, 1519. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ H: 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ C: 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<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>Na: 295.1422, found: 295.1417, [M + Na]<sup>+</sup>.
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