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One pot synthesis of α,α-bis(*N*-arylamido) lactams via iodide-catalyzed rearrangement of β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetals

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ABSTRACT

Five and six-membered cyclic ketene-*N,O*-acetals, generated in situ from 2,3-dimethyl-2-oxazolinium iodide or 2,3-dimethyl-2-oxazinium iodide and triethylamine, reacted with aryl isocyanates in refluxing THF producing α,α-bis(*N*-arylamido) lactams via the iodide-catalyzed rearrangement of β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetal intermediates. The cyclic ketene-*N,O*-acetal generated in situ from 2,3,4,4-tetramethyl-2-oxazolinium iodide reacted with isocyanates to give β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetals, which do not readily rearrange. The two methyls at C-4 hindered the nucleophilic attack of iodide on C-5, which is required for rearrangement.

1. Introduction

Cyclic ketene acetals (Fig. 1) with two electron-donating heteroatoms are nucleophiles.[1] These two heteroatoms make the β-carbon more electron rich and nucleophilic than vinyl ethers or enamines. Cyclic ketene-*N,O*-acetals react with both aroyl and aliphatic acid chlorides,[2] isocyanates,[3] and isothiocyanates.[3a,b] Cyclic ketene-*N,O*-acetals were generated first in these previous reactions[2,3a,b] by reacting 2,3,4,4-tetramethyl-2-oxazolinium iodide **1** or 2,3-dimethyl-2-oxazinium iodide with sodium hydride. For example, an acidic 2-methyl proton of **1** was quantitatively deprotonated by NaH to form cyclic ketene-*N,O*-acetal **2** (Eq. 1). After purification of **2** by distillation, conversion into β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetals **3** was performed by reacting **2** with 2 equiv aryl isocyanates.

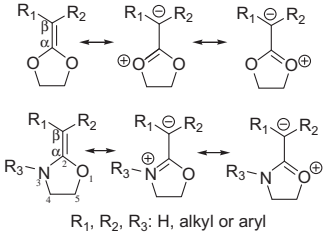
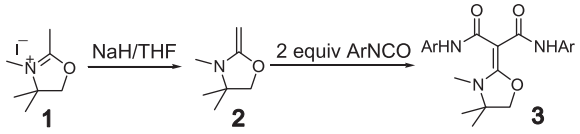
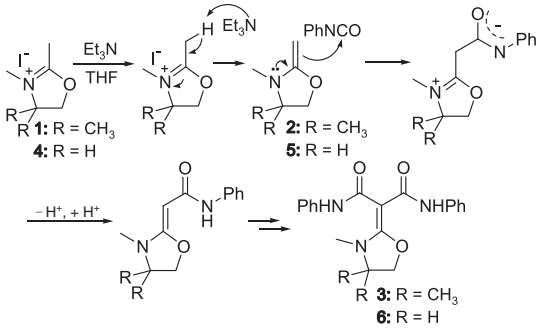


Figure 1. Five-membered cyclic ketene-*O,O*- and -*N,O*-acetals.



(1)

The 2-methyl group of **1** may also be reversibly deprotonated by triethylamine. Thus, we have now reacted **1** or its analog **4**, triethylamine and an aryl isocyanate in one pot to generate cyclic ketene-*N,O*-acetals **2** or **5** in situ (Scheme 1). Compound **2** or **5** then react further with the aryl isocyanate to form β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetals **3** or **6** without isolation and purification of **2** or **5**. A mechanism accounting for this substitution reaction is suggested below.



Scheme 1. Suggested mechanism for the one pot process to generate β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetals **3** or **6**.

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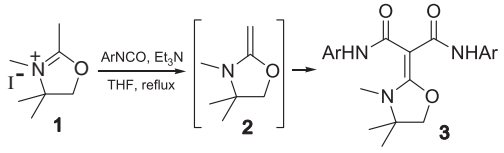
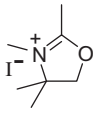
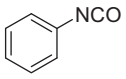
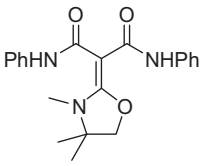
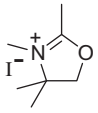
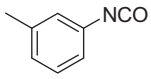
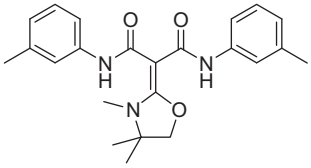
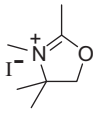
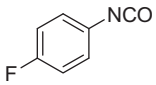
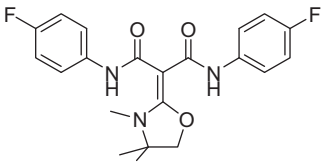
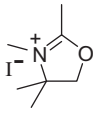
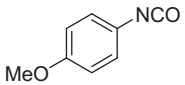
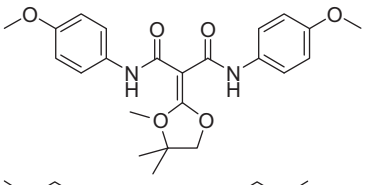
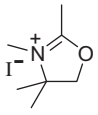
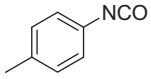
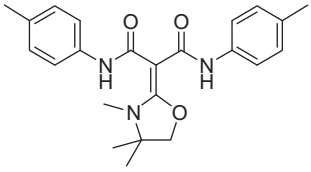
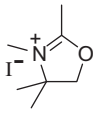
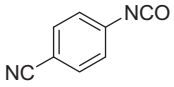
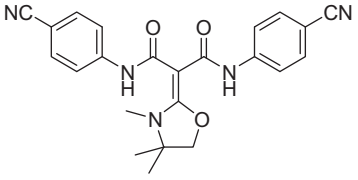
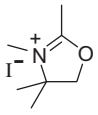
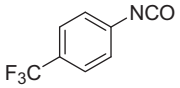
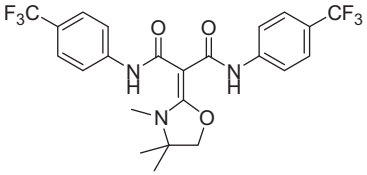
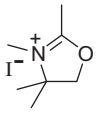
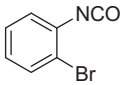
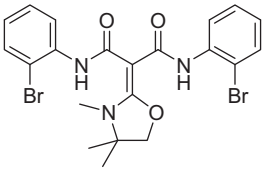
2. Results

Three cyclic ketene-*N*,*O*-acetals and eight aryl isocyanates were employed to explore this reaction. Selected results from these reactions are given in Table 1 and Table 2. All reactions in Table 1 proceeded through the 4,4-dimethyl-substituted cyclic ketene-*N*,*O*-acetal **2**.

The reaction sequence (Table 1) generated β,β-bis(*N*-arylamido) cyclic ketene-*N*,*O*-acetals **3** nicely after 5 h refluxing in THF where

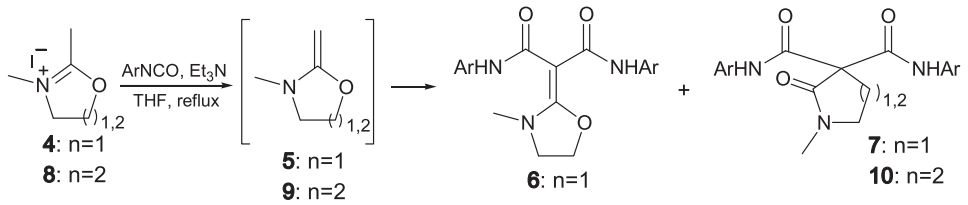
Table 1
Reactions of in situ generated cyclic ketene-*N*,*O*-acetal **2** with isocyanates to form *N*,*N*′-diaryl-2-(3,4,4-trimethyl-oxazolidin-2-ylidene)-malonamide **3**[a]



Entry	Iodide salt	Isocyanate	Product		Yield[b] (%)
1				**3a**	79
2				**3b**	76
3				**3c**	76
4				**3d**	64
5				**3e**	69
6				**3f**	36
7				**3g**	82
8				**3h**	76

[a] Reactions were run in refluxing THF for 5 h. Reactant molar ratio **1**/Et_3N/isocyanate = 1:1.3–1.5:2.2–2.3. Column chromatography (stationary phase: silica gel, eluting solvent: acetone/hexanes or ethyl acetate/hexanes) was used for purification.
[b] Isolated yield.

Table 2
Reactions of in situ generated cyclic ketene-*N*,*O*-acetals **5** and **9** with isocyanates[a]



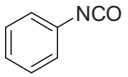
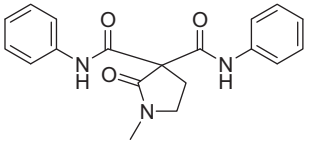
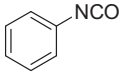
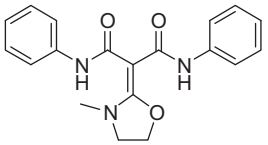
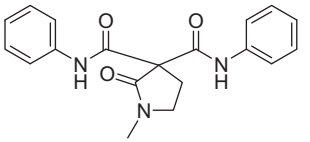
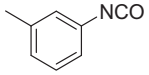
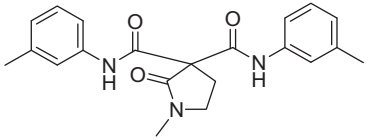
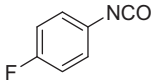
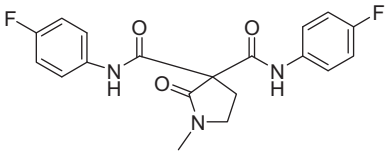
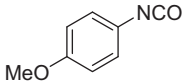
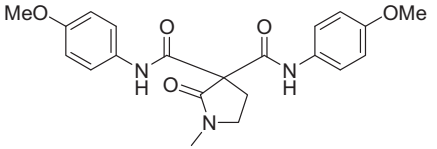
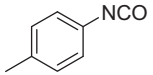
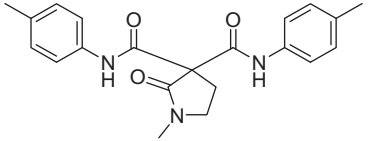
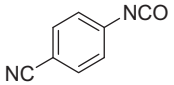
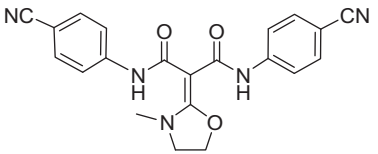
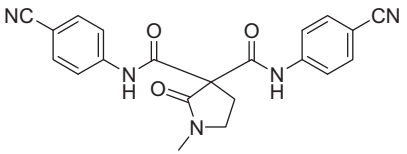
Entry	Iodide salt	Isocyanate	Product **6**		Yield[b] (%)	Product **7** or **10**		Yield[b] (%)
1[c]			None				**7a**	39
2[d]				**6a**	55		**7a**	Trace
3			None				**7b**	73
4			None				**7c**	85
5			None				**7d**	62
6			None				**7e**	67
7				**6f**	5		**7f**	28

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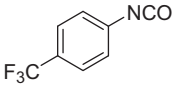
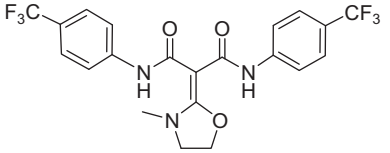
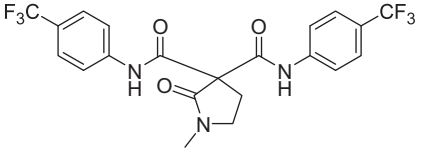
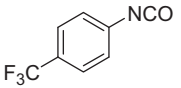
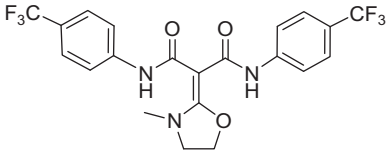
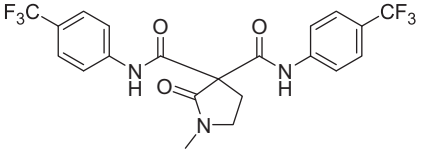
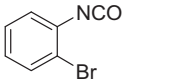
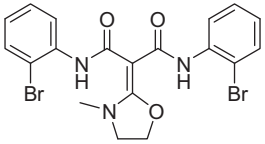
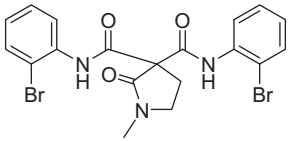
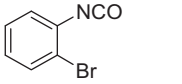
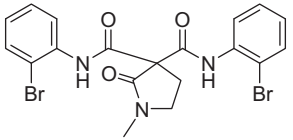
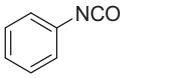
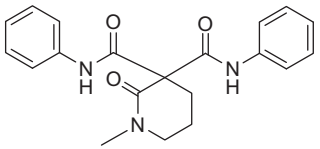
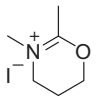
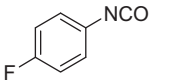
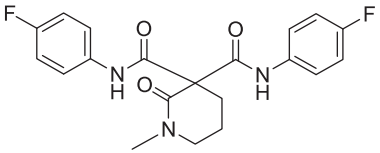
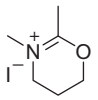
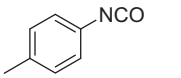
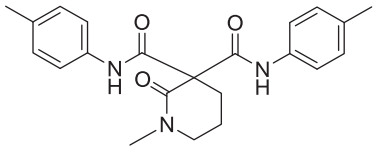
Table 2 (*continued*)

Entry	Iodide salt	Isocyanate	Product **6**		Yield[b] (%)	Product **7** or **10**		Yield[b] (%)
8				**6g**	14		**7g**	69
9[e]				**6g**	5		**7g**	75
10				**6h**	29		**7h**	42
11[f]			None				**7h**	68
12			None				**10a**	14
13			None				**10b**	21
14			None				**10c**	12

[a] Reactions were run in refluxing THF for 5 h. Reactant molar ratio **4** (or **8**)/Et_3N/isocyanate = 1:1.3–1.5:2.2–2.3. Column chromatography (stationary phase: silica gel, eluting solvent: acetone/hexanes or ethyl acetate/hexanes) was used for purification.

[b] Isolated yield.

[c] Reactant molar ratio: **4**/Et_3N/isocyanate = 1:1.3:1.1.

[d] Reaction was run in THF at room temperature where rearrangement to lactam is exceedingly slow. The product was purified by recrystallization from DCM.

[e] Reaction was run in refluxing THF for 13.5 h.

[f] Reaction was run in refluxing anhydrous 1,4-dioxane for 11.5 h.

R = methyl (Table 1, product **3**, entries 1–8). However, when R = H, the corresponding β,β-bis(*N*-arylamido) cyclic ketene-*N,O*-acetals **6** were not observed (Table 2, entries 1, 3–6) or only obtained in small amounts (Table 2, entries 7,8,10) after 5 h refluxing in THF. Unexpectedly, the rearranged α,α-bis(*N*-arylamido) lactams **7** (Table 2, entries 1, 3–8, 10) resulted when cyclic ketene-*N,O*-acetal **5**, without two methyl substituents on C-4, was used. The lactams were obtained even when using only 1 equiv of aryl isocyanate. This is shown for the reaction of phenyl isocyanate with 2,3-dimethyl-2-oxazolinium iodide **4** (Table 2, entry 1).

The lactams were readily characterized by NMR and FTIR spectroscopy. The ring methylene hydrogens adjacent to nitrogen of α,α-bis-substituted *N*-methyl-lactam **7a** (Ar = Ph) exhibited an NMR chemical shift at 2.7 ppm, sharply upfield from their original chemical shift of 4.1 ppm at the C-5 position of the precursor, 2-(3-methyl-oxazolidin-2-ylidene)-*N,N′*-diphenyl-malonamide, **6a**. This was characteristic of all the lactams **7a**–**h**. The FTIR spectrum of **7a** (Ar = Ph) exhibited a characteristic tertiary amide carbonyl stretching band[4] at 1696 cm^{-1}. X-ray crystallography confirmed this lactam's structure (Fig. 2).

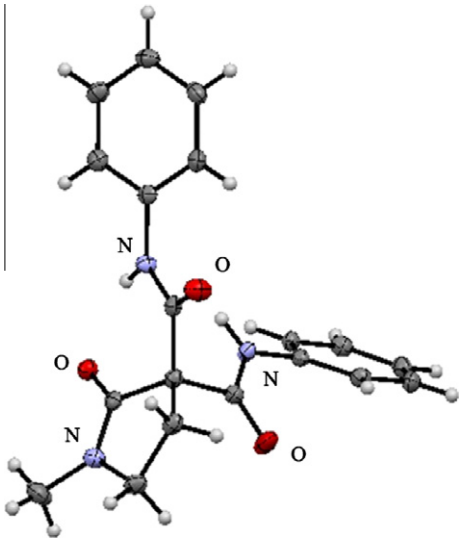


Figure 2. Crystal structure of α,α-bis(*N*-phenylamido)-γ-lactam **7a**, CCDC number 794113.

Rearrangement to lactam **7a** did not readily occur at room temperature. Cyclic ketene-*N,O*-acetal **5** reacted with 2 equiv of phenyl isocyanate (Table 2, entry 2) to give the β,β-bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **6a** almost exclusively at room temperature in THF. Only traces of the rearranged lactam **7a** were detected by TLC. The structure of **6a** was confirmed by X-ray crystallography (Fig. 3).

Somewhat slower rearrangement rates to lactams were found with aryl isocyanates carrying an electron withdrawing group on the phenyl ring (*p*-NC-PhNCO (Table 2, entry 7) and *p*-CF_3PhNCO (Table 2, entry 8)). Longer reaction times led to a higher rearrangement yield (*p*-CF_3PhNCO, Table 2, entry 9). *o*-Br-PhNCO also gave incomplete rearrangement after 5 h refluxing in THF (Table 2, entry 10). Using 1,4-dioxane, which has a higher boiling point (101 °C) than THF (66 °C), and longer reaction times drove the rearrangement of β,β-bis(*N*-*o*-bromophenyl amido) cyclic ketene-*N,O*-acetal **6h** to the lactam **7h** quantitatively (Table 2, entry 11).

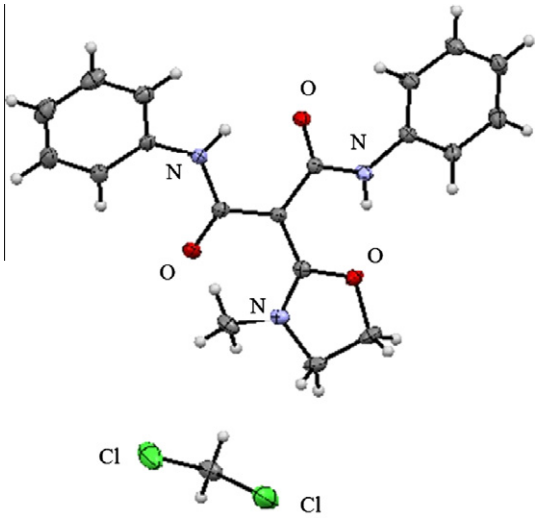
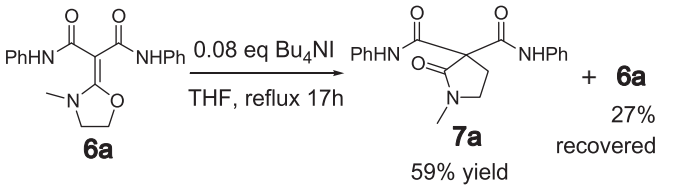


Figure 3. Crystal structure of 2-(3-methyl-oxazolidin-2-ylidene)-*N,N′*-diphenyl-malonamide **6a**, CCDC number 794114.

Six-membered ring cyclic ketene-*N,O*-acetal **9**, generated in situ from 2,3-dimethyl-2-oxazinium iodide **8**, reacted with aryl isocyanates giving rise to the rearranged lactams **10a–c** in refluxing THF (Table 2, entries 12–14) but in much lower yields compared to their five-membered ring analog **5**.

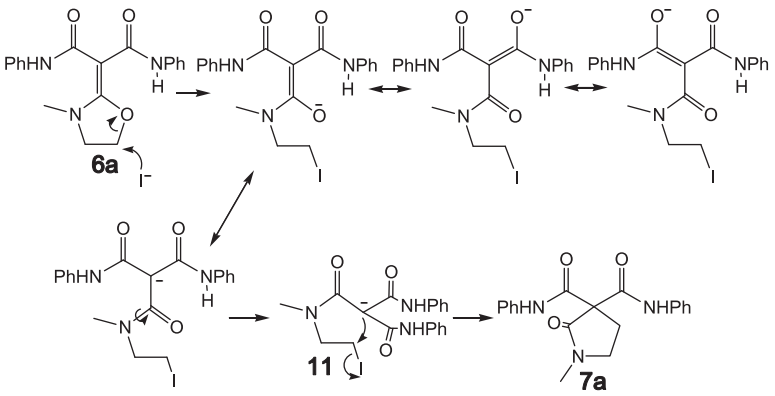
3. Discussion

To see if the rearrangement is a pure thermal process, the β,β-bis(*N*-phenylamido) cyclic ketene-*N,O*-acetal **6a** was refluxed in THF for 3 h, but **6a** was recovered and no **7a** formed. Thus, heating alone does not cause the rearrangement. Is this rearrangement catalyzed by a reaction component (triethylamine, iodide, triethylamine hydrochloride salt, 2,3-dimethyl-2-oxazolinium ion, and isocyanate)? Refluxing **6a** for 5 h in THF with triethylamine gave only recovered starting material. In contrast, refluxing **6a** in THF, in the presence of a catalytic amount (0.08 equiv) of tetrabutylammonium iodide, generated the rearranged product **7a** in 59% yield after 17 h (Eq. 2). Hence, this process is catalytic in iodide.



(2)

A mechanism is proposed in Scheme 2. Iodide attacks C-5 next to the ring oxygen in **6a**. This carbon is susceptible to nucleophilic attack by nucleophiles.[5] The negative charge on the ring-opened anion **11** is distributed over three oxygens and the β-carbon. After bond rotation, the negatively charged β-carbon of **11** does an S_N2 attack on the primary iodide-bearing carbon, displacing iodide, and generating the five-membered ring lactam **7a**. This catalytic process finds analogy to the iodide-induced rearrangement of [(*N*-aziridinomethylthio)methylene]-2-oxindoles to spiropyrrolidinyl-oxindoles,[6] where iodide attack on an aziridine ring set off a rearrangement process.



Scheme 2. Proposed mechanism for iodide-catalyzed rearrangement of 2-(3-methyl-oxazolidin-2-ylidene)-*N*,*N*′-diphenyl-malonamide **6a**.

It is likely that iodide attack is rate determining since the ring closure step is intramolecular. Reaction of **6a** with the cylindrical nucleophile, isothiocyanate, and SCN^- was conducted in refluxing THF (5 h). No ring opening was observed and **6a** was recovered. This emphasizes that a high anion nucleophilicity is needed to catalyze this conversion. Electron withdrawing groups on the aryl rings of **6f** (Ar = *p*-NC-Ph) and **6g** (Ar = *p*-CF_3-Ph) may stabilize the ring-opened anion **11** by slightly reducing the negative charge density on the nucleophilic β-carbon of **11**. However, these are distant functions and the anion is already highly stabilized. Compound **6h** with an *o*-Br-Ph function also rearranged to the lactam **7h** more slowly, perhaps due to steric or stereoelectronic factors.

In the presence of the two methyl groups on C-4, the incoming iodide is sterically hindered from attacking C-5 of **3a** (Fig. 4). The large iodide radius enhances this steric hindrance during nucleophilic attack on C-5. Thus, rearrangement in refluxing THF is not readily achieved.

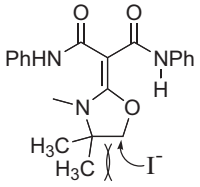


Figure 4. The 4,4-dimethyl groups prevent the iodide attack on C-5 of **3a**.

The formation of α,α-bis(*N*-phenylamido) lactam **7a** in the presence of only 1 equiv of phenyl isocyanate occurs because cyclic ketene-*N*,*O*-acetal **5** was generated in situ from **4** during the reaction. Thus, excess phenyl isocyanate was present as intermediate **5** was formed. Under these conditions the second substitution occurred to form β,β-bis(*N*-phenylamido) cyclic ketene-*N*,*O*-acetal **6a**, which rearranged to **7a**.

Whether this rearrangement reaction can be extended to aliphatic isocyanates and other electrophiles will be studied.

Acknowledgment

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Supplementary data

Supplementary data associated with (complete experimental synthetic descriptions and full characterizations of all the compounds) this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.148.

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