



Push–pull alkenes by reacting *N,N'*-dimethyl cyclic ketene *N,N'*-acetals with isocyanates: synthesis, structures, and reactivities

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ABSTRACT

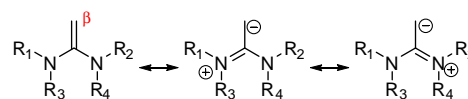
N,N'-Dimethyl cyclic ketene *N,N'*-acetals react with two or three equivalents of isocyanates to generate tetrasubstituted push–pull alkene derivatives in one-pot sequential reactions. X-ray crystallography showed significant elongations and out of plane distortions of the polarized carbon–carbon double bonds.

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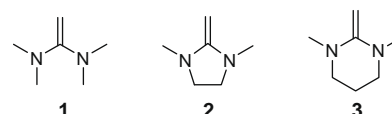
Ketene *N,N'*-acetals, which combine two enamine functions in one functional group structure, exhibit significant nucleophilicity at their β -carbons due to the delocalization of the lone-pair electrons on both the nitrogens into the C=C double bond (Scheme 1).

Cyclic ketene *N,N'*-acetals are generally more nucleophilic than acyclic analogs due to stereoelectronic effects. For example, five-membered cyclic ketene *N,N'*-acetal **2** exhibited much higher reactivity than its acyclic counterpart **1** in the inverse electron demand Diels–Alder reactions (Scheme 2).¹ The exceptional reactivity of **2** causes preparation, storage, and handling difficulties^{2,3} which account for how seldom they have been investigated in organic synthesis. The six-membered ring analog **3** (Scheme 2) has never been reported.

The electron-rich structures of cyclic ketene *N,N'*-acetals **2** and **3** make them ideal candidates for constructing push–pull alkenes but no such conversions appear in the literature. A typical push–pull alkene consists of electron-donating groups (push) and electron-withdrawing groups (pull) coupled through a double bond. Intramolecular charge transfer from the electron-donating groups to the electron-withdrawing groups leads to profound consequences on the molecular structure and properties. These include central double bond elongation,⁴ lowering of its rotational barrier,^{5,6} existence of strong charge-transfer absorption bands,⁷ large dipole moments,⁸ and high hyperpolarizabilities which are prerequisite for organic nonlinear optical materials.^{9–11} These special properties provided impetus for the synthesis, characterization, and applications of push–pull alkenes^{12–24} along with theoretical investigations to understand and predict these effects.^{25–31} Recently, Pittman's group^{32,33} reported the reactions of cyclic ketene-*N,X*-acetals (X = O, S) with isocyanates and isothiocyanates to generate push–pull alkenes in excellent yields. In this Letter, the conversion of cyclic ketene-*N,N*-acetals **2** and **3** to sterically



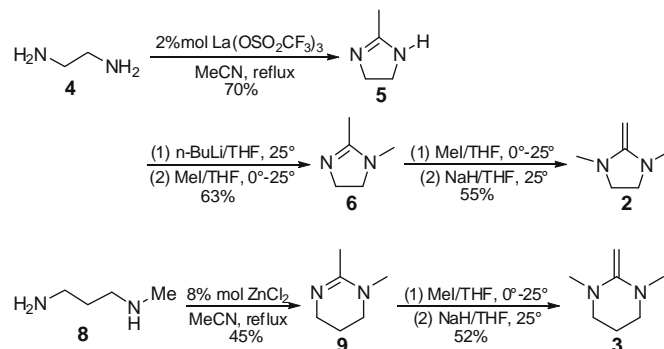
Scheme 1. Resonance structures of ketene *N,N'*-acetals.



Scheme 2. Ketene *N,N'*-acetals.

crowded push–pull alkenes via reactions with isocyanates will be demonstrated and discussed for the first time.

Cyclic ketene *N,N'*-acetals **2** and **3** were prepared from diamines (Scheme 3). The lanthanum(III) triflate-catalyzed condensation of



Scheme 3. Preparation of **2** and **3**.

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Table 1
Reactions of cyclic ketene *N,N'*-acetals with isocyanates

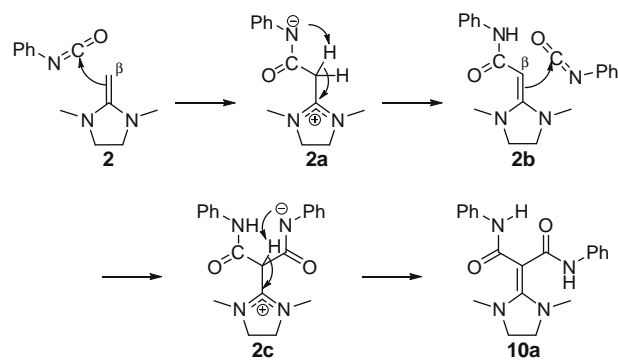
Substrate	Isocyanate	Product	Yield ^a (%)
			90
			93
			94
			95
			84
			81
			89
			93

^a Yields are based on substrate **2** or **3**.

ethylenediamine **4** with acetonitrile gave 2-methylimidazoline **5**,³⁴ which generated 1,2-dimethylimidazoline **6** upon deprotonation with butyllithium and subsequent methylation using MeI. Further methylation with MeI and deprotonation gave **2** in a moderate yield. The same sequence can be used to prepare the six-membered analog **3**. However, we discovered that 1,2-dimethyl-1,4,5,6-tetrahydro-pyrimidine **9** could be obtained directly from inexpensive *N*-methyl-1,3-propanediamine **8** in MeCN using ZnCl₂ catalysis (lanthanum(III) triflate is not effective for this conversion). This is the first example of a ZnCl₂-catalyzed synthesis of 1,2-dialkyl-1,4,5,6-tetrahydropyrimidines by condensation of *N*-alkyl-1,3-propanediamines with a nitrile.³⁵ Subsequent treatment of **9** with MeI/THF and NaH/THF furnished ketene acetal **3**.

Five-membered ring cyclic ketene-*N,N'*-acetal **2** and its six-membered analog **3**, were individually reacted immediately after synthesis with two equivalents of several different isocyanates in THF at the room temperature (Table 1). The expected but previously unreported tetrasubstituted push-pull alkenes **10a–d** and **11a–d** were isolated in excellent yields (Table 1). The electron-pushing five or six-membered cyclic ketene-*N,N'*-acetal moieties interact directly with the two amide groups in these push-pull alkenes.

The mechanism shown in Scheme 4 accounts for the formation of **10a**. Nucleophilic attack of the β-carbon in **2** on the first equivalent of phenyl isocyanate gives zwitterion **2a**, which rapidly removes the acidic hydrogen from the β-carbon intramolecularly to produce mono-adduct **2b**.



Scheme 4. Mechanism for the formation of push-pull alkene **2**.

Table 2
Reactions of push-pull alkenes with isocyanates

Substrate	R ^a	Product	Yield (%)
10a	Ph	No reaction	—
10b	<i>p</i> -CH ₃ C ₆ H ₄	No reaction	—
10c	<i>p</i> -MeOC ₆ H ₄	No reaction	—
10d	<i>p</i> -FC ₆ H ₄	No reaction	—
11a	Ph	13a	32
11b	<i>p</i> -CH ₃ C ₆ H ₄	13b	37
11c	CH ₂ =CH-CH ₂ -	No reaction	—
11d	<i>t</i> -Bu	No reaction	—

^a The R group in push-pull reagent alkenes and R group in isocyanates were the same for each reaction reported here.

then reacts with the second equivalent of phenyl isocyanate to generate zwitterion **2c**. Intramolecular proton abstraction in **2c** finally gives structure **10a**.

The isolated products **10a–d** and **11a–d**, previously unknown, were further treated with excess isocyanates to probe the reactivities of these tetrasubstituted polarized alkenes (Table 2). Triple adducts **13a** and **13b** were obtained from the six-membered systems **11a** and **11b**, respectively. However, **10a–d** and **11c–d** did not form analogous triadducts using the isocyanates examined herein.

The single crystal structure of **10d** was determined and shown in Figure 1. A remarkable feature in this crystal structure is the elongated central carbon–carbon double bond (C14–C16: 1.45 Å),

which is substantially longer than the normal carbon–carbon double bond of ethylene (1.34 Å).³⁶ In addition to the longer central carbon–carbon double bond, a concomitant twisting of this double bond occurs as shown in the dihedral angles C13–C14–C16–N2 (57.00°), C15–C14–C16–N1 (56.44°), C13–C14–C16–N1 (123.44°), and C15–C14–C16–N2 (123.12°). This is the synergistic outcome of (1) steric repulsion between the N-substituents and the β-carbon-substituents, and (2) the push–pull effect which reduces the C14–C16 bond order, making it easier to twist out-of-plane. The extent of twisting reflects a compromise between the relaxation of the steric hindrance (energy drop) and the deviation of the alkene substituents from the ideal co-planar geometry (energy rise).

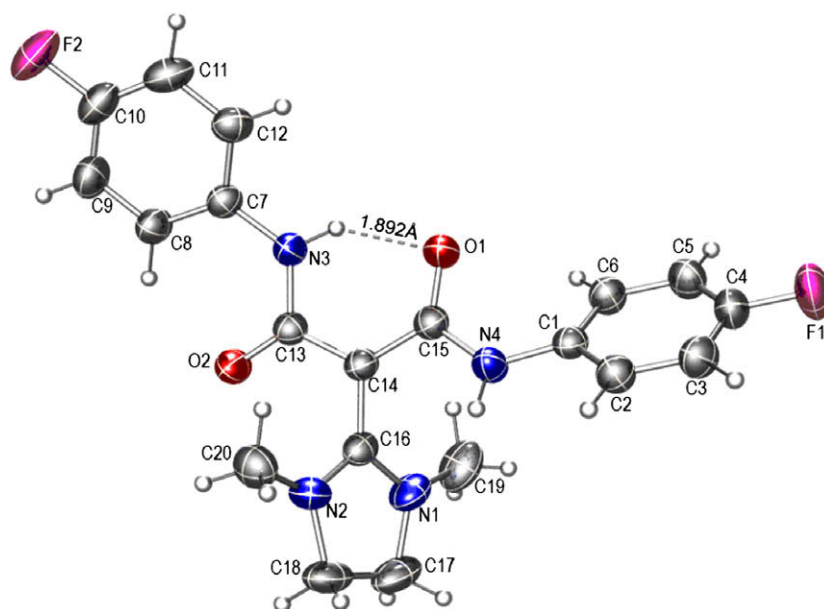


Figure 1. Crystal structure of **10d**. A water molecule is not shown for clarity. The thermal ellipsoids are drawn with 50% probability. CCDC: 689417.

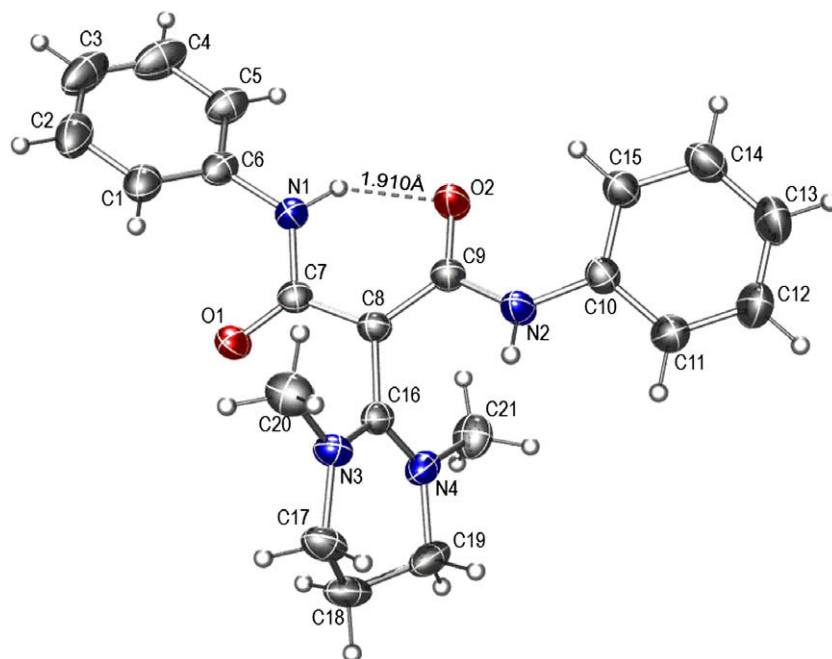
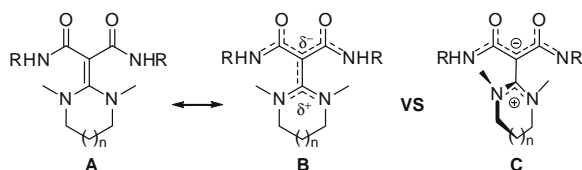


Figure 2. Crystal structure of **11a**. Disordered CHCl_3 molecules are present and not shown for clarity. The thermal ellipsoids are drawn with 50% probability. CCDC: 719324.



Scheme 5. The dependence of the charge separation on the geometry of a push-pull alkene. **A**: resonance structure showing no charge separation; **B**: resonance structure showing partial charge separation and a partial central double bond (central double bond may be twisted depending on steric factors); **C**: structure showing full charge separation in the 90° twisted geometry where the central bond is actually a zwitterionic single bond because no conjugation (π -bonding) is possible between donor and acceptor portions.

The short enamine carbon–nitrogen bonds (N1–C16: 1.33 Å; N2–C16: 1.32 Å) and the near planar configurations (versus pyramidal) of N1 and N2 suggest that N1–C16 and N2–C16 bonds have considerable double bond character. N1 and N2 are sp^2 -hybridized. An intramolecular hydrogen-bond exists in the crystal (O1···H–N3), which stabilizes the observed molecular geometry in the crystal.

The crystal structure of **11a** was also obtained (Fig. 2). Its central carbon–carbon double bond (C8–C16: 1.47 Å) is slightly longer (~ 0.02 Å) than that in **10d**. The length of the central double bond was recently demonstrated to be the sole parameter able to generally quantify the push–pull effect in push–pull alkenes based on NBO analysis (the longer the double bond, the stronger the push–pull effect).³⁰ The longer C=C bond length of **11a** versus **10d** helps to explain why the push–pull alkenes containing six-membered cyclic ketene-*N,N*-acetal donors (**11a** and **11b**) each underwent a further reaction with isocyanates (phenyl and *p*-tolyl, respectively), while those having five-membered cyclic ketene-*N,N*-acetal donors (**10a** and **10b**) did not.

The torsional angles about the central carbon–carbon double bond in **11a** (C7–C8–C16–N3: 67.87° ; C7–C8–C16–N4: 111.72° ; C9–C8–C16–N4: 67° ; C9–C8–C16–N3: 113.31°) have a larger twist ($\sim 10^\circ$) than that in **10d**. This enhanced twist is due to stronger

steric repulsions between donor and acceptor portions in **11a** versus that in **10d**. This larger twist angle is closer to the totally zwitterionic geometry (90° twist, Scheme 5). Thus, the minimum energy geometry of a push–pull alkene with six-membered ketene-*N,N*-acetal donor has more zwitterionic character than the five-membered analog. In other words, the acceptor portion of a six-membered push–pull alkene is more negatively charged and is more nucleophilic than the acceptor portions of the five-membered analog. This explains the different (higher) reactivities of **11a** and **11b** versus **10a** and **10b**.

The crystal structure of the triple adduct **13a** was determined (Fig. 3). Its central carbon–carbon double bond length (C8–C9: 1.47 Å) is comparable with that in **11a**, but this double bond is further twisted (C7–C8–C9–N2: 76.39° ; C7–C8–C9–N3: 100.72° ; C13–C8–C9–N2: 108.25° ; C13–C8–C9–N3: 74.65°) compared to **11a** due to **13a**'s larger acceptor groups. Two intramolecular hydrogen-bonds exist in the **13a** crystal structure (O3···H–N4 and O3···H–N1).

The five-membered ring *N,O*-analog, **14** (Fig. 4), was also synthesized according to a literature method.^{32,33} The crystal structure of **14** was determined in order to compare with those of **11d**, **11a**, and **13a**. The length of the central C6–C7 double bond in crystals of **14** (1.39 Å) is considerably shorter than those in **10d** (1.45 Å), **11a** (1.47 Å), and **13a** (1.47 Å). This was attributed to the weaker electron-donating ability of the *N,O*-ketene-acetal versus the stronger donation by cyclic ketene-*N,N*-acetals. The central carbon–carbon double bond of **14** is also less twisted versus those of **10d**, **11a**, and **13a** because one *N*-methyl group is replaced by oxygen atom. This dramatically reduced the donor–acceptor steric repulsions.

In summary, we have successfully demonstrated nucleophilic tandem reactions of cyclic ketene *N,N'*-acetals (**2** and **3**) with various isocyanates to construct new, unreported push–pull alkenes. The first $ZnCl_2$ -catalyzed condensation of an *N*-alkyl-1,3-propanediamine with nitrile was demonstrated to construct 1,2-dialkyl-1,4,5,6-tetrahydropyrimidine system. Significant elongations and torsions of the polarized carbon–carbon double bonds in these push–pull alkenes were observed using the X-ray crystallography. The stronger pushing effect of the six-membered cyclic ketene

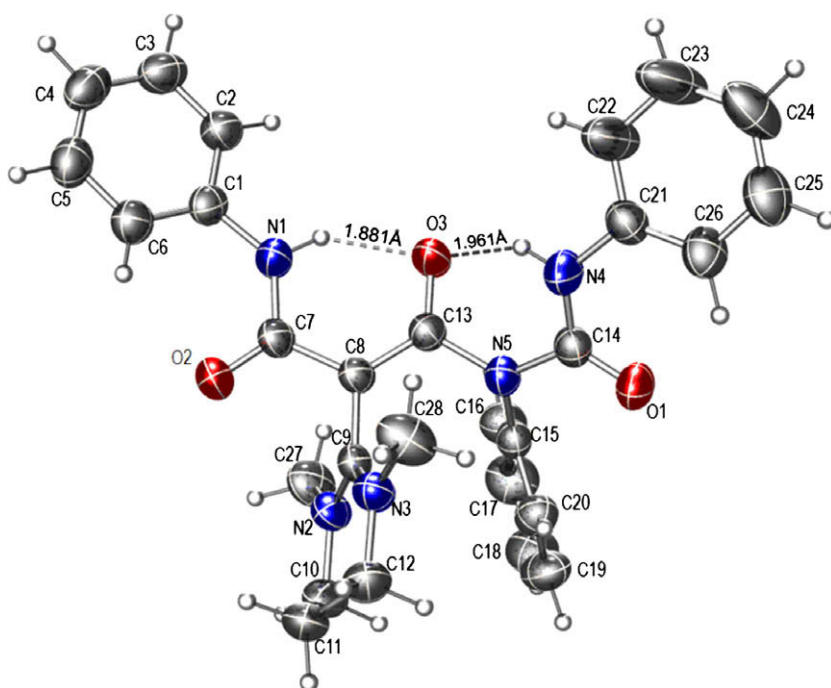


Figure 3. Crystal structure of **13a**. The thermal ellipsoids are drawn with 50% probability. CCDC: 689418.

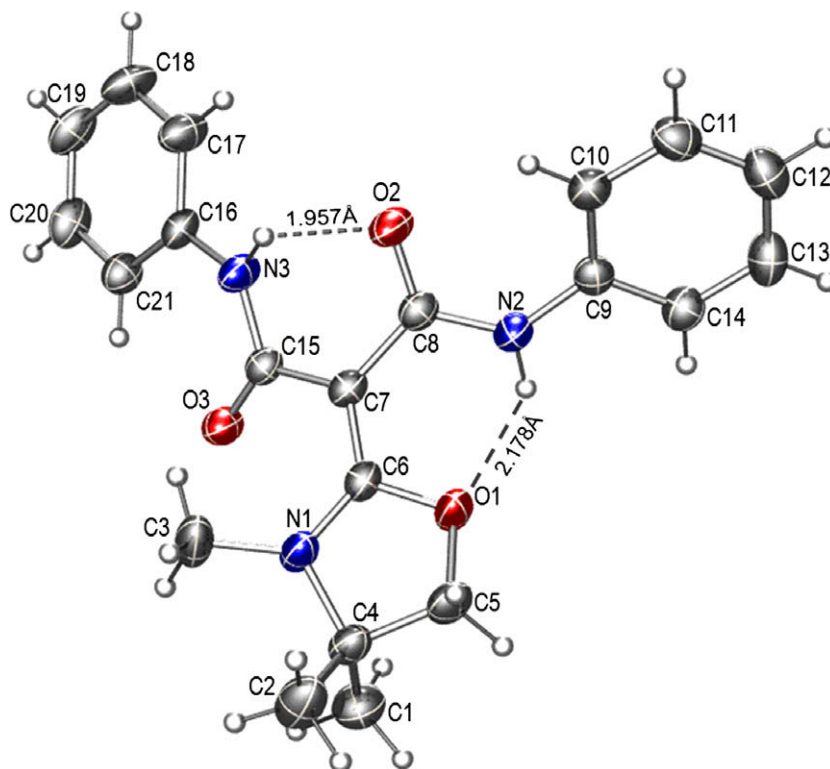


Figure 4. Crystal structure of **14**. The thermal ellipsoids are drawn with 50% probability. CCDC: 719325.

acetal portion in a push–pull alkene, versus the five-membered analog, was detected by reactivity differences for the first time.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.160.

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- Cyclic ketene *N,O*-ketene acetals can be stored under N₂ in base-treated glassware and they can coexist with NaH or *t*-BuOK for several months without appreciable deterioration.^{2h} However, in our experience, this method can only extend the life of the ketene *N,N'*-ketene acetals **2** and **3** (which are colorless liquids) for several days before they become dark brown viscous gels, presumably due to self-polymerization. It is best to use them as soon as they are synthesized.
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