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One-Pot Synthesis and Conformational Features of *N,N′*-Disubstituted Ketene Aminals

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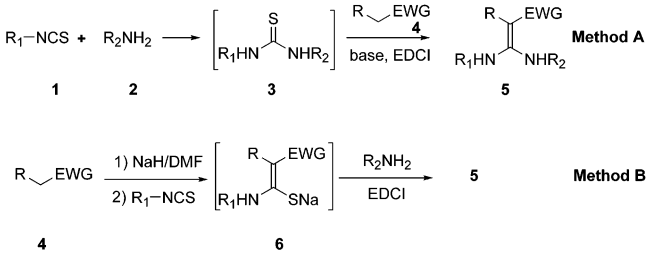
Abstract: *N,N′*-Disubstituted ketene aminals are bioisosteres of thioureas and are useful building blocks in many synthetic operations. A convenient one-pot synthesis of *N,N′*-disubstituted ketene aminals from activated methylene compounds and isothiocyanates is described. Most of these aminals exist in rotameric equilibrium around the central C═C bonds in solution, and the rotamers are stabilized by intramolecular hydrogen bonding both in solution and in solid states.

N,N′-Disubstituted ketene aminals are useful building blocks in many synthetic operations,[1] especially as the intermediates for construction of heterocyclic compounds.[2] They are also of general interest in medicinal and agricultural chemistry because they are possible bioisosteres of thioureas but with extra sites in the ketene that can be derivatized.[3] Like *N,N′*-disubstituted thioureas, their biologic activities rely on the stereochemistry of aminals because of possible *syn*/*anti* rotameric conformations. Typically, the synthesis of *N,N′*-disubstituted ketene aminals involves the stepwise or simultaneous displacement of both methylthio groups of ketene dithioacetals[4,2d] or the displacement of 2,2-dihalovinyl cyano or ketone compounds by nucleophilic amines.[5] However, these procedures usually lead to a mixture of mono- and disubstituted products and are only useful for the synthesis of symmetric *N,N′*-disubstituted products. Alternative methods involve the reaction of activated methylene compounds with isothioamide[6] or formamidinium salts.[7] All of these methods require the availability of necessary starting materials, which are often difficult to obtain or involve high temperature and the generation of noxious mercaptans.

SCHEME 1. One-Pot Synthesis of *N,N′*-Disubstituted Ketene Aminals



During our investigation of the synthesis of thiourea bioisosteres, we have previously demonstrated that 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) is an efficient thiocarbonyl activating agent[8] in the synthesis of *N,N′*-disubstituted cyanoguanidines,[9] acylguanidines,[10] sulfamoylguanidines, and sulfonylguanidines.[11] In this report, we disclose the EDCI-assisted one-pot synthesis of *N,N′*-disubstituted ketene aminals from activated methylene compounds and isothiocyanates.[3] We also consider the conformational features of these aminals.

As shown in Scheme 1, *N,N′*-disubstituted ketene aminals could be synthesized via two routes starting from the reaction of an isothiocyanate with a nucleophilic reagent, followed by the displacement of resulting thio group by another nucleophile. In the first route (Method

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TABLE 1. Synthesis of *N,N′*-Disubstituted Ketene Aminals (Scheme 1)

Entry	R_1	R_2NH_2 **2**	R EWG **4**	Method[a]	Yield (%)[b] of **5**
a	Ph	*n*-$BuNH_2$	NC, CO_2Me	A (DBU)	80
				B	91
b	*n*-Pr	4-$MeOC_6H_4NH_2$	NC, SO_2Ph	A (DBU)	80
				B	75
c	4-$MeOC_6H_4$	*n*-$BuNH_2$	NC, $CONMe_2$	A (DBU)	20
				A (NaH)	70
				B	75
d	4-ClC_6H_4	*t*-$BuNH_2$	NC, COPh	A (DBU)	10
				A (NaH)	55
				B	68
e	Ph	*t*-BuO, $CONH_2$	NC, COPh	A (DBU)	10
				A (NaH)	55
				B	65
f	Ph	*n*-$BuNH_2$	COPh	A (NaH)	5
				B	55

[a] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] All compounds were purified by silica gel column chromatography and characterized by ^1H NMR, ^{13}C NMR, and elemental analysis. All yields are isolated yields.

A), the intermediate thiourea could be condensed with an activated methylene anion to afford the *N,N′*-disubstituted ketene aminal with the assistance of a thiocarbonyl activating reagent. Since it has been reported that activated methylene compounds can react with isothioamide,[6] we first investigated the reaction of a thiourea **3a** (R_1 = Ph, R_2 = *n*-Bu) with methyl cyanoacetate **4a**. When the reaction was conducted in the presence of EDCI and triethylamine in methylene dichloride, the product **5a** was isolated in only 5% yield even after refluxing for 24 h. However, when DBU was employed as the base, compound **5a** was obtained in 80% yield after heating at 80 °C in DMF for 1 h. Similar results were obtained when mercury(II) chloride was employed as the thiocarbonyl activating agent (55%). This method appears to be general for highly activated methylene compounds, as shown in Table 1. For example, (phenylsulfonyl)-acetonitrile reacts with thiourea **3b** smoothly to afford **5b** in 80% yield after 1 h at 80 °C (entry b). The reaction of less activated methylene compounds with thioureas requires sodium hydride as the base (entries c−f). For example, 2-cyano-*N,N*-dimethyl-acetamide reacts with thiourea **3c** to afford **5c** in 70% yield when sodium hydride is used, compared to a 20% yield with DBU.

Alternatively, the isothiocyanate could first be condensed with an activated methylene anion to afford the intermediate thioamide anion **6**,[12] which provides the *N,N′*-disubstituted ketene aminal by the action of a

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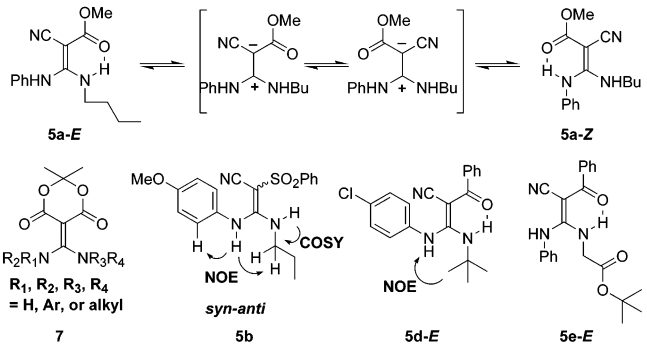
SCHEME 2. Solution Conformation of *N,N′*-Disubstituted Ketene Aminals



thiocarbonyl activating reagent and the requisite amine (Method B). Intermediate **6a** (R = cyano, R_1 = Ph, EWG = CO_2Me) was synthesized from methyl cyanoacetate sodium anion and phenyl isothiocyanate. The formation of intermediate **6a** was monitored by LC-MS or TLC analysis, which showed complete conversion of the starting phenyl isothiocyanate to **6a** in 30 min at 60 °C. After cooling to room temperature, the reaction mixture was treated with *n*-butylamine and EDCI to provide **5a** in 91% yield. As expected, we found that mercury(II) chloride[13] and 2-chloro-1-methylpyridinium iodide (Mukaiyama's reagent[14]) are also capable of converting intermediate **6a** to **5a** in 59% and 37% yields, respectively. This route appears to be general for a variety of activated methylene compounds as shown in Table 1. It should be noted that even acetophenone participates in the reaction to provide **5f** in good yield (55%).

Ketene aminals have been known to have fairly low rotational barriers around the C═C bond as a result of the push−pull effect of their substituents,[15,4f,7g] and a recent report suggests that derivatives of Meldrum's acid **7** (Scheme 2) also should undergo rapid rotation about the C═C bond at room temperature, giving rise to NMR signals from one average structure.[16] Spectral studies on compounds prepared in the present investigation indicated that they exist in the enamino form with strong intramolecular hydrogen binding. The IR spectra (KBr) strongly indicated a hydrogen-bonded NH stretching vibration at 3240−3330 cm^{-1}. The carbonyl stretching vibration in these compounds was merged with bands around and below 1600 cm^{-1}, reflecting the characteristic conjugation effect of the aminal group and strong intramolecular hydrogen bonding. The ^1H NMR of compound **5b** showed only one set of signals in either $CDCl_3$ or DMSO-d_6, indicating it is either a single stereoisomer or it has a very low rotational barrier around the C═C bond.[17] Although its stereochemistry about the ketene

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(17) The results from low temperature (10 to −40 °C in $CDCl_3$) NMR experiments are not conclusive because complex spectra arise from C−N bond rotamers.

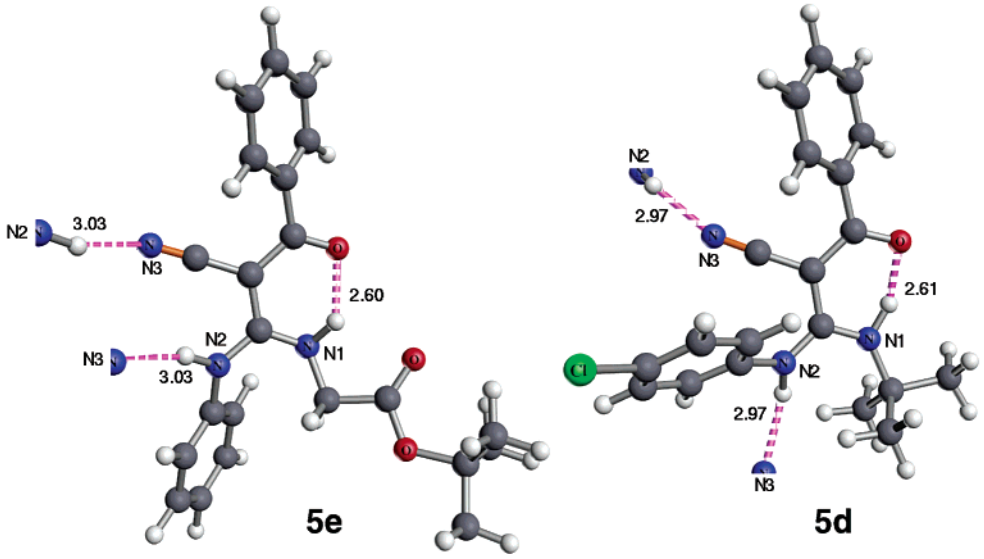
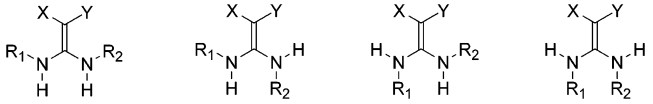


FIGURE 1. The molecular conformation and hydrogen bonding (dashed bonds) in the solvated crystal structures of **5d** (right) and **5e** (solvent molecules not shown). The angle of twist about the C═C bond is 10° and 3°, respectively, and the NCN angle is 121° in both.

double bond is not known, the conformation of the aminal group was determined to be *syn-anti* by observing common NOE correlations to the aniline N−H proton from both the N−CH_2 protons and the *ortho* protons of the aniline ring from a ^{1}H PSNOESY experiment in DMSO-d_6 (Scheme 2). For compounds **5a**, **5c**,[18] **5e**, and **5f**, our NMR experiments in $CDCl_3$ at room temperature indicated distinct, intramolecularly hydrogen bonded *Z* and *E* isomers. For example, the two N−H protons of **5a** showed four resonances at 10.54, 9.05, 6.65, and 4.95 ppm. While the two downfield signals can be assigned to the N−H protons that form hydrogen bonds with the carbonyl oxygen, the two upfield signals are due to N−H protons not associated with hydrogen bonds. The N−CH_2 protons also showed two broad peaks at 2.96 and 2.78 ppm, which are assigned to stereoisomers **5a**-*Z* and **5a**-*E* (ratio ∼1:1.3) on the basis of ^{1}H COSY NMR experiments (Scheme 2). Similarly, **5e** exists as a (∼2.3:1) mixture of *Z* and *E* isomers in $CDCl_3$, but only the *E* isomer is present in a single crystal (Figure 1).[19] This apparently is the first reported observation of distinct rotameric isomers for *N*,*N*′-disubstituted ketene aminals.

Except for **5f**, distinct isomers were not observed in strongly coordinating solvents such as CD_3CN or DMSO-d_6, most likely because of the disruption of the internal hydrogen bonds.[15b,20]

SCHEME 3. Possible Conformations of Aminals



By contrast, **5d** prefers a single configuration in both $CDCl_3$ and CD_3CN. The results of ^{15}N HMBC, ^{15}N HMQC, and NOE experiments[21] are consistent with the hydrogen-bonded *E* configuration observed in a single crystal (Figure 1).

In general, *N*,*N*′-disubstituted ketene aminals can have four extreme C−N rotameric conformations (*ss*, *as*, *sa*, and *aa*) as defined in Scheme 3. Each intramolecular hydrogen bond (NH−X or NH−Y) necessarily requires an antiperiplanar (*a*) rotameric conformation.

A survey of the Cambridge Structural Database (CSD)[22] revealed 19 examples of *N*,*N*′-disubstituted ketene aminals having acyclic C−N bonds, and most of them favor the *sa* (or *as*) conformation (16 out of 19 examples; see Supporting Information). All examples have the potential to form at least one intramolecular hydrogen bond involving an NH, and we note several correlations between their chemical structures and solid-state conformations: (a) Despite the potential to form *two*

(18) The rotamers observed for **5c** are not due to the rotation of the amide bond since only one resonance is observed for methyl groups on the amide nitrogen.

(19) H-bond distances designate O···N separation (Å). For **5d**, colorless rods from CH_2Cl_2/hexanes: $T = -70$ °C, $a = 23.1020(6)$, $b = 11.9057(3)$, $c = 19.4958(5)$, $\beta = 105.563(1)$, $V = 163.4(2)$, *C*2/*c*, $Z = 8$, $R = 0.13$, $R_w = 0.21$ for 2477 observed intensities at with $I \geq 3\sigma(I)$. The crystals are unstable at room temperature, and the solvent positions were poorly defined and partially occupied. Only the chlorine position for the CH_2Cl_2 site was obvious. For **5e**, colorless prisms from CH_2Cl_2: $T = -40$ °C, $a = 10.100(1)$, $b = 10.539(1)$, $c = 12.136(2)$, $\alpha = 75.10(1)$, $\beta = 83.93(1)$, $\gamma = 71.38(1)$, $V = 1182.6(3)$, *P*1*bar*, $Z = 2$, $R = 0.08$, $R_w = 0.13$ for 3166 observed intensities at with $I \geq 3\sigma(I)$, mp 110−40 °C. Crystallographic data (excluding structure factors) for the above compounds have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CDC-212560 (**5d**) and -212561 (**5e**). Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB21EZ, U.K. (Fax: (+44)1223-336-033. E-mail: deposit@ccdc.cam.ac.uk).

(20) It has been shown by AM1 calculation that the rotation barriers of Meldrum's acid derivatives decrease dramatically in a dielectric filed ($e = 40$) as the result of a much more effective stabilization of the zwitterionic transition state. See ref 16.

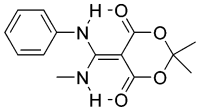
(21) ^{15}N HMBC and HMQC NMR experiments correlate the non-hydrogen bonded N-*H* (s, 6.97 ppm) and the 2′-*H* (7.27 ppm) of the 4′-chlorophenyl group to the same nitrogen (95.0 ppm), and the hydrogen bonded N-*H* (s, 11.15 ppm) and *tert*-butyl group to the other nitrogen (129.7 ppm). The NOE observed between N−H proton (6.97 ppm) of aniline and *t*-butyl group protons indicates it is the *E* stereoisomer.

(22) Allen, F. H.; Kennard, O. *Chem. Des. Autom. News* **1993**, *8*, pp 1, 31−37, Version 524.

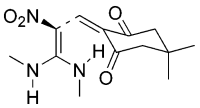
intramolecular hydrogen bonds and maintain an essentially planar conformation, all but 1 of the 10 examples are instead twisted more than 70° about relatively long (1.45−1.49 Å) C═C bonds and adopt *sa* or *ss* conformations without any intramolecular hydrogen bonds. The sole exception (X = 2-benzothiazole, Y = NO_2, $R_1 = R_2$ = Ph)[23] has an almost planar aminal with *two* intramolecular hydrogen bonds and the rare, sterically demanding *aa* conformation. It therefore appears that unfavorable steric interactions between R_1 and R_2 in *aa* conformation outweigh the two stabilizing intramolecular hydrogen bonds for most of these compounds. (b) The remaining 9 examples have the potential to form *one* intramolecular hydrogen bond. All but one[24] of the them are only slightly twisted (<6°) with correspondingly shorter C═C bonds (1.39−1.42 Å), and the intramolecular hydrogen bonds are evident. Examples **5d** and **5e** fall into this category (with a C═C length of 1.428 and 1.426 Å, and a twist angle of 10° and 3°, respectively). Interestingly, **5e** is the first example with an *aa* (R_1, R_2 = alkyl, aryl) conformation and only *one* stabilizing intramolecular hydrogen bond. All of the other examples in this category have a *sa* (or *as*) conformation. (c) No *aa* conformation is known when both R_1 and R_2 are alkyl, probably because of unfavorable steric factors. In contrast, all rotameric conformations have been reported when R_1 and R_2 are either aryl or one is aryl.

In conclusion, we have demonstrated two efficient routes (Methods A and B) for the synthesis of *N*,*N*′-disubstituted ketene aminals from activated methylene compounds and isothiocyanates. Most of these aminals exist in rotameric equilibrium around the central C═C bonds in solution, and the rotamers are stabilized by intramolecular hydrogen bonding both in solution and in solid states.

(23) Another example of an aminal with an *aa* solid-state conformation has been reported recently. Its structure is shown below (See ref 16).



(24) In the solid state, this aminal is severely twisted (66°) about the long (1.47 Å) C═C bond and forms no intramolecular hydrogen bond, its structure is shown below (also see Supporting Information).



Experimental Section

General Procedure for Method A. To a solution of an isothiocyanate **1** (1.0 mmol) in dry DMF (2 mL) was added an amine **2** (1.0 mmol). After 20 min of stirring, sodium hydride (95%, 38 mg, 1.5 mmol) or DBU (1.5 mmol) was added under nitrogen. The mixture was stirred for 5 min, and an activated methylene compound **4** (1.5 mmol) and EDCI (288 mg, 1.5 mmol) were added in that order. The reaction was heated to 80 °C for a period of 1−12 h. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate (3 × 5 mL). The organic phase was washed with saturated sodium chloride aqueous solution and dried over magnesium sulfate. The solvent was removed to give a crude product. Purification of the crude product on a silica gel column with 20−50% EtOAc in hexanes provided pure **5**.

General Procedure for Method B. To a solution of an activated methylene compound **4** (1.5 mmol) in dry DMF (2 mL) was added sodium hydride (95%, 38 mg, 1.5 mmol) under nitrogen. After 5 min of stirring, an isothiocyanate **1** (1.0 mmol) was added. The mixture was stirred for 30 min at 60 °C. An amine **2** (1.5 mmol) and EDCI (288 mg, 1.5 mmol) were added in that order. The reaction was heated to 80 °C for a period of 1−12 h. After cooling to room temperature, the reaction was quenched with water and extracted with ethyl acetate (3 × 5 mL). The organic phase was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was removed to give a crude product. Purification of the crude product on a silica gel column with 20−50% EtOAc in hexanes provided pure **5**.

Acknowledgment. We thank Dr. Vikram A. Roongta for helpful discussions about NMR experiments.

Supporting Information Available: Experimental details for Schemes 1, full characterization of compounds **5a**−**f**, X-ray crystallographic files for **5d** and **5e**, and structural information and references of 19 compounds obtained from CSD. This material is available free of charge via the Internet at http://pubs.acs.org.

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