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N-Pyrrolylketene: A Nonconjugated Heteroarylketene

Mohammad Reza Islami,[⊥], Annette D. Allen, Sinisa Vukovic and Thomas T. Tidwell*

Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6 Canada

ttidwell@chem.utoronto.ca

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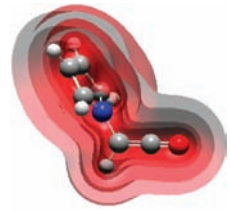
ABSTRACT



***N*-Pyrrolylketene (5) is calculated to be destabilized and nonconjugated, with a preferred geometry with the pyrrolyl ring orthogonal to the ketenyl group. Ketene 5 is generated from *N*-pyrrolylacetic acid (7) with use of Mukaiyama's reagent, and reacts with imines forming *β*-lactams 10, with a product ratio correlation of log(cis/trans) with σ^+. Photolysis of *N*-diazoacetylpyrrole (14) in MeOH gives methyl *N*-pyrrolylacetate (15) from 5 and also ester 17, evidently by trapping of 2-(1-pyrrolylketene) (21), formed by a new vinylogous Wolff rearrangement.**

β-Lactam (azetidinone) formation by ketene [2 + 2] cycloaddition with imines is of continuing interest because of the medicinal properties of penicillin and the cephalosporins. These have nitrogen substitution on the carbon adjacent to the carbonyl group, so ketenes with amino, acylamino, and azido groups are particularly useful.[1] Herein we report application of a new and unusual type of nitrogen-substituted ketene in *β*-lactam synthesis.

Furyl and thienyl ketenes have been generated and directly observed, and also utilized in synthesis.[2a] Pyrrolylketenes are an attractive target because of the many synthetic uses of pyrroles, and *N*-ketenylpyrrole offers the feature of attachment to heteroaryl nitrogen, while nitrogen-substituted ketenes are of great current interest because of their demonstrated interconversion with stable carbenes.[1e−h] Evidence for pyrrole-substituted ketenes is sparse,[2b] but includes[2c,d] thermal ring-opening of *N*-pyrrolylcyclobutenone **1** forming *N*-vinylpyrrolyl ketene **2** (eq 1). *N*-Pyrrolyl chromium carbene complex **3** revealed ketene-like reactivity in photochemical [2 + 2] imine cycloaddition forming *β*-lactam **4** (eq 2), and with alkenes forming cyclobutanones.[2e]

To assist understanding the chemistry of *N*-pyrrolylketene the structure was calculated with the MP2/6-31G+d and B3LYP/6-31G+d methods,[3] which predict that the twisted structure **5a**, with the pyrrolyl plane perpendicular to the ketene plane, is more stable, by 4.89 and 3.91 kcal/mol, respectively, than planar structure **5b**, which is a transition state for rotation

[⊥] Present address: Chemistry Department, Shahid Bahonar University of Kerman, Kerman 76169 Iran.

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(3) (a) Details are given in the Supporting Information. (b) *Gaussian 98*, Revision A-9; Gaussian, Inc., Pittsburgh, PA, 1998.

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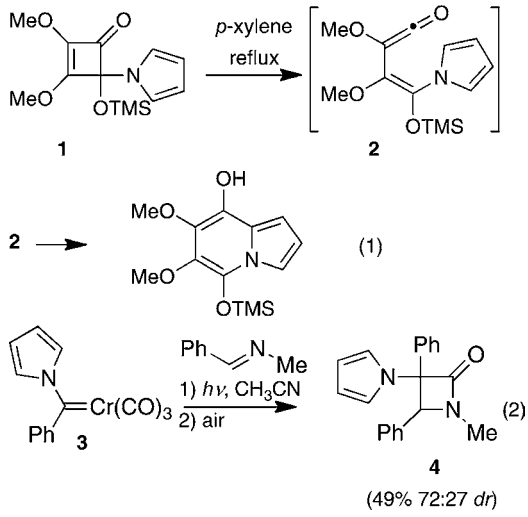
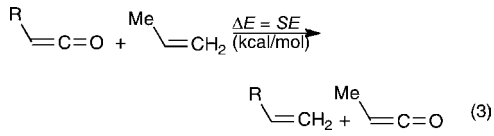
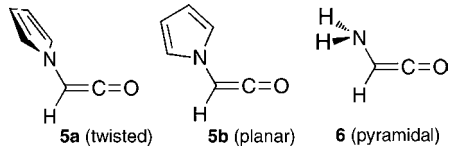


around the ketenyl−pyrrolyl bond. Calculated substituent effects on ketene stability evaluated as stabilization free energies (SE) from isodesmic energy comparisons by eq 3[4] are summarized in Table 1.



For R = *N*-pyrrolyl values of −7.1 (MP2) and −8.2 kcal/mol (B3LYP) are found, as compared to −9.3 (MP2) and −7.2 (HF) for NH_2. Thus **5** is remarkably destabilized, comparably to aminoketene (**6**),[4a,b] which has the nitrogen pyramidalized, with the lone pair twisted out of conjugation with the ketenyl π system. The destabilized and nonconjugated structure **5a** is in stark contrast to the significantly more stabilized furyl-[2a] thienyl-,[2a] ferrocenyl-,[4c] and phenylketenes[4a,b] (Table 1), with aryl groups coplanar and conjugated with the ketenyl group. There is no evidence in **5** for any bonding interaction between the ketenyl group and the pyrrolyl π system, as shown by the electronic contour depicted above.



N-Vinylpyrrole is more stable in the planar conformation, with a barrier for bond rotation of 3.9 (MP2) or 5.5 (B3LYP) kcal/mol. Thus planar *N*-pyrrolylketene is disfavored by 8.8 kcal/mol (MP2) or 9.4 kcal/mol (B3LYP) relative to planar *N*-vinylpyrrole. *N*-Ketenylpyrrole **5** is also calculated to be less stable than the C-2- and C-3-ketenyl isomers by 12.0 and 11.7 kcal/mol, respectively (B3LYP),[3] a result attributable to the destabilizing electronegativity of the pyrrole nitrogen relative to carbon. However the C-2- and C-3-ketenyl isomers are also calculated to be nonplanar.

Table 1. Ketene Stabilization Energies (SE, kcal/mol), Eq 3, for Groups R in RCH=C=O (B3LYP/6-31G(*d*))[2a,4]

R	SE	R	SE
N-pyrrolyl	−8.2	2-furyl	−1.4
Ph	1.3	3-furyl	−0.6
2-thienyl	−0.6	ferrocenyl	−0.3
3-thienyl	0.0	NH_2	−9.3 (MP2)

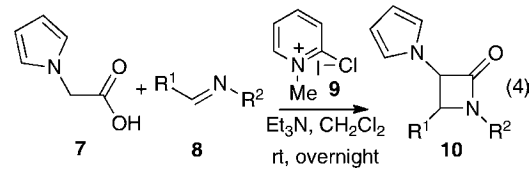
Table 2. β-Lactams **10** from *N*-Pyrrolylketene and Imines **8**

	R^1	R^2	cis/trans[a]	yield[b] (%) cis	yield[b] (%) trans
10a	Ph	Ph	55:45	37	29
10b	Ph	4-$MeOC_6H_4$	95:5	71	1.2
10c	Ph	4-$O_2NC_6H_4$	14:86	5	34
10d	Ph	4-MeC_6H_4	73:27	23	8
10e	Ph	*t*-Bu	97:3	74	
10f	4-$MeOC_6H4$	Ph	69:31	19	48
10g	4-O_2NC_6H4	Ph	100:0	43	

[a] From ^{1}H NMR of crude product. [b] Isolated yield of pure product.

The use of metal carbene complexes[2e] for possible preparation of *N*-pyrrolylketenes (eq 2) for mechanistic and synthetic studies is restricted by the very limited number of useable complexes available, and by uncertainty as to whether the unobserved ketenes are actual intermediates in the reactions. Therefore we have examined carboxylic acid derivatives and diazo ketones for this purpose, as these are the most used precursors to ketenes.

Reaction of *N*-pyrrolylacetic acid (**7**)[5a−c] with Mukaiyama's reagent (**9**)[5d−f] and Et_3N in CH_2Cl_2 in the presence of imines **8** gave azetidinones **10** as cis/trans mixtures (Table 2), indicating the intermediacy of *N*-pyrrolylketene **5** (eq 4). The cis:trans product ratios were determined by ^{1}H NMR of the crude reaction products from the signals of the 3- and 4-ring protons identified by their characteristic coupling constants, and the pure isomeric products were isolated by chromatography.



It is generally accepted that the stereochemistry in ketene−imine cycloaddition involves initial attack of the imine with formation of zwitterionic intermediates **11a** which undergo competitive ring closure to *cis*-β-lactams **12** and isomerization to less crowded intermediates **11b** and ring closure to *trans*-β-lactams **12** (Scheme 1).[1a,b,6]

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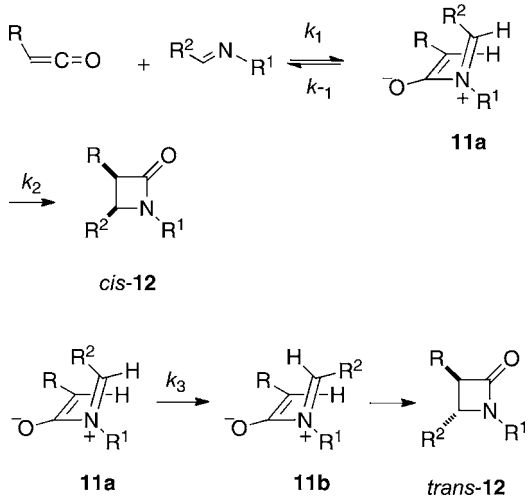
Scheme 1



A plot of log(cis/trans) for the product β-lactams **10** from reaction of imines PhCH═NAr versus σ^+_p values for the aryl substituents gives a good correlation, with $\rho^+ = 1.3$, $r = 0.993$ (Figure 1).

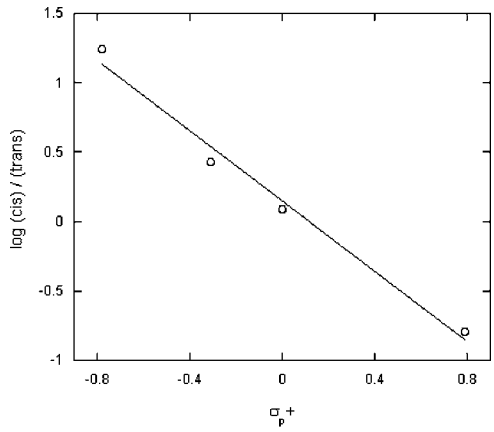
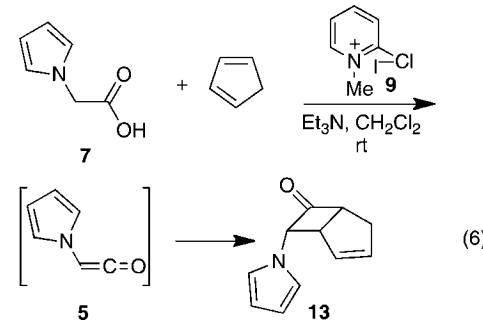


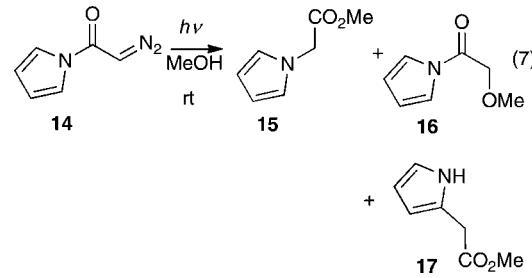
Figure 1. Correlation of σ^+_p values for reaction of **5** with ArN═CHPh versus log(cis/trans) for product β-lactams **10**.

By contrast reaction of PhSCH═C═O generated by thermal Wolff rearrangement with imines 4-$O_2NC_6H_4$-CH═NAr at 140° gives $\rho = -1.1$, with opposite slope of lesser magnitude than found for **5**.[6a] However, cis/trans selectivity can be strongly temperature sensitive; for example, phthalimidoketene reverses cis/trans selectivity for reaction with 4-$O_2NC_6H_4$CH═N−Pr-*i* from 87:13 at 40 °C to 4:97 at 150 °C.[6d] Thus caution is needed in predicting or interpreting such substituent effects.

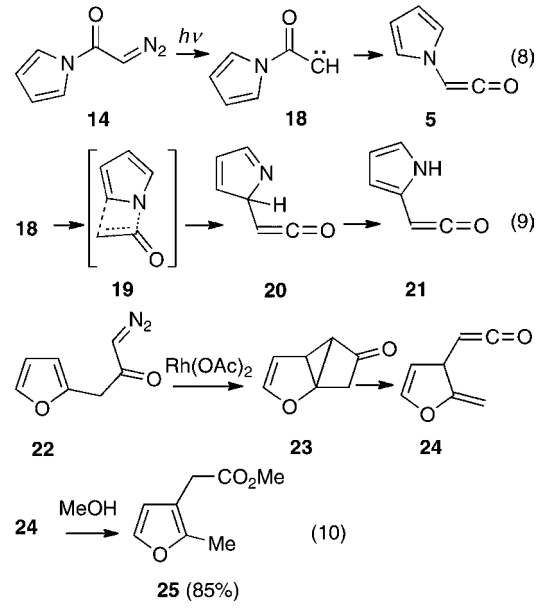
Addition of acid **7** to Mukaiyama's reagent (**9**) in CH_2Cl_2 and addition of cyclopentadiene led to the formation of *endo*-7-*N*-pyrrolylbicyclo[3.2.0]hept-2-en-6-one (**13**) in 17% yield as the only observed product (eq 6). The formation of **13** provides further confirmation of the intermediacy of ketene **5**.



N-Diazoacetylpyrrole (**14**) was obtained from the acid[7] by reaction with isobutyl chloroformate and diazomethane, and upon photolysis at 300 nm in MeOH led to isolation of not only the pure normal Wolff rearrangement product **15** and carbene derived product **16**, but also rearranged methyl ester **17**, in a 28:25:47 ratio by ^{1}HMR analysis of the crude product (eq 7).



Wolff rearrangement leading to **15** is calculated to proceed by formation of keto carbene **18**, which forms ketene **5** with a barrier of 7.52 kcal/mol (B3LYP) or 5.95 kcal/mol (MP2) (eq 8).[3] Ester **17** would form from rearranged ketene **21**, and computations suggest reaction involving a new type of vinylogous Wolff rearrangement[8] with a barrier of 5.23 (B3LYP) or 7.18 kcal/mol (MP2) through transition state **19**, which rearranges to ketene **20**, which tautomerizes to **21** (eq 9). Previous examples of such rearrangements include the proposal that 1-diazo-3-(2-furyl)-2-propanone (**22**) forms ester **25** via ketene **24** (eq 10).[8b]



In conclusion *N*-pyrrolylketene has been generated and shown to be unique among known arylketenes as exemplified by its instability, nonplanar structure, and unusual reactivity.

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Supporting Information Available: Experimental procedures, spectra, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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