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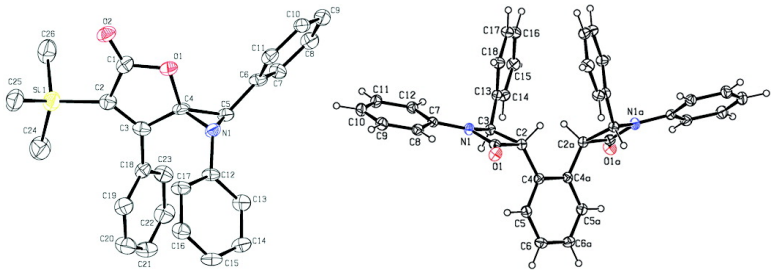

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Spiro-Aziridine and Bislactam Formation from Bisketene−Imine Cycloadditions

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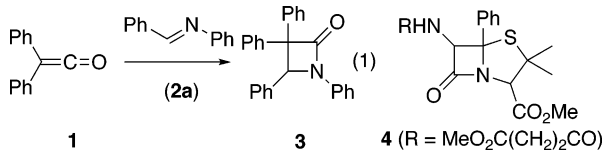
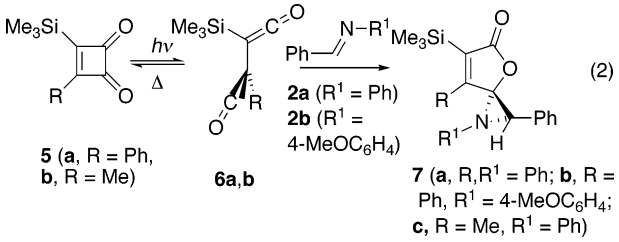
Reaction of diphenylketene (**1**) with imine **2a** forming **3** reported 100 years ago (eq 1) was the first synthesis of a β-lactam and, with the reaction of **1** with aldehydes forming β-lactones and with alkenes forming cyclobutanones, was the first example of [2 + 2] cycloaddition.[1] This reaction took on great interest after the discovery of penicillin in 1928 and its identification as the first β-lactam antibiotic.[2a−c] The β-lactam structure of the penicillins was proposed in the 1940s,[2c] and synthesis of penam **4**, which differs from the natural penicillins by the presence of the 9-phenyl group, was achieved in 1950 by using ketene−imine cycloaddition.[2d,e]



Subsequently, there has been immense effort devoted to β-lactam synthesis,[2f,g] including preparation of bis(β-lactams) by ketene reactions with bis(imines),[3a−c] photolysis of bis(carbene) complexes in the presence of imidazolines,[3d,e] and dehydration of diacids with Mukaiyama's reagent in the presence of imines.[3f] The presence of bisketene intermediates in these reactions was, however, not established, and the goal of the current research is to study imine−bisketene reactions in circumstances where bisketenes are proven to be intermediates, so that the course of the reactions can be followed with certainty.

Photolysis of cyclobutenedione **5a** formed bisketene **6a**, which with imine **2a** gave aziridine *trans*-(±)-**7a** in 78% yield (eq 2). The stereochemistry was proven by X-ray (Figure 1). Imine **2b** with **6a** gave *trans*-(±)-**7b**, also characterized by X-ray. Generation of **6b** (R = Me) and reaction with imine **2a** gave the aziridine **7c**, which was unstable to chromatography but was identified by NMR.



A conceivable pathway for formation of aziridines **7** is cyclization of bisketenes **6** to highly reactive carbene lactones **8** in low concentration, so that reaction proceeds through this channel rather than thermal reversion to **5** (eq 3). However, B3LYP/6-31G(d) computations[4] of interconversion of **5a**, **6a**, and **8a** show the carbene lactone **8a** is 30.7 kcal/mol higher in energy than **6a**, with a 36.7 kcal/mol barrier for reaction, showing that formation of **8a** is not a viable route to **7a**.

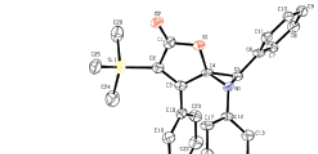
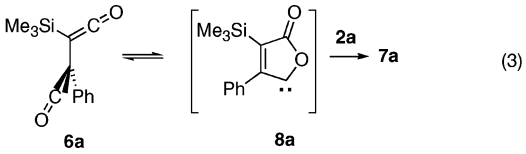
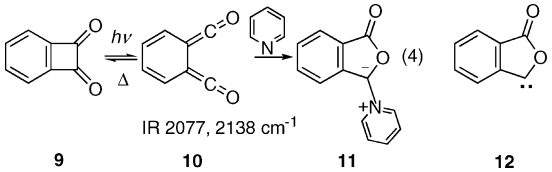


Figure 1. X-ray structure of aziridine **7a**.



Lactone derivatives analogous to **7** have been formed previously in the reactions of 1,2-bisketenes,[5,6] originally in the reactions of bisketene **10** formed by photolysis of benzocyclobutadienone (**9**), which for example reacts with pyridine to form the zwitterion **11** (eq 4).[6g] Computations[4] now show the unobserved carbene lactone **12** to be 4.0 kcal/mol more stable than the bisketene **10**, but the barrier calculated for return of the bisketene **10** to cyclobutenedione **9** is lower than that for formation of the more stable carbene lactone **12** by 4.5 kcal/mol, thereby accounting for the failure to observe **12**.



Two reaction paths have been calculated[4] for reaction of bisketene **6a** with imine (*E*)-**2a**, which is more stable than (*Z*)-**2a** by 6.6 kcal/mol. These include the possibility that reaction occurs by initial conversion of (*E*)-**2a** to (*Z*)-**2a** followed by reaction with the ketene, as reported[7] for other such reactions. The rate-limiting step for bisketene **6a** reaction with (*E*)-**2a** giving aziridine **7a** is calculated to be formation of zwitterionic intermediate (*E*)-**13**, followed by cyclization to lower energy intermediate (*E*)-**14** (eq 5). This is less than the corresponding barrier for reaction via (*Z*)-**2a** by 1.0 kcal/mol, but within the accuracy of the computations, reaction by one or the other route, or both, is not proven.

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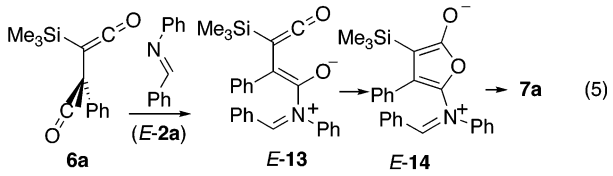
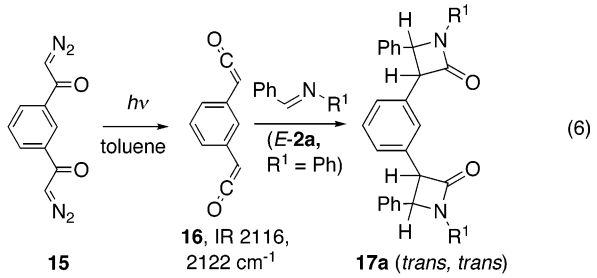


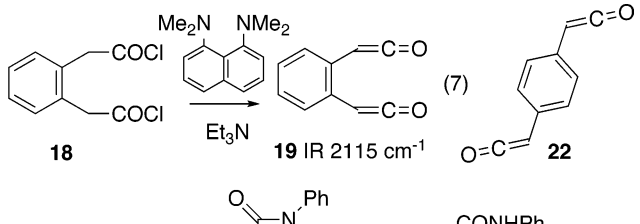
(5)

Experimental demonstration of bislactam formation by reaction of the observable 1,3-bisketenylbenzene **16**[8] generated by Wolff rearrangement of 1,3-bis(diazoacetyl)benzene (**15**) by continuous photolysis, followed by addition of imine (*E*)-**2a**, led to a product identified by the characteristic *trans* H,H NMR couplings as the chiral (±) and achiral *trans*,*trans*-diastereomers of bislactam **17a** as a 1:1 mixture (eq 6). *trans*-Stereochemistry has been reported for the *β*-lactam from imine (*E*)-**2a** and phenylketene generated photochemically or by dehydrochlorination.[9]



(6)

Observable 1,2-bisketenylbenzene **19**[8] generated by dehydrochlorination of bis(acyl chloride) **18** with 1,8-bis(dimethylamino)-naphthalene and catalytic Et_3N in toluene (eq 7) was captured by imine (*E*)-**2a**, giving four isolated products, identified as chiral (±) and meso *trans*,*trans*-bis(*β*-lactams) **20a**,**b**, *cis*/*trans*-isomer **20c**, and (±)-lactam **21**, in a 73:12:4:11 ratio by NMR analysis (eq 8). Similar methodology gave **16** from the 1,3-bis(acyl chloride), which with (*E*)-**2a** formed **17a**, while **16** and PhCH═NBn (*E*)-**2c**, gave **17b** (R^1 = Bn) as two diastereomers in a 2:1 ratio. 1,4-Bisketenylbenzene **22**, also generated by this protocol, reacted similarly with **2a** forming bis(*β*-lactams).[4a]



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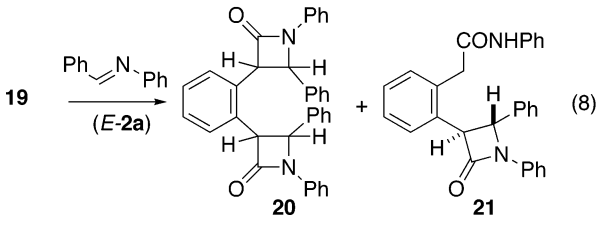

(8)

The structure of the major product in eq 8, chiral (±) *trans*,*trans*-**20a** determined by X-ray (Figure 2) displayed 2-fold symmetry and a striking molecular cleft, suggesting potential use as a complexing agent. Such proximate *β*-lactam groups are lacking in previously reported examples.[3] The simple method of synthesis also suggests that a variety of analogues with different substituents could be prepared.

In summary, reaction of 1,2-bisketenes **6** with imines (*E*)-**2a**,**b** forms aziridines **7**, providing a new method of aziridine synthesis,

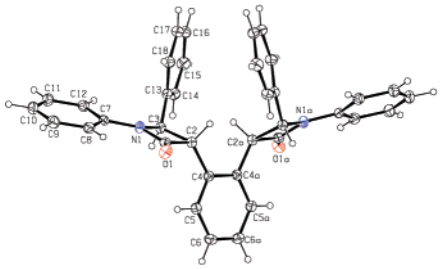

Figure 2. X-ray structure of chiral bis(*β*-lactam) **20a**.

as well as new structural types. A mechanism involving stepwise imine addition to the bisketene is proposed based on DFT computational studies. This argues against formation of carbene lactones in this process and against previous suggestions of carbene lactone **12** in the reactions of bisketene **10** from benzocyclobutenedione (**9**), even though **12** is calculated to be more stable than bisketene **10**. Bisketenylbenzenes **16**, **19**, and **22** react with imines **2** forming unique bis(*β*-lactams), including **17** and **20**, providing simple routes to these structurally interesting compounds.

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

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