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The Role of Hydrogen Bonding in the Intramolecular Cyclization of Carbenes

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The cyclization products from the photolysis of 3-arylamino-4-ethoxycarbonyl-2-heteroarylisoxazol-5(2*H*)-ones are interpreted as arising from intramolecular cyclization of carbenes. The mode of cyclization appears to be controlled by hydrogen bonding of the 3-NH group with either the 2-heteroaryl group or the 4-ethoxycarbonyl group.

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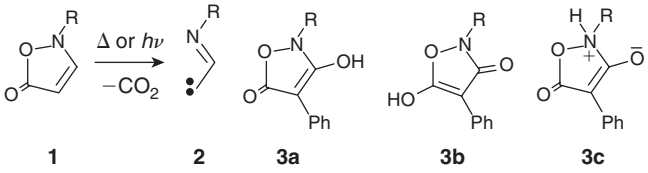
Introduction

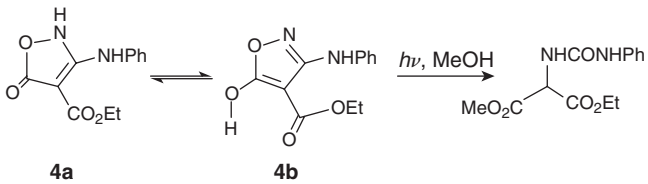
We have reported a considerable number of photolysis and pyrolysis reactions of isoxazol-5(2*H*)-ones **1** (Scheme 1),[1–3] in which the common intermediate is generally the imidoylcarbene **2**. When a C(3) hydoxyl group[4,5] or amino group[6] was present, however, the pathway was often complicated by the presence of several tautomers, each of which followed its own decomposition pathway, particularly on photolysis.

Thus the presence of a 3-hydroxyl group led to separate photolysis pathways from the three tautomers **3a**–**3c**,[4,5] and the 3-phenylamino analogue **4a** gave a single photolysis product via tautomer **4b** (Scheme 2),[6] which, however, does not involve a carbene intermediate.

The photolysis of *N*-heteroaryl derivatives of **4a** was intriguing in two ways. Firstly, photolysis now occurred exclusively through the lactone form, resulting in carbene-derived products. Secondly, the carbene intermediate was captured either by the nitrogen atom of the 2-heteroaryl group, to form an imidazopyridine,[7,8] or by the 3-arylamino group, leading to an indole. However, the less nucleophilic 3-nitropyridyl derivative **5** gave exclusively the imidazopyridine **6**,[7] whereas the more nucleophilic isoquinolinyl derivative **7** gave both imidazoquinoline **8** and indole **9** in a 2 : 1 ratio (Scheme 3).[6] Since this distribution of products appeared counter-intuitive, we have investigated the photolysis of this system in further detail.



Scheme 1.



Scheme 2.

Results and Discussion

Since isoxazolone **4a** underwent photolysis as its hydroxyisoxazole tautomer **4b**, and its 2-aryl derivative **5** as the lactone tautomer, we first examined the effect of having a methyl group at N(2). Methylation of **4a** with base and methyl iodide gave the same product as from the reaction of *N*-methylhydroxylamine with the thioamide **10**, namely the 2-methylated material **11** (Scheme 4). This product gave a single compound on photolysis, but the spectroscopic data did not allow unequivocal assignment of structure. X-ray analysis* showed the structure to be **12**, which, like the product from **4**, is consistent with its origin from the 5-hydroxy tautomer. As we were interested in the synthetic applications of possible polycyclic heterocycles from this system, we have now concentrated on the 2-aryl compounds.

While the isoxazolone **5** gave only the imidazopyridine **6** on photolysis (Scheme 5), we hoped that the presence of a more electron-rich *N*-aryl group at C(3) would promote formation of the indole. However, photolysis of isoxazolone **13** once again gave only the corresponding imidazopyridine **14**.

* We thank Dr M. R. Taylor for determining the single crystal X-ray structure, which is unequivocal, but the quality of the crystal precludes publication of the data.

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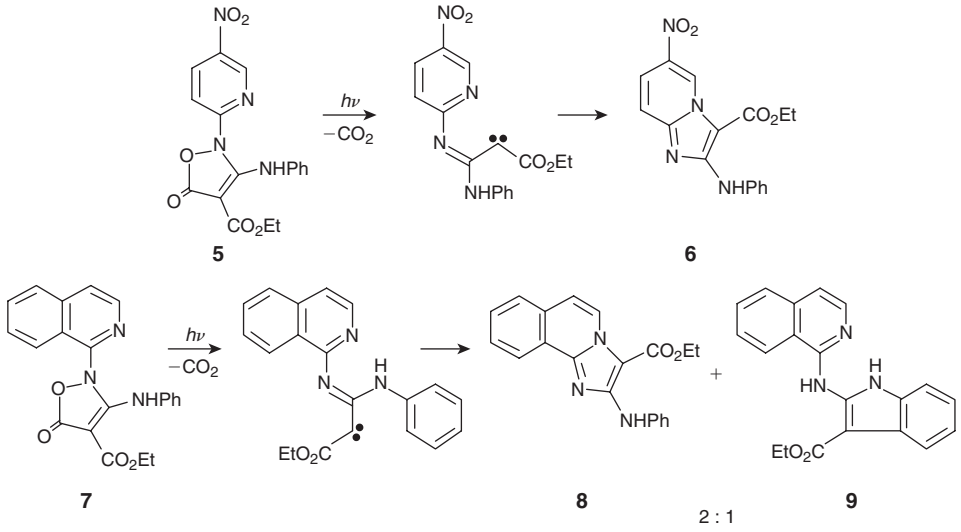
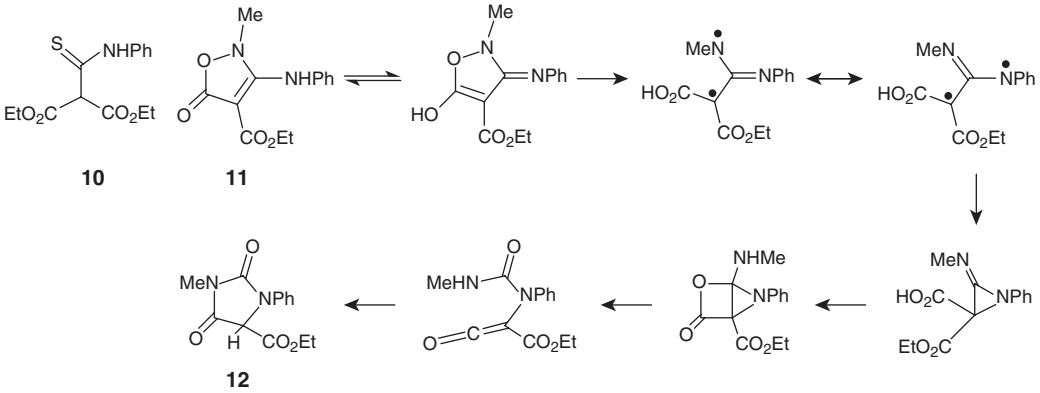
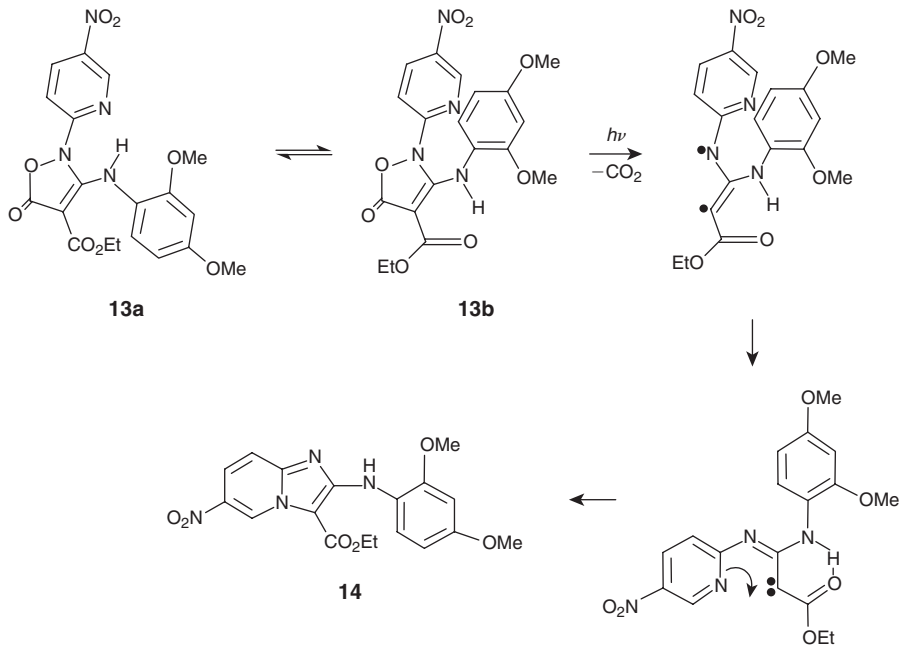


Scheme 3.



Scheme 4.



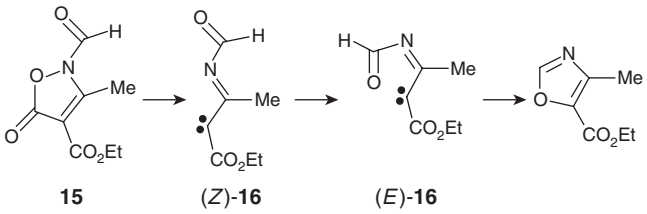
Scheme 5.

Since electronic factors in the 3-arylamino group now appeared to be only secondary, we considered the possibility that hydrogen-bonding factors were paramount. If hydrogen bonding in the reactants could be maintained throughout the formation of the carbene intermediate, the formation of the imidazole from the weakly hydrogen-bonding nitropyridine group could be understood by the preference for the conformation **13b**.

Since there is evidence to suggest that the carbene formation from an isoxazolone is a stepwise process initiated by homolysis of the N—O bond,[9] the initially formed carbene is likely to be a triplet. While triplet carbonylcarbenes are planar, the corresponding singlet carbenes are nonplanar,[10] with nearly orthogonal RCCO dihedral angles. The latter orientation allows overlap of the in-plane oxygen lone pair of the carbonyl group with the empty p-orbital of the singlet carbene, as well as the π-bond of the carbonyl group to conjugate with the filled carbene orbital.[10] Wang and co-workers have shown that the singlet–triplet gap in aryl(methoxycarbonyl) carbenes depends on the substituent in the aryl group, the triplet being of lower energy with electron-withdrawing groups and the singlet with electron-donating groups.[11] In addition, the bond angle about the triplet carbene carbon is larger than that of the singlet.[12] Polar solvents also favour the singlet state.

We also have carried out several AM1-level geometry optimization calculations on the decomposition of the system **15** to (*Z*)-**16** and to (*E*)-**16**,† representing a typical system in which the carbene is captured by a nucleophile attached to the nitrogen. While AM1 energies are unlikely to be very accurate, they are adequate for our purpose here in rationalizing the preference of different conformers. The calculations are collected in Table 1, and the general situation is summarized in Scheme 6. The initially formed triplet carbene (*Z*)-**16** is lower in energy by 110 kJ mol^{-1} than its singlet state. On the other hand, the energy of the triplet state of the carbene (*E*)-**16** is almost identical with that of triplet (*Z*)-**16**, and hence there will be a minimal energy barrier to their interconversion. With the carbene (*E*)-**16**, however, the singlet state is of considerably lower energy (by 177 kJ mol^{-1}), and this leads to essentially spontaneous cyclization of a nucleophile with the carbene, Scheme 7. Consistent with the previously cited calculations,[10–12] the triplet states of (*Z*)-**16** and (*E*)-**16** have larger angles than the corresponding singlet states. The ester carbonyl group in the initially formed triplet (*Z*)-**16** is not coplanar with the carbene, unlike its (*E*)-isomer, although the ester and carbene groups are orthogonal in singlet (*Z*)-**16** as expected.[10] On the other hand, the conformation of the singlet (*E*)-**16** is essentially planar, due to the overriding interaction of the formyl π-bond with the empty carbene π-orbital.

We have also carried out similar calculations on the carbenes derived from 3-aminoisoxazolones. In the simplest case, that of the carbene **18** derived from the isoxazolone **17** (Scheme 8), the calculations are compiled in Table 2. The amino group clearly does not influence the conformation of the carbene (*Z*)-**18** formed from it, and hydrogen bonding of the NH with the ester group is precluded by the large carbene bond angles. However, after isomerization to (*E*)-**18**,



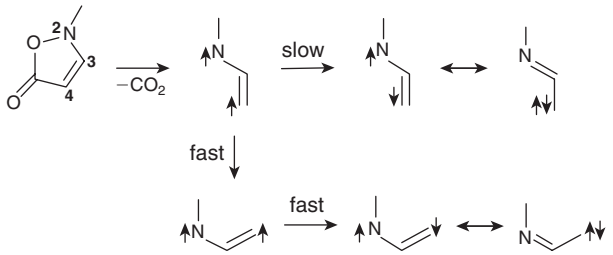
15 (*Z*)-**16** (*E*)-**16**

Scheme 6.

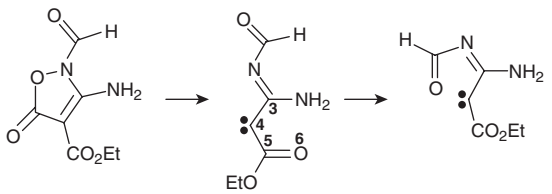
Table 1. AM1-calculated parameters for carbene 16

	(*Z*)-**16**		(*E*)-**16**	
	Triplet	Singlet	Triplet	Singlet
Carbene angle [°]	155.2	133.6	149.9	131.0
Dihedral angle 3-4-5-6 [°][A]	43.15	91.0	9.6	14.4
Energy [kJ mol^{-1}][B]	0	+110	+6	−171

[A] Atom 6 is the ester carbonyl group. [B] Relative values.



Scheme 7.



17 (*Z*)-**18** (*E*)-**18**

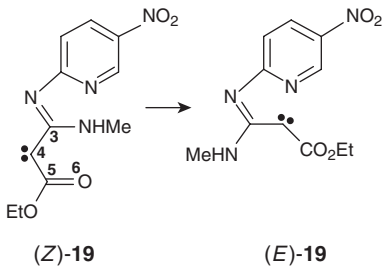
Scheme 8.

Table 2. AM1-calculated parameters for carbene 18

	(*Z*)-**18**		(*E*)-**18**[A]	
	Triplet	Singlet	Triplet	Singlet
Carbene angle [°]	150.1	124.6	146.1	134.6
Dihedral angle 3-4-5-6 [°]	43.5	84.2	176.5	177.3
NH–ester distance [Å]	Very large	3.76 (C=O)	2.39 (OEt)	2.31 (OEt)
Energy [kJ mol^{-1}][B]	0	+105	+7	−188

[A] Lowest energy (*E*) conformation. [B] Relative values.

† The terms (*Z*) and (*E*) refer to the geometry about the C=N bond. While the designations to carbene **16** are not correct, we wish to enable subsequent comparison with the carbenes **18**, **19**, **20**, and **24**.



(*Z*)-**19** (*E*)-**19**

Scheme 9.

Table 3. AM1-calculated parameters for carbene 19

	(*Z*)-**19**		(*E*)-**19**	
	Triplet	Singlet	Triplet	Singlet
Carbene angle [°]	147.9	122.1	153.9	132.6
Dihedral angle 3-4-5-6 [°]	6.63	100.5	28.9	135.5
NH–$N_{(pyr)}$ distance [Å]	2.3	2.3	4.75	4.25[A]
Energy [kJ mol^{-1}][B]	0	+101	+21	−146.1

[A] $N_{(pyr)}$–carbene 2.6 Å. [B] Relative values.

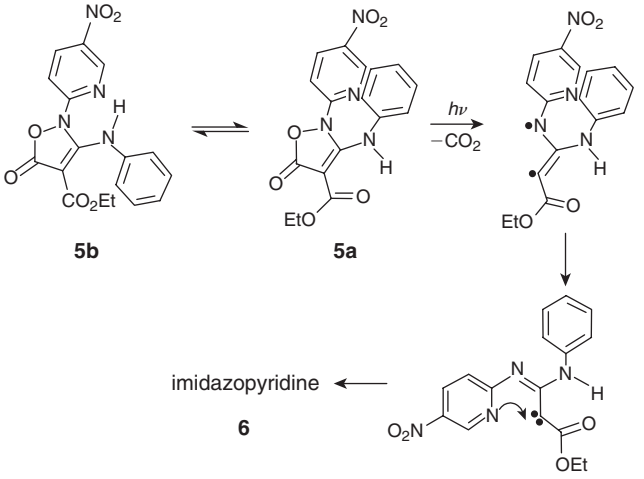
such hydrogen bonding is possible although unlikely to be significant.

For the model carbene **19** (Scheme 9), the corresponding values for the lowest-energy conformer are shown in Table 3. In the carbene (*Z*)-**19**, hydrogen bonding of the amino NH group and the pyridine N atom is made possible by the large carbene bond angle; hydrogen bonding with the ester group is precluded.

Ab initio geometry optimization calculations at the AM1 level (*Gaussian98W*) show that the hydrogen-bonded conformation of the ester for isoxazolone **5a** is 35.9 kJ mol^{-1} lower in energy than the hydrogen-bonded conformation of the pyridyl for **5b**, Scheme 10. However, since this is not maintained in the carbene, and pyridine N─NH bonding will be weak, the facile isomerization of the (*Z*)- to the (*E*)-carbene occurs and leads to exclusive formation of the imidazopyridine **6**.

With **7**, on the other hand, while the energy difference between the quinolinyl hydrogen-bonded system in the isoxazolone **7b** and the ester hydrogen-bonded conformer of the isoxazolone **7a** is essentially the same as above (36.1 kJ mol^{-1}), the singlet carbene (*Z*)-**20** is stabilized by hydrogen bonding between the NH and the isoquinoline N atom, and hence the singlet–triplet barrier for the carbene **20** is now significantly decreased, with respect to the isomerization of the carbene (*Z*)-**20** to (*E*)-**20**, allowing the formation of some indole (Scheme 11).‡

Similar calculations for the *N*-(4-quinolinyl)isoxazolone **21** confirm that hydrogen bonding in the isoxazolone and aromatic π-interactions[13] result in the conformation shown (**21**) being preferred by 28.2 kJ mol^{-1}. In support of this, the ^{1}H NMR spectrum of the isoxazolone **21**[8] showed the presence of a one-proton doublet of doublets due to H(6′) at

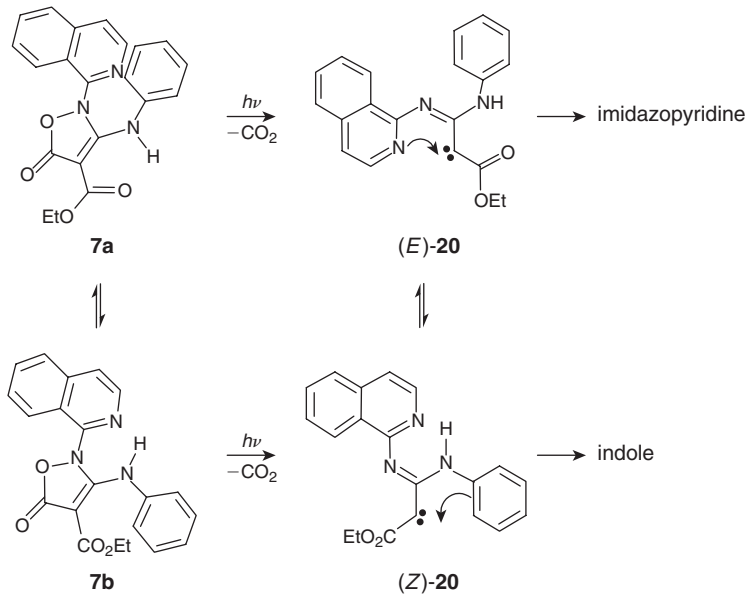


Scheme 10.

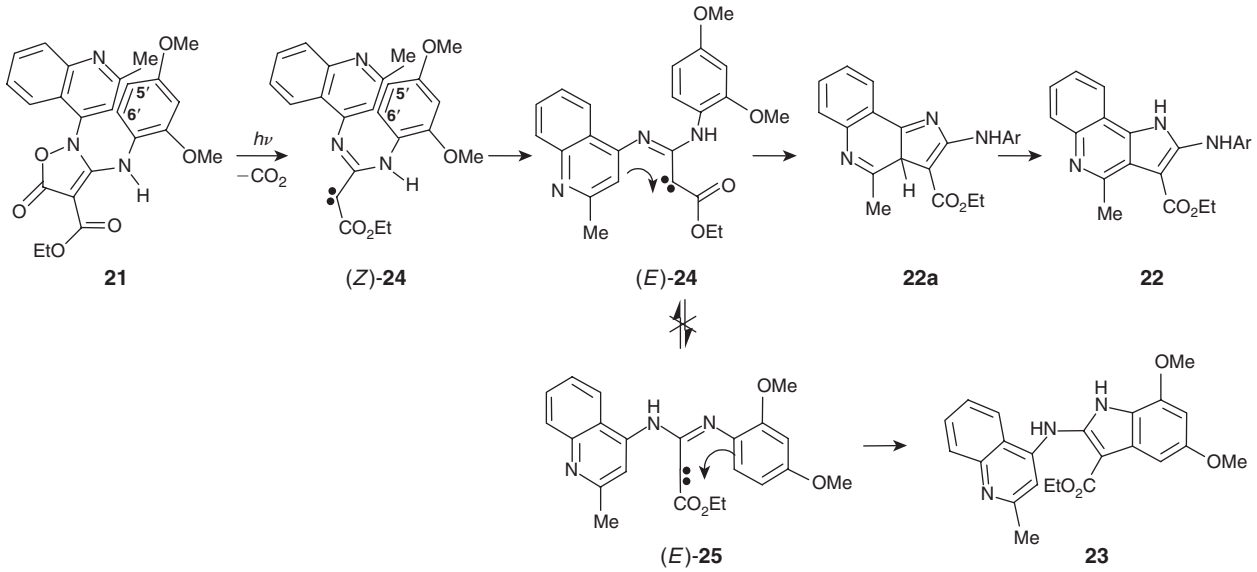
5.8 ppm and the doublet of doublets due to H(5)′ at 6.0 ppm, considerably upfield from their usual positions and indicating that the quinoline and dimethoxybenzene rings were now constrained to stacking. The isoxazolone **21**[8] was photolyzed in acetone at 300 nm to give a single product **22.** No significant quantity of **23** was isolated. This is of synthetic interest, as it complements the base-catalyzed reaction of **21**, which leads only to **23**.[8] We suspect that hydrogen bonding and π-stacking in **21** might promote carbene formation from this conformer, leading to (*Z*)-**24** and (*E*)-**24a** and then rapidly to pyrroloquinoline **22** (Scheme 12). Ab initio geometry calculations on the singlet carbene (*E*)-**24** showed that regardless of the extent of rotation about the C(3)─NH bond, the carbene would spontaneously collapse to the tautomer of **22**, namely **22**a, and not to the indole **23**. This suggests that the carbene cascade leading to the carbene (*E*)-**24** and thus to **22** is faster than the tautomerization of (*E*)-**24** to (*E*)-**25**, which could give the indole **23**.

To further probe the importance of hydrogen bonding in the choice of products, several attempts have been made to synthesize other *N*-arylated derivatives, **26**, of **4** (Scheme 13). The thioamide **10** and its *S*-methylated derivative were treated with phenylhydroxylamine under varying conditions but failed to react. In an alternative approach, phenylhydroxylamine was first treated with phenylisothiocyanate to form the *N*-hydroxythiourea **27**,[14] but all attempts to react this with ethyl malonyl chloride to give **28** were unsuccessful. Other unsuccessful approaches to obtain **26** included the treatment of **4** with 5-chloro-1,3-dimethoxybenzene in the presence of lithium diisopropyl amide, with the diazonium salts from aniline or 3-methoxyaniline, or with 2,4-dinitrofluorobenzene. In addition, several attempts have been made to trap the intermediate carbene **24** with the highly reactive bicyclopropylidene **29**,[15–17] but the (presumably) bimolecular reaction was unable to compete with the intramolecular reactions of the carbene, and the product composition was unchanged.

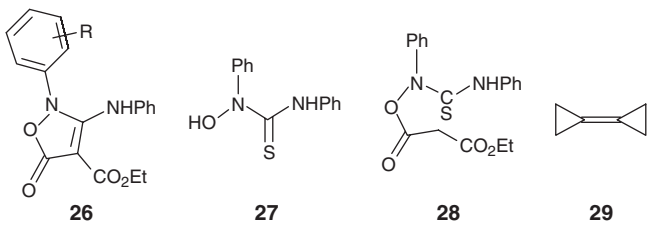
‡ At this stage we cannot rule out the possibility that the indole is the result of insertion of the carbene **20** into a C–H bond of the phenyl ring, but this would appear to give no role to the N(2) aryl group.



Scheme 11.



Scheme 12.



Scheme 13.

Conclusions

2-Aryl-3-arylamino-4-ethoxycarbonylisoxazol-5(2*H*)-ones undergo photolytic extrusion of CO_2 to give carbenes which insert into either the 2-aryl or 3-arylamino groups. Such insertions are not dictated by purely electronic factors. Hydrogen bonding of 3-NHAr and the CO_2Et groups is not maintained after formation of the carbene. But the 3-NH group does continue to hydrogen bond with the 2-heteroaryl N-atom. Combined with the effects of π–π stacking, this can direct the conformation of the carbene and drive its mode of cyclization.

Experimental

Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^1H and ^{13}C (300 and 75.5 MHz) NMR measurements were recorded on a Gemini Varian 300 spectrometer in deuteriochloroform with tetramethylsilane as internal standard, unless otherwise stated. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer using fused sodium chloride cells, measured as Nujol mulls or films. Electrospray ionization (ESI) mass spectra were recorded at Monash University, Melbourne. The protonated molecular ion (MH^+) mass to charge ratio (m/z) is reported. Microanalyses were performed at the University of Otago, New Zealand. Gas chromatography–mass spectrometry data was recorded on a Varian

Saturn 4D GC/MS/MS fitted with a Zebron 30 m × 0.25 mm ID 5% phenyl polysiloxane column. X-ray crystal data were recorded by the University of Canterbury, New Zealand, and the crystal structures solved by Dr Max Taylor. AM1 calculations were carried out using *MacSpartan* (**15** and **16**) or *Gaussian 98W*. Details are available in the Accessory Materials.

*Ethyl 2-Methyl-5-oxo-3-phenylamino-2,5-dihydroisoxazole-4-carboxylate **11***

To a stirred solution of isoxazolone **4a**[6] (0.300 g, 1.21 mmol) in acetone (10 mL) under an atmosphere of nitrogen was added triethylamine (200 μL, 1.45 mmol). The solution was stirred for 10 min at room temperature before methyl iodide (300 μL, 4.83 mmol) was added dropwise, and the resulting solution was stirred for 67 h. The solvent was removed in vacuo, yielding a yellow solid which was extracted into EtOAc and washed with 1 M HCl (5 mL) and brine (3 × 50 mL). The organic extracts were dried ($MgSO_4$), the solvent removed, and the yellow solid was recrystallized from ethanol to give the *isoxazolone* **11** as colourless crystals (0.201 g, 63%). mp 142–143°C. (Found: C 59.2, H 5.4, N 10.6%. $C_{13}H_{14}N_2O_4$ requires C 59.5, H 5.4, N 10.7%). ν_{max}/cm^{-1} 3416, 1756, 1673, 1582. δ_H 9.40 (1H, bs), 7.47–7.36 (2H, m), 7.32–7.20 (3H, m), 4.35 (2H, q, *J* 7.2), 3.02 (3H, s), 1.37 (3H, t, *J* 7.2). δ_C 167.9, 165.4, 164.9, 136.2, 129.9, 126.7, 122.7, 77.8, 60.6, 39.9, 14.4.

Alternative Preparation: Methylhydroxylamine hydrochloride (570 mg, 6.8 mmol) in ethanol (40 mL) was neutralized with excess of potassium carbonate, and the solution filtered. Diethyl phenylthiocarbamoylmalonate (1.0 g, 3.3 mmol)[18] was added to the filtrate, and the solution refluxed for 20 h. The solvent was evaporated, water (20 mL) and 3 M HCl (10 mL) were added, and the mixture was extracted with ethyl acetate. The dried extract was evaporated to a pale yellow oil (65%), which slowly crystallized. The crystals had identical spectral properties to the sample above.

*Ethyl 1-Methyl-2,5-dioxo-3-phenyl-2,3,4,5-tetrahydroimidazole-4-carboxylate **12***

Isoxazolone **11** (0.070 g, 0.267 mmol) was dissolved in anhydrous acetone (150 mL) and photolyzed at 300 nm for 2.5 h. The solvent was removed in vacuo, yielding a yellow oil which was triturated with and recrystallized from ethanol to give the *title compound* **12** as colourless crystals (0.013 g, 22%). mp 110–112°C. (Found: C 58.9, H 5.4, N 10.6%. $C_{13}H_{14}N_2O_4$ requires C 59.5, H 5.4, N 10.7%). ν_{max}/cm^{-1} 3400, 1774, 1742, 1716, 1599. δ_H 7.51–7.33 (4H, m), 7.24–7.14 (1H, m), 5.13 (1H, s), 4.35–4.13 (2H, m), 3.14 (3H, s), 1.22 (3H, t, *J* 7.0). δ_C 164.9, 164.0, 153.0, 136.4, 129.4, 125.4, 119.9, 63.8, 63.2, 25.5, 13.9.

*Photolysis of Isoxazolone **13***

Isoxazolone **13**[8] (100 mg) in acetonitrile (150 mL) was photolyzed at 300 nm under nitrogen for 1 h through pyrex. The solvent was removed to yield a red solid, which was recrystallized from ethanol to give ethyl 6-nitro-2-(2,4-dimethoxyphenyl)aminoimidazo[1,2-*a*]pyridine-3-carboxylate **14** as red needles (61 mg, 68%). mp 220°C (lit.[8] 218–221°C), identical with an authentic sample.[8]

*Ethyl 4-Methyl-2-(2,4-dimethoxyphenyl)aminopyrrolo[2,3-c]-quinoline-3-carboxylate **22***

N-aryl isoxazolone **21**[8] (0.100 g, 0.222 mmol) was photolyzed at 300 nm under a nitrogen atmosphere in acetone (150 mL) for 4 h. The solvent was removed in vacuo to yield a brown solid, which was recrystallized from ethanol to give the *title compound* as brown crystals (0.061 g, 68%). mp 114–117°C. (Found: $[M+H]^+$ (ESI) 406.1768. $C_{23}H_{24}N_3O_4^+$ requires 406.1766). ν_{max}/cm^{-1} 1643, 1601, 1558, 1419, 1349, 1234, 1204, 1075. δ_H ($CDCl_3$/TFA) 11.44 (1H, s), 9.05 (1H, bs), 7.95 (1H, d, *J* 7.2), 7.62 (1H, d, *J* 8.1), 7.38–7.27 (3H, m), 6.62 (1H, d, *J* 2.4), 6.57 (1H, dd, *J* 8.4, 2.4), 4.46 (2H, q, *J* 7.1), 3.87 (3H, s), 3.85 (3H, s), 3.06 (3H, s), 1.49 (3H, t, *J* 7.1). δ_C ($CDCl_3$/TFA) 165.0, 160.0, 154.7, 154.0, 147.9, 136.0, 133.0, 129.4, 126.9, 126.4, 121.8, 119.1, 118.5, 116.9, 113.0, 104.7, 100.0, 86.8, 60.6, 55.7, 55.5, 21.8, 14.4.

*Attempts to Trap Photolysis Intermediates from **21***

A mixture of isoxazolone **21** (50 mg, 0.13 mmol) and bicyclopropylidene (103 mg, 1.28 mmol) was photolyzed in anhydrous acetone (20 mL) by sunlight through pyrex for 5 d. The solvent was removed to yield a red solid. ^1H NMR and TLC analysis indicated the presence of **21** and the pyrroloquinoline **22**, and polymerization products of the bicyclopropylidene.

Accessory Materials

AM1-level ab initio calculations for **5a**, (*Z*)-**5a**, **5b**, (*E*)-**5b**, **7a**, (*Z*)-**7a**, **7b**, **13a**, **13b**, **21a**, and **21b** are available from the author or, until May 2009, from the *Australian Journal of Chemistry*.

Acknowledgments

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