Intermolecular Reactions of β-Lactam-4-ylidenes with Alkenes, Alcohols, and Acetic Acid. Spiro-Fused β-Lactam Cyclopropanes, 4-Alkoxy β-Lactams, and a 4-Acetoxy β-Lactam

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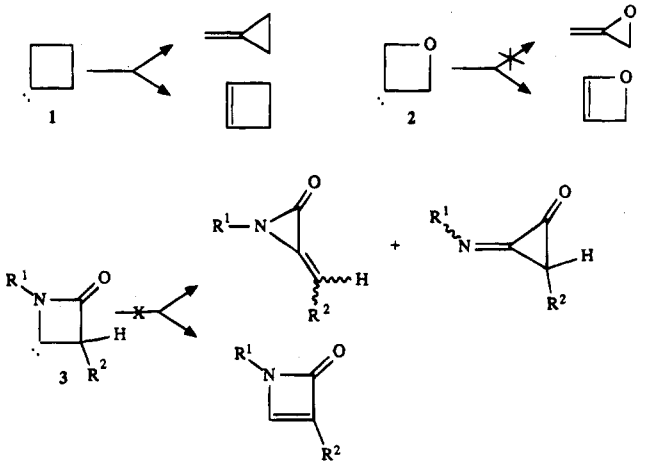
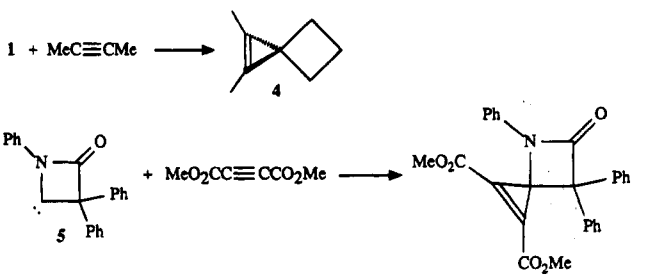
Thermolysis of spiro-fused β-lactam oxadiazolines in the presence of alkenes gave spiro-fused β-lactam cyclopropanes. The latter arise through a sequence of reactions beginning with 1,3-dipolar cycloreversion of an oxadiazoline to form N_2 and a short-lived carbonyl ylide. The latter fragments to acetone and a β-lactam-4-ylidene, which adds to the alkene. Stereospecific additions to dimethyl fumarate and to dimethyl maleate are consistent with a concerted mechanism of cyclopropanation. The ylidenes also form cyclopropanes with alkenes that are not Michael acceptors, including styrene and 4-bromo-1-butene. Thermolysis of β-lactam oxadiazolines in the presence of hydroxylic compounds led to capture of β-lactam-4-ylidenes by OH insertion, essentially in quantitative yields, as expected for reaction of singlet β-lactam-4-ylidenes.

Introduction

The properties of intermediates that have a carbene center in a four-membered ring are of considerable interest. Singlet cyclobutylidene[1] (**1**) rearranges primarily to methylenecyclopropane and affords cyclobutene as a minor coproduct.[2-4] 3-Oxacyclobutylidene (**2**), on the other hand, apparently does not undergo ring contraction but only 1,2-H migration to afford oxetene.[5] A β-lactam-4-ylidene (**3**) undergoes neither ring contraction nor 1,2-H migration fast enough to complete with intermolecular reactions.[6]



Before about 1984, only intramolecular reactions of **1** were known. In that year, Brinker and Boxberger[7] reported stereospecific addition of **1** (carbenoid from reaction of 1,1-dibromocyclobutane with MeLi) to simple alkenes and to styrenes. Moreover, the same species was shown to react with 2-butyne[4] to afford 1,2-dimethylspiro-[2.3]hex-1-ene (**4**). A similar cycloaddition of **5** (an analogue of **3**) to dimethyl acetylenedicarboxylate had been demonstrated,[8] but it was not established whether



or not β-lactam-4-ylidenes add to unactivated alkenes, nor was the stereochemistry of their additions to isomeric unsaturated substrates, such as maleates and fumarates, known. The stereochemistry of such addition is a strong criterion of a cycloaddition mechanism, formation of both *cis* and *trans* adducts from a *Z*-alkene or an *E*-alkene, being incompatible with a concerted mechanism.

Whether or not β-lactam-4-ylidenes add to simple alkenes, as well as to those substituted with electron-withdrawing groups, was also of interest. Although they are formally aminocarbenes, the nitrogen is relatively nonbasic in an amide and therefore a β-lactam-4-ylidene cannot be expected to be distinctly nucleophilic but, perhaps, ambiphilic[9] or electrophilic. We now report that β-lactam-4-ylidenes react with both activated and unactivated alkenes and that the addition to dimethyl maleate occurs with retention of stereochemical integrity, suggesting a concerted mechanism. The same β-lactam-4-ylidenes, formed by thermolysis of spiro-fused β-lactam oxadiazolines in the presence of hydroxylic compounds, including alcohols and acetic acid, afford the products

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(1) Different methods of preparation may generate cyclobutylidene as the free carbene or as a complex (carbenoid). Such intermediates presumably are chemically different, at least in terms of quantitative aspects. Moreover, reaction temperatures for the various approaches to the carbene (carbenoid) can be very different. These features make it difficult to ascertain the relative selectivities of carbenes and carbenoids.

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(3) Schoeller, W. *J. Am. Chem. Soc.* 1979, *101*, 4811.

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(7) Brinker, U. H.; Boxberger, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 974.

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(9) (a) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15. (b) Moss, R. A.; Young, C. M.; Perez, L. A.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1981**, *103*, 2413.

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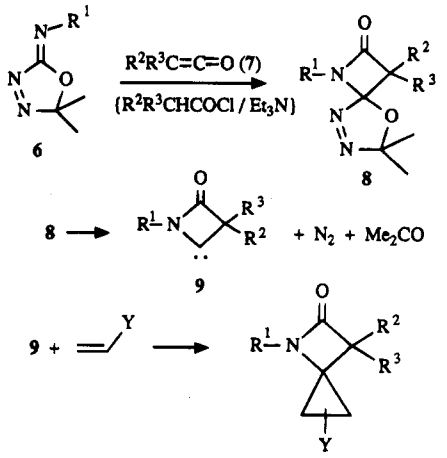
Scheme 1

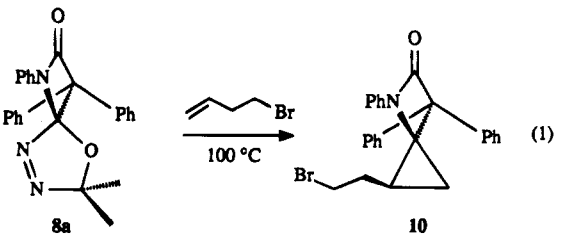


expected of carbene insertion into an O—H bond. All of the chemistry of the ylidenes appears to be that of the singlet state.

Methods, Results, and Discussion

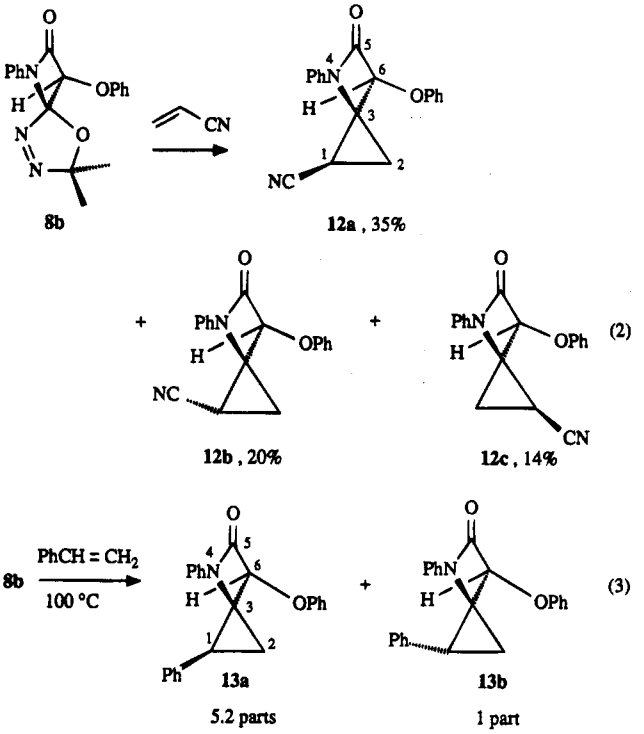
β-Lactam-4-ylidenes **9** were generated by thermolysis of β-lactam oxadiazolines **8**, which were prepared by formal [2 + 2]-cycloaddition of ketenes **7** to iminooxadiazolines **6**, Scheme 1. The carbenophile, present for the thermolysis step, captured the carbene to form the cyclopropane product(s) (Scheme 1). The synthesis of **8**[10] and rate constants for their thermolysis[11] have been published. Thermolyses of **8** in the presence of a carbenophile were run at 100 °C in evacuated, sealed, glass tubes to five or six half-lives of **8**, and reaction products were separated by chromatography and identified by means of infrared spectroscopy, ^1H and ^{13}C NMR spectroscopy, and mass spectrometry. Assignments of stereochemistry to isomeric products are based, in part, on the assumption that their yields are in inverse proportion to the steric crowding in them, and on ^1H NMR chemical shifts and coupling constants. Although those assignments are likely to be correct, they should be regarded as tentative until at least some of the structures are confirmed by X-ray crystallography.

Thermolysis of **8a** in neat 4-bromo-1-butene at 100 °C afforded one major product, 4-aza-1-(2-bromoethyl)-4,6,6-triphenylspiro[2.3]hexan-5-one (**10**), in 60% yield, eq 1. From models, it is clear that the *trans* isomer would be considerably more hindered than **10**. Although only one adduct was found, its geometric isomer could have been missed at the 1 or 2% level. Overall carbon—bromine bond insertion, either concerted or stepwise (Scheme 2)



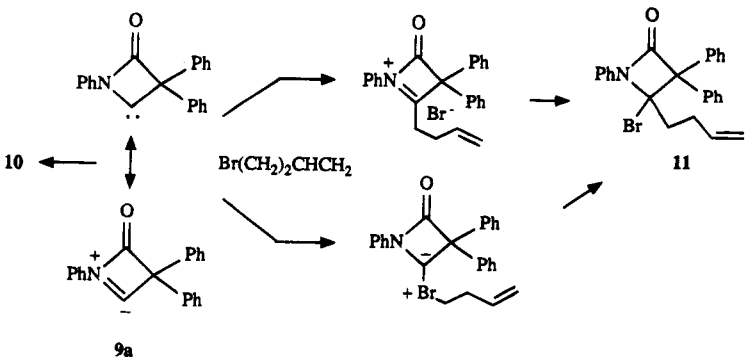
would produce an unstable product **11**. While minor competition from such processes cannot be ruled out because **11** was not found, the high yield of cyclopropanation product suggests that **9** is an electrophilic or ambiphilic carbene rather than a nucleophilic carbene or a dipole.

Thermolysis of **8b** in neat acrylonitrile at 100 °C for 55 min afforded three products (69% yield) that were identified as the stereoisomers **12a—c**, eq 2. Thermolysis of **8b** in styrene afforded two of the four possible isomers, in an overall yield of 74% and in the ratio **13a**:**13b** = 5.2:1, eq 3.



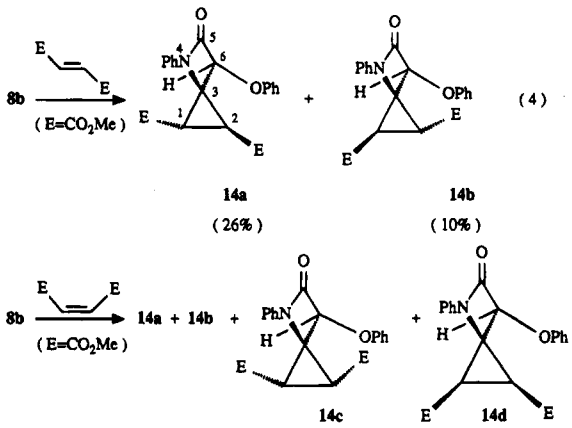
Assignment of the structure of **13b** is based on the shielding of C6-H (δ = 4.99) in the isomer labeled **13b**

Scheme 2



vs $\delta = 5.50$ in **13a**. From an examination of models, such shielding of C6-H is more likely for isomer **13b**.

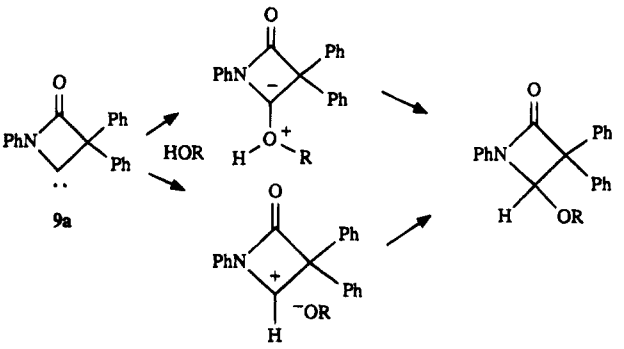
Dimethyl fumarate and **8b**, heated at 111 °C for 55 min, led to formation of two *trans* isomers, **14a** and **14b**, in the ratio 2.7:1; total yield 36%, eq 4. Dimethyl maleate (Aldrich, 96% pure), on the other hand, on heating with **8b** at 100 °C for 55 min, afforded four products. These were **14a** (19%) and **14b** (5%), both also obtained from reaction between dimethyl fumarate and **8b**, as well as the *cis* isomers **14c** (13%) and **14d** (6%), eq 5. The *cis*



isomers showed stronger coupling between the cyclopropane hydrogens (11 Hz), in keeping with the mutual eclipsing of the CH bonds. Heating of the commercial dimethyl maleate at 100 °C for 1 h did not lead to a detectable increase (^{1}H NMR spectroscopy) in the concentration of dimethyl fumarate, in agreement with a literature report of the stability of diethyl maleate toward similar conditions.[12] Moreover, the adducts **14a–d** were found to be thermally stable under the conditions of their formation. One explanation for the four products therefore would invoke a stepwise mechanism of addition and in the case of maleate-derived intermediate, rotation to relieve steric interactions between the ester groups. Such an intermediate could be described as a dipolar adduct, from addition of the carbene as nucleophile, or as a diradical adduct from electron transfer (the carbene acting as reducing agent) followed by bond formation between radical cation and radical anion. Another explanation, that could account for the result in terms of concerted cyclopropanation, would require the dimethyl fumarate present in the sample of dimethyl maleate to have a much higher reactivity toward the β-lactam-4-ylidene.

The second explanation was found to be correct. First, thermolysis of **8b** in a 50:50 solution of dimethyl maleate in dimethyl fumarate gave only **14a** and **14b**. Second, synthesis of dimethyl maleate by adaptation of a literature[13] procedure gave material in which the extent of contamination by fumarate was only 0.4%. When **8b** was thermolyzed in that sample of diester, all four products **14a–d** were again obtained but the yields of the *trans* isomers (**14a**:**14b** = 2.8:1.0) were reduced relative to those of the *cis* isomers (**14c**:**14d** = 10.3:3.0); overall ratio *trans:cis* = 1.0:3.5. Convincing evidence for the origin

Scheme 3



of **14a** and **14b** came from the simple expedient of recycling the leftover ester solvent for a second and a third thermolysis of **8b**. The yields of **14a** and **14b** dropped with each cycle to the point where the overall *trans:cis* ratio was 1.0:31. That result is consistent with fast reaction of fumarate to form *trans* adducts, and much slower reaction of maleate to form *cis* adducts.

The enhanced reactivity of fumarates, compared to that of maleates, in cyclopropanations has been observed before.[14] It may be a consequence of increased steric interactions between the ester groups, during addition to maleate, as the central carbons rehybridize from sp^2 (*ca.* 120° angles) to sp^{2+}, in the cyclopropane-like transition state. Although the retention of stereochemistry implies a concerted reaction of the singlet carbene, the converse, that a singlet must react with retention of stereochemistry, does not follow. There are now several precedents for stepwise cyclopropanation reactions of singlet carbenes. Aryl chlorocarbenes add to diethyl maleate to form two *cis* adducts and one *trans* adduct, and to diethyl fumarate to form *trans* adduct only.[12] Phenylchlorocarbene may react in two steps with alkenes, as inferred from the observation of negative free energies of activation.[15] The two steps were described as reversible complex formation, by charge transfer from alkene to carbene, followed by ring closure in the complex,[15] as concluded also on the basis of theory.[16,17] Benzylchlorocarbene reacts with tetramethylethylene or diethyl fumarate in competition with unimolecular rearrangement to *E*- and *Z*-β-chlorostyrenes.[17] Complex formation between carbene and alkene was inferred from a dependance of the *E:Z* ratio on alkene concentration.[15,18] There is also at least one example of nonstereospecific, intramolecular cyclopropanation of an unactivated alkene from reaction of dibromocyclopropane with methyllithium.[19]

Although either a concerted mechansim, or a stepwise mechanism with a very fast second step, can account for the sterospecific additions observed in the present case, such reactions are usually described as concerted reactions until compelling evidence for a stepwise process emerges. Extrapolating from the results with dimethyl maleate and fumarate, we assume that reactions of **9** with acrylonitrile, styrene, and 4-bromo-1-butene are also concerted.

Thermolyses of spiro-fused β-lactam oxadiazolines in media containing hydroxyl functions led to efficient overall OH insertions. In the case of electrophilic singlet carbenes, such reactions are believed to involve initial nucleophilic attack by an oxygen lone pair, at the carbene's electrophilic vacant coordination site (Scheme 3), to generate an ylide. The latter than rearranges, by

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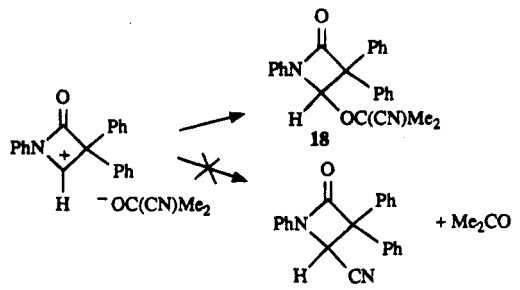
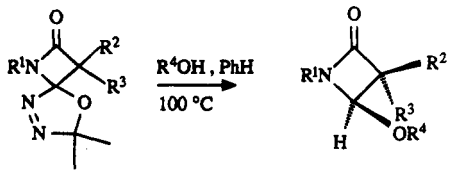
(13) Raber, D. J.; Gariano, P., Jr.; Brod, A. O.; Gariano, A. L.; Guida, W. C. *Org. Syntheses;* Noland, W. E.; Ed., Wiley: New York, **1988**; Collect. Vol. VI, p 576.

Scheme 4



Scheme 5



8a: $R^1 = R^2 = R^3 = Ph$
b: $R^1 = Ph, R^2 = OPh, R^3 = H$
15: $R^1 = R^2 = R^3 = Ph, R^4 = Me$
16a: $R^1 = Ph, R^2 = OPh, R^3 = H, R^4 = Me$
16b: $R^1 = Ph, R^2 = H, R^3 = OPh, R^4 = Me$
17a: $R^1 = Ph, R^2 = OPh, R^3 = H, R^4 = Et$
17b: $R^1 = Ph, R^2 = H, R^3 = OPh, R^4 = Et$
18: $R^1 = R^2 = R^3 = Ph, R^4 = C(CN)Me_2$
19: $R^1 = R^2 = R^3 = Ph, R^4 = COMe$

proton transfer, to the observed product of overall OH insertion. For a nucleophilic carbene, a proton transfer mechanism, leading to an ion pair, is an alternative (Scheme 3). Similar but concerted mechanisms would have O to C bond formation more advanced at the transition state than for H to C bond formation for insertions of electrophilic carbenes and the reverse order for nucleophilic carbenes.

Acetone cyanohydrin was used to probe for the ion pair mechanism of Scheme 3. The cyanohydrin is more acidic than simple alcohols and, in addition, it has the potential for leading to a nitrile instead of, or in addition to, an ether (Scheme 4). The cyano lactam was not found but only the ether. This failure to observe branching to two products does not eliminate the ion pair mechanism, of course, because collapse of that pair to form the ether could be much faster than extrusion of CN^- from the cyanohydrin anion. The detailed mechanism of the OH insertions remains unknown but it is interesting that essentially quantitative yields of carbene insertion products were found (Scheme 5). This could mean that the ylide precursors of the carbenes are very short-lived or else that they are unreactive toward alcohols and acetic acid. The latter option is not realistic, given the known chemistry of carbonyl ylides,[20] and we conclude that ylide fragmentation must be very fast.

In summary, a β-lactam-4-ylidene cyclopropanates both simple alkenes and those with electron-withdrawing substituents, suggesting electrophilic or ambiphilic properties for the carbene. Stereospecific addition to dimethyl maleate and fumarate, as well as efficient insertion into OH bonds, indicates that the reacting species is the singlet carbene, but those observations do not require that the singlet be the ground state.

Experimental Section

β-Lactam Oxadiazolines 8. These compounds were prepared from 2-(phenylimino)-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline by treatment with the appropriate acid chloride and triethylamine, as described in the literature.[10]

Procedure for Cyclopropanations. Most reactions were carried out on a small scale. A spiro β-lactam oxadiazoline(**8**) (0.1 mmol) and alkene (0.5 mL) were introduced into a medium-walled NMR tube. After three freeze-pump-thaw cycles the tube was sealed under reduced pressure (10^{-2} Torr) and then placed in a constant temperature (100 + 0.2 °C) oil bath for a period of time equivalent to about 5 half lives of the oxadiazoline.[11] The tube was then cut, excess alkene was removed by bulb to bulb distillation at 10^{-2} Torr pressure (or less), and the residue was chromatographed (Chromatotron, 2 mm silica plate) with ether in hexane as eluent.

In the case of dimethyl fumarate, a solid alkene melting at 103–104 °C, the oxadiazoline, also solid, was mixed with the fumarate and the solid mixture was degassed as such and sealed into the NMR tube. To ensure a homogeneous, free-flowing melt the temperature for thermolysis was 111 °C instead of 100 °C. Workup was without bulb to bulb distillation, by chromatography only.

Addition to 4-Bromo-1-butene. 4-Aza-1-(2-bromoethyl)-4,6,6-triphenylspiro[2.3]hexan-5-one (**10**): yield 60%; IR (KBr) ν 1755 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (m, 1H, cyclopropyl), 1.30 (m, 2H, cyclopropyl), 1.76 (m, 2H), 3.14 (m, 2H, CH_2Br), 6.90–7.42 (m, 15H), assignments based in part on two dimensional $^{13}C-^1H$ correlations; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.80 (+ve, C2), 19.47 (-ve, C_1), 31.81 (+ve, CH_2), 31.90 (+ve, CH_2), 60.71 (+ve, C3 or C6), 70.02 (+ve, C6 or C3), 124.22, 127.05, 127.53, 127.65, 128.07, 128.22, 128.64, 128.82, 129.54 (all -ve, Ar), 135.82 (+ve, C1, aryl), 137.72 (+ve, C1, aryl) 138.18 (+ve, C1, aryl), 168.81 (+ve, CO); MS (EI) m/z 433/431 (M^+, 2%), 405/403 (M^+ − CO, 14%), 314/312 (M^+ − PhNCO, 8%), 269 (40%), 205 (49%), 165 ($C_{13}H_9$ = 9-fluorenyl, 100%), 115 (11%), 77 (39%); MS (CI, NH_3) m/z 451/449 ($M^+ + NH_4$, 56%), 434/432 (M^+ + H, 100%), 404 (14%), 354 (33%), 352 (30%), 316 (13%), 270 (17%), 205 (11%), 165 (19%), 94 (13%); MS (HR) m/z for $C_{25}H_{22}BrNO$ calcd 431.0885, found 431.0883.

Addition to Acrylonitrile. 4-Aza-1-cyano-6-phenoxy-4-phenylspiro[2.3]hexan-5-ones **12**. Four fractions were obtained by chromatography but the first was too small for IR and NMR spectroscopic identification.

Fraction 2 (**12c**): 14% yield; IR (film) 1775 cm^{-1} (CO), 2260 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 (dd, J = 6.9, 7.9 Hz, 1H), 2.14 (dd, J = 7.9, 10 Hz, 1H), 2.50 (dd, J = 6.9, 10.0 Hz, 1H), 5.61 (s, 1H), 7.08–7.38 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 2.96, 10.25, 54.31, 82.71, 117.85, 116.26, 118.67, 123.12, 126.27, 129.79, 129.83, 134.89, 156.90, 162.72; MS (EI) m/z 290 (M^+, 2%), 262 (M^+ − CO, 31%), 233 (48%), 194 (10%), 180 (30%), 165 (6%), 144 (12%), 117 (65%), 104 (33%), 77 (100%); MS (CI, NH_3) m/z 308 ($M^+ + NH_4$, 100%), 262 (6%), 199 (8%); MS (HR) m/z for $C_{18}H_{14}N_2O_2$ calcd 290.1055, found 290.1050.

Fraction 3 (**12a**): 35% yield; IR(KBr) 1760 cm^{-1} (CO), 2240 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.82–1.92 (m, 1H), 2.00–2.13 (m, 2H), 5.43 (s, 1H), 7.05–7.45 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 4.33, 10.42, 54.08, 83.37, 116.85, 115.61, 122.99, 123.15, 127.73, 129.43, 129.84, 133.51, 156.78, 163.39; MS (EI) m/z 290 (M^+, 3%), 262 (M^+ − CO, 48%), 233 (68%), 209 (6%), 180 (36%), 144 (11%), 117 (61%), 104 (29%), 77 (100%); MS (CI, NH_3) m/z 308 ($M^+ + NH_4$, 100%), 291 (M^+ + H, 4%), 263 (M^+ + H − CO, 6%), 199 (10%); MS (HR) m/z for $C_{18}H_{14}N_2O_2$ calcd 290.1055, found 290.1047.

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Fraction 4 (**12b**): yellow oil, 20% yield; IR (film) 1790 cm^{-1} (CO), 2260 cm^{-1} (CN); ^1H NMR (200 MHz, $CDCl_3$) δ 1.85 (dd, J = 7, 10 Hz, 1H), 2.09 (dd, J = 7, 10 Hz, 1H), 2.24 (t, J = 7 Hz, 1H), 5.39 (s, 1H), 7.05–7.47 (m, 10H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 2.44, 12.68, 54.87, 82.28, 119.37, 115.71, 116.31, 123.14, 127.33, 129.53, 129.90, 133.86, 156.72, CO not found; MS (EI) m/z 290 (M^+, 3%), 262 (M^+ – CO, 68%), 233 (100%), 209 (8%), 180 (52%), 144 (16%), 117 (93%), 104 (40%), 103 (20%), 84 (41%), 77 (92%); MS (CI, NH_3) m/z 308 ($M^+ + NH_4$, 100%), 291 (M^+ + H, 13%), 263 (10%), 233 (6%), 216 (8%), 199 (79%), 183 (8%), 160 (18%), 94 (27%); MS (HR) m/z for $C_{18}H_{14}N_2O_2$ calcd 290.1055, found 290.1060.

Addition to Styrene. 4-Aza-6-phenoxy-1,4-diphenylspiro-[2.3]hexan-5-ones, **13**. Major isomer **13a**: white solid, 62% yield; mp 136 °C; IR (KBr) 1760 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.67 (dd, J = 7.6, 10.1 Hz, 1H), 1.84 (t, J = 7.6 Hz, 1H), 2.72 (dd, J = 7.6, 10.1 Hz, 1H), 5.50 (s, 1H), 6.70–7.35 (m,15H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 7.40, 24.08, 55.79, 84.19, 115.78, 122.39, 122.53, 125.77, 127.07, 128.28, 128.46, 129.46, 129.69, 135.25, 135.36, 157.56, 164.90; MS (EI) m/z 313 (M^+ – CO, 4%), 238 (10%), 196 (100%), 165 (25%), 144 (6%), 104 (21%), 77 (45%); MS (CI, NH_3) m/z 359 ($M^+ + NH_4$, 8%), 342 (M^+ + H, 100%), 3.14 (M^+ + H – N_2, 29%), 248 (12%), 196 (8%), 94 (6%); MS (HR) m/z for $C_{22}H_{19}NO = C_{23}H_{19}NO_2$ – CO 313.1467, found 313.1457.

Minor isomer (**13b**): white solid, 12% yield; mp 162 °C; IR (KBr) 1758 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.75 (dd J = 7.4, 7.9 Hz, 1H), 2.13 (dd, J = 7.9, 10.3 Hz, 1H), 3.10 (dd, J = 7.4, 10.3 Hz, 1H), 4.99 (s, 1H), 7.05–7.41 (m, 15H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 9.48 (C2), 20.86, 56.42, 81.45, 116.48, 117.04, 118.40, 122.51, 125.13, 126.63, 126.93, 128.77, 129.53, 136.42, 137.42, 157.35, 164.22; MS (EI) m/z 313 (M^+ – CO, 1%), 238 (11%), 196 (100%), 165 (22%), 100 (16%), 75 (13%); MS (CI, NH_3) m/z 359 ($M^+ + NH_4$, 11%), 342 (M^+ + H, 100%) 314 (M^+ + H – N_2, 10%), 250 (9%), 196 (14%), 167 (13%), 134 (12%), 94 (33%), 72 (15%); MS (HR) m/z for $C_{22}H_{19}NO = C_{23}H_{19}NO_2$ – CO calcd 313.1467, found 313.1453.

Addition to Dimethyl Fumarate. 4-Aza-1,2-bis (methoxycarbonyl)-6-phenoxy-4-phenylspiro[2.3]hexan-5-ones **14**. Chromatography, with 25% ethyl acetate in hexane as eluent, gave two fractions. The first fraction was dimethyl fumarate and the second was a mixture of *trans* cyclopropanation products in the ratio 2.7:1; total yield 36%.

Major isomer (**14a**): yield 26.3%; IR (film) 1775 (CO, lactam), 1730 cm^{-1} (CO, esters); ^1H NMR (200 MHz, $CDCl_3$) δ 2.99 (d, J = 7 Hz, 1H), 3.23 (d, J = 7 Hz, 1H), 3.22 (s, 3H), 3.78 (s, 3H), 5.52 (s, 1H), 7.00–7.41 (m, 10 H); MS (EI) m/z 381 (M^+, 0.5%), 353 (M^+ – CO, 30%), 293 (19%), 262 (M^+ – PhNCO, 13%), 234 (M^+ – PhNCO – CO, 27%), 228 (13%), 188 (28%), 175 (53%), 144 (53%), 129 (14%), 104 (31%), 77 (100%), 51 (40%).

Minor isomer (**14b**): yield 9.7%; IR (film) 1775 (CO lactam), 1730 cm^{-1} (CO, esters); ^1H NMR (200 MHz), $CDCl_3$) δ 2.96 (d, J = 7 Hz, 1H, CH), 3.27 (d, J = 7 Hz, 1H, CH), 3.39 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 5.38 (s, 1H, C6 – H), 7.00–7.36 (m, 10 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 26.86 (-ve, C1 or C2), 26.97 (-ve, C2 or C1), 52.20 (-ve, OCH_3), 52.63 (-ve, OCH_3), 59.75 (+ve, C3), 82.74 (-ve, C6), 117.42, 123.03, 123.81, 127.43, 129.09, 129.63 (-ve, 6CH, aryl), 134.10 (+ve, N – C1, aryl), 157.62 (+ve, O – C1, aryl); 165.14 (CO), 167.45 (CO), 168.87 (CO); MS (EI) m/z 353 (M^+ – CO, 10%), 293 (9%), 262 (M^+ – PhNCO, 8%), 234 (M^+ – CO – PhNCO, 11%), 175 (35%), 149 (41%), 91 (42%), 77 (100%); MS (CI, NH_3) m/z 419 (20%, impure ?), 382 (M^+ + H, 17%), 354 (M^+ + H – CO, 28%), 313 (83%), 286 (100%), 194 (23%), 166 (7%), 134 (6%), 108 (36%), 91 (13%); MS (HR) m/z for $C_{20}H_{19}NO_5 = C_{21}H_{19}NO_6$ – CO) calcd 353.1263, found 353.1258.

Addition to 96% Dimethyl Maleate. 4-Aza-1,2-bis-(methoxycarbonyl)-6-phenoxy-4-phenylspiro[2.3]hexane-5-ones **14**. Chromatography with 25% ether in hexane separated four minor impurities from **14**. Use of 25% ethyl acetate in hexane eluted three further fractions, nos. 5, 6, and 7. Fraction 5: colorless oil, in 5% yield; IR and NMR spectra identical to those described above for **14b**.

Fraction 6: yellow oil, in 32.5% yield, mixture of **14a** (1.6 parts, eluting first) and a *cis* isomer **14c** (1 part) by GC; IR (film) of the mixture: 1775 cm^{-1} (br, CO, lactam), 1730 cm^{-1} (br, CO, esters); ^1H NMR (500 MHz, $CDCl_3$) of **14c**; δ 2.93 (d, J = 11 Hz, 1H), 3.00 (d, J = 11 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 6.24 (s, 1H), 7.00–7.41 (m, 10H); MS (EI) m/z 381 (M^+, 1%), 353 (M^+ – CO, 19%), 293 (18%), 262 (M^+ – PhNCO, 14%), 234 (M^+ – PhNCO – CO, 23%), 200 (23%), 175 (44%), 169 (39%), 144 (40%), 104 (25%), 77 (100%), 51, (31%).

Fraction 7: yellow oil (**14d**) in 6.5% yield; IR (film) 1775 cm^{-1} (CO, lactam), 1730 cm^{-1} (CO, esters); ^1H NMR (200 MHz, $CDCl_3$) δ 2.63 (d, J = 11 Hz, 1H), 2.66 (d, J = 11 Hz, 1H), 3.45 (s, 3H), 3.52 (s, 3H), 5.38 (s, 1H), 7.03–7.38 (m, 10H); the chemical shifts δ 2.63 and 2.66 assigned with use of the equation $\delta_A - \delta_B = [(\nu_4 - \nu_1)(\nu_3 - \nu_2)]^{1/2}$; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.37, 26.46, 51.92, 52.04, 58.01, 83.51, 115.86, 122.93, 127.94, 128.46, 128.54, 129.82, 133.94, 156.97, 165.99, 166.00, 166.50; MS (EI) m/z 381 (M^+, 1.5%), 353 (M^+ – CO, 21%), 293 (13%), 262 (M^+ – PhNCO, 9%), 234 (M^+ – PhNCO – CO, 7%), 149 (25%), 77 (100%); MS (CI, NH_3) m/z 399 ($M^+ + NH_4$, 7%), 382 (M^+ + H, 40%), 354 (M^+ + H – CO, 98%), 322 (36%), 290 (20%), 259 (10%), 228 (26%), 205 (11%), 175 (18%), 119 (PhNCO, 42%), 94 (100%), MS (HR) m/z for $C_{20}H_{19}NO_5 = C_{21}H_{19}NO_6$ – CO, calcd 353.1264, found 353.1275.

Dimethyl Maleate of High Purity. The procedure of Raber and co-workers[13] gave, from maleic acid (1.16 g, ≥99.5% purity) and trimethyloxonium tetrafluoroborate (3.26 g), dimethyl maleate (1.0 g, 69%). Integration of a ^{13}C satellite at δ 3.54, of the carbomethoxy singlet from dimethyl maleate, against the olefinic signal of dimethyl fumarate at δ 6.86, gave the maleate:fumarate ratio as 99.6:0.4.

Additions to Maleate Depleted of Fumarate. Thermolysis of **8b** (64 mg, 0.20 mmol) in dimethyl maleate (576 mg, 4.0 mmol) gave two *cis* adducts **14c**:**14d** = 10.3:3.0 and two *trans* adducts **14a**:**14b** = 2.8:1.0, overall *trans*:*cis* = 1:3.5. The excess maleate, separated by Kugelrohr distillation and containing less than 0.2 % fumarate (by NMR, as described above) was used as solvent and trap for a further thermolysis of **8b**; **8b** (32 mg, 0.1 mmol) in 220 mg (1.5 mmol) of recovered maleate. The product ratios were **14c**:**14d** = 20.3:7.1 and **14a**:**14b** = 3.4:1; overall *trans*:*cis* = 1:6.2.

Recovered maleate (150 mg, 1.0 mmol) was used in a further thermolysis of **8b** (16 mg, 0.05 mmol) to afford three products in relative proportions **14c**:**14d**:**14a** = 24:7.0:1.0; overall *trans*:*cis* = 1:31. The minor *trans* product (**14b**) was not found.

Insertions into OH Bonds. The general procedure involved the thermolysis of spiro β-lactam oxadiazoline **8** (0.1 mmol) in a solution made by dissolving the hydroxy compound (1.0 mmol) in 0.25 mL of C_6D_6 unless otherwise specified. Reactions were carried out in sealed, medium-walled NMR tubes as described above and the product was isolated by distilling off excess trap and solvent by the bulb to bulb method on a vacuum line. Unless otherwise noted, the residue was the expected product of carbene insertion into the OH bond of the trapping agent and it was pure.

Trapping with Methanol. 4-Methoxy-1,3,3-triphenylazetidin-2-one (**15**). The above procedure afforded the 4-methoxy β-lactam **15** as a white solid, in >95% yield; mp 89–90 °C; IR (KBr) 1753 cm^{-1} (CO); ^1H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 5.75 (s, 1H), 7.1–7.6 (m, 15H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 54.81, 71.86, 90.68, 117.42, 124.79, 127.61, 127.76, 127.93, 128.24, 128.67, 128.93, 129.21, 136.23, 137.21, 138.25, 166.13; MS (EI) m/z 329 (M^+, 5%), 210 (M^+ – PhNCO, 68%), 194 (Ph_2CCO, 100%), 165 (78%), 105 (18%), 77 (36%); MS (HR) m/z for $C_{22}H_{19}NO_2$ calcd 329.1416, found 329.1411.

Trapping with Methanol. 4-Methoxy-3-phenoxy-1-phenylazetidin-2-ones **16a** (*cis*) and **16b** (*trans*). Removal of the volatiles from thermolysis of **8b** in the presence of methanol left a residue that consisted of only (by ^1H NMR spectroscopy) **16a** and **16b** in the ratio 1:2 as a yellow oil in >95% yield. Those products were not separated and spectral lines of the composite spectra were assigned, where possible, to the components present. IR (film) 1770 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 3.55 (s, both isomers), 5.28 (d, J = 0.8 Hz, *trans* isomer), 5.33 (d, J = 3.6 Hz, *cis* isomer), 5.46 (d, J = 0.8 Hz, *trans* isomer), 5.71 (d, J = 3.6 Hz, *cis* isomer), 7.06–7.57 (m); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 53.83 (*trans* isomer), 54.53 (*cis* isomer), 81.79 (*cis* isomer), 83.67 (*trans* isomer), 84.61 (*trans*

isomer), 88.23 (*cis* isomer), these last four assignments tentative, 115.56, 115.70, 117.47, 117.57, 122.55, 125.31, 125.34, 129.31, 129.65, 129.76, 136.70, 157.07, 157.40, 160.94, 163.07.

Trapping with Ethanol. 4-Ethoxy-3-phenoxy-1-phenylazetidin-2-ones **17a** (*cis*) and **17b** (*trans*). The 4-ethoxy β-lactams were obtained in quantitative yield in the ratio *cis*:*trans* = 1:4. All spectra and properties refer to the product mixture: yellow oil; IR (film) 1770 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, J = 7 Hz, *cis*), 1.30 (t, J = 7 Hz, *trans*), 3.78 (m, signals of *cis* and *trans* overlapped), 5.24 (s, br, *trans*), 5.30 (d, J = 3.6 Hz, *cis*), 5.46 (s, br, *trans*), 5.70 (d, J = 3.6 Hz, *cis*), 7.06–7.55 (m, ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 15.24 (presumably both isomers), 63.04 (*trans*), 63.26 (*cis*), 81.61 (*cis*), 84.01 (*cis*), 84.54 (*trans*), 87.55 (*trans*), 112–113.5, 115.62, 117.46, 117.66, 122.49, 125.24, 129.28, 129.61, 129.74, 136.62, 161.15 (presumably CO, only one found); MS (EI) m/z 283 (M^+, 15%), 164 (M^+ − PhNCO, 100%), 149 (10%), 136 (53%), 121 (17%), 107 (25%), 93 (16%), 77 (76%); MS (CI, NH_3) m/z 301 ($M^+ + NH_4$, 9%), 284 (M^+ + H, 100%), 164 (19%), 150 (7%), 94 (9%).

Trapping with Acetone Cyanohydrin. 4-[(1-Cyano-1-methyl)ethoxy]-1,3,3-diphenylazetidin-2-one (**18**). Treatment of β-lactam oxadiazoline **8a** (0.081 mmol) with acetone cyanohydrin (0.24 mmol) in C_6D_6 (0.5 mL) as described above led to a crude product still containing some cyanohydrin. Chromatography on a 2 mm silica plate (Chromatotron apparatus) with 25% ethyl acetate in hexane afforded **18** as a white solid, mp 155–156 °C, in >95% yield; IR (KBr) 2240 cm^{-1} (CN), 1767 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.51 (s, 3H), 3.39 (s, 1H), 7.17–7.67 (m, 15H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 27.44, 27.90, 70.34, 72.99, 86.32, 120.23, 118.16, 125.24, 127.79, 127.89, 128.12, 129.03, 129.13, 129.24, 130.08, 136.00, 136.24, 136.59, 166.45; MS (EI) m/z 383 (M^+ + H, 1–5%), 382 (M^+, 1%), 263 (M^+ − PhNCO, 24%); 205 (6%), 194 (100%), 165 (93%), 152 (22%), 139 (7%), 115 (6%), 93 (12%), 77 (19%); MS (CI, NH_3) m/z 400 ($M^+ + NH_4$, 3%), 383 (M^+ + H, 100%), 342 (14%), 325 (18%), 300 (15%), 270 (16%), 194 (23%), 167 (71%), 119 (13%), 94 (34%); MS (HR) m/z for $C_{25}H_{22}N_2O_2$ calcd 382.1681, found 382.1696.

Trapping with Acetic Acid. 4-Acetoxy-1,3,3-triphenylazetidin-2-one (**19**). Oxadiazoline **8a** (0.064 mmol) in C_6D_6 (0.5 mL) containing acetic acid (0.19 mmol) gave, following the procedure described above, the expected 4-acetoxy-β-lactam as a thick, colorless oil in quantitative yield: IR (film) 1768 cm^{-1} (CO), 1745 cm^{-1} (CO); ^1H NMR (200 MHz, $CDCl_3$) δ 1.72 (s, 3H), 7.02 (s, 1H), 7.16–7.85 (m, 15H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.38, 72.87, 83.22, 117.08, 125.07, 127.84, 127.91, 127.96, 128.24, 128.66, 128.90, 129.31, 135.92, 136.38, 137.08, 165.57, 170.07; MS (EI) m/z 270 ($M^+ - CH_3CO_2$ − CO, 2%), 238 (M^+ − PhNCO, 12%), 196 (100%), 165 (32%), 84 (23%); MS (CI, NH_3) m/z 358 (M^+ + H, 18%), 315 (M^+ + H − CH_3-CO, 11%), 298 ($M^+ - CH_3CO_2H$, 100%), 270 (80%), 238 (8%), 196 (47%), 167 (15%), 136 (6%), 94 (7%).

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