Reactions of nucleophilic carbenes with enols

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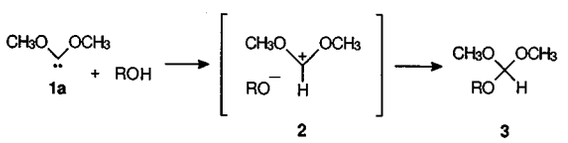
The formal insertion of dimethoxycarbene (1a) into the acidic C–H bond of pentane-2,4-dione (9a), methyl acetoacetate (9b), 3-methylpentane-2,4-dione (9c) and 1,3-diphenylpropane-1,3-dione (9d) is reported as well as the insertion of 3-benzoyloxazolidin-2-ylidene (1b) into 9c. The β-dicarbonyl compounds 9 are known to be equilibrated with their corresponding enols in benzene solution and the insertions appear to proceed by proton abstraction from the enol tautomers of 9 to generate enolate anions and either a dimethoxymethyl cation (from 1a) or a 3-benzoyloxazolidin-2-ium cation (from 1b). Collapse of these ion pairs at the carbon atom of the enolate yields the major product. Formal insertion of 1a into the O–H bond of the enol tautomer of anthrone (12) is also reported.

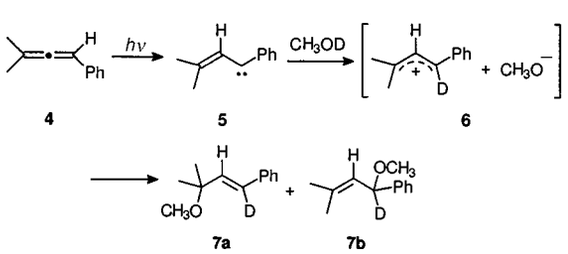
Investigations of the reactions of carbenes with alcohols and phenols have resulted in a better understanding of the mechanisms of insertion of carbenes into the O–H bond.[1] There is good evidence for a mechanism in which nucleophilic carbenes such as dimethoxycarbene (**1a**, Scheme 1) abstract the O–H



Scheme 1

proton of an alcohol to generate an ion pair (**2**) that collapses to yield an orthoformate (**3**). For example, absolute rate constants for the reaction of dimethoxycarbene with a variety of alcohols are correlated to the ionization constants of the alcohols.[2] A large primary deuterium kinetic isotope effect ($k_H/k_D = 3.3$) has been measured for the insertion of dimethoxycarbene into the O–H bond of methanol.[3] In addition, the cationic intermediates resulting from protonation of several nucleophilic carbenes have been detected spectroscopically by means of laser flash photolysis.[4,5] These results are all in keeping with the mechanism in Scheme 1 for the insertion of dimethoxycarbene into an O–H bond.

Proton transfer to the nucleophilic carbene generates the cation–anion pair (**2**) in intimate contact. These carbene-generated contact ion pairs have been shown to lead to scrambling when the cationic portion is delocalized. Thus, photolysis of the phenylallene **4** results in rearrangement to the vinylcarbene **5** which has been shown to abstract a proton from methanol to yield the allyl cation–methoxide ion pair **6** (Scheme 2).[5] The methoxide ion bonds to either C-1 or C-3 of the allyl



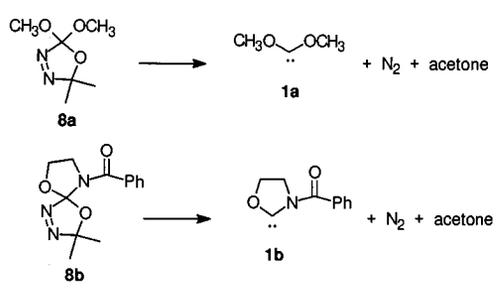
Scheme 2

cation to generate the isomeric ethers **7a** or **7b** in a 1:2.8 ratio. In addition, the allyl cation has been observed as a transient during laser flash photolysis and it has been characterized by means of extensive deuterium labelling experiments.[5]

Reports of reactions of nucleophilic carbenes with compounds having a high enol content have not appeared. Deprotonation of an enol by a nucleophilic carbene should yield an enolate and a stabilized carbocation (*e.g.* dimethoxymethyl cation in the case of **1a**). Such an ion pair could collapse to afford either the product of *O*-alkylation or that of *C*-alkylation. Which process predominates is not known because carbene generated ion pairs in which the anionic portion is an enolate have apparently not been reported.

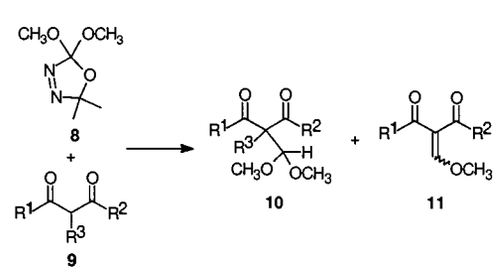
Results and discussion

General thermolysis of 2,2-dimethoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**8a**)[6] and 3,4,9-triaza-9-benzoyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene (**8b**)[7] (Scheme 3) resulted in the gener-



Scheme 3

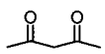
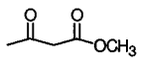
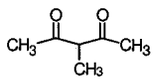
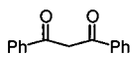
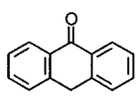
ation of stabilized carbenes (**1a** and **1b**).[6,7] Typically, a solution of an oxadiazoline (0.05 M) in dry benzene containing one equivalent of a β-dicarbonyl compound (**9a–d**) was heated at 110 °C for 20 h in the case of **8a** or at 90 °C for 24 h for **8b**. The major products from dimethoxycarbene (**10**, Scheme 4) result from carbene insertion into a C–H bond of the keto tautomers



Scheme 4

of **9a–d** (see Table 1). In the cases of **9a** and **9b**, the reaction mixture also contained the products **11a** and **11b** which arose from elimination of methanol from **10a** and **10b**, respectively. Product **11b** was a mixture of *E* and *Z* isomers in roughly equal

Table 1 Yields of products of dimethoxycarbene trapping (**10a–d**, **11a–b** and **13**) with activated methylene compounds **9a–d** and **12**

Methylene compound		Product(s)	Yield[a]
9a		**10a** **11a**	17 8
9b		**10b** **11b** (*E*, *Z* isomers)	29 14
9c		**10c**	26
9d		**10d**	56
12		**13**	30

[a] Yield, by NMR spectroscopy, is based on oxadiazoline.

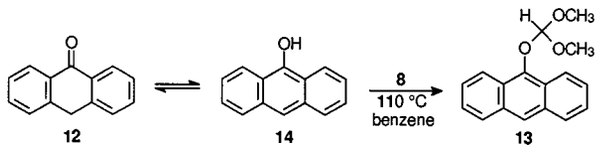
proportions. The reaction mixture from trapping with **9c** did not contain such products because the methyl group ($R^3 = CH_3$) blocked elimination. Evidence for formation of **11d** from the reaction of **1** with **9d** was not found in our analysis of the reaction mixture. For the traps **9a** and **9b**, the ratios of primary products (**10**) to products of methanol loss (**11**) were 2.2:1 and 4.7:1, respectively. Yields of carbene-derived products based on oxadiazoline, determined by NMR spectroscopic analysis of the reaction mixtures containing an internal standard, are given in Table 1.

The crude samples from trapping of dimethoxycarbene with **9a–c** (1 equiv.) were analyzed directly by GC and GC–MSD. Reaction products were then concentrated by removal of the solvent, along with much of the excess β-dicarbonyl compound, under vacuum. The product from dimethoxycarbene trapping by **9d** was identified by ^{1}H NMR spectroscopy on the reaction mixture which still contained leftover trap. Nearly total conversion of **9d** to **10d** was achieved by conducting a thermolysis with a 2.5-fold excess of oxadiazoline **8a**.

Mixtures resulting from trapping of **1a** by **9a** and **9b** could be converted entirely to the products of methanol loss (**11a** and **11b**) by adding a catalytic amount of pyridine (5 μl in 25 ml) and reheating the mixture to 110 °C for 20 h (unoptimized conditions). However, addition of pyridine prior to thermolysis (so that it was present during carbene generation) resulted in lowered yields of carbene-derived products. The cause is unlikely to be competitive trapping of the carbene with pyridine,[8] as trapping of a nucleophilic carbene by pyridine is expected to be quite slow. Rather, pyridine results in full elimination of methanol, with the methanol produced intercepting some ion pairs (or dimethoxycarbene), thus lowering yields of products of type **10**. For instance, trimethyl orthoformate was observed in about 43% yield (^{1}H NMR, *p*-xylene as reference) from a reaction involving pentane-2,4-dione **9a** (0.29 M) and oxadiazoline **8a** (0.24 M) in [$^2H_6$]benzene even in the absence of pyridine. This explanation does not account for the poor yield of **10c** from 3-methylpentane-1,3-dione **9c**, however.

Similar methods were used to examine the trapping of **1a** with anthrone **12**. Solutions of 0.05 M oxadiazoline, 1 equiv. of anthrone **12** and a catalytic amount of pyridine were heated at 110 °C for 20 h. The reaction mixture contained a single anthrone-derived product **13**, formally generated from insertion of dimethoxycarbene into the O–H bond of the enol tautomer, anthranol **14** (Scheme 5). In that case addition of pyridine prior to thermolysis was effective in increasing the yield of **13** (from <10% in the absence of pyridine), presumably by catalyzing the keto–enol equilibration, without the complication from formation of methanol.

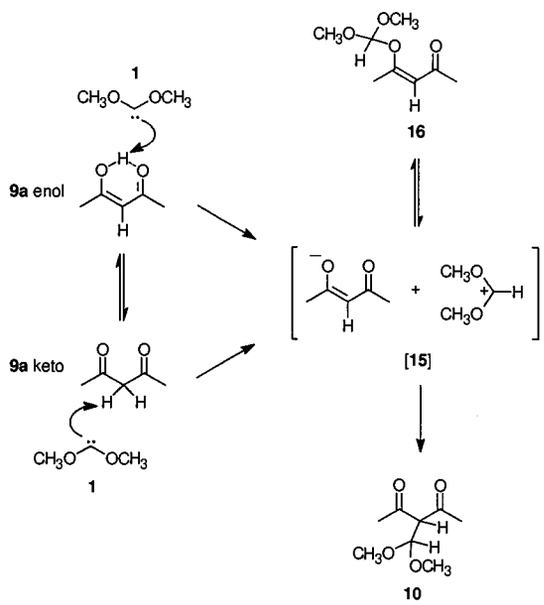
Trapping studies with other activated methylene compounds



Scheme 5

were informative. Methyl cyanoacetate (**9e**), malononitrile (**9f**) and dimethyl malonate (**9g**) all proved to be ineffective agents for trapping of **1a**. Only trace amounts of likely products of trapping could be detected in the GC–MSD traces of the crude reaction mixtures. Addition of pyridine in various amounts had little effect on the trapping efficiency of **9e**.

Since carbonyl compounds **9** exist in equilibrium with the corresponding enols, there are two pathways, both involving proton abstraction, to achieve overall C–H insertion (Scheme 6). As discussed above, there is a body of evidence to suggest



Scheme 6

that the O–H insertion reactions of dialkoxycarbenes are stepwise in nature and progress through an ion pair intermediate. However, proton abstraction from either the keto form or the enol form of **9a**, for example, leads to the same ion pair intermediate **15**. Although collapse of the ion pair could lead to a structure of either type **10** or **16**, only **10** and its analogues were observed from reaction of **1a** and **9**.

The observation of predominant *C*-alkylation is in keeping with the greater thermodynamic stability of **10** compared to **16**. *C*-Alkylation products are generally more stable than *O*-alkylation products, largely because of the greater bond energy of a C=O double bond compared to a C=C double bond (a difference of *ca.* 100 kJ mol^{-1}). Whether or not *C*-alkylation is preferred kinetically, as observed for soft electrophiles such as alkyl iodides,[9] cannot be determined from these data. If *O*-alkylation is kinetically preferred (the more likely alternative) then the observation of exclusive *C*-alkylation must mean that **16** is unstable to the reaction conditions. Return to the ion pair **15**, because the enolate anion of β-dicarbonyl systems is a good leaving group, would ultimately afford the thermodynamically favoured *C*-alkylation product (**10**).

Fortunately, the type of tautomer involved in the reaction with the carbene could be deduced. Tautomerization equilibrium constants in benzene and pK_as in water of some of the carbonyl compounds are presented in Table 2. For **9a–d**, the enolic tautomer is known to be plentiful in non-polar solvents such as benzene. We confirmed the presence of the enolic forms

Table 2 Physical properties of carbonyl compounds **9a–f**

Compound	K_T [a]	pK_a [f]
9a	14.7 [b]	9 [g]
9b	0.26 [b]	11 [g]
9c	0.67 [c]	—
9d	22.8 [c]	—
9e	2.6×10^{-10} [d]	9 [h]
9f	n/a	13 [h]
12	0.0025 [e]	—

[a] Equilibrium constant for tautomerization; K_T = [enol]/[keto]. [b] In [$^2H_6$]benzene, from ref. 10. [c] In $CDCl_3$ at 40 °C, from ref. 11. [d] In dioxane–water for the ethyl ester from ref. 12. [e] In [$^2H_8$]toluene, from ref. 10. [f] pK_a in H_2O. [g] From ref. 10. [h] From ref. 13.

of **9a–d** by ^{1}H NMR spectroscopy of [$^2H_6$]benzene solutions, which had been freshly prepared at approximately the thermolysis concentration from the pure carbonyl compounds, and then dried with $MgSO_4$. As expected, the hydrogen bonded proton of each enol appeared at high frequency as a singlet (**9a**, 86%, δ 16.17; **9b**, 16%, δ 12.67; **9c**, 48%, δ 17.10; **9d**, 100%, δ 17.72) and concentrations were relatively close to the equilibrium values in Table 2.

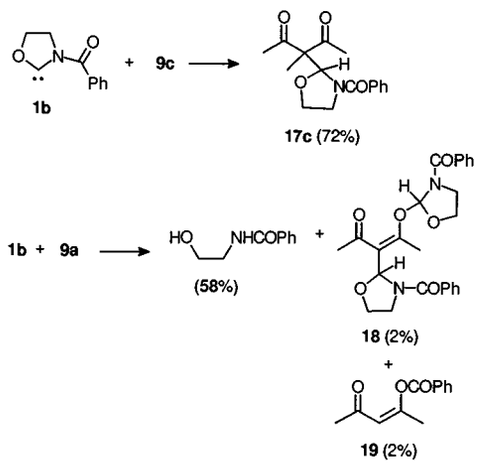
These data favour a mechanism in which proton abstraction from the enol is the source of the ion pair intermediate. In the cases of active methylene compounds with at least one ketone functional group (**9a–d**), the enol content (Table 2) is sufficient for the well precedented abstraction of a proton from an O–H group. Analogous abstraction from carbon is unlikely because the pK_a values of methyl cyanoacetate and of pentane-2,4-dione are similar in aqueous solution, and yet the former is a poor trap for carbene **1a**, whilst the latter is very effective. Since the carbenes reactivity toward hydroxy protons has been correlated to the pK_a values of corresponding acids,[2] one might expect similar trapping efficiencies for methyl cyanoacetate and pentane-2,4-dione if abstraction from the keto tautomer occurred. Although values for the ionization constants of these two β-dicarbonyl compounds in benzene are not available, and are likely to be significantly different from those in water, the order of carbon acid acidity is likely to remain the same. On the other hand, pentane-2,4-dione exists largely as the enol tautomer while the concentration of the enol tautomer of methyl cyanoacetate is vanishingly small, presumably because the enol cannot be stabilized by intramolecular H-bonding to the cyano group. Thus the enol concentration at equilibrium is more important for successful trapping of **1a** than the pK_a of the carbon acid.

The mechanism of elimination of methanol from **9a** and **9b** is of some interest even though the products (**11**) are known. The synthesis of compounds such as **11** from the action of trimethyl orthoformate and acetic anhydride on β-dicarbonyl compounds has been known for over a century.[14] The mechanism of the formation of these compounds in the reaction mixtures studied here was probed with **9a** as a model. A GC trace of the reaction mixture from thermolysis of **8** in the presence of **9a**, showed that **10a** and **11a** were present in a 1:1 ratio. Reheating of that mixture at 130 °C for 20 h did not cause a significant change in the GC trace. Thus, **11** did not arise from **10** as a result of the thermal instability of the latter. Complete conversion of **10a** and **10b** to **11a** and **11b** could be achieved by reheating the sample in the presence of pyridine. Thus the 1:1 ratio of **10a** to **11a** is not the equilibrium value and **11a** must come from a process related to the presence of the carbene intermediate.

Our interpretation of these results invokes occasional proton transfers between an ion pair intermediate **15** and a β-dicarbonyl compound **9** or the corresponding initial product **10**. Although the lifetime of an ion pair in benzene is expected to be short, the lifetime of **15** is probably extended through its regeneration from its reservoir **16**. Thus, the enolate anion of the ion pair (or a solvent separated analogue) could abstract a proton from **10** to afford a new ion pair with the potential for loss of methoxide, affording **11**. Methoxide could then become a chain carrier, either by direct proton abstraction from **10** or its enol, or through formation of the enolate from **9**. Thus the anions could also serve to catalyze the tautomerization of keto-**9** to enol-**9**. Dimethoxycarbene itself could also deprotonate the enol of **10**, thus leading to overall removal of methanol. In keeping with the observed results, this mechanism predicts that once the production of carbene has ended, and the source of the ion pairs is gone, the conversion of **10** to **11** ends. The expected trimethyl orthoformate, from capture of dimethoxycarbene or of dimethoxymethyl cation by methanol, was a major product in the one case where that product was sought (above).

Exclusive *O*-alkylation of anthrone **12** is opposite to the behaviour of the other active methylene compounds. The lower enol content of **12** is presumably sufficient to trap the carbene which is generated over the course of 20 h. Although the product **13** was formed in benzene alone, the addition of a drop of pyridine resulted in improved yields. This is likely to be the result of an acceleration of the known slow rate of tautomerization of anthrone in non-polar solvents,[15] thereby replenishing the enol as it is consumed by the carbene. The predominance of *O*-alkylation could again be the result of either kinetic or thermodynamic control but in this case both thermodynamics and kinetics are likely to favour *O*-alkylation. Although the product could isomerize by reforming the ion pair from which it was born, the enolate of anthrone **12** is probably less stable than that of pentane-2,4-dione in benzene solution.

The carbene **1b** was intercepted efficiently by the enol **9c**, to afford **17c** in 72% yield (Scheme 7). That acetal-like compound



Scheme 7

could be purified by careful chromatography, presumably by virtue of the benzoyl substituent. The enol of pentane-2,4-dione (**9a**) was probably effective also in trapping **1b**, but in that case the major initial product (**17a**, assumed but not characterized) hydrolyzed upon exposure to the atmosphere, affording *N*-(2-hydroxyethyl)benzamide (58%). In the case of **9a**, two interesting minor products were also identified as **18** and **19**, both isolated in 2% yield. Compound **18** is clearly the product of bis-alkylation of **9a**, and that process presumably has to occur in the order: *C*-alkylation, re-enolization and *O*-alkylation, as *O*-alkylation first can only result in bis-alkylation by return to the ion pair and subsequent *C*-alkylation. The *E* geometry was assigned on the basis of both a lesser steric interaction and the assumption that the enolic precursor was H-bonded to the carbonyl oxygen. The origin of **19** is very likely the initial ion pair. In addition to collapsing to **17**, that species could find an alternative path, namely benzoyl group transfer from the cation to the oxygen of the anion. Although benzoyl group transfer to carbon of the enolate may compete, the anticipated product was not found, nor was the expected co-product, oxazoline,

identified. It is likely that a product analogous to **18** was among the many components of the complex mixtures that generally resulted from trapping of **1a**.

In summary, reactions of nucleophilic carbenes with some active methylene compounds indicate that such carbenes can abstract a proton from an enol to generate a contact ion pair in which the anion is an enolate. The ion pair collapses to form the eventual product of formal carbene insertion into the C–H bond of the keto tautomer in the cases of **9a–d** or into the O–H bond of the enol tautomer of **12**. Elimination of methanol from insertion products arising from **1a** and **9a** (or **9b**) appears to be carbene initiated.

Experimental

Typical thermolyses were performed with an oxadiazoline concentration between 0.03 and 0.10 M in dry benzene and one equivalent of trap. Samples were sealed into a resealable thermolysis tube and heated in a constant temperature oil bath at 110 °C for 20 h, unless otherwise indicated. For reactions of dimethoxydimethyloxadiazoline **8a**, the crude product mixtures were analyzed by GC–MSD and GC–FTIR. The acetals **10** and the enol ethers **11** are not stable to chromatography. Excess trap in the reaction mixture, in the cases of **9a–c**, could be removed under vacuum to yield samples that could be analyzed by ^{1}H and ^{13}C NMR spectroscopy without the spectra being obscured by excess trap. In the case of **9d** and **12**, thermolyses of a sample with 2–3:1 ratio of oxadiazoline:trap resulted in products which were fairly free of excess trap. Yields reported in Table 1 were determined from an aliquot of the reaction mixture to which a non-volatile standard was added. The benzene was removed and the residue was dissolved in $CDCl_3$ and analyzed by integration of the ^{1}H NMR signals. The incomplete mass balance for reactions of **8a** is the result of formation of trimethyl orthoformate (where appropriate) and other uncharacterized volatile products. For **8b**, minor thermolysis pathways competing with formation of **1b** have been described.[7]

In general, the products **10** and **11** could not be stored as neat liquids due to their high susceptibility to hydrolysis from atmospheric moisture. In the cases where isolation of the products of trapping was not successful, spectroscopic analyses (^{1}H, ^{13}C, MS, FTIR) were performed on the crude reaction mixtures. Although **10a–d** and **13** are new compounds, their sensitivity to moisture (*i.e.* the compounds hydrolyzed on silica) meant that only **10c** could be isolated in sufficient purity for elemental analysis.

Unless otherwise stated for the particular compound, ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solvent with a Bruker AC-200 NMR spectrometer operating at 200 and 50.3 MHz, respectively, with residual $CHCl_3$ (δ_H 7.24) and the centre line of the $CDCl_3$ triplet (δ_C 77.0) as the internal standards; *J* values are given in Hz. Gas phase FTIR: Hewlett-Packard HP-5890 gas chromatograph connected to a Bio-Rad FTS-40 FTIR with a Bio-Rad GC/C 32 GC interface. MS(EI): HP-5890 Series II gas chromatograph with a 5971A mass selective detector or a VG Analytical ZAB-E double focusing mass spectrometer. MS(CI): VG Analytical ZAB-E double focusing mass spectrometer.

Thermolysis of dimethoxydimethyloxadiazoline (8a) in the presence of pentane-2,4-dione (9a)

A solution containing **8a** (0.13 g, 0.8 mmol) and **9a** (0.09 g, 0.9 mmol) in 25 ml of benzene was sealed into a thermolysis tube and heated at 110 °C for 20 h. The solvent and excess **9a** were removed under reduced pressure to give 0.05 g of a mixture. ^{1}H NMR analysis showed **10a** and **11a** in a 2.3:1 ratio. The total yield of carbene derived products was 25% by NMR spectroscopy, based on oxadiazoline (*p*-bromoacetophenone as internal standard). Spectral characteristics of **11a** were in keeping with those reported in the literature.[16]

3-(Dimethoxymethyl)pentane-2,4-dione (10a). ν_{max}(gas phase)/cm^{-1} 3005 (w), 2961 (m), 2944 (m), 2844 (w), 1718 (s), 1444 (w), 1363 (m), 1284 (w), 1199 (m), 1120 (s), 1084 (s); δ_H(300 MHz) 2.17 (6H, s, $COCH_3$), 3.31 (6H, s, OCH_3), 4.01 [1H, d, ^{3}J 8.4, $(CH_3CO)_2CH$], 4.94 [1H, d, ^{3}J 8.4, $(CH_3O)_2CH$]; δ_C(75.5 MHz) 30.2 (CH_3CO), 54.5 (OCH_3), 71.5 [$(COCH_3)_2CH$], 103.1 [$CH(OCH_3)_2$], 200.7 (C=O); *m*/*z* (EI) (%) 143 $[M - OCH_3]^+$ (4), 131 $[M - CH_3CO]^+$ (28), 127 (12), 101 (51), 85 (100), 83 (14), 75 $[(CH_3O)_2CH]^+$ (82), 69 (10), 55 (10), 47 (25), 43 (94).

3-(Methoxymethylene)pentane-2,4-dione (11a). ν_{max}(gas phase)/cm^{-1} 3017 (w), 2950 (w), 2856 (w), 1700 (s), 1610 (s), 1444 (w), 1369 (w), 1278 (s), 1191 (w), 1133 (s), 1066 (w), 995 (s), 958 (w); δ_H 2.24 (3H, s, $COCH_3$), 2.30 (3H, s, $COCH_3$), 3.96 (3H, s, OCH_3), 7.53 (1H, s, vinyl); δ_C 29.1 (CH_3), 32.0 (CH_3), 63.5 (OCH_3), 122.2 (vinyl), 166.9 (vinyl), 197.0 (C=O), 197.8 (C=O); *m*/*z* (EI) (%) 142 $[M]^+$ (5), 127 $[M - CH_3]^+$ (61), 85 (100), 69 (5), 43 (55); *m*/*z* (CI, NH_3) (%) 160 $[M + NH_4]^+$ (10), 143 $[M + H]^+$ (100).

Conversion of 10a to 11a with pyridine

Dimethoxydimethyloxadiazoline **8a** (0.10 g, 0.6 mmol) and pentane-2,4-dione (**9a**) (0.07 g, 0.7 mmol) were dissolved in 12.5 ml of benzene and sealed in a thermolysis tube. After heating at 110 °C for 20 h, 0.33 g of pyridine was added to the thermolysis tube and the mixture was heated again for 20 h. Conversion of the initial **10a** to **11a** was found to be complete after this time. The only product detectable by GC–MSD was **11a**; 0.03 g was isolated. Addition of the same quantity of pyridine before thermolysis of the oxadiazoline gave products of carbene trapping in trace amounts only.

Thermolysis of dimethoxydimethyloxadiazoline (8a) in presence of methyl acetoacetate (9b)

A solution containing 0.14 g (0.8 mmol) of dimethoxydimethyloxadiazoline **8a** and 0.09 g (0.8 mmol) of methyl acetoacetate (**9b**) in 25.0 ml of benzene was sealed into a thermolysis tube and heated at 110 °C for 20 h. Removal of the solvent and excess **9b** yielded 0.08 g of a mixture of **10b** and **11b**. Analysis by ^{1}H NMR spectroscopy showed a mixture of **10b** and **11b** in a 4.7:1 ratio. The total yield of carbene derived products was 43%, based on oxadiazoline and determined by ^{1}H NMR spectroscopy (*p*-bromoacetophenone as internal standard). Spectral data for **11b** were in agreement with those reported in the literature.[16]

Methyl 2-(dimethoxymethyl)-3-oxobutanoate (10b). ν_{max}(gas phase)/cm^{-1} 3004 (w), 2962 (m), 2845 (w), 1765 (s), 1737 (s), 1441 (w), 1364 (m), 1299 (w), 1195 (s), 1138 (m), 1117 (s), 1094 (s), 989 (w); δ_H 2.23 (3H, s, CH_3CO), 3.35 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.69 (3H, s, CO_2CH_3), 3.84 [1H, d, ^{3}J 8, $CH(CO)_2$], 4.91 [1H, d, ^{3}J 8, $CH(OCH_3)_2$]; δ_C 30.3 (CH_3CO), 52.4 (CO_2CH_3), 55.0 (OCH_3), 55.2 (OCH_3), 63.2 (COCHCO), 103.2 [$C(OCH_3)$], 166.7 (CO_2CH_3), 199.8 ($COCH_3$); *m*/*z* (EI) (%) 147 $[M - CH_3CO]^+$ (<1), 143 (10), 131 (14), 117 (30), 115 (6), 101 (5), 85 (100), 75 (85), 69 (14), 59 (11), 47 (17), 43 (37).

(*E*/*Z*)-Methyl 2-(methoxymethylene)-3-oxobutanoate (11b). ν_{max}(gas phase)/cm^{-1} 3025 (w), 2955 (m), 2856 (w), 1736 (s), 1708 (s), 1615 (s), 1441 (m), 1374 (m), 1287 (s), 1267 (s), 1196 (s), 1140 (s), 1079 (m), 997 (m); δ_H 2.25 (3H, s, CH_3CO), 2.30 (3H, s, CH_3CO), 3.67 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.92 (3H, s, CO_2CH_3), 3.94 (3H, s, CO_2CH_3), 7.50 (1H, s, vinyl), 7.51 (1H, s, vinyl); δ_C 28.5 ($COCH_3$), 31.5 ($COCH_3$), 51.6 (CO_2CH_3), 51.7 (CO_2CH_3), 63.5 (OCH_3), 63.6 (OCH_3), 113.2 (vinyl), 114.0 (vinyl), 165.4 (C=O), 165.6 (vinyl), 165.8 (C=O), 166.7 (vinyl), 195.0 (C=O), 196.5 (C=O); *m*/*z* (EI) (%) 158 $[M]^+$ (4), 143 $[M - CH_3]^+$ (58), 127 $[M - OCH_3]^+$ (17), 85 (43), 75 (100), 69 (15), 43 (37); *m*/*z* (CI, NH_3) (%) 176 $[M + NH_4]^+$ (10), 159 $[M + H]^+$ (100).

Conversion of 10b to 11b with pyridine

Dimethoxydimethyloxadiazoline **8a** (0.10 g, 0.6 mmol) and methyl acetoacetate (**9b**) (0.08 g, 0.7 mmol) were dissolved in

12.5 ml of benzene and the solution was sealed into a thermolysis tube. After heating at 110 °C for 20 h, 0.33 g of pyridine was added to the thermolysis tube and the mixture was heated again for 20 h. Conversion of **10b** to **11b** was found to be complete. The only product detectable by GC–MSD was **11b**, isolated in 0.06 g yield. Addition of pyridine before thermolysis gave products of carbene trapping in trace amounts only.

Thermolysis of dimethoxydimethyloxadiazoline (8a) in presence of 3-methylpentane-2,4-dione (9c)

A solution containing 0.20 g (1.2 mmol) of dimethoxydimethyloxadiazoline **8a** and 0.14 g (1.2 mmol) of 3-methylpentane-2,4-dione **9c** in 25.0 ml of benzene was sealed into a thermolysis tube and heated at 110 °C for 20 h. Removal of the volatiles under vacuum yielded **10c**. The yield of **10c** (26%, based on oxadiazoline) was determined by ^{1}H NMR spectroscopy (*p*-dimethoxybenzene as internal standard).

3-Methyl-3-(dimethoxymethyl)pentane-2,4-dione (10c). ν_{max}(gas phase)/cm^{-1} 3002 (m), 2959 (b), 2943 (b), 2840 (m), 1712 (s), 1451 (b), 1360 (m), 1193 (m), 1110 (s), 1091 (s), 963 (w); δ_H 1.38 (3H, s, CH_3), 2.09 [6H, s, $(CH_3CO)_2C$], 3.49 [6H, s, $(CH_3O)_2C$], 4.90 [1H, s, $CH(OCH_3)_2$]; δ_C 13.3 (CH_3), 27.3 (CH_3CO), 58.6 [$C(OCH_3)_2$], 71.8 [$CH(CH_3)$], 107.8 [$C(OCH_3)_2$], 204.7 (CH_3CO); *m*/*z* (EI) (%) 145 (13), 115 (36), 114 (15), 99 (100), 97 (8), 75 (57), 47 (17), 43 (76) (Found: C, 57.3; H, 8.6%. Calc. for $C_9H_{16}O_4$: C, 57.4; H, 8.5%).

Thermolysis of dimethoxydimethyloxadiazoline (8a) in presence of 1,3-diphenylpropane-1,3-dione (9d)

A solution of dimethoxydimethyloxadiazoline (**8a**, 0.12 g, 0.8 mmol) and 1,3-diphenylpropane-1,3-dione (**9d**, 0.19 g, 0.8 mmol) in 25.0 ml of benzene was sealed into a resealable thermolysis tube and heated at 110 °C for 20 h. Removal of the solvent yielded 0.24 g of a mixture of product **10d** in 56% yield (*p*-bromoacetophenone as internal standard) and excess **9d**. Pure **10d** was obtained from another thermolysis in which an excess of oxadiazoline was used in order to convert **9d** more fully to **10d**. A solution of **8a** (0.15 g, 1.0 mmol) and **9d** (0.08 g, 0.4 mmol) in 25.0 ml of benzene, treated as described above, gave 0.14 g (50%) of **10d**.

2-(Dimethoxymethyl)-1,3-diphenylpropane-1,3-dione (10d). δ_H 3.4 [6H, s, $C(OCH_3)_2$], 5.32 (1H, d, ^3J 7.9), 5.71 (1H, d, ^3J 7.9), 7.35 (4H, m, aromatic), 7.48 (2H, m, aromatic), 7.94 (4H, m, aromatic); δ_C 56.7, 61.1, 106.2, 128.1, 128.6, 133.3, 136.5, 192.0; *m*/*z* (EI) (%) 267 $[M - OCH_3]^+$ (5), 193 $[M - C_6H_5CO]^+$ (40), 105 $[C_6H_5CO]^+$ (60), 77 $[C_6H_5]^+$ (25), 75 $[(CH_3O)_2CH]^+$ (100).

Thermolysis of dimethoxydimethyloxadiazoline (8a) in presence of anthrone 12

A solution containing 0.12 g (0.8 mmol) of dimethoxydimethyloxadiazoline **8a** and 0.15 g (0.8 mmol) of anthrone **12** in 25.0 ml of benzene containing one drop of pyridine was sealed into a resealable thermolysis tube and heated at 110 °C for 20 h. Removal of the solvent yielded 0.19 g of a mixture of **13** and excess **12**. The yield (30%, based on oxadiazoline) was determined by NMR spectroscopy after the addition of an internal standard. A similar thermolysis in which the oxadiazoline (0.15 g, 1.0 mmol) was in excess over **12** (0.11 g, 0.6 mmol) in 25.0 ml of benzene containing two drops of pyridine afforded 0.17 g of **13** (89%, based on anthrone) which was pure enough to characterize by NMR spectroscopy although it still contained a detectable amount of anthrone.

9-Anthracenyl dimethyl orthoformate (13). δ_H 3.54 [6H, s, $C(OCH_3)_2$], 5.74 [1H, s, $CH(OCH_3)_2$], 7.45 (2H, m, aromatic) 7.5 (2H, m, aromatic), 7.95 (2H, m, aromatic), 8.23 (1H, s, 10-H), 8.50 (2H, m, aromatic); δ_C 51.3 [$C(OCH_3)_2$], 116.4 [$C(OCH_3)_2$], 122.9, 123.1, 125.2, 125.3, 128.0, 132.0, 146.4; *m*/*z* (EI) (%) 268 $[M]^+$ (2), 237 $[M - OCH_3]^+$ (9), 221 (5), 193 (38), 165 (71), 164 (18), 163 (31), 139 (12), 115 (5), 75 (100), 63 (5), 47 (30).

Synthesis of spiro oxadiazoline 8b

As briefly described in ref. 7, the synthesis of **8b** involved the transamination of acetone semicarbazone with ethanolamine to acetone 4-(2-hydroxyethyl)semicarbazone. Oxidation of the latter with $PhI(OAc)_2$ gave a spiro oxadiazoline unsubstituted at N, which was then benzoylated with PhCOCl to afford **8b**.

Acetone 4-(2-hydroxyethyl)semicarbazone. The procedure for the preparation of this semicarbazone is based on that of Iwao.[17] A solution of the semicarbazone of acetone (19.6 g, 0.170 mol) and ethanolamine (11.1 g, 0.182 mol) was refluxed in toluene (55 ml), under dry nitrogen, for 7 h. The solution was allowed to cool to room temperature and precipitation of the product occurred within a few hours. The product was then collected by filtration and washed well with diethyl ether to give 22.0 g (81%) of a pale yellow solid, mp 89–94 °C (lit.,[17] 94–96 °C). ν_{max}(KBr)/cm^{-1} 3379 (s), 3317 (s), 3210 (s), 3070 (m), 2927 (m), 2869 (w), 1652 (s), 1554 (s), 1458 (w), 1427 (m), 1365 (m), 1337 (m), 1281 (w), 1254 (m), 1212 (m), 1157 (w), 1132 (m), 1088 (w), 1068 (m), 980 (w), 884 (w), 836 (w), 773 (w), 722 (w); δ_H 1.84 (3H, s, CH_3), 1.97 (3H, s, CH_3), 3.39–3.53 (2H, m, NCH_2), 3.69–3.82 (2H, m, OCH_2), 6.56 [1H, br s, C(O)NHC], 8.02 [1H, br s, C(O)NHN] (OH caused a slight distortion in the baseline between 3 and 4 ppm); δ_C 16.36 (CH_3), 25.20 (CH_3), 42.85 (NCH_2), 63.35 (OCH_2), 147.85 (C=N), 157.88 (C=O).

3,4,9-Triaza-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene. Iodobenzene diacetate[18] (7.47 g, 23 mmol), dissolved in dichloromethane (150 ml), was added dropwise over 1–2 h, to a stirred solution of acetone 4-(2-hydroxyethyl)semicarbazone (3.50 g, 22 mmol) in dichloromethane (200 ml) at 0 °C, under nitrogen. After addition was complete, the solution was kept in the ice bath for another 2 h, and was then allowed to warm to room temperature overnight. After evaporating approximately one half of the solvent *in vacuo*, the solution was washed, first with ice-cold aqueous $NaHCO_3$ (5%) and then with ice-cold brine, before it was dried over $MgSO_4$. Evaporation of the solvent afforded an oil (*ca.* 6 g), consisting of the oxadiazoline and iodobenzene, which was generally used without purification in the next step.

3,4,9-Triaza-9-benzoyl-2,2-dimethyl-1,6-dioxaspiro[4.4]non-3-ene (8b). The crude mixture containing the NH oxadiazoline was dissolved in dichloromethane (25 ml), and pyridine (1.10 g, 13.9 mmol) was added. Benzoyl chloride (1.86 g, 13.2 mmol) was added dropwise to this stirred solution over *ca.* 10 min. After stirring at room temperature for another 30 min, the solution was diluted with dichloromethane and washed successively with water, aqueous $NaHCO_3$ (5%) and brine. The organic phase was dried over $MgSO_4$, the solvent was evaporated, and hexane was added to the crude product to induce crystallization. Recrystallization from methanol–ethyl ether yielded 1.41 g (25%, from the semicarbazone) of **8b** as a white solid, mp 108–110 °C (dec.). ν_{max}(KBr)/cm^{-1} 2994 (w), 2902 (w), 1655 (s), 1578 (w), 1453 (w), 1389 (s), 1272 (m), 1222 (m), 1162 (m), 1115 (m), 1081 (w), 1046 (w), 1011 (w), 973 (w), 921 (m), 856 (w), 817 (w), 798 (w), 722 (m); δ_H(300 MHz) (broad peaks caused by slow exchange) 1.20–1.80 (6H, br m, 2 × CH_3), 3.85–4.00 (1H, m, NCH_2), 4.05–4.20 (1H, m, NCH_2), 4.25–4.45 (2H, m, OCH_2), 7.35–7.60 (5H, m, aromatic); δ_C(75 MHz) 21.40 (CH_3), 25.19 (CH_3), 47.35 (NCH_2), 65.40 (OCH_2), 120.41 [$C(CH_3)_2$], 127.26 (aromatic C2, C6), 128.36 (aromatic C3, C5), 130.94 (aromatic C4), 133.22 (spiro C), 135.40 (aromatic C1), 169.00 (C=O); *m*/*z* (EI) (%) 233 $[M - N_2]^{\cdot+}$ (0.9), 192 $[M - N_2 - C_3H_5^{\cdot}]^+$ (5), 175 $[M - N_2 - C_3H_6O]^{\cdot+}$ ($C_{10}H_9NO_2$) (27), 174 (30), 147 (15), 146 (10), 145 (12), 131 (43), 117 (20), 105 $[C_6H_5CO^+]$ (100), 103 (21), 88 (25), 77 $[C_6H_5^+]$ (35), 51 (21).†

† Mass spectrometric experiments on this oxadiazoline involved LRP and HRP electron impact (EI), collisional activation (CA) spectrometry and chemical ionization (CI) using ammonia.[7]

Thermolysis of 8b with 3-methylpentane-2,4-dione (9c)
A solution containing **8b** (0.13 g, 0.50 mmol) was thermolyzed with **9c** (0.069 g, 0.61 mmol) in 10 ml of benzene. The major product, **17c**, was obtained as a colourless oil in 72% yield after purification by radial chromatography (Chromatotron apparatus, silica gel-coated glass plate) with 10–30% ethyl acetate in hexane as elution solvent.

3-[2-(3-Benzoyl)oxazolidinyl]-3-methylpentane-2,4-dione (17c). $\nu_{max}(CCl_4)/cm^{-1}$ 2991 (w), 2950 (w), 2885 (w), 1800 (w), 1705 (s), 1650 (s), 1581 (w), 1497 (w), 1449 (w), 1416 (m), 1377 (m), 1356 (m), 1296 (w), 1203 (m), 1157 (w), 1081 (m), 1029 (w), 958 (w), 909 (w); δ_H(300 MHz) 1.44 (3H, s, CH_3), 2.24 (3H, s, $COCH_3$), 2.29 (s, 3H, $COCH_3$), 3.58–3.66 (2H, m, NCH_2), 3.67–3.81 (1H, m, OCH_2), 4.04–4.19 (1H, m, OCH_2), 6.28 [1H, s, oxazolidine C(2)H], 7.35–7.57 (5H, m, aromatic); δ_C(75.5 MHz) 13.22 (CH_3), 27.72 ($COCH_3$), 28.12 ($COCH_3$), 48.90 (NCH_2), 66.55 (OCH_2), 71.19 {$[CH_3C(O)]_2C$}, 90.75 (oxazolidine C2), 127.43 (aromatic C2, C6), 128.41 (aromatic C3, C5), 131.08 (aromatic C4), 135.18 (aromatic C1), 169.78 (NC=O), 203.25 (C=O), 204.26 (C=O), diastereotopicity not detected in the NMR spectra; *m*/*z* (EI) (%) 246 (7), 176 (benzoyloxazolidinium cation) (16), 148 (7), 105 $[PhCO]^+$ (100), 77 (41), 51 (10), 47 (27); *m*/*z* (CI, NH_3) (%) 290 $[M + H]^+$ (7), 176 (benzoyloxazolidium cation) (100).

Thermolysis of 8b with pentane-2,4-dione (9a)
A solution of **8b** (0.26 g, 1.0 mmol) was heated with **9a** (0.11 g, 1.1 mmol) in 20 ml of benzene. The thermolysis products were separated by radial chromatography, by elution with ethyl acetate–hexane mixtures or 8% MeOH in $CHCl_3$. The fractions had to be rechromatographed several times in order to achieve a good separation.

***N*-(2-Hydroxyethyl)benzamide.** White solid (58% yield), mp 60.5–61.5 °C (lit.,[19] 60 °C); ν_{max}(KBr)/cm^{-1} 3100–3600 (br), 1637 (s), 1542 (s), 1491 (w), 1310 (m), 1067 (m), 712 (m); δ_H 3.09 (1H, br s, OH), 3.56–3.66 (2H, m, NCH_2), 3.75–3.84 (2H, m, OCH_2), 6.84 (1H, br s, NH), 7.30–7.57 (3H, m, aromatic *meta*, *para*), 7.73–7.81 (2H, m, aromatic *ortho*); δ_C 42.74 (NCH_2), 61.83 (OCH_2), 126.93 (aromatic C2, C6), 128.47 (aromatic C3, C5), 131.57 (aromatic C4), 134.00 (aromatic C1), 168.68 (C=O); *m*/*z* (EI) (%) 165 $[M^+]$ (2), 147 (12), 134 (10), 122 (19), 105 $[PhCO]^+$ (100), 84 (16), 77 (61), 51 (28). *m*/*z* (CI, NH_3) (%) 166 $[M + H]^+$ (100).

Compound 18. Isolated as a single diastereomer, in 2% yield, after up to six separations by chromatography. $\nu_{max}(CCl_4)/cm^{-1}$ 1669 (s), 1636 (m), 1617 (m), 1523 (m), 1486 (w), 1385 (m), 1288 (w), 1262 (m), 1149 (m), 1094 (m), 1024 (m), 965 (w), 909 (s), 849 (w); δ_H(300 MHz) 2.25 (3H, s, CH_3), 2.31 (3H, s, CH_3), 3.60–4.30 (8H, m, NCH_2, OCH_2), 5.25 [1H, br s, 2-alkyloxazolidine C(2)H], 7.20–7.65 [9H, m, 2-alkoxyoxazolidine C(2)H, aromatic], 7.85–7.94 (2H, m, aromatic); δ_C(75.5 MHz) 15.14 (C=C*C*H_3), 29.18 ($COCH_3$), 40.11 (NCH_2), 47.40 (NCH_2), 65.60 (OCH_2), 69.81 (OCH_2), 82.46 (2-alkyloxazolidine C2), 113.75 (2-alkoxyoxazolidine C2), 116.84 (CO*C*=C), 127.05 (aromatic C2, C6, 2 coincident signals from analogous carbons), 128.12 (aromatic C3, C5), 128.48 (aromatic C3, C5), 131.13 (aromatic C4), 131.39 (aromatic C4), 134.39 (aromatic C1), 135.31 (aromatic C1), 167.35, 167.68, 168.76 (COC=*C*, 2 × NCO), 193.78 (CH_3CO); *m*/*z* (EI) (%) 303 (3), 286 (5), 260 (3), 244 (4), 214 (2), 198 (3), 180 (5), 148 (66), 105 $[PhCO]^+$ (100), 77 (43); *m*/*z* (CI, NH_3) (%) 468 $[M + NH_4]^+$ (4), 451 $[M + H]^+$ (14), 286 (100).

(*Z*)-1-Methyl-3-oxo-1-enyl benzoate (19).[20] Colourless oil isolated in 2% yield. $\nu_{max}(CCl_4)/cm^{-1}$ 1741 (s), 1706 (w), 1673 (m), 1637 (w), 1451 (w), 1426 (w), 1378 (w), 1359 (w), 1262 (s), 1195 (m), 1177 (w), 1153 (m), 1082 (m), 1065 (m), 1024 (w); δ_H 2.18 (3H, s, CH_3), 2.22 (3H, s, CH_3), 5.92 (1H, s, vinyl), 7.45–7.70 (3H, m, aromatic *meta*, *para*), 8.08–8.16 (2H, m, aromatic *ortho*); δ_C 21.51 (C=C*C*H_3), 31.03 ($COCH_3$), 117.40 (CO*C*=C), 128.67 (aromatic C2, C6), 129.02 (aromatic C4), 130.20 (aromatic C3, C5), 133.81 (aromatic C1), 158.14, 163.50 [OC=O, O=C–C(H)=*C*], 195.56 (CH_3C=O); *m*/*z* (EI) (%) 204 $[M]^+$ (<1), 161 (1), 105 $[PhCO]^+$ (100), 77 (48), 51 (18), 43 (17). *m*/*z* (CI, NH_3) (%) 222 $[M + NH_3]^+$ (13), 205 $[M + H]^+$ (13), 105 $[PhCO]^+$ (100).

Preparation of authentic (*Z*)-1-methyl-3-oxo-1-enyl benzoate (19)
Benzoyl chloride (0.74 g, 5.3 mmol) was added to a solution of pentane-2,4-dione **9a** (0.50 g, 5.0 mmol) and pyridine (0.42 g, 5.3 mmol) in 10 ml of CH_2Cl_2. After stirring at room temperature overnight, the solution was diluted with 10 ml of CH_2Cl_2 and washed with water (2 × 10 ml), aq. $NaHCO_3$ (5%, 2 × 10 ml), and water (10 ml) again, before it was dried over $MgSO_4$. Purification of **19** was done by chromatography (10–20% ethyl acetate in hexane); ^1H and ^{13}C spectra were identical to those of **19** isolated from thermolysis of **8b** in the presence of **9a**.

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