# Intramolecular Reactivity of Triplet Carbonylcarbenes

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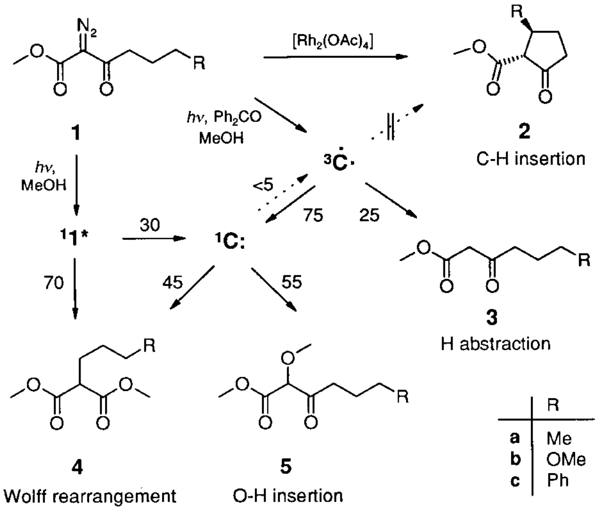
$\alpha$-Diazocarbonyl compounds have a long history of useful applications in organic chemistry.[1] Intramolecular insertion into C–H bonds and addition to $\pi$ systems is mediated by transition metal catalysts, such as $[Rh_2L_4]$.[2] These reactions involve metal carbenoids and provide opportunities for asymmetric syntheses with a chiral catalyst. The Wolff rearrangement is the major reaction induced by photolysis or thermolysis of $\alpha$-diazo ketones.[1, 3] The [1,2] shift that leads to ketenes proceeds in the singlet state, accompanying or following the loss of $N_2$. The ground state of carbonylcarbenes is triplet, as attested by ESR spectroscopy.[4] However, the reactivitiy of triplet carbonylcarbenes has received little attention, except that nonstereospecific addition reactions with alkenes and abstraction of hydrogen from the solvent were observed in sensitized photolyses of diazomalonates.[5] Our studies of functionalized arylcarbenes revealed that geometrical constraints affect the participation of singlet and triplet states.[6] This experience prompted us to explore the intramolecular reactivity of triplet carbonylcarbenes.

The photolysis of methyl 2-diazo-3-oxoheptanoate (**1a**)[7] in methanol afforded **4a** (86%, Wolff rearrangement) and **5a** (14%, O–H insertion).[8] In the presence of benzophenone as a sensitizer **3a** was formed in addition to **4a** and **5a** (Scheme 1). Neither direct nor sensitized photolysis induced cyclization to give **2a**, although **2a** is readily obtained from **1a** under $Rh^{II}$ catalysis.[7] To facilitate the intramolecular abstraction of hydrogen, methoxy and phenyl groups were introduced. However, **1b** and **1c** behaved very much like **1a**.[9] On sensitization the amount of **3** (a triplet product) and **5** (a singlet product) increase at the expense of **4**, as illustrated for **1a** in Figure 1.[10] These observations indicate that 1) on direct photolysis a large fraction of **4** arises from the excited diazo compound $^1\mathbf{1}^*$ and 2) spin inversion of the triplet carbene is faster than hydrogen abstraction from the solvent, $k_{TS} > k_T$. A quantitative evaluation is shown in Scheme 1; the numbers are averages for **1a**–**c** from which the individual species differ by ±2. Conformational effects suggested earlier that the Wolff rearrangement can proceed in concert with the extrusion of nitrogen.[11] This notion is fully confirmed by the present, entirely different, approach.



Scheme 1. Reaction pathways for the decomposition of methyl 2-diazo-3-oxo-6-R-hexanoates (**1**) in methanol. Numbers are averages for **1a**–**1c**.

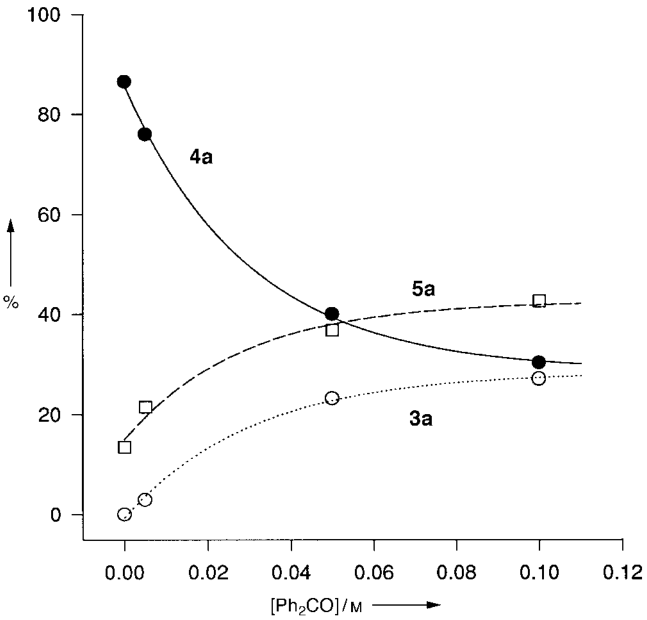


Figure 1. Photolyses of **1a** in methanol with benzophenone as sensitizer. Product distributions (%) are shown as functions of the concentration of benzophenone.[8, 10]

With unsaturated analogues of **1**, such as methyl 2-diazo-3-oxo-6-heptenoate (**6a**),[12] the triplet carbene undergoes intramolecular addition to the double bond to give **9a** (Scheme 2). As shown in Figure 2, benzophenone sensitization minimizes the Wolff rearrangement (→9%) and O–H insertion (→3%), so that $k_{TS} < k_T$. Relative to intramolecular addition, abstraction of hydrogen from the solvent is negligible in methanol (<0.01), competitive in ethanol (0.68), and predominant in 2-propanol (1.8). The stereochemistry of the cyclopropanation was probed with **6b**[12] and **6c**.[13] Incomplete retention of configuration was observed in direct photolyses, whereas complete sensitization led to nearly stereorandom addition (Table 1).[14] The data indicate that small amounts of intersystem crossing occurs in both directions; the numbers recorded in Scheme 2 are averages for **6b** and **6c**.

If the double bond is separated from the carbene by four rather than three carbon atoms, the intramolecular addition is only slightly affected (**10a**[15] →**11a** versus **6a**→**9a**). With five carbon atoms interposed, however, the yield of the bicyclic

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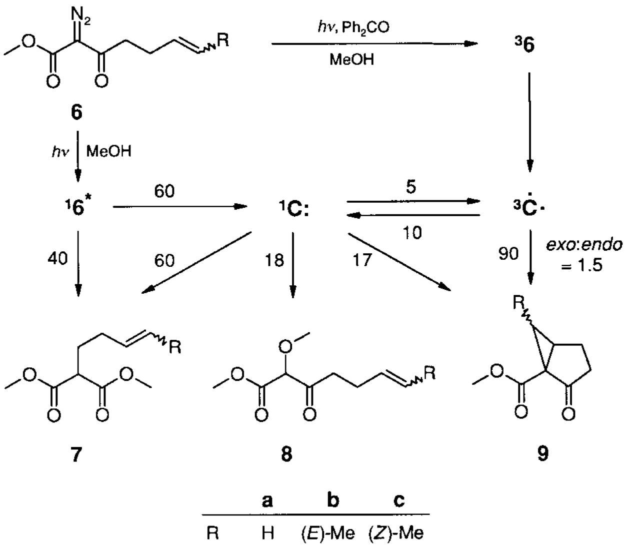


Scheme 2. Reaction pathways for photolyses of **6** in methanol. Numbers are averages for **6b** and **6c**.

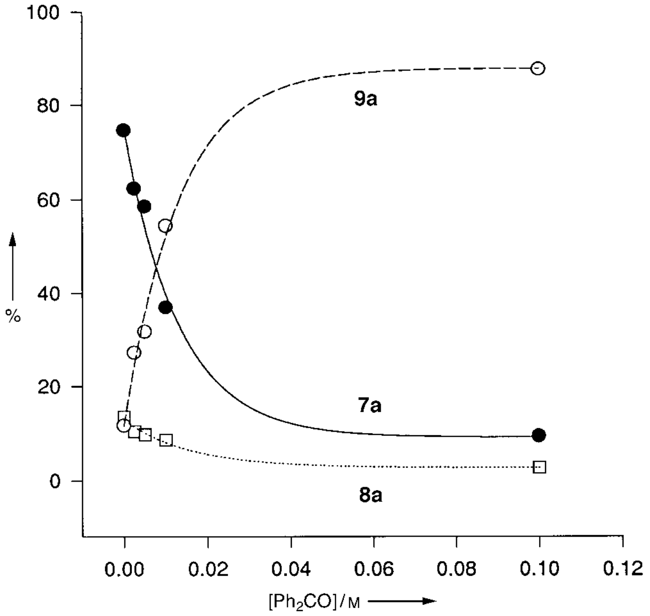


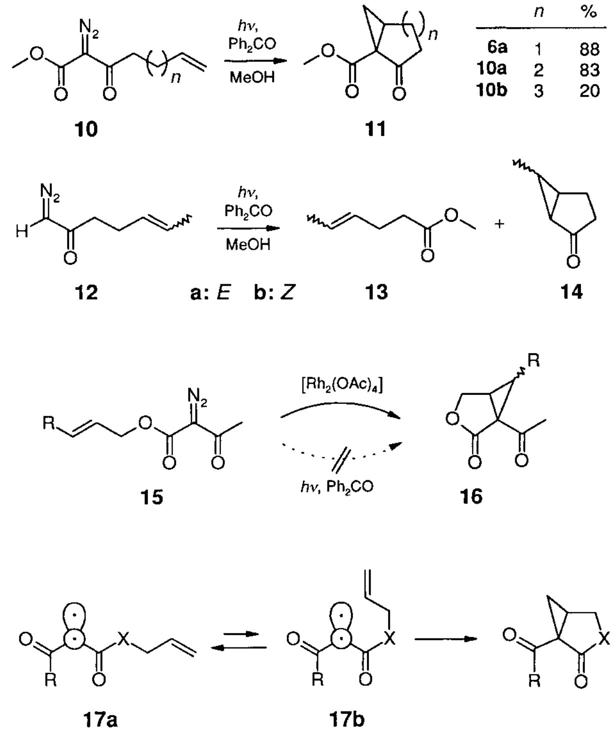
Figure 2. Photolyses of **6a** in methanol with benzophenone as sensitizer. Product distributions (%) are shown as functions of the concentration of benzophenone.[8, 10]

Table 1. Photochemically induced intramolecular addition reactions of carbonylcarbenes.[a]

| Precursor | Product | [Ph$_2$CO] = 0 | | [Ph$_2$CO] → ∞ | |
|---|---|---|---|---|---|
| | | [%] | exo:endo | [%] | exo:endo |
| **6b** | **9** | 11.3 | 15 | 91.3 | 1.6 |
| **6c** | **9** | 13.8 | 0.14 | 92.8 | 1.4 |
| **12a** | **14** | 2.5 | 11 | 46.7 | 2.3 |
| **12b** | **14** | 3.0 | 0.30 | 51.4 | 1.7 |

[a] Solvent: methanol. Product distributions extrapolated to $t = 0$.

adduct drops to 20% (**10b**[9] →**11b**). The remaining products arise by abstraction of hydrogen atoms from the solvent (11%) and intersystem crossing, which leads eventually to O–H insertion (37%) and Wolff rearrangement (32%, Scheme 3). The methoxycarbonyl group present in **6** and **10** assists the intramolecular addition but is not indispensible. Triplet carbonylcarbenes, generated by sensitized photolyses of 1-diazo-5-hepten-2-ones (**12**),[16] cyclize less efficiently than analogous dicarbonylcarbenes (Table 1). Approximately 50% of Wolff rearrangement and divergent stereoselectivities of **12a** and **12b** point to substantial triplet →singlet interconversion ($k_{TS} \approx k_T$).



Scheme 3. Structural and conformational effects influencing the intramolecular reactivity of triplet carbonylcarbenes.

Sensitized photolyses of 2-alkenyl 2-diazo-3-oxobutanoates (**15**)[17] by benzophenone do not give rise to the bicyclic lactones **16** (which are formed, however, under Cu[17] or Rh$^{II}$ catalysis). The product distributions obtained from **15** are similar to those from **1**, rather than to those from **6**. The failure of the intermediate triplet carbenes to attack the double bond is attributed to conformational effects. The X–C bond of **17** must assume the s-E conformation ($X = O$, $\sphericalangle$O-C-O-C = 180°) or the skew conformation **17b** ($X = CH_2$, $\sphericalangle$O-C-C-C = 120°) in order for the alkene to approach the half-filled σ orbital, which is the reactive site of the triplet carbene. Relative to the most stable s-Z conformer **17a** ($\sphericalangle$O-C-X-C = 0°), the energy difference is much smaller for ketones (for example, $\Delta E \approx 8$ kJ mol$^{-1}$ for 2-butanone)[18] than for esters (for example, $\Delta E \approx 35$ kJ mol$^{-1}$ for ethyl acetate).[19, 20]

In summary, in contrast to 2-alkylarylcarbenes[6] triplet carbonylcarbenes do not abstract hydrogen from δ- or ε-C–H bonds. Intramolecular addition to double bonds, leading to five- and six-membered rings, occurs with dicarbonylcarbenes RCO-C-CO-CH$_2$(CH$_2$)$_n$CH=CHR' and (less readily) with carbonylcarbenes H-C-CO-CH$_2$(CH$_2$)$_n$CH=CHR', but fails with (alkenyloxycarbonyl)carbenes RCO-C-CO-O-

$(CH_2)_nCH{=}CHR'$. Intersystem crossing to the singlet state is a major reaction of all triplet carbonylcarbenes that are not rapidly scavenged intramolecularly. Thus, with the exceptions outlined above, the lifetimes of carbonylcarbenes are controlled by the rate of spin inversion rather than by the reactivity of the triplet ground state.

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[10] The dependence of product distributions on the concentration of benzophenone is reasonably approximated by exponential functions, $f = a \pm b\exp(-c[Ph_2CO])$ (lines in Figures 1 and 2). Data for complete sensitization ($[Ph_2CO] \rightarrow \infty$) were obtained by extrapolation; for example 28% of **2a**, 29% of **4a**, and 43% of **5a** from **1a**.

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## A New Heterocyclic Multicomponent Reaction For the Combinatorial Synthesis of Fused 3-Aminoimidazoles**

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Combinatorial chemistry and high-throughput screening have changed, and are still changing, the face of modern drug discovery.[1] From the organic chemist's point of view, these new approaches emphasize the need for highly efficient and expeditious protocols. Multicomponent reactions—which combine two major principles of organic synthesis, convergence and atom economy—were prone to be recognized and used in library syntheses.[2] A prototypical example is the Ugi four-component reaction (Scheme 1),[3] though several other classical heterocyclic syntheses have also been used.[4] However, these transformations, which are of enormous potential value, remain scarce.[5] We therefore embarked on a program aimed at finding and exploiting *new* and *high-yielding* multicomponent reactions. Here we disclose our first results in this domain.

To be of industrial relevance, a multicomponent reaction should possess the following characteristics:

- It must be general enough to create libraries with 10000 to 100000 compounds (not a trivial situation!).
- It must be reliable (i.e., give high yields within its reactivity domain).
- It must be amenable to high-throughput automated synthesis (i.e., with a simple reaction protocol; ideally one would like to simply mix reactant solutions).

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