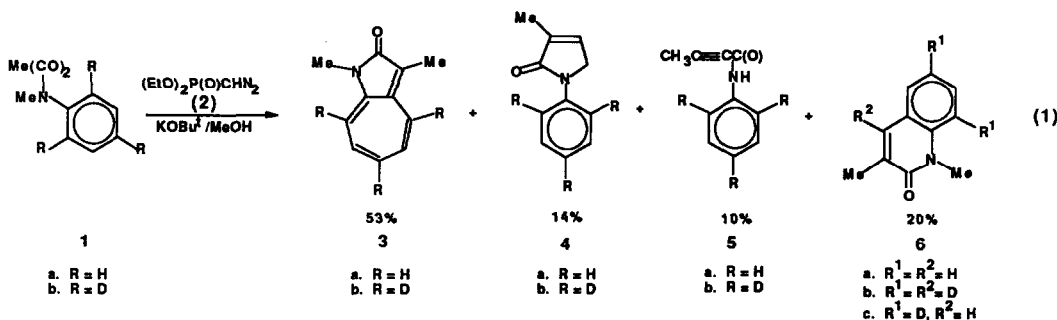


FORMAL 1,6-INSERTION OF AN ALKYLIDENECARBENE INTO A CARBON-HYDROGEN BOND. UNVEILING OF A STEPWISE REACTION MECHANISM.¹

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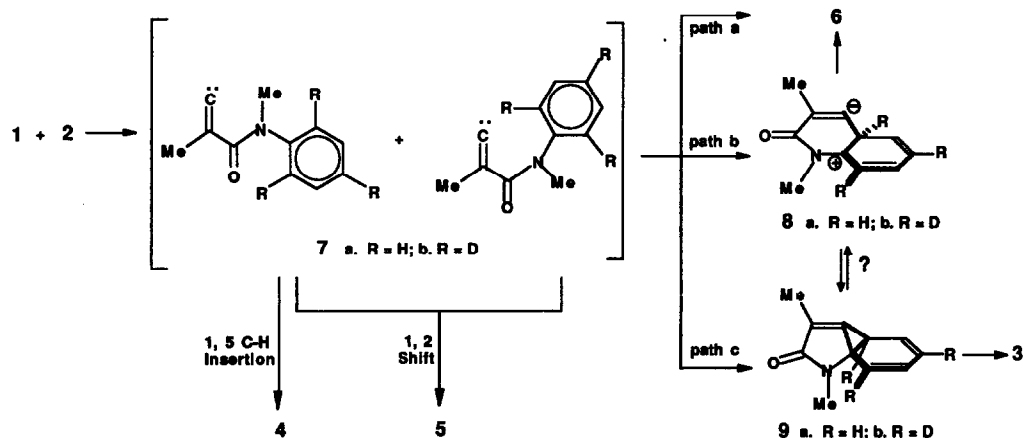
Abstract: The formation of 1,3-dimethylquinol-2-one (**6a**) by reaction of *N*-methyl-*N*-phenyl-2-oxopropanamide (**1a**) with diethyl (diazomethyl)phosphonate (**2**), an apparent C-H insertion by an alkylidenecarbene, is shown to involve a stepwise rather than a concerted reaction pathway.

We earlier reported reaction of *N*-methyl-*N*-phenyl-2-oxopropanamide (**1a**) and diethyl (diazomethyl)phosphonate (**2**, DAMP) in acetonitrile as a novel method for the preparation of cyclohepta[b]pyrrol-2-one (**3a**).³ We have now found that repetition of the reaction, but with methanol as solvent, yields **3a** accompanied by *N*-methylaniline (probably derived by alcoholysis of **1a**), pyrrolone **4a** and butynamide **5a** (eq. 1). The latter two compounds are products characteristic of reaction of **2** with *N,N*-dialkylpropanamides in acetonitrile as solvent.⁴ Unexpectedly, 1,3-dimethylquinol-2-one (**6a**) is also produced in modest yield, and the mechanism of its formation is the subject of this communication.



The alkylidenecarbene **7a**, two conformations of which are shown in Scheme 1, is a key transient intermediate anticipated⁵ to be generated under our reaction conditions, and products **3-6** are all derivable from it, as indicated in the scheme. Conversion of **7a** to **6a** is *formally* the result of an intramolecular 1,6-insertion of the carbenic center into an aromatic C-H bond (path a, Scheme 1). However, formulation of this step as a *concerted* process begs precedent. To the extent that *aliphatic* systems can serve as models for the present system, it is known that reaction conditions like those leading to **6a** give 1,5 C-H insertion products, to the *exclusion* of the analogous 1,6 process.⁶ Moreover yields of products from the 1,5 mode of reaction in aliphatic systems are *inversely* related to the dissociation energy of the C-H bond undergoing insertion.^{6,7} Assuming that 1,6 C-H insertion reactions, were they to occur at all, would show the same trend, the high (103 kcal/mol⁸) bond dissociation energy of an *aromatic* C-H bond would militate against such a process since 1° aliphatic C-H bonds, with their lower bond dissociation energies of *ca.* 98 kcal/mol,⁸ are unreactive to alkylidenecarbenes under our conditions.

Alternative mechanisms for the generation of **6a** were therefore considered. In the most attractive of these, we posit a *stepwise* sequence that passes through the zwitterionic intermediate **8a** (Scheme 1). This zwitterion might arise directly from interaction between the electrophilic⁹ carbene **7a** and the aromatic ring (path b) or indirectly by heterolytic cleavage of the norcaradiene, **9a**, that could result from intramolecular [2+1]-cycloaddition of **7a** to the ring (path c).¹⁰



Scheme 1. Mechanistic Pathway to Rationalize Products from Reaction of 1 and 2.

Evidence for a stepwise mechanism was sought by careful examination of the reaction between **1a** and **2** in aprotic media. Formation of quinolone **6a** necessitates a proton transfer from the postulated zwitterion **8a**, and its yield should be diminished in aprotic solvents, owing to a lowered efficiency of the key prototropic step(s) (Scheme 1, path b); presumably, the yield of **3a** would increase as a consequence.¹¹ Indeed, when the reaction was performed in THF or acetonitrile the yield of **6a** decreased to 2% and 0%,¹² respectively, and that of **3a** increased concomitantly (Table 1).

| Compound | MeOH ^a | THF ^a | MeCN ^b |
|--------------------------|-------------------|------------------|-------------------|
| 3 | 53 | 64 | 82 |
| 4 | 14 | 8 | — |
| 5 | 10 | 9 | — |
| 6 | 20 | 2 | — |
| <i>N</i> -Methyl-aniline | 5 | 15 | — |

^aIsolated yield (%) based on amount of **1** consumed by reaction with **2**.

^bIsolated yield (%) based on recovered starting material.

Table 1. Product Distribution as Function of Solvent.

More compelling evidence for a stepwise mechanism was obtained from the reaction of DAMP (**2**) with *N*-methyl-*N*-(2,4,6-trideuteriophenyl)-2-oxopropanamide (**1b**). If quinolone **6** were formed by concerted 1,6 C-H insertion of the alkylidene carbene (Scheme 1, path a), trideuterated product **6b** would result. Were solvent-assisted proton transfer obligatory to the formation of **6** (Scheme 1, path b), however, one deuterium atom would potentially be lost to bulk solvent and **6c** would result.

Experimentally, reaction between **1b** and DAMP in methanol afforded the same spectrum of products as those derived from **1a** (eq. 1).¹³ Analysis of the appropriate spectral data (mass, ¹H- and ¹³C-NMR) showed that the level of deuteration of compounds **3b-5b** matched that of the starting propanamide **1b**. This result was consistent with the outcome of a prior control experiment that proved that base-catalyzed H-D exchange in **1a** involved *only* the acetyl methyl group.¹⁶ It also precluded such exchange in any of the precursors. *e.g.*, **9b**, of these products.

In contrast, the data obtained for the quinolinone that was isolated dictated its assignment as **6c**. Analysis by mass spectrometry proved that this product contained only *two* deuterium atoms, and their location at C-6 and C-8 was signalled by its ¹³C-NMR spectrum, wherein resonances for these carbon atoms appeared as triplets (¹J_{C,D} = 28.0 and 26.0 Hz, respectively). The presence of protium at C-4 was evident from both ¹H- and ¹³C-NMR spectral data.¹⁷ The results of a control experiment demonstrated that **6c** did *not* undergo H-D exchange under the reaction conditions, thus ensuring that the presence of protium at C-4 was *not* the result of selective exchange phenomena.

The *complete* loss of one deuterium atom in the conversion of **1b** to **6c** clearly cannot be reconciled with a concerted insertion reaction. Conversely, the results observed are entirely consistent with a stepwise sequence by way of the zwitterionic intermediate **8**.¹⁸ The loss of deuterium, as noted earlier, would occur during the collapse of **8b** to **6c** (Scheme 1, path b).

The details of this final stage of the mechanism are presently unclear. It is conceivable that the process represents an example of a "conducted tour" of a proton, wherein a single methanol molecule abstracts a hydrogen (deuterium) atom from C-5 of **8** in concert with delivery of its original proton to C-4 of the zwitterion. Stereoelectronic considerations make synchronicity of such a process highly improbable, yet the complete absence of any deuterium label at C-4 of **6b** would seem to require precisely this if a conducted tour is operative. A more probable scenario, in our opinion, is delivery of protium and abstraction of deuterium by different solvent molecules.^{19,20}

References and Notes

1. Respectfully dedicated to Professors Wolfgang Kirmse and Sara Jane Rhoads on the occasion of their 60th and 70th birthdays, respectively.
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10. The norcaradiene **9a** has been proposed before to rationalize the formation of cyclohepta[b]pyrrol-2-one (**3a**), the major product of the reaction between **1a** and **2** (eq. 1).⁵ Formation of similar norcaradienes by addition of alkylidenecarbenes to aromatic π -systems has been postulated by others: Brown, R.F.C.; Eastwood, F.W.; Harrington, K.J.; McMullen, G.L. *Aust. J. Chem.* **1974**, *27*, 2393.
11. Others have postulated ylids analogous to **8** to rationalize C-H insertion reactions (see Jefford, C.W.; Tang, Q; Zaslona, A. *Helv. Chim. Acta* **1989**, *72*, 1749, for example), but have not defined the course of the insertion process.
12. The previously reported⁴ reaction of **1** and **2** in acetonitrile was performed without an authentic specimen of **6** in hand. Repetition of the reaction showed that **6** was not produced within the limits of detection (tlc and ¹H-NMR spectral analysis of the crude reaction mixture).
13. Compound **1b** was prepared by reaction of 2,4,6-trideuterio-*N*-methylaniline¹⁴ and pyridinium hydroxymaleic anhydride.¹⁵ Spectroscopic analyses (¹H-NMR spectroscopy and mass spectrometry) of **1b** indicated that 86% of it was totally deuteriated at each of the *ortho* positions, the remaining 14% being monodeuteriated at these sites.
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16. Analysis (¹H-NMR spectroscopy) of a sample of **1** that had been treated with KOBU^t in methanol-*O*-d showed that 81% of the theoretical level of incorporation had occurred at the acetyl methyl group; no measurable amount of deuterium was found at the *ortho* positions.
17. Selected spectral data for **6c**: ¹H-NMR (CDCl₃) 7.55 (bs, 1 H, C-4 H), 7.48 (bs, 2 H, C-5 and C-7 H), 3.74 (s, 3 H, NCH₃), 2.27 (s, 3 H, CH₃C=); ¹³C-NMR (CDCl₃) 162.92 (C-2); 139.20 (C-4), 135.58 (C-9), 130.15 (C-7), 129.03 (C-3), 127.68 (C-5), 121.61 (t, C-6), 120.83, (C-10), 113.57 (t, C-8), 29.67 (*N*-methyl), 17.64 (C-3 methyl); ²H-NMR (CCl₄, ref. acetone-*d*) 7.29, 7.16; MS *m/z* 175 (M⁺, 100), 146 (46.8), 132 (19.9).
18. A referee has suggested that **6** is formed as a consequence of diazonium ion chemistry. We dismiss this possibility on the grounds (1) that **6** is produced in THF (Table 1) and (2) the intervention of such an ion would be expected to produce enol ethers derived from attack of methanol (or methoxide) on the vinyl cation arising by loss of dinitrogen from the diazonium ion.
19. The absence of product(s) ascribable to insertion of **7** into the O-H bond of methanol is remarkable, and presumably reflects the powerful influence of entropy on the fate of the carbene.
20. The financial support of this research by the National Institutes of Health (GM-29972) and the Robert A. Welch Foundation (F-815) is gratefully acknowledged.

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