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Ipso Aromatic Substitution from Reaction of a Carbene with DMAD

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Abstract: An aryloxy(methoxy)carbene reacted which DMAD (dimethyl acetylenedicarboxylate) by overall ipso aromatic substitution.

Keywords: aromatic substitution; carbene

Carbenes that are nucleophilic, because of stabilization of the singlet state by donor substituents, are intriguing intermediates with unusual reaction characteristics. New and useful synthetic applications of dimethoxycarbene, for example, have emerged recently [1].

Here we report a novel aromatic substitution from reactions of bis(oxadiazoline) **2**, (Scheme 1). Thermolysis of **2** generated carbene **4** (Scheme 2) which attacked dimethyl acetylenedicarboxylate (DMAD), resulting in *ipso* substitution at the oxygen-bearing carbon of the aryl ring. An analogous carbene (**11**) from the second oxadiazoline moiety reacted intramolecularly with the α,β-unsaturated ester group formed from the first carbene and DMAD. These novel sequential reactions resulted in a one-pot assembly of the fused, 3-ring heterocyclic system **12** (Scheme 2).

Bis(oxadiazoline) **2** was prepared from **1** by an acid catalysed exchange reaction [2] with catechol (Scheme 1). By-product **3** [3] was isolated by extraction into base. Pure **2** (40%) was obtained by chromatography [4].

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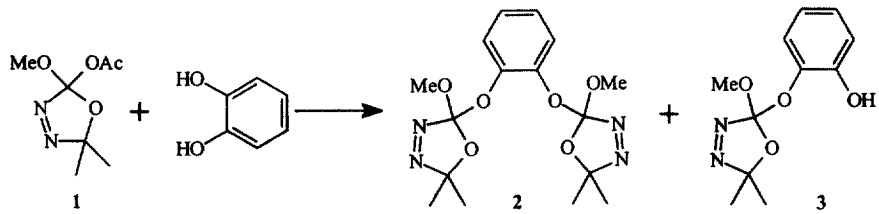
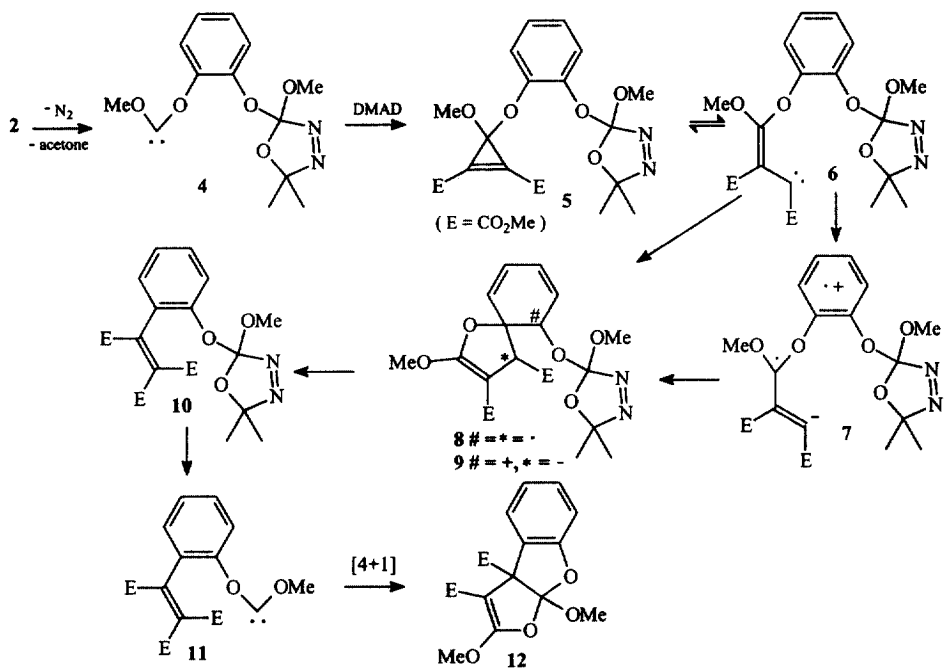
Scheme 1



Heating of **2** with DMAD in dry benzene in a sealed tube (110 °C, 24 h) afforded a product (40%, m/z= 336), derived formally from reaction of DMAD with the bis-carbene available from **2**. Its ^{1}H and ^{13}C NMR spectra were compatible with several potential structures. Crystals from hexane/benzene gave structure **12** [5].

Scheme 2

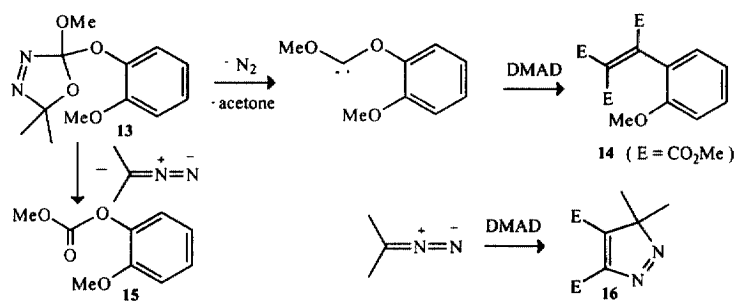


Striking features of **12** are the ketene-acetal-like functionality, in which one oxy-group is part of an orthoester, and the fact that it is a substituted phenol rather than a substituted catechol. The *ipso* aromatic substitution can be rationalized with the mechanism in Scheme 2, based on precedence for formation of a nucleophilic [1,6] carbene (**4**) and its addition to DMAD to afford cyclopropene **5** and carbene **6** (dipolar

contributor not shown) by reversible ring opening of **5**. Such equilibration of analogous 3,3- dialkoxycyclopropenes with vinylcarbenes is well known [7]. The next step, however, is not. We postulate that **6** undergoes either an electron transfer to generate radical-ion centers (**7**), leading to **8**, or that intramolecular attack by the arene ring at the formally-vacant p-orbital of **6** affords **9**, in a step like σ-bond formation in electrophilic aromatic substitution. Intermediate **8** or **9** subsequently opens to **10**. Sequential loss of N_2 and acetone from **10** would afford carbene **11**, for a precedented [8] [4+1] cycloaddition to give **12**.

Experimental support for the major part of the reaction path came from thermolysis of oxadiazoline **13** [9], prepared by the approach in Scheme 1. At 110 °C, in benzene containing DMAD, it afforded **14** (60%), Scheme 3 [10]. Carbonate **15**, presumably from 1,3-dipolar cycloreversion of **13** to 2-diazopropane, was isolated along with **16**; both in *ca.* 5% yield.

Scheme 3



In summary, the efficiency of the cascade leading to **12** from **2**; a process involving several consecutive reactions in one pot, is comparable to that of cascades involving dialkoxycarbenes with a tethered triple bond [11], and may find some applications in synthesis. Aryloxy(methoxy)carbenes with substituents in various positions of the arene ring (e.g. **13** and analogues) are under investigation as potential probes of mechanism.

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References and Notes:

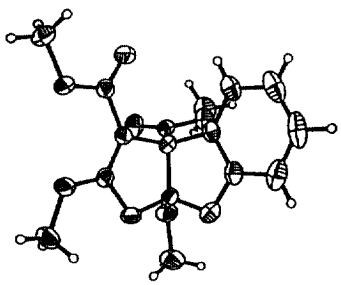
[1]. (a). Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.*, **1996,** *118*, 12848-12849. (b). Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.*, **1998**, *120*, 3664-3670.

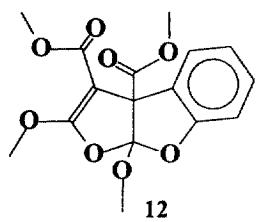
[2]. Kassam, K.; Pole, D. L.; El-Saidi, M.; Warkentin, J. *J. Am. Chem. Soc.* **1994**, *116*, 1161-1162.

[3]. **3**. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25 (s, 3H), 1.56 (s, 3H), 3.62 (s, 3H), 6.09 (s br,1H), 6.75-6.84 (m, 1H), 6.93-7.14 (m, 3H); ^{13}C NMR (50 MHz) δ: 23.31, 23.96, 52.71, 116.56, 120.02, 121.07, 123.45, 126.38, 137.08, 138.44, 148.87.

[4]. Diastereomers **2**. Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ:1.25 & 1.27 (s, total 6H), 3.64 (s, 6H), 7.00-7.09 (m, 2H), 7.23-7.33 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.22(-), 24.16(-), 120.69(+), 122.59(-), 124.62(-), 136.73(+), 143.88(+), 143.98(+); MS (electrospray) m/z: 373.1 (M+ Li)$^+$, 389.1 (M+ Na)$^+$, 405.1 (M+ K)$^+$.

[5]. **12**. mp 107.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.718/ 3.721 (2s, 6H), 3.76 (s, 3H), 4.02 (s, 3H), 6.86 (d, 1H), 6.91-7.04 (m, 1H), 7.19-7.27 (m, 1H), 7.52-7.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 50.93, 52.50, 53.10, 57.63, 83.77, 109.68, 122.61, 126.94, 127.70, 128.62, 129.28, 156.59, 163.83, 165.15, 168.47; MS (EI) m/z: 336 (M$^+$), 305, 277 (100%); crystal structure shown below.





12

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[9]. Oxadiazoline **13**. Liquid. IR(CCl_4) cm^{-1}: 1771, 1598; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.21(s, 3H), 1.51(s, 3H), 3.65 (s, 3H), 3.82 (s, 3H), 6.80-6.92 (m, 2H), 7.04-7.13 (m, 1H), 7.19-7.24 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.14, 24.15, 52.42, 55.85, 112.44, 120.27(C5), 123.43, 125.55, 137.08(C2), 140.72, 152.41.

[10]. Triester **14**. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 52.3(-), 52.7(-), 52.83(-), 55.58(-), 111.02(-), 120.61(-), 122.94(+), 129.75(-), 130.60(+), 131.50(-), 142.85(+), 156.75(+), 164.41(+), 164.54(+), 166.96(+); HRMS calcd for $C_{15}H_{16}O_7$ 308.0896; found 308.0896.

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