J. Am. Chem. Soc. 1982, 104, 4953-4954

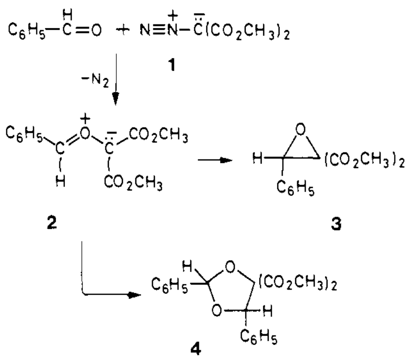
Three-Component Reactions of Diazomalonic Ester, Benzaldehyde, and Electrophilic Olefins

Rolf Huisgen* and Pedro de March

Institut für Organische Chemie der Universität München
D-8000 München 2, West Germany

Received April 26, 1982

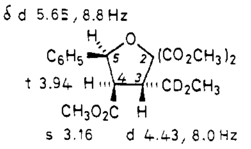
The reaction of dimethyl diazomalonate (**1**) with an excess of



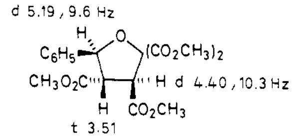
benzaldehyde with or without metal catalyst furnished the diastereomeric 1,3-dioxolanes **4** and the oxirane **3**; evidence for the occurrence of the carbonyl ylide **2** as an intermediate was presented.[1] Benzaldehyde plays a double role, first as a constituent of the carbonyl ylide and, subsequently, as a dipolarophile in the trapping of **2**.

We report here on the separation of the two functions, which is of mechanistic significance and gives access to substituted tetrahydrofurans.[2] Carbonyl ylides combine especially well with α,β-unsaturated carboxylic esters,[3,4] which however, are not favored reaction partners of the highly electrophilic bis(methoxycarbonyl)carbene. The 1,3-dipolar cycloadditions of **1** are mainly LUMO (1,3-dipole)–HOMO (dipolarophile) controlled;[5] the slow reaction with dimethyl fumarate (13 days, 80 °C) provided 73% tetramethyl 2-pyrazoline-3,4,5,5-tetracarboxylate.[6] The low nucleophilicity of **1** was responsible for its choice as carbene generator in this study.

A mixture of 17 mmol each of **1** and benzaldehyde was introduced dropwise in 4 h into 17 mmol of benzaldehyde, 67 mmol of dimethyl fumarate, and 30 mg of copper powder stirred at 125 °C. The N_2 evolution was quantitative and, after removal of the excess of reactants, ^{1}H NMR analysis with standard indicated 58% of **5** and **6** in the ratio 54:46. The tetrahydrofurans **5** (mp 114.5–115.5 °C) and **6** (mp 88–89 °C), 1:1:1 products minus N_2,[7] crystallized from methanol. Both **5** and **6** possess four nonequivalent ester groups, but only the ^{1}H NMR ($CDCl_3$) of **5** shows a high-field OCH_3 (δ 3.16), which we assign to 4-CO_2CH_3 located cis-vicinal to the 5-phenyl group. The stronger deshielding of 4-H in **5** (3.94) compared with 4-H in **6** (3.51) is in consonance with the effect of *trans*- and *cis-vic*-C_6H_5.

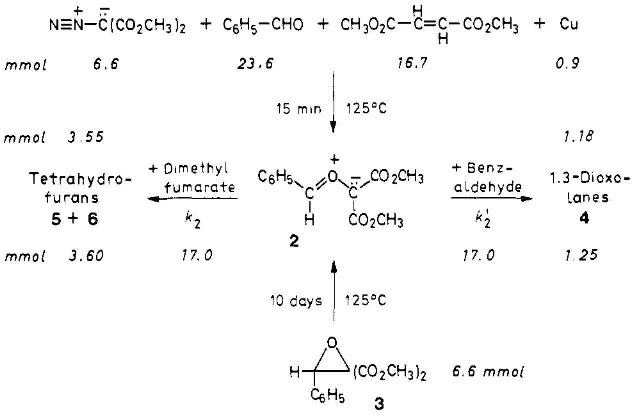


5



6

Scheme I

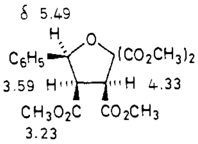


Copper catalysis is not a prerequisite of the three-component reaction, but it improves the yield. When dimethyl diazomalonate was heated with 6 equiv each of benzaldehyde and dimethyl fumarate for 11 h at 125 °C, 79% N_2 evolved, and ^{1}H NMR analysis revealed 18% **5** and **6** and 2% dioxolanes **4**.

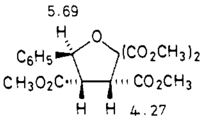
The 54:46 ratio of **5** and **6** signifies a low diastereoselectivity for the cycloaddition of **2** to dimethyl fumarate. The attractive π overlap between C_6H_5 of **2** and an ester group of the dipolarophile outweighs the steric repulsion in the transition state.

Benzaldehyde and dimethyl fumarate compete as dipolarophiles for the carbonyl ylide **2**. The results of a quantitative competition experiment (Scheme I) provided $k_2/k_2' = 3.3$, i.e., dimethyl fumarate intercepts **2** 3.3 times faster than benzaldehyde: 100% N_2 after 15 min at 125 °C signaled the disappearance of **1**, whereas an analogous competition experiment with **3** as the source of **2** required 10 days at 125 °C. Nevertheless, $k_2/k_2' = 3.0$ in the latter case intimates the identity of the reactive intermediate involved in both conversions; also the absolute yields of cycloadducts (72% and 74%) were similar.

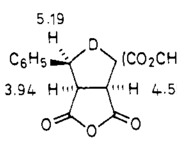
The use of dimethyl maleate (Cu(I) triflate, 80 °C), which is not as good a dipolarophile as fumaric ester, diminished the yield of interception product to 24% **7** (mp 137–138 °C) and **8** in a 55:45 ratio; **3** and **4** occurred as side products. Maleic anhydride afforded 42% **9** (mp 119–119.5 °C), which was converted to **7** by methanol and diazomethane. *N*-Methylmaleimide gave rise to 49% **10** (mp 146–147 °C) and 10% **11**, which were separated on SiO_2. Analogously, *N*-phenylmaleimide afforded 57% dia-



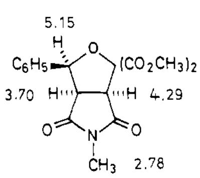
7



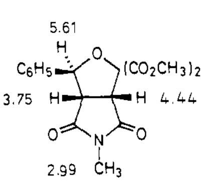
8



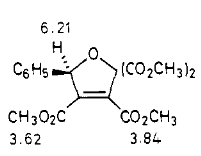
9



10



11



12

---

(1) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* preceding paper in this issue.

(2) Bermes, R. Ph.D. Thesis, University of Munich, 1963. Bermes reacted diethyl diazomalonate and diethyl fumarate with benzaldehyde and anisaldehyde, respectively, under Cu catalysis at 145 °C, and obtained oily products that correctly analyzed for 1:1:1 products minus N_2. The results were not published because the structural evidence was inconclusive.

(3) Hamberger, H.; Huisgen, R. *J. Chem. Soc., Chem. Commun.* **1971**, 1190–1192. Dahmen, A.; Hamberger, R.; Huisgen, R.; Markowski, V. *Ibid.* **1971**, 1192–1194. Markowski, V.; Huisgen, R. *Ibid.* **1977**, 439–440.

(4) Review: Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572–585.

(5) Bihlmaier, W.; Huisgen, R.; Reissig, H.-U.; Voss, S. *Tetrahedron Lett.* **1979**, 2621–2624.

(6) Reissig, H.-U. Ph.D. Thesis, University of Munich, 1978; pp 64, 201.

(7) Satisfactory elemental analyses were obtained for all new compounds.

0002-7863/82/1504-4953$01.25/0

stereomeric 1:1:1 products in a 5:1 ratio. Despite the fact that dimethyl acetylenedicarboxylate is a fairly good dipolarophile vs. **1**,[5,6,8] the copper-catalyzed procedure provided 58% of the dihydrofuran derivative **12** (mp 89–90 °C). Methyl phenylpropiolate, however, no longer successfully competed with benzaldehyde for the high-energy intermediate **2**.

Benzaldehyde has been replaced by anisaldehyde, 4-chlorobenzaldehyde, and furfural in analogous three-component reactions. For example, anisaldehyde, dimethyl fumarate, and **1** (Cu, 45 min, 125 °C) yielded 68% **5** and **6**, p-$C_6H_4OCH_3$ instead of C_6H_5 (mp 113.5–115 °C and 144–145 °C), in a 54:46 ratio, and the carbonyl ylide **2**, p-$C_6H_4OCH_3$ instead of C_6H_5, combined with fumaric ester 7.2 times faster than with anisaldehyde. Is it possible to substitute diazoacetic ester for diazomalonic ester? The pyrazoline formation with α,β-unsaturated carboxylic esters becomes the prominent reaction. Nevertheless, the Cu-catalyzed reaction of benzaldehyde, dimethyl fumarate, and methyl diazoacetate at 90 °C gave 14% of a tetrahydrofuran as 1:1:1 product. Experiments with more active metal catalysts are under way.

Registry No. 1, 6773-29-1; **3**, 82545-15-1; *cis*-**4**, 82545-16-2; *trans*-**4**, 82545-17-3; **5** (Ph), 82545-18-4; **5** ($C_6H_4OCH_3$-p), 82545-26-4; **6** (Ph), 82545-19-5; **6** ($C_6H_4OCH_3$-p), 82545-27-5; **7**, 82545-20-8; **8**, 82545-21-9; **9**, 82545-22-0; **10** (N-Me), 82545-23-1; **10** (N-Ph), 82545-24-2; **11** (N-Me), 82597-22-6; **11** (N-Ph), 82597-23-7; **12**, 82545-25-3; benzaldehyde, 100-52-7; dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6; maleic anhydride, 108-31-6; N-methylmaleimide, 930-88-1; N-phenylmaleimide, 941-69-5; dimethyl acetylenedicarboxylate, 762-42-5; p-anisaldehyde, 123-11-5; methyl diazoacetate, 6832-16-2.

---

(8) Bramley, R. K.; Grigg, R.; Guilford, G.; Milner, P. *Tetrahedron* **1973**, *29*, 4159–4167.

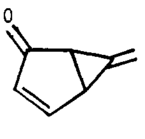
Chemistry of the Energy-Rich *m*-Quinomethane System. Formal (3 + 2) Cycloadditions to Olefins via a Singlet Intermediate

Albert R. Matlin, Thomas A. Inglin, and Jerome A. Berson*

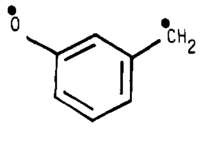
Department of Chemistry, Yale University
New Haven, Connecticut 06511

Received April 15, 1982

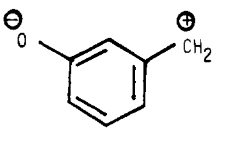
m-Quinomethane, a new non-Kekulé system, has been generated in two valency tautomeric forms, the bicyclic dienone **1** and the triplet state **2T** of the monocyclic biradical **2**.[1-3] The present paper reports a series of novel cycloadditions of this system and implicates a third species, a monocyclic singlet, **2S** or **3**, as the actual reactive intermediate.



1

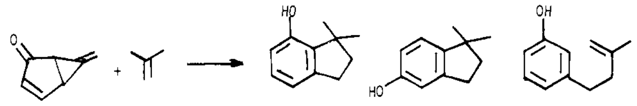


2T: triplet
2S: singlet



3

Although **1** fails to give adducts with dimethyl acetylenedicarboxylate or dimethyl maleate, facile additions to electron-rich olefins occur either thermally (110 °C in benzene solution) or photochemically (0 °C in benzene solution, 300-nm radiation). With isobutylene, for example, three 1:1 adducts **4–6**, are formed in the kinetically controlled proportions 1.9:1.0:1.9, respectively.

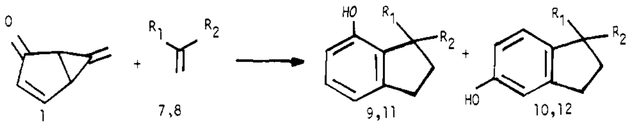


1 4 5 6

Their structures are established by elemental compositions, spectroscopic properties, and independent syntheses.[4] At low conversion (3.7% depletion of **1**), the absolute yield of 1:1 cycloadducts in the thermal reaction is 86 ± 15% by gas chromatographic (GC) analysis. This drops to 24% at 100% conversion, although the proportions of products **4**:**5**:**6** change only slightly (2.2:1.0:2.6). The photochemical reaction gives 54% yield of the same cycloadduct mixture after 100% conversion.

The diminished yields of 1:1 adduct in the high-conversion runs are caused by a secondary reaction in which another molecule of enone alkylates the first product either on oxygen or on carbon to give a 2:1 adduct. This problem can be mitigated in the photochemical addition by in situ protection of the 1:1 adducts. Inclusion of 6 equiv of trimethylsilyl chloride (Me_3SiCl) and 9 equiv of 2,6-lutidine in the reaction mixture traps the initial adducts **4–6** as their Me_3Si ethers, which under these conditions are relatively resistant to attack by a second molecule of **1**. Methanolysis of the Me_3Si ethers at 45 °C gives **4–6** in the combined yield of 70°.[5]

The highly specific Markovnikov-like orientation observed in the isobutylene additions occurs also in the reactions with isoprene (**7**) and with ethyl vinyl ether (**8**), which give products **9** + **10** (about equal amounts) and **11** + **12** (about 2:1), respectively. Without the Me_3SiCl in situ protection, the (unoptimized) absolute yields of **9** + **10** are 22% and 30% in the thermal and photochemical modes, respectively; **11** + **12** are correspondingly formed in 37% and 51% yields. O-methylation of **11** and **12** and of the dihydro derivatives of **9** and **10** give the corresponding ethers. Independent syntheses[4] of the latter confirm the spectroscopically based structural assignments. Products resulting from formal (3 + 2) addition to the conjugated diene system of isoprene, if present, constitute <3% of the adduct mixture.



1 7,8 9,11 10,12

7, 9, 10, R_1 = Me; R_2 = CH=CH_2
8, 11, 12, R_1 = H; R_2 = OEt

Superficially, the cycloaddition reactions leading to phenolic indans and the hydrogen-transfer process leading to the olefin **6** resemble a Diels–Alder reaction and a vinylogous ene reaction, respectively, in which a σ bond plays a π-like role. However, the analogy implies a bimolecular mechanism, which is now shown to be incompatible with the kinetics of the thermal reaction.

Disappearance of enone **1** in benzene solution in the presence of a large excess of methanol or isoprene follows clean pseudo-first-order kinetics (analyses by GC and NMR). Measurements at seven temperatures between 100 and 129 °C give the Arrhenius equation $k = 10^{14.0} \exp(-30600 \pm 600\ (\text{cal/mol})/RT)\ \text{s}^{-1}$. At high methanol concentration a trace of 4-methoxy-6-methylenebicyclo[3.1.0]hexan-2-one is formed. Otherwise, the sole product in the methanol reaction is *m*-hydroxybenzyl methyl ether. The rate is *independent of the methanol concentration* in the range 0.0–1.73 M. At 105 °C, the rate in the presence of 0.5 M isoprene is the same as that in the presence (or absence) of methanol.

These data suggest that unimolecular formation of a reactive intermediate is the rate-determining step. A priori, the candidates

---

(1) Rule, M.; Matlin, A. R.; Hilinski, E. F.; Dougherty, D. A.; Berson, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 5098.

(2) Seeger, D. E.; Hilinski, E. F.; Berson, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 720.

(3) Rule, M. Matlin, A. R.; Seeger, D. E.; Hilinski, E. F.; Dougherty, D. A.; Berson, J. A. *Tetrahedron* **1982**, *38*, 787.

(4) Methyl ethers of compounds **4** and **5** by H_2SO_4-catalyzed cyclization of 4-(3-methoxyphenyl)-2-methyl-2-butanol; methyl ether of compound **6** by Wittig methylenation of 4-(3-methoxyphenyl)-2-butanone; methyl ethers of dihydro-**9** and of dihydro-**10** by acid-catalyzed cyclization of 1-(3-methoxyphenyl)-3-hydroxy-3-pentane.

(5) The method fails in the thermal mode, however, because **1** reacts with Me_3SiCl at 110 °C to give a high yield of *m*-(trimethylsiloxy)benzyl chloride.

0002-7863/82/1504-4954$01.25/0 © 1982 American Chemical Society