Competing Formations of Oxonium and Carbonyl Ylides with Carbonylcarbenes

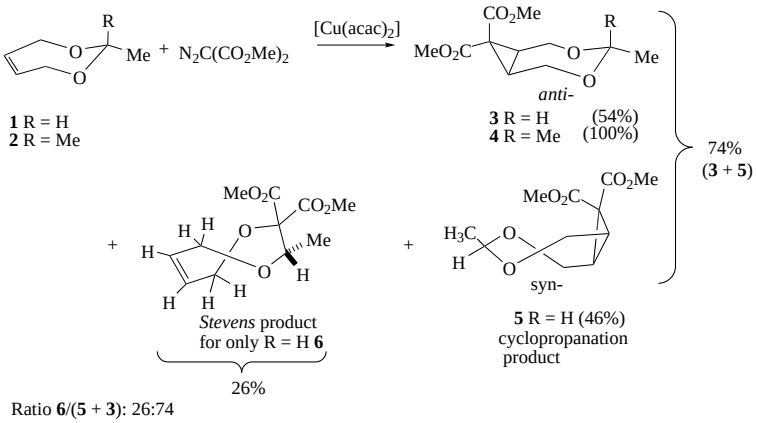
by **E. Naciye Talinli***, **Olcay Anaç**, and **I. Volkan Kumbaracı**

Istanbul Technical University, Faculty of Sciences, Department of Chemistry, 34469 Maslak, TR-Istanbul

A series of 2-mono- and 2,2-disubstituted 1,3-dioxepin derivatives, two of which also had a carbonyl function in one of their 2-R groups, were prepared and reacted with dimethyl diazomalonate with copper(II) acetylacetonate as a catalyst. Ylide formation probabilities with allyl ether and/or carbonyl functions were investigated. A chemoselectivity in favor of carbonyl ylide was observed.

Introduction. – The reactions of carbenes with open-chain ethers and acetals have been extensively studied [1]. Only a few have been recorded regarding their reaction with cyclic ethers and cyclic acetals [2]. For the open-chain analogues, cyclopropanations and *Stevens* reactions compete with 2,3-sigmatropic shifts in certain cases. In our previous work, we reacted 1,3-dioxepin derivatives (unsaturated cyclic acetals) with dimethyl diazomalonate (DMDM) copper(II) acetylacetonate [$Cu(acac)_2$] as a catalyst to investigate the formation of oxonium-ylide-originated products, along with cyclopropanation and β-H elimination reactions [3] (*Scheme 1*). We reported that *i*) increased bulk near the O-atom promoted the cyclopropanation reaction, and *ii*) *Stevens* reaction occurred only at the O–C–O bonds as claimed by *Doyle et al.* for open-chain analogues [4][5].

Scheme 1

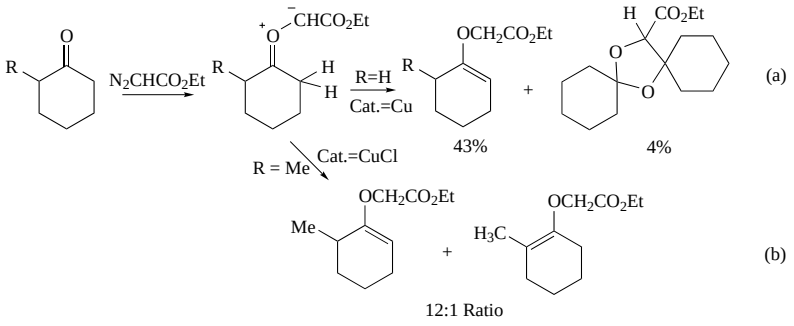


In this study, as a part of our continuing interest in this field, we worked on similar reactions of 2-mono- and 2,2-disubstituted 1,3-dioxepin derivatives. Furthermore, we

investigated the probabilities of additional pathways *via* carbonyl ylides in the case of 2-R groups having C=O functions, and also wanted to compete the ylide formation of allyl ether and C=O functions residing in the same molecule.

As known, one characteristic reaction of carbonyl ylides consists of an intramolecular H-transfer to give enol ethers [6] along with the formation of dioxole and epoxide derivatives. Treatment of ethyl diazoacetate in cyclohexanone derivatives with catalytic amounts of Cu powder or CuCl was reported to afford moderate yields of H-transfer products (β-H elimination; *Scheme 2*, *a* and *b*) [7].

Scheme 2



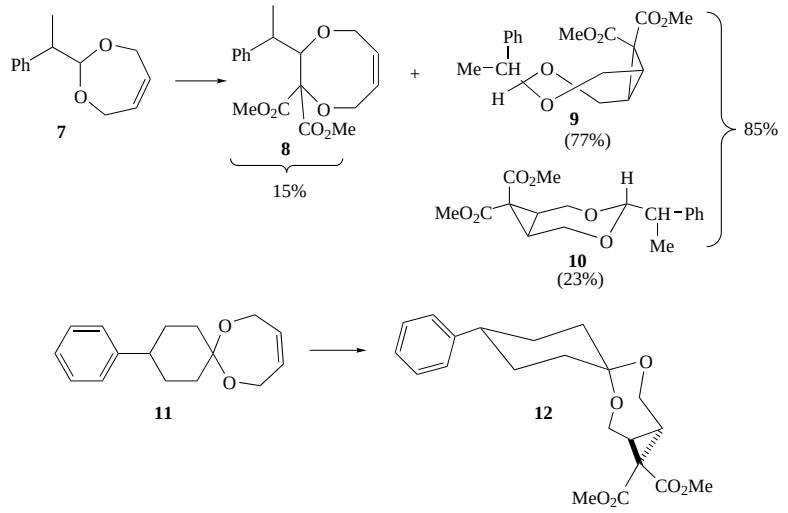
The H-transfer was also found to proceed with high regiospecificity: when unsymmetric ketones were used, formation of the least-substituted enol ether is the dominant pathway (*Scheme 2*, *b*). The regiochemistry observed can be accommodated by considering various reasonable starting configurations or conformations for the essential carbonyl ylide in which the C–H bond of the migrating H is approximately perpendicular to the plane of the ylide. Minimization of steric interactions of various groups rationalizes the high regioselectivity encountered [8].

Results and Discussions. – For the first part of the work, compounds **7** and **11** were chosen as the starting materials and were synthesized according to the methods described in [9][10] (*Scheme 3*).

Three products were obtained from the reaction of 4,7-dihydro-2-(1-phenylethyl)-1,3-dioxepin (**7**) with DMDM. Although the ^{13}C-NMR spectrum gave a clue about the presence of three compounds, GC analysis showed only two products, one of which contained two unresolved isomeric cyclopropane derivatives, and the other one was a *Stevens* product with the ratio of 85:15. The ratio of the isomers of cyclopropane product, **9**/**10**, was found to be 77:23 according to the integrals of the signals of the bridgehead H-atoms from ^{1}H-NMR spectrum of the crude reaction mixture. However, the increased crowding at C(2) of 1,3-dioxepin caused an additional decrease in the relative amount of the *Stevens* product when compared with the results in *Scheme 1*.

In the reaction of 3-phenyl-7,12-dioxaspirododec-9-ene (**11**), with DMDM, the compound **12** was obtained as the sole product. As expected, steric hindrance prohibited the *Stevens* rearrangement. ^{1}H-NMR Spectrum and geometry-optimization

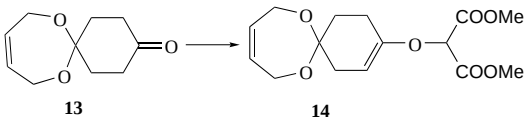
Scheme 3



studies (with 'Desktop Molecular Modeller' on PC-Windows platform) indicated that **12** had a chair-chair conformation (*Scheme 3*).

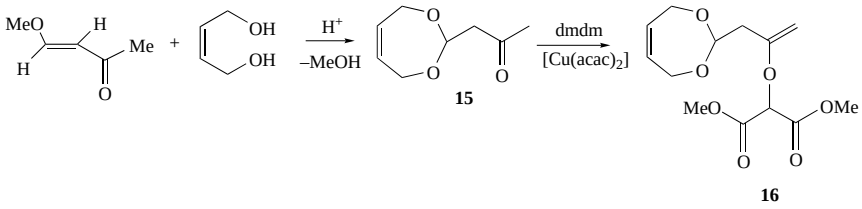
For the second part of the study, compound **13** was chosen as the substrate for DMDM. Compound **13** represented a pattern having two substituents at the acetal C-atom, thus greatly eliminating the possibility of a *Stevens*-type reaction. The probable reactions to compete with cyclopropanation were reactions *via* a carbonyl ylide, and, surprisingly, this latter pathway led to the only product of the reaction, *i.e.*, the β-H-eliminated product **14** (*Scheme 4*).

Scheme 4



To gather more supporting data related to this β-H elimination, another dioxepin derivative, 1-(4,7-dihydro-1,3-dioxepin-2-yl)propan-2-one (**15**), was reacted with DMDM. Compound **15** [11] was prepared from 2-methoxyvinyl methyl ketone by a *trans*-acetalization-like reaction (*Scheme 5*). In contrast to **13**, compound **15** with a mono-substituted acetal C-atom might also have produced oxonium-ylide-originated products as **7** did. Compound **15**, again, gave only a β-elimination product in high yield, and products from any other possible reactions (such as cyclopropanation, *Stevens* rearrangement, [2,3]-sigmatropic rearrangement, dioxole and/or epoxide formation) were not detected (*Scheme 5*).

Scheme 5



In accordance with the previous reports [6], this H-transfer reaction proceeded with high regioselectivity to yield the least-substituted enol ether. Apparently, the sterically crowded carbonyl ylide could not reach the CH_2 H-atoms, thus, it preferred the unhindered Me H-atoms. In this reaction, the β-H elimination occurred, again with 100% chemoselectivity. Therefore, we can easily conclude that, under our experimental conditions, these two reactions of **13** and **15**, which include both carbonyl and allyl ether functions, were totally chemoselective in favor of carbonyl-ylide formation.

In conclusion, intermolecular ylide-forming competition between ether and C=O functions, both residing in the same molecule, is reported for the first time.

Experimental Part

General. Dimethyl diazomalonate (DMDM) and the dioxepins were prepared according to literature methods. Product distributions were established by GC and NMR, and are rather relative than isolated yields. IR: *Jasco FT-IR-5300* apparatus. NMR ($CDCl_3$): 250-MHz *Bruker AC-3000* apparatus, TMS as internal standard, δ in ppm, J in Hz. GC: *Philips PU4400* instrument with 3% *OV17*-packed column. GC/MS: *Hewlett-Packard* instrument with a 24-m *HP-1* capillary column, packed with cross-linked methyl(phenyl)siloxane as the liquid phase, EI-MS detector; column conditions *I:* 150° for 30 min, then 15°/min to 280° (for compounds **8**–**10**, and **12**); column conditions *II:* 90° for 5 min, then 20°/min to 280° (for **13**–**16**).

Reaction of DMDM and Dioxepins: General Procedure. A soln. of 1 equiv. of DMDM in benzene (2 mmol/1 ml benzene) was added very slowly within 48 h to a refluxing benzene soln. of dioxepin (3 equiv.; 1 mmol/1 ml benzene) and [Cu(acac)$_2$] (0.005 equiv.) under N_2. Consumption of DMDM was monitored by IR. After disappearance of the band at 2130 cm^{-1}, the mixture was passed through a column of neutral aluminium oxide to remove the catalyst and highly colored impurities. Then, the solvent was evaporated, and the residue was purified with prep. TLC or column chromatography (AcOEt/hexane 20:80).

Dimethyl 5,8-Dihydro-3-(1-phenylethyl)[1,4]dioxocine-2,2-dicarboxylate (**8**): ^{1}H-NMR: 7.25 (*m*, Ph); 5.63 (br. *d*, *J* = 6.16, H–C(6), H–C(7)); 4.65–4.3 (*m*, H–C(3), 2 H–C(5), 2 H–(8)); 3.71, 3.70 (2*s*, 2 MeO); 2.85 (*dq*, *J* = 7.2, 7.16, PhC*H*); 1.40 (*d*, *J* = 7.16, Me). ^{13}C-NMR: 168 (C=O); 123–127 (Ph), 108, 107 (C(6), C(7)); 77 (C(3)); 67.9 (C(5), C(8)); 52.3 (MeO); 31 (Ph*C*); 14.6 (Me). EI-MS: 334 (1, M^+), 200 (10), 145 (8), 134 (25), 117 (12), 105 (100), 91 (25), 77 (45), 59 (50), 54 (95). HR-MS: 334.3621 (M^+, $C_{18}H_{22}O_6^+$; calc. 334.3637).

syn-*Dimethyl 4-(1-Phenylethyl)-3,5-dioxabicyclo[5.1.0]octane-8,8-dicarboxylate* (*syn*-**9**): ^{1}H-NMR: 7.25 (*m*, Ph); 4.3–4.2 (*m*, H–C(4), 2 H–C(6), 2 H–C(2)); 3.72, 3.69 (2*s*, 2 MeO); 3.05 (*dq*, *J* = 8.2, 7.0, PhC*H*); 2.1 (br. *d*, *J* = 9.4, H–C(1) or H–C(7)); 2.0 (br. *d*, *J* = 9.4, H–C(7) or H–C(1)); 1.36 (*d*, *J* = 7.0, Me). ^{13}C-NMR: 168 (C=O); 123–127 (Ph); 102 (C(4)); 68.8 (C(2); C(6)); 52.9 (MeO); 43.8 (Ph*C*); 39 (C(8)); 31.55 (C(7) or C(1)); 31.5 (C(1) or C(7)); 15.7 (Me). EI-MS: 334 (2, M^+), 304 (10), 230 (100), 202 (4), 197 (10), 183 (30), 169 (70), 151 (40), 137 (70), 125 (35), 113 (55), 105 (95), 91 (50), 77 (75), 69 (40), 59 (100). HR-MS: 334.3621 (M^+, $C_{18}H_{22}O_6^+$; calc. 334.3637).

anti-*Dimethyl 4-(1-Phenylethyl)-3,5-dioxabicyclo[5.1.0]octane-8,8-dicarboxylate* (*anti*-**10**): ^{1}H-NMR: 7.25 (*m*, Ph); 4.5–4.3 (*m*, H–C(4), 2 H–C(6), 2 H–C(2)); 3.74, 3.73 (*s*, 2 MeO); 2.96 (*dq*, *J* = 7.1, 6.1, PhC*H*); 2.14 (br. *s*, H–C(1), H–C(7)); 1.18 (*d*, *J* = 7.1, Me). ^{13}C-NMR; 167 (C=O); 123–127 (Ph); 101 (C(4)); 68.4 (C(2), C(6)); 52.6 (MeO); 42.8 (Ph*C*); 34 (C(8)); 31.9 (C(1), C(7)); 14.8 (Me). EI-MS: 334 (2, M^+), 304 (10), 230 (100), 202 (4), 197 (10), 183 (30), 169 (70), 151 (40), 137 (70), 125 (35), 113 (55), 105 (95), 91 (50), 77 (75), 69 (40), 59 (100). HR-MS: 334.3621 (M^+, $C_{18}H_{22}O_6^+$; calc. 334.3637).

Dimethyl 4-Phenylspiro[cyclohexane-1,4′-[3,5]dioxabicyclo[5.1.0]octane]-8′,8′-dicarboxylate (**12**): ^{1}H-NMR: 7.2 (*m*, Ph); 4.2 (*m*, 2 H−C(2), 2 H−C(6)); 3.77 (*s*, MeO); 3.7 (*s*, MeO); 2.48 (*tt*, *J* = 11.8, 3.7, H−C(4)); 2.14 (*ddd*, *J* = 13.04, 6.3, 3.17, 1 H, CH_2(2)); 2.01 (*ddd*, *J* = 13.0, 6.3, 3.2, 1 H, CH_2(6)); 2.02 (br. *s*, H−C(1′), H−C(7′)); 1.24–1.78 (*m*, 1 H−C(2), CH_2(3), CH_2(5), 1 H−C(6)). ^{13}C-NMR: 170.8; 167.4 (2 CO); 146 (quat. olef. C); 128.3; 126.7; 126.03 (Ph); 102 (C(4)); 56.8; 56.5 (C(2), C(6)); 52.8; 52.4 (2 MeO); 43.6 (C(4)); 31 (C(1′), C(7′)); 34.8, 32.8, 32.3, 30.2 (C(2′), C(3′), C(5′), C(6′)). EI-MS: 374 (7, M^+), 343 (14), 255 (100), 242 (10), 201 (50), 183 (25), 174 (30), 157 (50), 139 (30), 125 (25), 117 (70), 104 (90), 91 (80), 81 (40), 77 (35), 69 (30), 59 (85). HR-MS: 374.4261 (M^+, $C_{21}H_{26}O_6^+$; calc. 374.4275).

7,12-Dioxaspiro[5.6]dodec-9-en-3-one (**13**): ^{1}H-NMR: 5.64 (*s*, H−C(9), H−C(10)); 4.26 (*s*, 2 H−C(11), 2 H−C(8)); 2.37 (*t*, *J* = 6.72, 2 H−C(1), 2 H−C(5)); 2.06 (*t*, *J* = 6.72, 2 H−C(2), 2 H−C(4)). EI-MS: 182 (20, M^+), 125 (80), 112 (15), 84 (20), 70 (20), 55 (100), 39 (85). HR-MS: 182.2156 (M^+, $C_{10}H_{14}O_3^+$; calc. 182.2164).

Dimethyl 2-[(7,12-Dioxaspiro[5,6]dodeca-2,9-dien-3-yl)oxy]propanedioate (**14**): ^{1}H-NMR: 5.64 (br. *s*, H−C(9), H−C(10)); 4.92 (*s*, CHO); 4.40 (*t*, *J* = 3.75, H−C(2)); 4.23 (br. *s*, 2 H−C(8), 2 H−C(11)); 3.78 (*s*, 2 MeO); 2.34 (*d*, *J* = 3.8, 2 H−C(1)); 2.30 (*t*, *J* = 6.5, 2 H−C(4)); 1.93 (*t*, *J* = 6.5, 2 H−C(5)). ^{13}C-NMR: 130; 128 (C(9), C(10)); 167 (2 C=O), 153 (C(3)); 116 (C(2)); 100.9 (C(6)); 61.2 (C(8), C(11)); 52.2 (MeO); 32 (C(1)); 28.2 (C(5)), 25.7 (C(4)). EI-MS: 294 (7), 281 (5), 255 (12), 253 (7), 243 (65), 211 (30), 181 (90), 151 (20), 141 (25), 132 (30), 111 (100), 83 (35), 69 (30), 59 (25), 55 (28). HR-MS: 312.3140 (M^+, $C_{15}H_{20}O_7^+$; calc. 312.3151).

1-(4,7-Dihydro[1,3]dioxepin-2-yl)propan-2-one (**15**): ^{1}H-NMR: 5.61 (br. *s*, H−C(5), H−C(6)); 5.08 (*t*, *J* = 5.7, H−C(1)); 4.30 (*dd*, *J* = 14.65, 5.15, H_{ax}−C(4), axial H_{ax}−C(7)); 4.11 (*dd*, *J* = 14.7, 5.2, H_{eq}−C(4), H_{eq}−C(7)); 2.72 (*d*, *J* = 5.7, CH_2); 2.09 (*s*, Me). EI-MS; 141 (1), 102 (5), 87 (15), 70 (20), 58 (35), 54 (20), 43 (100). HR-MS: 156.1782 (M^+, $C_8H_{12}O_3^+$; calc. 156.1791).

Dimethyl 2-[2-(4,7-Dihydro[1,3]dixepin-2-yl)-1-methylideneethoxy]propanedioate (**16**): ^{1}H-NMR: 5.7 (br. *s*, H−C(5″), H−C(6″)); 5.08 (*t*, *J* = 5.8, H−C(2″)); 4.97 (*s*, H−C(2)); 4.38 (br. *d*, *J* = 14.6, H_{ax}−C(4″), H_{ax}−C(7)); 4.19 (br. *d*, *J* = 14.6, H_{eq}−C(4), H_{eq}−C(7)); 4.12, 3.91 (2 *d*, *J* = 3.5, =CH_2); 3.75 (*s*, 2 MeO); 2.55 (*d*, *J* = 5.8, CH_2). ^{13}C-NMR: 189.4 (*C*=CH_2); 167.3 (2 C=O); 129.3 (C(5″), C(6″)); 105.9 (C(2)); 101 (C(2″)); 71 (=CH_2); 65.6 (C(4″), C(7″)); 53 (2 MeO), 51.1 (CH_2). EI-MS: 286 (7, M^+), 241 (2), 217 (30), 189 (25), 171 (25), 157 (35), 143 (7), 138 (25), 132 (12), 114 (15), 99 (70), 71 (90), 69 (75), 59 (45), 53 (25), 41 (100), 39 (95). HR-MS: 286.2769 (M^+, $C_{13}H_{18}O_7^+$; calc. 286.2778)

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