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Dihydrofurans from α-Diazoketones: Facile Rearrangement of Donor-Acceptor Cyclopropanes

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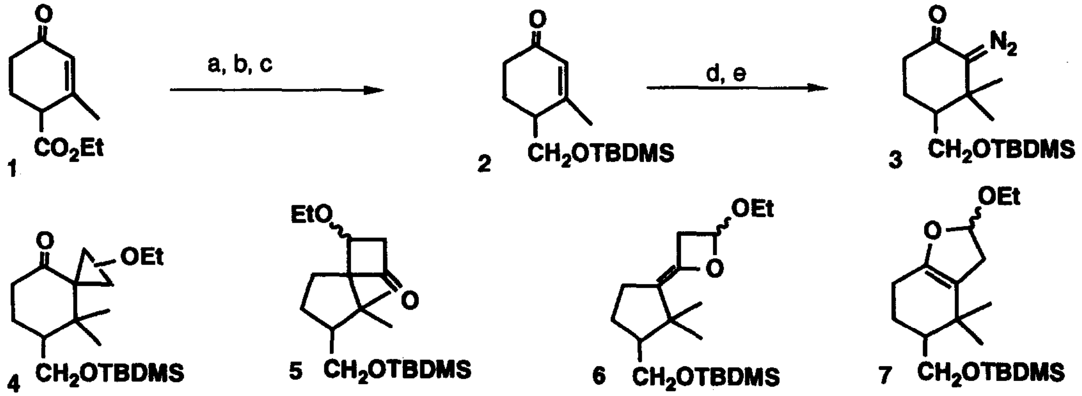
Abstract: The direct synthesis of dihydrofurans **7**, **11**, and **23**- **25** from α-diazoketones **3**, **8**, and **20**-**22** is described. The cyclopropane intermediates generated upon treatment of the α-diazoketones with metal catalysts in the presence of ethyl vinyl ether rearranged spontaneously. Sensitized irradiation of **3** afforded **7** plus cyclobutanone **5** while direct photolysis gave the cyclobutanones **5**, and **26**-**28**.

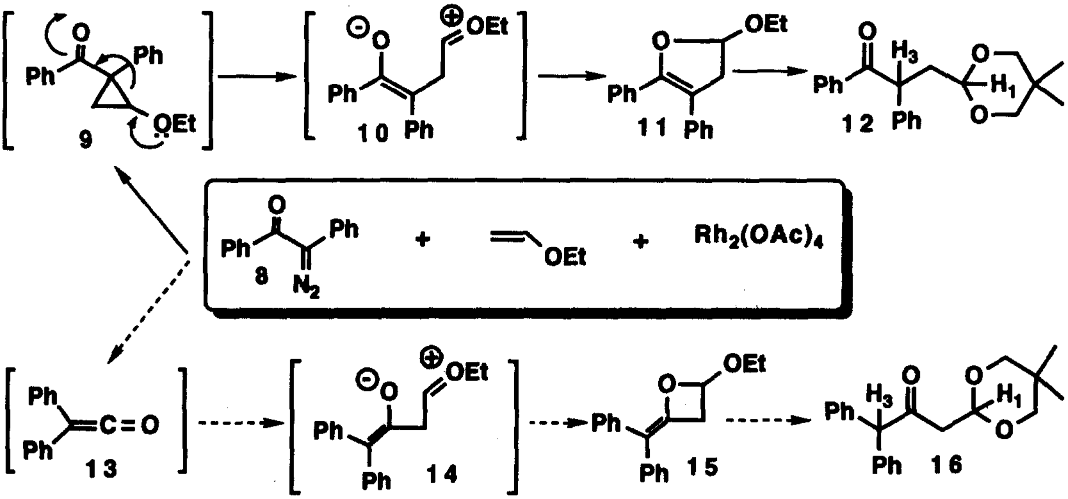
In connection with a synthetic approach we are developing[1] to the potent anti-tumor agent taxol,[2,3] α-diazoketone **3** was prepared from Hagemann's ester (**1**) by the reduction, oxidation, conjugate addition, enolate trapping-diazo transfer sequence illustrated. Treatment of **3** with $Rh_2(OAc)_4$ (2 mol %, 21 °C) in the presence of excess ethyl vinyl ether afforded neither the expected cyclopropylcyclohexanone **4** nor the cyclobutanone **5** that would have arisen from Wolff rearrangement followed by conventional [2 + 2] cycloaddition. Instead, a new compound was isolated that contained two tertiary vinyl carbons (^{13}C NMR δ 102.4, 148.3 ppm), an acetal carbon (δ 104.6) and an attached proton (^1H NMR δ 5.45 ppm). These features were consistent with both the oxetane structure **6** and the dihydrofuran system **7** which could have arisen from ring opening-rearrangement of



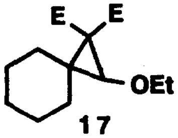
(a) DIBAL, C_6H_6, 0°C, 2h, 96%; (b) DDQ, dioxane, 25°C, 24h, 92%; (c) TBDMSCl, imidazole, DMF, 24h, 95%;
(d) Me_2CuLi, ether, 0°C, 1.5h, HCO_2Et, 0.5h; (e) Et_3N, TsN_3, CH_2Cl_2, -15° to +21°C, 2h, KOH(aq), 15min, 20% from 2
DIBAL = Diisobutylaluminium hydride; DDQ = 2,3-Dichloro-5,6-dicyanoquinone; DMF = Dimethylformamide;
TBDMSCl = t-Butyldimethylsilylchloride.

the intermediate cyclopropyl ketone **4**. In spite of the visual difference between these ring systems various NMR experiments were inconclusive and standard hydrolytic and oxidative cleavage reactions gave mixtures. Thus establishing the structure unambiguously with only one compound available required acid catalyzed hydrolysis and *in situ* trapping of the resulting keto-aldehyde.

Discrete ketene carbonyl cycloadditions are rare. The two previously reported cases involved strong electron withdrawing groups in the ketene (the reaction of bis(trifluoromethyl)ketene with vinyl benzoate)[4] or sterically hindered ethers (diethylketene with the silyl enol ether of pinacolone).[5] In addition, *ab initio* molecular orbital calculations considered alkene addition to the ketene carbonyl to be energetically disfavoured relative to cyclobutanone formation.[6]



Direct pathways to the dihydrofuran **11** or the oxetane **15** from the diphenyl diazoketone **8**[7] are feasible after initial reaction of the carbenoid intermediate. Both of these products may arise from the intermediacy of 1,3-zwitterions such as **10** and **14** which posses both enolate and oxacarbenium character. Generally cyclopropanes with single electron donating and electron withdrawing groups (*e.g.*, 1-ethoxy-2-carboethoxycyclopropane) are stable at room temperature and require more forcing conditions for rearrangement . Thus, direct rearrangement usually requires either two donor or two acceptor groups. The ease with which the initial cyclopropane undergoes a 1,3-sigmatropic shift is therefore both substituent and substrate dependent.[8] For example, the spirosystem **17** may be isolated, but the related cyclopropane **18** was not detected when dimethyl diazomalonate reacted in the presence of copper.[9] Other methoxy cyclopropanes also rearranged more readily than the corresponding ethoxy substituted isomers.[10] However, the reaction conditions markedly influence the course of diazo rearrangements, particularly solvent polarity (pentane versus CH_2Cl_2)[11] and the catalyst ($Rh_2(OAc)_4$ versus $Rh_2(OPiv)_4$).[12] Cyclopropanated 2,3-dihydrofurans were the presumed intermediates generated from cyclic diazo-β-diketones in the presence of furans and rhodium carboxylate salts.[13] In the case of **3**, the major product from the reaction with ethyl vinyl ether was independent of the catalyst. Reaction with $Pd(OAc)_2$ or CuCl afforded the acetal product in isolated yields of 72% and 30% respectively, while the cyclopropyketone **19** was isolated in 65% yield with $Rh_2(OAc)_4$ and 2,5-dihydrofuran.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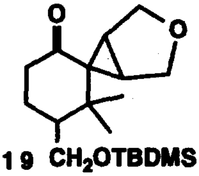
E = CO_2Me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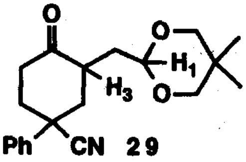
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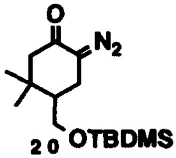
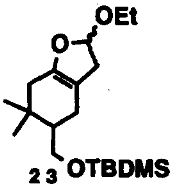
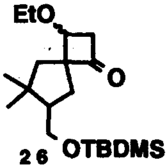
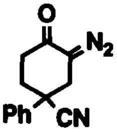
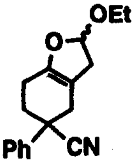
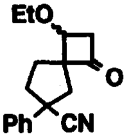
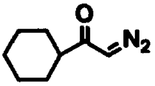
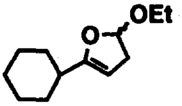
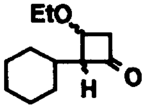
The cyclic α-diazoketones **20**, **21** and the acyclic systems **8** and **22** displayed similar behaviour with ethyl vinyl ether and metal catalysts to afford acetals **23-28** and **11** whose dihydrofuran structures were established as follows. Treatment of **11** with *p*-toluenesulfonic acid in the presence of 3,3-dimethyl-1,3-propanediol generated a keto-acetal that, on the basis of its NMR features, was assigned structure **12** rather than the isomer **16**. (H_1 δ 4.92 coupled to both the adjacent methylene protons plus H_3, a relationship that does not occur in **16**)[14] Compound **29** derived from **24** displayed similar characteristics.[15]

Table: Metal Catalyzed and Direct Photochemical Reactions in Ethyl Vinyl Ether

Substrate	Catalyst	Yield[a]	Dihydrofuran	Photolysis Yield	Cyclobutanone
3	$Rh_2(OAc)_4$ $Pd(OAc)_2$ CuCl	70% 72% 30%	7	88%	5
 20	$Rh_2(OAc)_4$ $Pd(OAc)_2$ CuCl	75% 72% 35%	 23	88%	 26
 21	$Rh_2(OAc)_4$ $Pd(OAc)_2$ CuCl	40% 36% 10%	 24	60%	 27
 22	$Rh_2(OAc)_4$ $Pd(OAc)_2$	[b]71% [b]37%	 25	80%	 28

[a] Isolated Yield [b] GC Yield

The use of benzophenone as a triplet sensitizer during the photolysis of α-diazo ketones is known to promote cyclopropane formation,[16] although a large excess of sensitizer is required.[17] It was hoped these mild conditions would allow detection of the cyclopropane. Benzophenone (10 equiv.) sensitized photolysis of **3** failed to provide the cyclopropane **4**. A mixture of cyclobutanone **5** (30%) and dihydrofuran **7** (25%) was formed instead. This result was surprising since Wolff rearrangement is considered to arise only from the singlet carbene.[17,18] Upon direct irradiation, no acetals could be detected and clean conversion to the cyclobutanones **5**

26, **27**, and **28** from [2 + 2] cycloaddition to the ketene double bond was observed. Decomposition of **8** under various conditions ($Rh_2(OAc)_4$, pentane:ethyl vinyl ether, 30:1, 0 °C; $Rh_2(OPiv)_4$, pentane:ethyl vinyl ether, 30:1, 0 °C)[11,12] known to promote cyclopropanation also afforded **11** as the major product. A similar result was obtained with $Rh_2(OAc)_4$ in ethyl vinyl ether at -78 °C.[19]

The formation of these dihydrofurans could be considered concerted 1,3-dipolar cycloadditions but this has been shown to be unlikely in metal catalyzed systems.[20] Rather cyclopropanation of enol ethers, followed by rearrangement, has been established as the preferred pathway.[10,21-23] This is consistent with the behaviour of the α-diazoketones above, although the mild conditions (21 °C or less) for the rearrangement are noteworthy.

In summary, spontaneous dihydrofuran formation from α-diazoketones usually requires diactivated cyclopropyl carbonyl systems. This mild route from cyclic α-diazoketones via monoactivated cyclopropyl ketones provides an attractive sequence to generate compounds for further synthetic manipulation in view of the widespread occurrence of five-membered oxygen-containing heterocyclic ring systems in nature.[24]

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(14) **12** key signals ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.92 (dd, 1H, J = 7.8, 7.0 Hz, HC-acetal), 4.31 (dd, 1H, J = 5.6, 4.9 Hz, HC-Ph), 2.60 (ddd, 1H, J = 13.8, 7.9, 5.8 Hz, HC-CH_2-CH), 2.15 (ddd, 1H, J = 13.8, 6.8, 4.8 Hz,HC-CH_2-CH).
(15) **29** key signals ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.58 (dd, 1H, J = 5.8, 3.9 Hz, HC-acetal), 3.25 (m, 1H, H-C-C=O), 2.33 (m, 1H, HC-CH_2-CH), 1.45 (m, 1H, HC-CH_2-CH).
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(19) Cyclopropanation is favoured by non polar solvents (pentane)[11] and catalysts such as $Rh_2(OPiv)_4$.[12] At temperatures below 0 °C the pentane solution became heterogeneous and the results were inconclusive. The polarity of ethyl vinyl ether appears to encourage rearrangement since GC-MS analysis of the total reaction at -78 °C (diethyl ether) indicated the presence of a minor component (~10%) consistent with the cyclopropane **9** but it could not be isolated and rigorously identified.
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