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OXYGEN TRANSFER DURING THE COPPER INDUCED REACTION OF α,β-EPOXY DIAZOMETHYL KETONES

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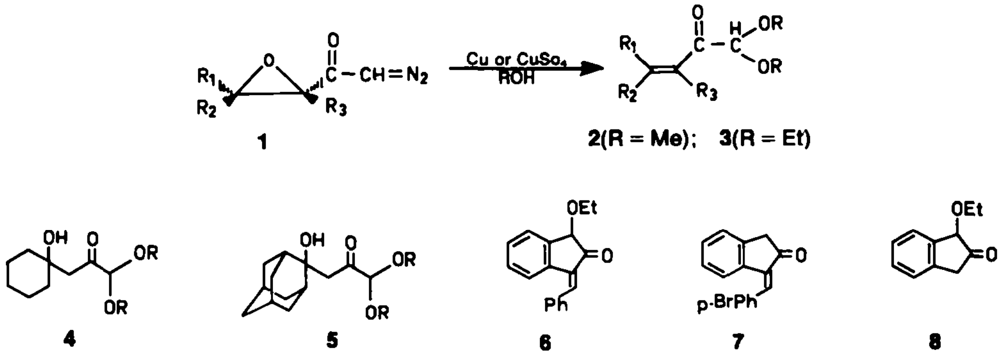
Abstract—Reactions of α,β-epoxy diazomethyl ketones **1a–i** with activated copper powder or copper(II) sulfate in methanol (or ethanol) lead to 1,1 - dialkoxy - but - 3 - ene - 2 - ones **2** (or **3**) in good yields. This process of oxygen transfer proceeds *via* initially generated keto-carbenoids which react intramolecularly with the epoxide function to give bicyclic intermediates **10**. Release of strain and subsequent ring opening produces but - 3 - ene - 1,2 - diones which acetalise to give the ultimate reaction products **2** (or **3**). With copper as catalyst byproducts were isolated, *viz* 1,1 - dialkoxy - 4 - hydroxy - butane - 2 - ones (**4** and **5**), and indanone derivative **6**. An explanation for these side reactions has been given.

Epoxy diazomethyl ketones **1** are of interest as they enable the study of intramolecular interactions as well as selective transformations of the epoxide and the diazoketone function. These compounds are now readily available by the reaction of glycidic carbonic anhydrides[1,2] or glycidyl chlorides[2] with diazomethane and by Darzens condensation of 3 - chloro - 1 - diazopropanone with aromatic aldehydes.[3,4] In a previous report[1] we showed that epoxy diazomethyl ketones selectively react with hydrogen chloride in ether at the diazoketone moiety, whereas with boron trifluoride etherate[5] a selective reaction takes place at the epoxide function. Photochemical triggering of the diazoketone group leads to ketocarbenes that undergo a Wolff rearrangement to epoxyketenes.[6] During irradiation in benzene these reactive intermediates cyclise to butenolides,[6] while in methanol these ketenes solvolyse to γ-hydroxycrotonates.[6]

The use of metal catalysts in the reaction of diazoketones is recognized as a general method to generate ketocarbenes, or rather ketocarbenoid species, of which the proclivity to undergo a Wolff rearrangement is suppressed. By performing the reaction in an alcoholic medium diazomethyl ketones are usually converted into alkoxymethyl ketones.[7] It is also known that a carbethoxycarbenoid can de-oxygenate epoxides.[8] The aim of the present study is to establish whether a selective reaction of the diazoketone moiety in α,β-epoxy diazomethyl ketones **1** with copper and copper salts can be accomplished.

Treatment of **1a** with activated copper in refluxing methanol for 3 hr gave 1,1 - dimethoxy - 4 - phenyl - 3 - buten - 2 - one **2a** in a yield of 74% (Scheme 1, Table 1). The structure of this product is based on the spectral data which are in full accordance with those reported in literature.[4]† Similarly, diazoketone **1a** gave in refluxing ethanol diethoxy analogue **3a** (80%). This product was derivatised by a Michael addition with *p*-toluenesulfinic acid to give 1,1 - diethoxy - 4 - phenyl - 4 - *p* - tolylsulfonyl - butan - 2 - one whose m.p. and spectral features were identical with those reported by Schank *et al.*[9] Substrate **1b** reacted with copper to give products **2b** and **3b**, respectively, in moderate yields. However, when anhydrous copper sulfate was used as catalyst cleaner reactions and better yields were obtained (see Table 1). The results with other epoxy diazomethyl ketones are collected in Table 1.

In some cases byproducts were isolated when copper was used as catalyst. Substrate **1e** gave, besides **2e**, also γ-hydroxy compound **4**. Similarly, **1g** led to **2g** and **5**. The structures of **4** and **5** were apparent from their spectra (Experimental). An entirely different type of an additional product was obtained by treatment of **1b** with



Scheme 1.

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†The same product **2a** was obtained by Woolsey and Khalil[4] by refluxing epoxy diazomethyl ketone **1a** in methanol for 48 hr. These authors suggest that a ketocarbene is not intermediate in this thermolysis reaction.

Table 1.

Starting Material				Products	
	R_1	R_2	R_3	with Cu/ROH	with $CuSO_4$/ROH
1a	H	Ph	H	2a (3 hr, 74%), 3a (3 hr, 80%)	
1b	H	Ph	Ph	2b (1 hr, 45%), 3b (1 hr, 44%)*	2b (1 hr, 65%), 3b (1.5 hr, 72%)
1c	Ph	H	Ph		2b (2 hr, 56%)
1d	H	H	Ph_2CH	2d (1 hr, 87%), 3d (1 hr, 78%)	
1e	$-(CH_2)_5-$		H	2e (4 hr, 32%)**	2e (1.5 hr, 57%)
1f	$-(CH_2)_4-$		H		2f (1 hr, 46%)
1g			H	2g (3 hr, 35%)***	2g (1.5 hr, 80%)
1h	H	Ph	p-MePh	3h (6 hr, 42%)	
1i	Me	Me	Ph	3i (5 hr, 21%)	2i (1 hr, 61%)

All reactions were performed in refluxing alcohol ROH.

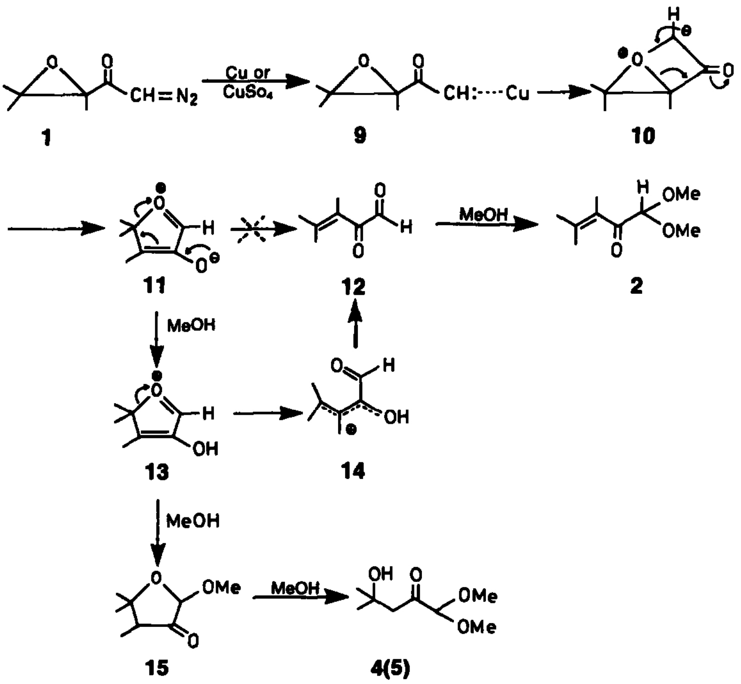
* Along with 6 (35%).

** Along with 4 (43%).

***Along with 5 (16%).

copper in refluxing ethanol. In a yield of 35% a yellow compound was isolated (besides **3b**) to which structure **6** was assigned on the basis of a correct elemental analysis and the following spectral data: IR ν_{max}^{KBr}: 1708 (C=O), 1625 (C=C) cm^{-1}; *m/e*: 264 (M^+); ^{1}H-NMR ($CDCl_3$): δ 1.22 (t, 3 H, $CH_2C\underline{H}_3$); 3.50–4.17 (m, 2 H, $C\underline{H}_2CH_3$), 4.78 (s, 1 H, methine proton), 6.96–7.75 (m, 10 H). In the latter multiplet the signal of an olefinic proton was hidden as was revealed by using shift reagent Pr(fod)$_3$. These spectral features were compared with those of related compounds **7** (ν_{max}^{KBr} 1730, 1625 cm^{-1})[10] and **8** [ν_{max} 1755 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3 H, $CH_2C\underline{H}_3$), 3.27–4.22 (m, 2 H, $C\underline{H}_2CH_3$), 4.79 (s, 1 H, methine proton)]. Furthermore, on catalytic hydrogenation with Pd(C)/H_2 one equiv. of hydrogen was taken up; the resulting reduced product showed a CO absorption at 1755 cm^{-1}.

The results described above clearly reveal that both the diazoketone and epoxide function are involved in these copper and copper sulfate catalysed reactions of epoxy diazoketones. The products formed can be rationalized as is pictured in Scheme 2. Intramolecular reaction of the initially formed electrophilic carbenoid **9** with the epoxide function leads to bicyclo intermediate **10** which conceivably releases strain to give intermediate **11**. Subsequent ring opening gives unsaturated α-oxoal-



Scheme 2.

dehyde **12** which then acetalises rapidly under the conditions of the reaction.[4] However, this reaction sequence does not take into account that the diasteromeric substrates **1b** and **1c** lead to the same product **2b** when treated with copper sulfate in methanol. This stereochemical result can be understood by invoking a stepwise non-synchronous solvolysis of **11**. Protonation of **11** by methanol produces **13** which then opens to mesomeric cation **14**. In the latter species isomerisation at C_4 can be readily envisaged. Loss of a proton again leads to α-oxoaldehyde **12**. Although a direct conversion of **11** to **12** with product isomerisation afterwards cannot be excluded, the route *via* **13** and **14** is preferred.

The γ-hydroxy compounds **4** and **5** most likely arise from reaction of oxononium intermediates **13** with methanol at C_1 to give mixed acetals **15** which then undergo a transacetalisation with methanol to the products isolated. An alternative, *viz* Michael addition of water to **2**, was ruled out by the complete recovery of **2e** and **2g** from an attempted reaction with water/methanol in the presence of activated copper. It should also be noted that the hydroxy compounds **4** and **5** are stable under the conditions of the reaction, no conversion to alkene oxoacetals **2** was observed.

From the structure of indanone derivative **6** it is apparent that its formation involves an intramolecular electrophilic aromatic substitution of the C_3-phenyl group. Probably, the required electrophilic precursor $PhCH{=}CPhC({=}O)CH{=}\overset{\oplus}{O}Et$ is formed from **12** by reaction with ethanol. In a separate experiment it was ascertained that the acetal **3b** under the condition of the reaction (or by catalysis with an acid such as *p*-toluenesulfonic acid) does not cyclise to **6**.

In summary, epoxy ketocarbenoids generated from epoxy diazomethyl ketones with copper undergo an intramolecular oxygen transfer to give alkene oxoacetals as the ultimate products.

EXPERIMENTAL

All m.ps are uncorrected and were determined on a Reichert m.p. microscope. IR Spectra were run on a Perkin-Elmer 257 grating spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 using TMS as internal standard. Elemental analyses were carried out by Mr. J. Diersmann (Micro Analytical Department of our University). α,β-Epoxy diazomethyl ketones were prepared as described in the accompanying paper.[2] Anhydrous $CuSO_4$ was dried at 110° for 2 hr prior to use. Activated copper powder was prepared according to Vogel.[11]

Reactions of epoxy diazomethyl ketones **1** *with* $CuSO_4$ *or activated* Cu.

General procedure. A soln of **1** (1–2 mmole) in MeOH (or EtOH) (25 ml) containing $CuSO_4$ (200 mg) (or activated Cu powder, 200 mg) was heated at reflux. The progress of the reaction was followed by concentrating an aliquot at intervals and recording an IR spectrum. When the diazo absorption had disappeared the reaction was complete. After cooling, filtration and removal of the solvent the residue was chromatographed on silicagel using dichloromethane as eluent. Most products **2** were obtained as oils. Compounds **2b** and **2d** were crystallised from EtOH (correct elemental analyses were obtained). The respective reaction times and yields are collected in the Table. The spectral features read as follows. [IR: ν(C=O), ν(C=C); ^{1}H-NMR: C_1-H, olefinic H, remaining prot.]: **2a**: IR (neat): 1660–1690, 1600 cm^{-1}; ^{1}H–NMR (CCl_4): δ 4.49 (s, 1 H), 6.98 + 7.69 (ABq, 2 H, J 17 Hz), 3.44 (s, 6 H), 7.05–7.80 (m, 5 H). **2b**: IR (KBr): 1690, 1600 cm^{-1}; NMR ($CDCl_3$): δ 4.95 (s, 1 H), 7.89 (s, 1 H), 3.37 (s, 6 H), 6.87–7.58 (m, 10 H). **2d**: IR (KBr): 1670, 1620 cm^{-1}; NMR (CCl_4): δ 4.67 (s, 1 H), 5.48 (s, 2 H), 6.60 (s, 1 H), 3.34 (s, 6 H), 6.80–7.33 (m, 10 H). **2e**: IR (neat): 1690, 1620 cm^{-1}; NMR (CCl_4): δ 4.22 (s, 1 H), 6.12 (s, 1 H), 3.35 (s, 6 H), ~1.4–2.8 (m, 10 H). **2f**: IR (neat): 1690, 1620 cm^{-1}; NMR (CCl_4): δ 4.28 (s, 1 H), 6.44 (br. s, 1 H), 3.33 (s, 6 H), 1.40–3.0 (m, 8 H). **2g**: IR (neat): 1680, 1610 cm^{-1}; NMR (CCl_4): δ 4.25 (s, 1 H), 6.25 (s, 1 H), 3.35 (s, 6 H), 1.63–2.15 (m, 12 H), 2.41 (br. s, 1 H), 4.10 (br. s, 1 H). **2i**: IR (neat): 1690, 1600 cm^{-1}; NMR ($CDCl_3$): δ 4.43 (s, 1 H), 1.66 (s, 3 H), 2.05 (s, 3 H), 3.18 (s, 6 H), 7.03–7.44 (m, 5 H).

3a: IR (neat): 1690, 1620 cm^{-1}; NMR (CCl_4): δ 4.61 (s, 1 H), 7.00 + 7.70 (ABq, 2 H, J 15 Hz), 1.23 (t, 2x 3 H), 3.18–4.04 (m, 2x 2 H), 7.10–7.75 (m, 5 H). **3b**: IR (neat): 1670–1700, 1610 cm^{-1}; NMR (CCl_4): δ 4.80 (s, 1 H), 7.78 (s, 1 H), 1.22 (t, 2x 3 H), 3.13–3.97 (m, 2x 2 H), 6.72–7.45 (m, 10 H). **3d**: IR (neat): 1670, 1600 cm^{-1}; NMR (CCl_4): δ 4.71 (s, 1 H), 5.44 (s, 2 H), 1.15 (t, 2x 3 H), 3.14–3.90 (m, 2x 2 H), 6.65 (s, 1 H), 7.10 (br. s, 10 H). **3h**: IR (neat): 1680, 1600 cm^{-1}; NMR ($CDCl_3$): δ 4.93 (s, 1 H), 7.77 (s, 1 H), 1.18 (t, 2x 3 H), 3.19–3.84 (m, 2x 2 H), 2.33 (s, 3 H), 6.89–7.50 (m, 9 H). **3i**: IR (neat): 1690, 1600 cm^{-1}; NMR ($CDCl_3$): δ 4.57 (s, 1 H), 1.09 (t, 3 H), 1.67 (s, 3 H), 2.04 (s, 2x 3 H), 3.13–3.70 (m, 2x 2 H), 6.84–7.50 (m, 5 H).

Reaction of **1b** *with* Cu *in* EtOH. A soln of **1b** (500 mg, 1.9 mmole) in abs EtOH (400 ml) containing freshly activated Cu-powder (150 mg) was refluxed for 1 hr. After filtration and concentration the residue was chromatographed on plates (SiO_2, CH_2Cl_2). The upper band gave after extraction with ether solid **6** (175 mg, 35%), m.p. *ca* 115° (light yellow crystals from EtOH–H_2O). (Found: C, 81.64; H, 5.96; Calc. for $C_{18}H_{16}O_2$: C, 81.82; H, 6.06%) Spectra see text. The lower band gave after extraction with ether oily **3b** (259 mg, 44%), spectra *vide supra*.

Catalytic reduction of indanone **6**. A soln of **6** (153 mg) in MeOH (25 ml) to which a small amount of Pd(C) was added, was exposed to H_2 (1 atm) for 1 hr; slightly more than one equiv of H_2 was consumed. Work-up gave a colourless oil (141 mg), IR ν_{max}: 1755 (C=O) cm^{-1}, no absorption of a C=C band.

1 - *Ethoxy - indane* - 2 - *one* (**8**). 2 - Bromo - indane - 2 - ol[12] (21.3 g, 0.10 mole) was added to a soln of NaOEt (from 2.5 g Na) in EtOH (50 ml). The reaction mixture then was heated under reflux for 16 hr (under N_2). Evaporation of solvent gave a residue which was extracted with ether. The ether soln was washed (H_2O) and dried ($MgSO_4$) and concentrated. The residue was distilled, b.p. 112–116°/1 mm Hg, yield 8.24 g (47%). ^{1}H-NMR ($CDCl_3$): δ 1.28 (t, 3 H, $CH_2C\underline{H}_3$), 2.35 (s, 1 H), OH), 2.48–3.50 (d of q, 2 H, $C\underline{H}_2$), 3.75 (q, 2 H, $C\underline{H}_2CH_3$), 4.22–4.77 (m, 2 H, methine H's), 6.93–7.42 (m, 4 H).

Oxidation to **8**. CrO_3 (3.0 g, 30 mmole) was added to a soln of pyridine (4.75 g) in CH_2Cl_2 (75 ml), after stirring for 15 min a soln of 1-ethoxy-indanol-2 (980 mg, 5.0 mmole) in CH_2Cl_2 (5 ml) was added. After stirring for 15 min, extraction with ether (50 ml) and washing of the ether extracts with 5% NaOH aq (3 × 50 ml), 5% HCl aq (50 ml), 5% $NaHCO_3$ aq (50 ml), satd NaCl aq (50 ml), drying ($MgSO_4$) and concentration an oil was obtained (644 mg). Tlc (SiO_2, CH_2Cl_2) gave **8** (253 mg, 29%); spectra see text.

Reaction of **1e** *with* Cu *in* MeOH. A soln of **1e** (367 mg, 2.15 mmole) in MeOH (25 ml) containing freshly activated Cu-powder (200 mg) was heated under reflux for 4 hr. Filtration and removal of solvent gave a residue which was chromatographed (SiO_2, CH_2Cl_2) affording **2e** (138 mg, 32%). Elution with CH_2Cl_2–ether 1:1 gave **4** as an oil (200 mg, 43%); IR (neat): ν_{max} 3520–2560 (OH), 1730 (C=O) cm^{-1}; ^{1}H–NMR (CCl_4): δ 0.70–1.80 (m, 10 H), 2.56 (s, 2 H, CH_2), 3.04 (br. s, 1 H, OH), 3.35 (s, 6 H, 2x Me), 4.20 (s, 1 H, C–$\underline{H}$).

Reaction of **1g** *with* Cu *in* MeOH. A soln of **1g** (300 mg, 1.3 mmole) in MeOH (40 ml) containing freshly activated (Cu-powder (150 mg) was heated under reflux for 3 hr. Work-up (*vide supra*) and chromatography (alumina, CH_2Cl_2) gave a 1:1 mixture of **2g** and **5** (265 mg, 79%). Crystallization from petroleum ether (60–80) gave **5** (55 mg, 16%), m.p. 60–60.5°; IR ν_{max}^{KBr}: 3540 (OH), 1720 (C=O) cm^{-1}; ^{1}H–NMR (CCl_4); δ 1.19–2.59 (m, 14 H), 2.90 (s, 2 H, CH_2), 3.30 (br. s, 1 H, O$\underline{H}$), 3.40 (s, 6 H, 2x Me), 4.20 (s, 1 H, C–$\underline{H}$). (Found: C, 69.20; H, 8.94; Calc. for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01%) From the mother liquor, thick layer chromatography (SiO_2, CH_2Cl–ether 10:1) gave oily **2g** (111 mg, 35%).

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