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CYCLOPROPANATION REACTIONS WITH α,β-EPOXY DIAZOMETHYL KETONES AND REARRANGEMENT OF α,β-EPOXY CYCLOPROPYL KETONES

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Abstract—The cyclopropanation reactions of α,β-epoxy diazomethyl ketones **1** with olefins using $Pd(OAc)_2$ as catalyst is described. Differently substituted epoxy diazo ketones **1a-f** give with cyclohexene *exo*-norcarane derivatives. 3, 3-Diphenyloxiranyl-2 diazomethyl ketone **1a** reacts with olefins like isobutene, *E*- and *Z*-butene-2 to give epoxy cyclopropyl ketones. 3, 3-Diphenyloxiranyl-2 cyclopropyl ketones **2a** and **9** undergo two consecutive rearrangement reactions with BF_3 as catalyst. In the first step an epoxide rearrangement of **9** takes place to give β-ketoaldehyde **10**, which in a second step rearranges to enolester **12**. The latter reaction is most likely restricted to β-ketoaldehydes which have a quaternary α-C atom. A rationale for this unusual reaction has been proposed.

IN THE course of our study of selective transformations with α,β-epoxy diazomethyl ketones we previously showed that a primary reaction at the diazomethyl ketone moiety takes place upon treatment with light[1] or proton acids,[2,3] whereas a Lewis acid preferentially reacts with the epoxide function.[4] Reaction of epoxy diazo ketones with copper bronze or copper sulfate in an alcoholic solvent led to the formation of the acetal of α-oxo-β,γ-unsaturated aldehydes by an intramolecular interaction of initially formed epoxyketocarbenoid with the epoxide O atom.[5]

The objective of the present investigation is to generate and to trap a ketocarbenoid species without disturbing the epoxide function. Cyclopropanation with alkenes is most appropriate for this purpose. The products that will result from such a cyclopropanation are ketones in which the CO group is flanked by an epoxide and a cyclopropyl ring. Of such epoxyketones only one example was reported so far.[6]

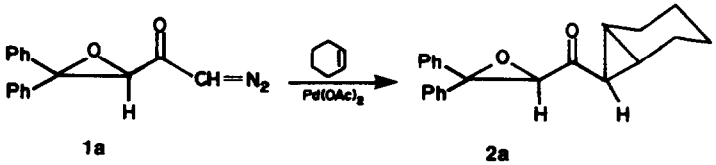
Cyclopropanation was first attempted by reacting epoxy diazo ketone **1a** with copper sulfate in the presence of a large excess of cyclohexene. However, no desired cyclopropane derivative could be detected. Besides resinous material only 20% of the butenolide 5,5-diphenyl-furan-2(5H)-one, arising from a Wolff rearrangement and subsequent cyclization,[1] was isolated.

In view of the report of Paulissen[7] who obtained excellent cyclopropanation reactions with ethyl diazoacetate using $Pd(OAc)_2$ as catalyst, epoxy diazo ketone **1a** was refluxed in cyclohexene containing 1 mole % of $Pd(OAc)_2$. After work-up a colourless crystalline compound was obtained in a yield of 53.5%, which was characterized as the desired norcarane derivative **2a** (Scheme 1). Spectral data reveal the presence of only one diastereomer to which the *exo*-structure was assigned.

To acquire some information about steric and electronic influences of the olefinic reactant a variety of alkenes was subjected to cyclopropanation with compound **1a**. The resulting product mixtures were rather complex and the epoxy cyclopropyl ketones had to be isolated by thick layer chromatography. The yields were moderate in most cases (Table 1). At least two factors contribute to the complexity of the reaction mixtures. Firstly, the reaction times required for complete conversion of the diazo compounds are rather long, during which decomposition of the diazo substrates cannot be prevented. Secondly, as will be shown below the resulting products undergo a thermal rearrangement. In most cases the epoxy cyclopropyl ketones were obtained as mixtures of diastereomers (with cyclohexene only the *exo*-isomer was formed). Separation of diastereomeric pairs could only be accomplished for the adduct **7**, arising from isobutene, while one of the isomeric products **9** (from *Z*-butene-2) could be obtained pure. The diastereomeric composition could be deduced from ^{1}H-NMR spectra for the products **5**, **7**, **8** and **9**. The results obtained for *E*- and *Z*-butenes reveal that the alkene geometry is retained in the cycloadduct, suggesting[8] the formation of the cyclopropyl ring through a singlet carbenoid species.

Steric hindrance probably is responsible for the failure of the cyclopropanation with 2, 3-dimethylbutene-2 (see Ref. 9). An electron-rich olefin as exemplified by isopropenyl acetate also does not react.

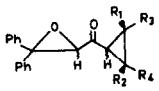
Cyclopropanation of a series of differently substituted epoxy diazo ketones was performed with cyclohexene as the olefin (Table 2). These reactions were followed by monitoring the diazo absorption in the IR. In all cases only one diastereomer (*exo*) was obtained. Variation of the epoxide substituents hardly affects the yields on epoxy cyclopropyl ketones. When a larger amount of



1a **2a**

Scheme 1.

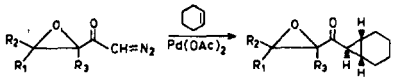
Table 1.



Nr.	R_1	R_2	R_3	R_4	temp. (°C)	time	ratio of diastereomers	yield (%)
2a	$-(CH_2)_4-$	H	H		83	5 h	*exo* only	53.5
3	Ph	H	H		20	10 days	mixt. of 4	16
4	AcO	H	H		80	0.5 h	-	-
5	$-(CH_2)_3-$	H	H		44	6 h	5:1	25
6	Me	Me	Me	Me	73	6 h	-	-
					20	7 days	-	-
7	Me	H	Me	H	85[a]	6 h	1:1	48
8	Me	H	H	Me	85[b]	7 h	1:1	41
9	Me	Me	H	H	85[b]	7 h	1:2	38

a: Reaction in a sealed tube, pressure 10 atm.
b: Reaction in a sealed tube, pressure 5 atm.

Table 2.

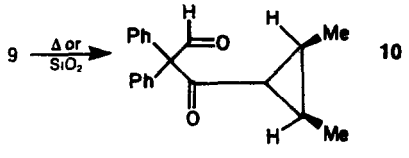


Substrate	R_1	R_2	R_3	time (h)	mol% catalyst	product	yield (%)	m.p. (°C)
1a	Ph	Ph	H	5	1	2a	53.5	124-126
1b	$-(CH_2)_4-$		Me	2.5	1	2b	48.5	31-34
1c	$-(CH_2)_4-$		H	1.5	1	2c	62.5	59.5-61
1d	Ph	Me	Me	5.5	1	2d	38.5	38-39.5
1e	Ph	H	H	0.5	4	2e	33	33.5-35.5
1f	Ph	H	Ph	0.5	4	2f	41	101.5-103

All reactions were performed in refluxing cyclohexene (83°C).

catalyst was used, a considerable acceleration in the consumption of the diazo substrate was observed. However, the yields of adducts did not increase.

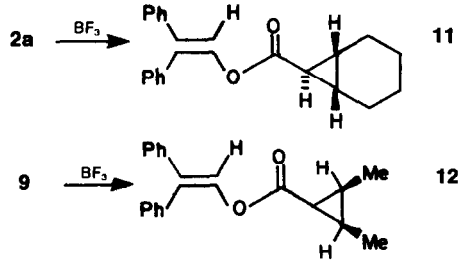
During efforts to separate the diastereomeric cycloadducts **9** a mixture of new diastereomers was obtained. One of the newly formed diastereomers could be isolated by thick layer chromatography (m.p. 60–60.5°) and was assigned structure **10** on the basis of spectral data (Scheme 2). Such a rearrangement of epoxy ketones to 1,



Scheme 2.

3-diketones is frequently encountered.[10] By monitoring this rearrangement by ^{1}H-NMR a half life time of 50 hr at 50° was estimated. Probable a conversion to β-ketoaldehydes as shown in Scheme 2 also occurs during the isolation procedures. Formation of keto aldehydes was observed for the adducts **7**, **8** and **9**, although the amount present in the product mixture was rather small due to their instability under the condition of the reaction and the isolation method.

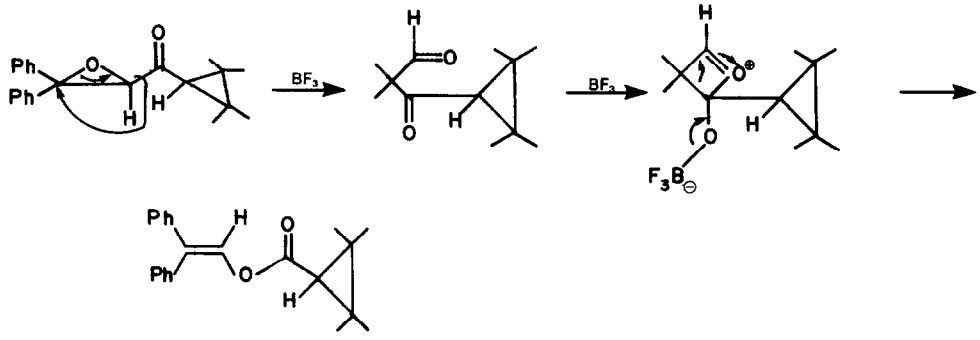
Epoxide rearrangement of the type shown in Scheme 2 also can be induced by a Lewis acid catalyst.[10] However, treatment of epoxy cyclopropyl ketone **2a** with 0.1 equiv of $BF_3.Et_2O$ in benzene did not lead to a β-ketoaldehyde but quantitatively to enol ester **11** instead (Scheme 3).



Scheme 3.

Similarly, the adduct **9** rearranged to enol ester **12**. Unambiguous structure proof was provided by comparing the spectral data of this enol ester with those obtained from the enol ester $Ph_2C{=}CHOC(=O)CH(CH_2)_2$ which was prepared from diphenylacetaldehyde and cyclopropanecarbonyl chloride.[11]

The conversion of epoxy cyclopropyl ketones to enol esters occurs *via* the intermediacy of a β-ketoaldehyde as is apparent from the observation that β-ketoaldehyde **10** rearranged to enol ester **12** upon treatment with $BF_3.Et_2O$. A rationale for the two consecutive rearrangements of epoxy cyclopropyl ketones is pictured in Scheme 4.



Scheme 4.

As stated above the first reaction is an acyl migration commonly observed for epoxy ketones.[10] To explain the second rearrangement complexation of BF_3 with the keto CO function followed by a nucleophilic reaction of the aldehyde oxygen to give a 4-membered ring intermediate must be involved. Only then the necessary C–C bond cleavage can be envisaged. In the literature only one precedent for the conversion of an epoxy ketone to an enol ester was mentioned, namely the formation of 3, 4 - benzo - 5,6 - diphenyl - pyran - (2H)2 - one from 2,3 - diphenyl - 2,3 - epoxy - indanone by BF_3 catalysis.[12] However, no mechanistic explanation has been given.

The rearrangement shown in Scheme 4 was up till now observed for β,β-diphenyl substituted epoxy ketones only. Probably, the presence of a quaternary central C atom in the intermediate 1,3-diketone is required for the rearrangement to enol ester to occur. Otherwise, the formation of an enolic chelate will be favoured.

EXPERIMENTAL

All m.ps are uncorrected and were determined on a Reichert melting point microscope. IR spectra were run on a Perkin–Elmer 257 grating spectrometer. NMR spectra were recorded on a Varian EM-390 or T-60 instrument using TMS as internal standard. Preparative thick layer chromatography (ptlc) was performed with self-made silicagel and alumina plates (20 × 20 cm, thickness 2 mm), or silicagel plates (20 × 20 cm, thickness 0.5 or 2 mm) purchased from E. Merck. Cyclohexene contained 0.1% of hydroquinone as stabilizer. Epoxy diazomethyl ketones were prepared as described previously.[13]

Cyclopropanation reactions of **1a**

With cyclohexene. A mixture of **1a** (264 mg, 1.0 mmole) and $Pd(OAc)_2$ (2 mg, 0.01 mmole) in cyclohexene (50 ml) was heated under reflux for 5 hr. According to tlc all **1a** had reacted. After removal of solvent an oil (365 mg) remained which was subjected to ptlc (SiO_2, 0.5 mm, pentane–ether 2:1). A colourless oil (170 mg, 53.5%) was obtained (**2a**) which crystallized on standing, m.p. 124–126° (from pentane). IR ν_{max}^{KBr}: 1675 (C=O) cm^{-1}; NMR (CCl_4) δ 0.8–2.1 (m, 11H), 3.58 (s, 1H), 7.25 (m, 10H). (Found: C, 82.96; H, 7.07. Calc. for $C_{22}H_{22}O_2$: C, 82.99: H, 6.96%).

With sytrene. A mixture of **1a** (264 mg, 1.0 mmole), $Pd(OAc)_2$ (2 mg), sytrene (5 g, 50 mmole) and CH_2Cl_2 (70 ml) was stirred for 10 days at room temp. Removal of volatiles gave a brown oil (340 mg) from which with ptlc (Al_2O_3, 2 mm, pentane–ether 2:1) an oil (85 mg) was separated consisting of diastereomeric epoxy cyclopropyl ketones **3** contaminated with some benzophenone. IR (neat) ν_{max}: 1685 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 0.7–3.0 (m, cyclopropyl H), 3.92 + 3.95 (2 × s, epoxy H, ratio 3:1), 7.21 (m, arom. H); *m/e*: 340 (M^+).

With isopropenyl acetate. A soln of **1a** (264 mg) in isopropenyl acetate (50 ml) containing $Pd(OAc)_2$ (2 mg) was refluxed for 30 min. Removal of solvent gave a brown oil (425 mg) from which with ptlc no pure product could be obtained.

With cyclopentene. A soln of **1a** (264 mg) in cyclopentene (50 ml containing 2 mg of catalyst) was refluxed for 6 hr. Removal of solvent gave a brown oil (438 mg) which contained **5** in 31% (NMR). With ptlc (Al_2O_3, pentane–ether 2:1) a colourless oil (85 mg) was obtained (diastereomeric mixture of **5**) contaminated with some benzophenone. IR (neat) ν_{max}: 1680 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 0.60–2.03 (m, 9H), 3.80 + 3.84 (2 × s, ratio 1:5), 7.28 (m, 10H).

With 2, 3-*dimethylbutene-2.* Refluxing of **1a** in this olefin (+ $Pd(OAc)_2$) resulted in decomposition, no cyclopropyl ketone could be isolated.

With isobutene. A mixture of **1a** (264 mg), $Pd(OAc)_2$ (10 mg) and isobutene was heated at 80° for 7 hr (autoclave, pressure 10 atm). Removal of excess olefin gave a brown oil (300 mg), containing 48% of **7** as a diastereomeric mixture (NMR). Ptlc (SiO_2, 2 mm, pentane–ether 2:1) gave 140 mg (48%) of oily **7** (isomer ratio 1:1). By careful crystallization from pentane the two diastereomers could be separated.

Isomer **A**: m.p. 74–76.5°; IR ν_{max}^{KBr}: 1678 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 0.61 (s, 3H, CH_3), 0.71 (s, 3H, CH_3), 1.12 (dd, 1H, J_{vic} 5.3 Hz, J_{gem} 3.4 Hz, cyclopropyl methylene H *anti* to methine H), 0.90 (dd, 1H, J_{vic} 8.0 Hz, J_{gem} 3.4 Hz, cyclopropyl methylene H *syn* to methine H), 1.93 (dd, 1H, J_{syn} 8 Hz, J_{anti} 5.3 Hz, cyclopropyl methine H), 3.96 (s, 1H, epoxy H), 7.25 (m, 10H).

Isomer **B**: m.p. 84–85°: IR ν_{max}^{KBr}: 1700 (C=O) cm^{-1}; NMR (CCl_4): δ 1.00 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 0.87 (dd, 1H, J_{vic} 5.3 Hz, J_{gem} 3.5 Hz, cyclopropyl methylene H *anti* to methine H), 0.29 (dd, 1H, J_{vic} 7.5 Hz, J_{gem} 3.5 Hz, cyclopropyl methylene H *syn* to methine H), 1.55 (dd, 1H, J_{syn} 7.5 Hz, J_{anti} 5.3 Hz, cyclopropyl methine H), 3.66 (s, 1H, epoxy H), 7.30 (m, 10H).

With E-*butene-2.* A mixture of **1a** (264 mg), $Pd(OAc)_2$ (10 mg) and *E*-butene-2 (20 ml) was heated in an autoclave at 80° for 7 hr (press. 5 atm). Removal of volatiles gave an oil (343 mg) containing 43% of **8**. Ptlc (SiO_2, 2 mm, pentane–ether 2:1) gave **8** as a mixture of diastereomers (41%), m.p. 70–75° (from pentane). IR ν_{max}^{KBr}: 1675 (C=O) cm^{-1}; NMR (CCl_4): δ 0.2–1.9 (m, 9H), 3.68 + 3.74 (2 × s, ratio 1:1, epoxy H), 7.28 (m, 10H); *m/e*: 292 (M^+). (Found: C, 82.39; H, 7.09. Calc. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90%).

With Z-butene-2. A mixture of **1a** (264 mg), $Pd(OAc)_2$ (10 mg) and *Z*-butene-2 (25 ml) was heated in an autoclave for 7 hr at 85° (press. 5 atm). After work-up an oil containing 38% (NMR) of **9** (mixture of diastereomers) was obtained. Ptlc (SiO_2, pentane–ether 2:1) gave 110 mg of oily **9**, diastereomeric ratio 1:1.7, which crystallized from pentane, m.p. 73.5–78.5°; IR ν_{max}^{KBr}: 1673 (C=O) cm^{-1}; NMR (CCl_4): δ 0.2–1.8 (m, 9H), 0.32 + 0.95 (2 × d, Me integrated with multiplet), 3.64 (s, 1H, epoxy H), 7.30 (m, 10H). *m/e*: 292 (M^+). Found: C, 81.55; H, 6.90. Calc. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90%.

Cyclopropanation reactions of **1b-f** *with cyclohexene*

General procedure. A soln of epoxy diazomethyl ketone (1.0 mmole) in cyclohexene (50 ml) containing $Pd(OAc)_2$ was refluxed for the period indicated in Table 2. After removal of the solvent the residue was chromatographed (ptlc, SiO_2, pentane–ether 2:1) and the product crystallized from pentane at low temp. Spectral data: **2b**: IR (neat) ν_{max}: 1680 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 0.8–2.3 (m, 21H), 1.45 (s, 3H, CH_3). **2c**: IR ν_{max}^{KBr}: 1682 (C=O) cm^{-1}; NMR (CCl_4): δ 1.0–2.2 (m, 21H), 3.03 (s, 1H, epoxy H). **2d**: IR (neat) ν_{max}: 1678 (C=O) cm^{-1}; NMR (CCl_4): δ 1.10–2.10 (m, 10H), 1.01 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.23 (t, 1H, cyclopropyl H), 7.17 (s. 5H, arom. H). **2e**: IR ν_{max}^{KBr}: 1680 (C=O) cm^{-1}; NMR (CCl_4): δ 0.90–2.16 (m, 11H), 3.30 (d, 1H, *J* 1.5 Hz, epoxy H), 3.88 (*d, 1H, J* 1.5 Hz, *epoxy H*), 7.18 (*m*, 5H, arom. H). **2f**: IR ν_{max}^{KBr}: 1680 (C=O) cm^{-1}; NMR (CCl_4): δ 0.70–1.90 (m, 10H), 2.04 (m, 1H, $\diagup$C–H), 4.00 (s, 1H, epoxy H), 7.07–7.73 (m, 10H, arom. H).

2, 2-*Diphenylethenyl*-1 *cyclopropanecarboxylate.* An emulsion of NaH (16.5 mmole) in mineral oil was added to a soln of diphenylacetaldehyde (3.3 g, 16.5 mmole) in ether (50 ml) at 0°. After stirring overnight at room temp the mixture, containing a white ppt, was cooled to 0° and a soln of cyclopropanecarbonyl chloride (2.93 g, 28 mmole) was gradually added. After stirring for 20 min at room temp *i*PrOH and then H_2O was added. The organic layer was washed with H_2O, sat $NaHCO_3$ aq and sat NH_4Cl aq, dried ($MgSO_4$) and concentrated. The resulting oil (4.44 g) was chromatographed (medium pressure liquid chromatography, 18 cm column, ϕ 4 cm, SiO_2-type H60, iPr_2O-hexane 1:10, piston press. 6 atm, eluent press. 5 atm, flow 18 ml/min) affording 2.3 g (53%) of the enol ester as an oil which was crystallized from hexane, m.p. 38.5–40°. IR (neat) ν_{max}: 1735 (C=O), 1632 (C=C) cm^{-1}; NMR ($CDCl_3$): δ 0.75–1.21 (m, 4H), 1.42–1.75 (m, 1H), 7.22 (m, 10H), 7.58 (s, 1H, =CH).

Isomerization of epoxy cyclopropyl ketone **9** *to ketoaldehyde* **10.** A mixture of **9** (140 mg, 0.48 mmole), silicagel (500 mg, type 60H, Merck) and CH_2Cl_2 (10 ml) was stirred at room temp for 5 days. After filtration and concentration oily **10** (130 mg, mixture of isomers) was obtained, crystallization from pentane gave a single isomer, m.p. 78–81°. IR ν_{max}^{KBr}: 1736 (HC=O), 1674 ($\diagup$C=O) cm^{-1}; NMR (CCl_4): δ 0.78 (m, 6H), 1.14 (t, 1H, O=C–C(H)cyclopropyl), 1.54 (m, 2H, cyclopropyl H), 7.28 (m, 10H, arom. H), 9.90 (s, 1H, CH=O).

Formation of enol ester **12** *from ketoaldehyde* **10.** To a soln of **10** (130 mg, 0.45 mmole, mixture of isomers) in CH_2Cl_2 (5 ml) was added 1.0 ml $BF_3.Et_2O$ (1molar) at 0°. After stirring for 15 min sat $NaHCO_3$ aq (25 ml) was added. Extraction with ether (3 × 50 ml), washing with sat $NaHCO_3$ aq and sat NH_4Cl aq, drying ($MgSO_4$) and concentration gave crude **12** (130 mg, oil) which was purified by medium pressure liquid chromatography (28 cm column, ϕ 4 cm, SiO_2 type H60, iPr_2O-hexane 1:4, flow 18 ml/min), yield: 70 mg (54%) oil which crystallized from pentane, m.p. 50–51.5°. IR (neat) ν_{max}: 1735 (C=O), 1635 (C=C) cm^{-1}; NMR (CCl_4): δ 0.91–1.70 (m, 9H), 7.25 (m, 10H, arom. H), 7.58 (s, 1H, =CH–). In addition, some diphenylacetaldehyde (33 mg) was isolated.

Formation of enol ester **11** *from cyclopropyl ketone* **2a.** $BF_3.Et_2O$ (2 drops) was added to a soln of **2a** (90 mg, 0.28 mmole) in benzene (5 ml). After stirring for 10 min at room temp the soln was washed twice with 5% $NaHCO_3$ aq (3 ml). The aq layer was extracted with ether and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting oil (100%) was crystallized from pentane, m.p. 109.5–110.5°. IR ν_{max}^{KBr}: 1730 (C=O), 1635 (C=C) cm^{-1}; NMR (CCl_4): δ 0.90–2.10 (m, 11H), 7.24 (m, 10H, arom. H), 7.47 (s, 1H, =CH–); *m/e*: 318 (M^+). Found: C, 82.79; H, 6.82. Calc. for $C_{22}H_{22}O_2$: C, 82.99; H, 6.98%.

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