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A Novel One-Step Conversion of α,β–Epoxy Ketones to *o*-Dichlorobenzaldehydes by the Vilsmeier Reaction

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Abstract: A novel, versatile one-step synthesis of *o*-dichlorobenzaldehydes has been developed. Acyclic α,β-epoxy ketones undergo the Vilsmeier reaction to afford *o*-dichlorobenzenemono- and dicarboxaldehydes whereas cyclic α,β-epoxy ketones gave *o*-dichlorobenzenecarboxaldehydes and chlorobenzenedicarboxaldehydes.

The wide synthetic potential of the versatile Vilsmeier reaction has been known for years and its utility for achieving different synthetic transformations has been amply demonstrated.[1] Recently the application of this reaction (by our group and others) to acyclic unsaturated ketones,[2] cyclohexenones[3] and methoxy cyclohexadienes[4] has furnished chlorobenzenecarboxaldehydes in all cases. During the course of these studies we decided to investigate the application of this reaction to α,β-epoxy ketones. Though the Vilsmeier reaction has also been applied to epoxides,[5] to the best of our knowledge it had never been studied with α,β-epoxy ketones.

As a continuation of our studies of the Vilsmeier reaction, we wish to report a novel one-step synthesis of *o*-dichlorobenzenecarboxaldehydes with 1,2,3-, 1,2,3,4- and 1,2,3,5-substitution pattern from α,β-epoxy ketones (see table) which are easily accessible from the corresponding α,β-unsaturated ketones by treatment with alkaline hydrogen peroxide.[6] Acyclic α,β-epoxy ketone **1** gave *o*-dichlorobenzenemono- and dicarboxaldehydes **7**[7] and **8**.[8] Compounds **2** and **3** furnished only *o*-dichlorobenzenecarboxaldehydes **9**[8] and **10**[8] respectively. Chlorobenzenedicarboxaldehyde **11**[2] was obtained from **4**. Cyclic α,β-epoxy ketones **5** and **6** afforded *o*-dichlorobenzenecarboxaldehydes **7** and **9** as well as chlorobenzenedicarboxaldehydes **12**[8] and **13**.[2]

Based on the known course of the Vilsmeier Reaction[1] the formation of **9**, **7** and **12** can be rationalized as shown in the scheme. Under the Vilsmeier reaction conditions the α,β-epoxy ketone undergoes ring opening

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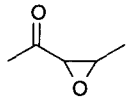
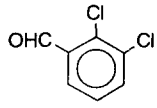
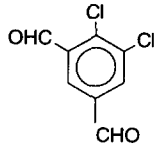
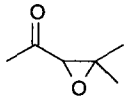
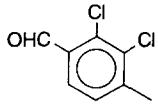
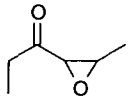
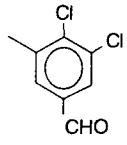
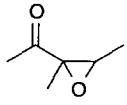
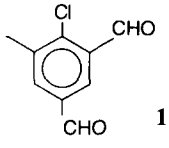
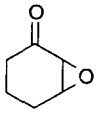
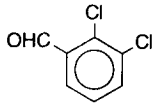
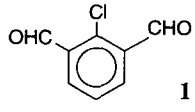
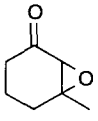
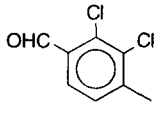
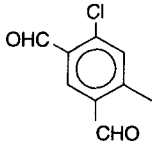
Table: *o*-Dichlorobenzenecarboxaldehydes from α,β-Epoxy Ketones

Entry#	Substrate	Products (Yield%)
I	 **1**	 **7** (18%)  **8** (30%)
II	 **2**	 **9** (45%)
III	 **3**	 **10** (38%)
IV	 **4**	 **11** (24%)
V	 **5**	 **7** (13%)  **12** (24%)
VI	 **6**	 **9** (11%)  **13** (19%)

of the epoxide to give the equivalent of *o*-dichlorodiene species **14** or **15** (X= Cl / $OPOCl_2$). Iminoalkylation of **14** followed by electrocyclisation and hydrolysis then gives the final product **9**. In the case of cyclic systems further iminoalkylation of **16** gives **17** which eliminates HCl to give aromatic species such as **12**.

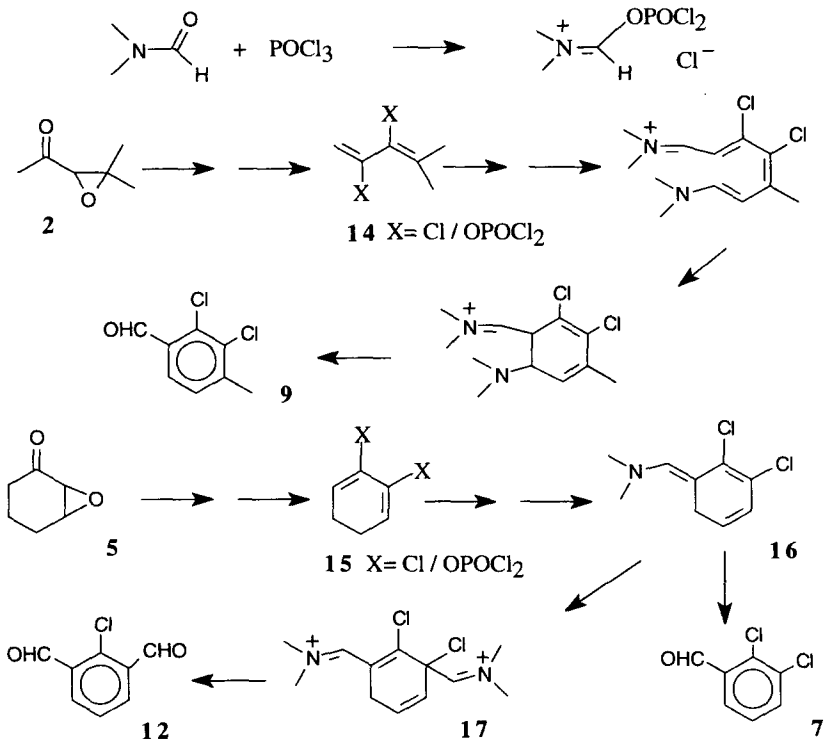
The Vilsmeier reaction of α,β-epoxy ketones shows several notable features:

- the regiospecific opening of the epoxide
- the introduction of two chlorine atoms adjacent to each other
- the introduction of one or more formyl groups and
- the transformation of aliphatic acyclic and cyclic systems to benzenoid compounds.

It is interesting to see that substitution at the α-position in the case of **4** gives exclusively chlorobenzenedicarboxaldehyde **11**. Formation of monochlorobenzenoids **12** and **13** in major amounts in the

case of cyclic epoxy ketones **5** and **6** indicates that further iminoalkylation of **16** followed by elimination of HCl to give product **12** is preferred over its oxidative aromatization to **7**.

Scheme



The noteworthy features of the present investigation are the easy accessibility of the starting materials and the simplicity of the one-step procedure to yield monochloro- and o-dichlorobenzenecarboxaldehydes. The present synthetic procedure is of particular interest in view of the use of o-dichlorobenzenoids in the synthesis of diuretic drugs,[9] herbicides, inhibitors of phenolethanolamine-N-transferase[10] and their occurence in aromatic natural products.[11] Further synthetic applications of the Vilsmeier reaction are currently under investigation in our laboratories.

Vilsmeier reaction on 4-methyl-3,4-epoxypentan-2-one **2**; Typical procedure:

To a cooled (0°C) and stirred solution of the epoxy ketone **2** (1.14g, 10 mmol) in dimethylformamide (10 mL) was added slowly phosphorous oxychloride (3.8 mL, 40 mmol). The reaction mixture was stirred at room temperature for 30 min and maintained on a boiling water bath for 4- 4.5 h. The dark red solution was cooled and poured over crushed ice (20 g). After leaving it aside for 3-4 h, the reaction mixture was extracted with diethyl ether (20 mL X 4) washed with water (20 ml X 2) and dried. Evaporation of the solvent, purification of the residue by using silica gel column chromatography (eluant: petroleum ether / ethyl acetate 10:1) and crystallization (petroleum ether) gave 2,3-dichloro-4-methylbenzaldehyde **9** (0.78g, yield 45%, m.p. 80°C).

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8. All new compounds gave satisfactory C&H analysis.
   Compound **8**: mp 111°C (pet. ether); IR ($CHCl_3$) υ_{max} 1700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ: 10.4 (1H, s, CHO), 9.96 (1H, s, CHO), 8.3 (1H, d, *J*=2Hz, ArH_2), 8.18 (1H, d, *J*=2Hz, ArH_6).
   Compound **9**: mp 80°C (pet. ether); IR (Nujol) υ_{max} 1690 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ: 10.36 (1H, s, CHO), 7.67 (1H, d, *J*=8Hz, ArH_6), 7.2 (1H, d, *J*=8Hz, ArH_5), 2.5 (3H, s, CH_3).; ^{13}C NMR (Bruker 270 MHz, $CDCl_3$) δ: 188.5 (d, CHO), 144.5 (s, Ar1), 135.9 (s, Ar2), 133.6 (s, Ar3), 131.7 (s, Ar4), 128.7 (d, Ar6), 126.4 (d, Ar5), 21.3 (q, CH_3).
   Compound **10**: mp 73°C (pet. ether); IR (Nujol) υ_{max} 1700 cm^{-1}; ^1H NMR (60MHz, $CDCl_3$) δ: 9.9 (1H, s, CHO), 7.78 (1H,d, *J*=2Hz, ArH_2), 7.64 (1H, d, *J*=2Hz, ArH_6), 2.5 (3H, s, CH_3).
   Compound **12**: mp 138-139°C (pet. ether); IR (Nujol) υ_{max} 1680 cm^{-1}; ^1H NMR (60MHz, $CDCl_3$) δ: 10.5 (2H, s, 2x CHO), 8.1 (2H, d, *J*=8Hz, ArH4 & H6), 7.5 (1H, d, *J*=8Hz, ArH5) ; ^{13}C NMR (Bruker 270 MHz, $CDCl_3$) δ: 188.16 (d, CHO), 140.37 (s, Ar1 & Ar3), 134.52 (d, Ar4 & Ar6), 133.21 (s, Ar2), 127.43 (d, Ar5).
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