AN ANOMALOUS COURSE OF THE DARZENS REACTION CATALYZED WITH MAGNESIUM METHOXIDE

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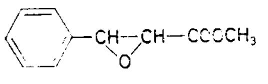
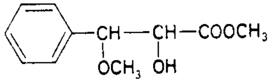
The reaction of benzaldehyde with methyl chloroacetate catalyzed with magnesium methoxide gave beside the expected methyl 2,3-epoxy-3-phenylpropanoate (*I*) also comparable amounts of methyl 2-hydroxy-3-methoxy-3-phenylpropanoate (*II*). The condensation was accompanied by a competing disproportionation of benzaldehyde giving methyl benzoate and benzyl alcohol. The course of the condensation reaction is discussed.

The Darzens condensation[1–4] represents a succesfully adopted method of homologization of carbon chain in synthetic organic and pharmaceutical chemistry[3,6]. This base-catalyzed reaction requires strong bases among which alkali metals and alkali hydrides, alkoxides and amides are the most important. As far as we know, magnesium alkoxides have not yet been used as the basic reagents in Darzens-type condensations, these reagents being useful (due to the chelatation properties of magnesium ion) in some condensation reactions of reactive carbonyl compounds[7–12]. To a limited extent they were adopted in intramolecular Dieckmann condensations of activated esters[13]. This present preliminary communication reports some surprising results of the reaction of benzaldehyde, methyl chloroacetate, and magnesium methoxide studied by us.

The reaction proper was carried out with equimolar amounts of the reactants at three different temperatures in all the cases. In the first case the reaction was carried out at 0–5°C 15 h and the reaction mixture was submitted to column chromatography to give the unreacted benzaldehyde (containing small amounts of methyl benzoate according to GLC analysis) and the expected methyl 2,3-epoxy-3-phenylpropanoate (*I*) in the yield of 9%. Beside that the following unexpected products were isolated in small amounts: methyl 2-chloro-3-hydroxy-3-phenylpropanoate



I



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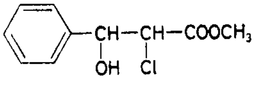

III

(*III*, c. 0·3%), methyl 2-hydroxy-3-methoxy-3-phenylpropanoate (*II*, 1%), and benzyl alcohol (6%). Whereas an increase in reaction temperature to 20 – 22°C had almost no effect on the composition of reaction mixture, at 50°C the reaction was fast and the conversion was complete. The products contained beside the expected epoxyester *I* (yield 29%) and methoxyester *II* (22%) also methyl benzoate (9%) and benzyl alcohol (14%). The chloroester *III* was not detected. These findings agree with earlier studies of mechanism of the Darzens reaction[2,14] which involves a primary attack of the carbonyl group by the respective carbanion giving a reactive intermediate with halogenhydrin structure which was isolated and identified in several cases[3,15,16]. The isolation of ester *III* in our case can be considered to be another support to correctness of the mechanism suggested earlier. It is supposed that the presence of halogenhydrin *III* in the reaction mixture can be ascribed to the mild reaction conditions.

We presumed that also the other unexpected reaction product – methoxyester *II* – was formed by subsequent reaction of epoxyester *I* with magnesium methoxide. An independent experiment really showed that only ester *II* was formed from epoxyester *I* on action of magnesium methoxide at the conditions of the condensation reaction. On the other hand, when using sodium methoxide we obtained a complex mixture of unidentified products from which only methoxyester *II* was isolated in a small amount. It is surprising that formation of such a compound in Darzens-type condensations has not yet been observed, and the compound itself is not described in literature. As the ester *II* is formed in the reaction mixture in comparable amounts like the ester *I*, the rate of oxirane ring opening must be at least the same as that of the condensation reaction itself. A similar regioselectivity in opening of oxirane grouping was observed[17–21] with applications of other nucleophilic reagents too.

Methyl benzoate and benzyl alcohol represent products of disproportionation of the starting benzaldehyde by action of base in the reaction medium. Such disproportionation with application of magnesium methoxide was observed in the case of formaldehyde only[22]. Formation of the above-mentioned products can be explained by the mechanism of both Cannizzaro and Tishchenko reactions. With regard to their complexity[23–27], similarity and different interpretation[28,29], it is very difficult to decide which of the mechanisms will be preferred. By an independent experiment we found that the reaction of benzaldehyde with magnesium methoxide smoothly gave methyl benzoate (yield 39%) and benzyl alcohol (46%) with total conversion of the starting aldehyde. If the Tishchenko reaction were operating, then the reaction mixture would contain at least a small amount of benzyl benzoate (whose subsequent transesterification gives the products mentioned), but its presence was not detected.

Hence the lower basicity of magnesium methoxide as compared with alkali alkoxides substantially changes the course of Darzens condensation. The rate lowering of the condensation proper has the consequence that other competing processes make themselves felt, and from synthetical standpoint application of this base to these condensations has no practical importance. The investigation of mechanism of the disproportionation reaction of benzaldehyde will be dealt with in our next communication.

EXPERIMENTAL

The temperature data are not corrected. The gas chromatography was carried out on a Chrom 5 apparatus (Laboratorní přístroje, Prague), FID, the stationary phase carrier Gaschrom Q. The IR spectra were measured with a Perkin-Elmer 325 apparatus in chloroform. The ^{1}H NMR spectra were measured with a Bruker 400 apparatus in deuteriochloroform using TMS as the internal standard. The mass spectra were measured with a JEOL DX-300 apparatus, the electron energy of 70 eV. Chemicals: Methyl 2,3-epoxy-3-phenylpropanoate[30] (*I*, b.p. 105–106°C/40 Pa) and benzyl benzoate (b.p. 168–170°C/1·6 kPa) were prepared by standard procedures. The methanol used in all the reactions was dried with magnesium. The identity of the known compounds was verified by comparison of their boiling points, IR, ^{1}H NMR, and mass spectra with those of the authentic standards.

Reaction of Benzaldehyde with Methyl Chloroacetate in the Presence of Magnesium Methoxide

Procedure A: During 15 min at 50°C a mixture of 5·0 g (47 mmol) benzaldehyde and 5·1 g (47 mmol) methyl chloroacetate was added dropwise to a solution of magnesium methoxide prepared from 1·15 g (50 mmol) magnesium and 70 ml methanol. After 2·75 h the reaction mixture was decomposed with 100 ml 5% sulfuric acid, diluted with 200 ml water and washed wtih 4 × 75 ml ether. The ethereal solution was washed with saturated aqueous solution of sodium hydrogen carbonate and with water, and dried with anhydrous magnesium sulfate. The solvent was evaporated, and the oily residue (7·5 g) was submitted to column chromatography (silica gel, gradient elution with toluene–ethyl acetate mixture) to give 0·53 g (8%) methyl benzoate, 2·4 g (29%) epoxyester *I*, 2·2 g (22%) methyl 2-hydroxy-3-methoxy-3-phenylpropanoate (*II*), m.p. 61–63°C, and 0·7 g (14%) benzyl alcohol. For compound *II* $C_{11}H_{14}O_4$ (210·2) calculated: 62·85%, 6·71% H; found: 62·58% C, 6·56% H. IR spectrum: 3 680, 3 550, 3 020, 2 965, 2 930, 2 850, 2 835, 1 740, 1 085. ^{1}H NMR spectrum: 2·98 bs, 1 H (OH); 3·31 s, 3 H (OCH_3); 3·68 s, 3 H (OCH_3); 4·46 d, 1 H (CH); 4·50 d, 1 H (CH); 7·20–7·40 m, 5 H (arom.). Mass spectrum: 167/1, 149/3, 121/100 ($C_8H_9O^+$), 105/8, 91/32, 77/37, 65/6, 51/6.

Procedure B: The same reaction carried out at 0°C for 15 h gave, on subsequent chromatography, a mixed fraction of benzaldehyde and methyl benzoate, epoxyester *I* (0·75 g, 9%), methyl 2-chloro-3-hydroxy-3-phenylpropanoate (*III*, 0·08 g, 0·03%), methoxyester *II* (0·22 g, 2%), and benzyl alcohol (0·31 g, 6%).

Reaction of Ester *I* with Magnesium Methoxide

At 0°C, 2·0 g (11 mmol) ester *I* was added to a solution of magnesium methoxide prepared from 0·26 g (11 mmol) magnesium and 20 ml methanol. The reaction mixture was stirred at room temperature 4 days and at 50°C 5 h. The reaction mixture was treated as in the above procedure to give 1·56 g (68%) ester *II* whose all physical data agreed with those of the above-described compound.

Reaction of Benzaldehyde with Magnesium Methoxide in Methanol

A solution of magnesium methoxide prepared from 0·6 g (25 mmol) magnesium and 40 ml methanol was treated with 2·5 g (24 mmol) benzaldehyde and the mixture was stirred at room temperature 6 days, whereupon in was decomposed by addition of 200 ml 3% hydrochloric acid, and washed with 3 × 30 ml ether. The ethereal solution was washed with saturated aqueous solution of sodium hydrogen carbonate, with water, and dried with anhydrous $MgSO_4$. The solvent was evaporated and the residue was submitted to column chromatography (silica gel, chloroform) to give 1·25 g (39%) methyl benzoate and 1·18 g (46%) benzyl alcohol.

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