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FORMYLATION AND DICHLOROMETHYLATION AS ALTERNATIVE DIRECTIONS OF RIECHE REACTION. A NOVEL APPROACH TO THE SYNTHESIS OF STERICALLY HINDERED AROMATIC DIALDEHYDES

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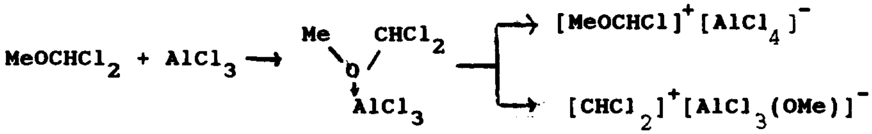
Abstract: *A previously unknown direction of Rieche reaction has been found: formylation of mesitylene, m-xylene, and durene with dichloromethyl methyl ether in the presence of aluminium trichloride and, to lesser extent, of titanium tetrachloride give the respective benzylidene dichlorides besides aldehydes. A novel approach to the synthesis of sterically hindered aromatic dialdehydes has been offered which involves the transformation of a monoaldehyde into the corresponding benzylidene dichloride, Rieche formylation of the latter, and hydrolysis of dichloromethyl aldehyde formed.*

Introduction

Studies of formylation of mesitylene with dichloromethyl methyl ether (DCME) in the presence of aluminium trichloride and, to lesser extent, of titanium tetrachloride[1] revealed that besides 2,4,6-trimethylbenzaldehyde (**1a**) the respective substituted benzylidene dichloride (**2a**), small amounts (1-3%) of 3-formyl-2,4,6-trimethylbenzylidene dichloride (**3a**) and bis-(dichloromethyl)mesitylene (**4a**) as well as traces of diformylmesitylene (**5a**) were formed. It was also shown[1] that under conditions used, 2,4,6-trimethylbenzylidene dichloride **2a** could not be formed either from the aldehyde **1a** or probably from its chloroacetal (chloroacetals are considered to be the intermediates of Rieche reaction[2-4]). Therefore formylation and dichloromethylation were assumed to be two parallel reactions corresponding to two alternative transformation routes of DCME - Lewis acid complex resulting in generation of two cations, i.e. chloro(methoxy)methyl and dichloromethyl ones.



$$MeOCHCl_2 + AlCl_3 \longrightarrow \underset{\downarrow AlCl_3}{Me\diagdown O \diagup CHCl_2} \longrightarrow \begin{cases} [MeOCHCl]^+[AlCl_4]^- \\ [CHCl_2]^+[AlCl_3(OMe)]^- \end{cases}$$

Results and Discussion

The aim of this paper is the study of effects of structure of the aromatic substrates and reaction conditions on formation of dichloromethyl-substituted derivatives, which has never been observed previously. Benzene and its homologues differing in their steric requirements and reactivities, viz. mesitylene, durene, and m-xylene were used as substrates. The reaction conditions were similar to those described in[1] with unusual order of reagent mixing (an aromatic substrate and DCME were added to a suspension of $AlCl_3$ in CH_2Cl_2) at ratios ArH : DCME : $AlCl_3$ = 1:1:2 and 1:4:8, the latter promoting formation of disubstituted products 3,4. As shown by our experiments and other data[5], hydrolysis of substituted benzylidene dichlorides on treatment of a reaction mixture with cold water does not actually occur. The results are presented in Table 1.

$$ArH \xrightarrow[AlCl_3]{DCME} \underset{1a\text{-}d}{ArCHO} + \underset{2a\text{-}c}{ArCHCl_2} + \underset{3a\text{-}c}{OHC\text{-}X\text{-}CHCl_2} + \underset{4a\text{-}c}{Cl_2HC\text{-}X\text{-}CHCl_2} +$$

$$+ \underset{5a}{OHC\text{-}X\text{-}CHO} + \underset{6c,d}{Ar_3CH} + \underset{7d}{Ar_2CHCl}$$

a Ar = 2,4,6-trimethylphenyl, X = 2,4,6-trimethyl-1,3-phenylene
b Ar = 2,3,5,6-tetramethylphenyl, X = 1,3,5,6-tetramethyl-1,4-phenylene
c Ar= 2,4-dimethylphenyl, X= 4,6-dimethyl-1,3-phenylene
d Ar = Ph

It follows from the data in Table 1 that dichloromethylation is quite natural, alternative direction of Rieche reaction and its products (compounds 2a,b) are formed in quantities comparable with those of the respective aldehydes (1a,b) if dichloromethyl group is sterically shielded and an excess of DCME is absent. The excess DCME leads to decrease in the yields of dichlorides 2a,b owing to further substitution resulting in the formation of compounds 3a,b and 4a,b. If steric shielding is low or absent (m-xylene and benzene) only traces of dichloromethyl-substituted derivatives are formed or cannot be found at all owing to their transformation into diarylchloromethanes and triarylmethanes under reaction conditions.

Table 1

Products Formed upon the Action of DCME on Benzene and Its Homologues in the Presence of $AlCl_3$

Aromatic substrate (ArH)	Molar ratios ArH:DCME:$AlCl_3$	Ratios of products, %				
		Aldehydes 1	Benzylidene dichlorides 2	Dichloromethyl-aldehydes 3	Bis-(dichloromethyl)-arenes 4	Coupling products 6,7
Mesitylene	1:1:2	60	40	-	-	-
	1:4:8	55	10	10	25	-
Durene	1:1:2	50	50	-	-	-
	1:4:8	40	15	15	30	-
m-Xylene	1:1:2	55	traces	-	-	45
	1:4:8	55	traces	5	10	30
Benzene	1:1:2	70	-	-	-	30
	1:4:8	60	-	-	-	40

Steric shielding of dichloromethyl group by adjacent alkyl substituents manifests itself in ^1H and ^{13}C NMR spectra of dichlorides **2a,b**: at -20 °C (for dichloromethyldurene **2b** even at room temperature) ortho-methyl groups are observed as two different signals[6]. Such phenomenon was described earlier for dichloromethylmesitylene[7,8] and caused by high rotation barrier (13.9±0.2 kcal/mol[7]) of dichloromethyl group around C_{Ar}-$CHCl_2$ bond resulting in non-equivalence of two adjacent methyl groups, the conformation with C-H bond of the $CHCl_2$ group coplanar to benzene ring being energetically the most advantageous one. Such steric shielding results also in broadening of signals of methyl groups of dichloromethyl-substituted aldehydes **3a,b** in ^1H NMR spectra. However, this broadening is absent in cases of dialdehydes **5a,b** (see Table 2).

It should be mentioned that the products of disubstitution **3a,b** and **4a,b**, which have never been discovered previously, resulted from the interaction of DCME not with monoaldehydes **1a,b** but with the respective dichlorides **2a,b**. Thus, as was shown by our experiments, second formyl group cannot be introduced in formylmesitylene **1a**, probably, because of strong deactivation of benzene ring by electron-withdrawing aldehyde group.

Table 2

^{1}H NMR Spectra of Dichloromethyl-Substituted Aldehydes 3a-c and Dialdehydes 5a-c

Compound	Chemical shifts, δ, (in $CDCl_3$, s)									
	2-Me	3-Me	4-Me	5-Me	6-Me	2-H	3-H	5-H	$CHCl_2$	CHO
3a	2.80 broad	-	2.50 broad	-	2.50 broad	-	6.95	6.95	7.25	10.59
3b	2.34 broad	2.48 broad	-	2.48 broad	2.34 broad	-	-	-	7.35	10.62
3c	-	-	2.52	-	2.64	8.19	-	6.92	7.11	10.23
5a	2.79	-	2.58	-	2.58	-	7.02	7.02	-	10.60
5b	2.35	2.35	-	2.35	2.35	-	-	-	-	10.61
5c	-	-	2.70	-	2.70	8.21	-	7.18	-	10.24

Data presented indicate that the presence of dichloromethyl group in benzene ring does not prevent Rieche formylation. This allows a novel method to be offered for preparation of sterically hindered aromatic dialdehydes bearing two aldehyde functions in one benzene ring, which has been briefly described in[9]. Caracteristic of the method is the use of dichloromethyl functionality for aldehyde group protection in Rieche formylation which cannot be accomplished for monoaldehydes like **1** owing to deactivating effect of formyl group. The method offered involves the following steps: (i) preparation of an aromatic monoaldehyde **1**; (ii) transformation of the latter into dichloromethyl-substituted derivative **2**; (iii) formylation of a dichloride **2** and hydrolysis of an intermediate dichloromethyl-substituted aldehyde **3** without its isolation to yield the target dialdehyde **5**. This reaction sequence was used for syntheses of 2,4,6-trimethylisophthalic (**5a**), 2,3,5,6-tetramethylterephthalic (**5b**), and 2,4-dimethylisophthalic (**5c**) dialdehydes from mesitylene, durene, and m-xylene, respectively.

$$\mathrm{Ar{-}H} \longrightarrow \underset{\mathbf{1a\text{-}c}}{\mathrm{Ar{-}CHO}} \longrightarrow \underset{\mathbf{2a\text{-}c}}{\mathrm{Ar{-}CHCl_2}} \longrightarrow$$

$$\longrightarrow \underset{\mathbf{3a\text{-}c}}{\mathrm{OHC{-}X{-}CHCl_2}} \longrightarrow \underset{\mathbf{5a\text{-}c}}{\mathrm{OHC{-}X{-}CHO}}$$

It should be mentioned that the preparation of sterically hindered alkyl-substituted aromatic dialdehydes is a rather difficult synthetic problem. The known methods are based on transformations of the corresponding bis-chloromethyl-substituted derivatives[10-14], the latter being prepared by chloromethylation of m-xylene, mesitylene, and durene with formaldehyde or its oligomers and HCl gas or concentrated hydrochloric acid[15-20]. Bis-chloromethyl-substituted derivatives are transformed further into target dialdehydes by direct oxidation[11-13,21] or via acetoxymethyl-substituted derivatives using hydrolysis of the latter and subsequent oxidation of carbinols formed[10,14].

Low total yields as well as the formation of mixtures with some hard-to-separate by-products are the main shortcomings of the methods cited. Thus, in preparation of trimethylisophthalic dialdehyde (5a)[10] the oxidation of the respective carbinol with lead tetraacetate proceded non-selectively and its product, as we have shown[1], consisted of ca. 85% of the target dialdehyde and ca. 15% of 3-hydroxymethyl-2,4,6-trimethylbenzaldehyde. The yield of pure dialdehyde did not exceed 50% owing to losses during chromatographic purification. Previously Grundmann and Dean[22] communicated on the presence of analogous admixture of 4-hydroxymethyl-2,3,5,6-tetramethylbenzaldehyde in tetramethylterephthalic dialdehyde obtained by oxidation of bis-(hydroxymethyl)durene with nitrobenzene according to procedure[11]. Individual dialdehyde could be isolated using recrystallization, however, losses reached 58%[22]. Taking into account that the starting bis-chloromethyl-substituted derivatives of benzene homologues could be isolated on chloromethylation of the latter in yields which, as a rule, are not higher than 50%[17,19,20,23], total yields of dialdehydes under consideration never exceed 40%.

The results presented in this paper (see Experimental) show that the use of dichloromethyl group as a protective one in preparation of sterically shielded aromatic dialdehydes not only simplifies the procedure and gives target compounds in pure state but also improves essentially the yields of dialdehydes 5a-c which are as high as 58-71% (based on the starting hydrocarbon) or 61-84% (based on monoaldehyde).

Our attempts to extend this scheme on sterically non-shielded aromatic substrates, such as thiophene, 2-methylthiophene, toluene, haphthalene, anthracene, proved to be unsuccessful: as could be seen from GLC data, formation of dialdehydes in these cases did not take place probably owing to intermolecular condensation of sterically unhindered dichloromethylarenes on the stage of repeated formylation.

Experimental

Analytical procedures were performed on a gas-liquid chromatograph (model 3700) using flame ionization detector and linear temperature programming over a range of 110-250 °C ($10^{o}.min^{-1}$), stainless steel column (2 x 1000 mm) packed with 5% SE-30 on Chromosorb P, N_2 as carrier gas, n-heptadecane as the internal standard as well as on GLC-MS Varian MAT 311A instrument (70 eV, 500 μA) with 25 m capillary column (SE-30).

Authentic samples, starting and intermediate compounds.

Aldehydes **1a-c** were prepared using reactions of mesitylene, durene and m-xylene with DCME and $TiCl_4$ in CH_2Cl_2 (see below).

Substituted benzylidene dichlorides **2a-c** were obtained from aldehydes **1a-c** upon the action of PCl_5 in CH_2Cl_2.

3-Dichloromethyl-2,4,6-trimethylbenzaldehyde **3a**, 4-dichloromethyl-2,3,5,6-tetramethylbenzaldehyde **3b** and 3-dichloromethyl-4,6-dimethylbenzaldehyde **3c** were prepared using the action of DCME with $TiCl_4$ in CH_2Cl_2 on respective dichlorides **2a-c** (see below), isolated in yields of 93-97% after evaporation of the solvent as unstable oils and characterized by ^1H NMR spectra (see Table 2), compound **3c** allowed to be distilled with partial decomposition, b.p. 145-150 °C (2 mm Hg) and isolated in 46% yield.

Bis-(dichloromethyl)mesitylene **4a** was isolated (column chromatography on silica, chloroform as eluent) from products of the reaction of DCME with mesitylene in the presence of $AlCl_3$, m.p. 165-165.5 °C (cf. Ref.[1]). The respective products (**4b,c**) formed from durene and m-xylene as well as coupling product **6c** were identified by GLC-MS.

Commercial specimens of benzaldehyde **1d**, diphenylchloromethane **7d** and triphenylmethane **6d** were also used.

Interaction of benzene and its homologues with DCME in the presence of aluminium chloride. A solution of 3.4 ml (0.04 mol) of DCME and 0.01 or 0.04 mol of an arene (in experiments with the ratio ArH:DCME:$AlCl_3$ = 1:4:8 and 1:1:2, respectively) was added to a stirred suspension of 11.2 g (0.08 mol) of $AlCl_3$ in 20 ml of CH_2Cl_2 at 20-25 °C. The mixture was stirred for 15 min and poured onto 200 g of crushed ice. The organic layer was separated, the aqueous one was extracted with chloroform (2 x 20 ml). The extracts were combined, washed with water, and analysed using GLC or GLC-MS methods. The results are presented in Table 1.

Formylation of mesitylene. A solution of DCME (30 ml, 0.33 mol) and mesitylene (23 ml, 0.17 mol) in CH_2Cl_2 (100 ml) was added at 20-25 °C for 5 min to a solution of $TiCl_4$ (73 ml, 0.67 mol) in CH_2Cl_2 (150 ml). The mixture was stirred for 15 min at room temperature and poured onto 0.5 kg of crushed ice. The organic layer was separated and the aqueous one extracted with $CHCl_3$ (2 x 50 ml). The extracts were combined, washed with water (3 x 100 ml) and the solvent was evaporated. The extract contained (by GLC) aldehyde **1a** (92%), dichloride **2a** (3%), dichlororomethyl-substituted aldehyde **3a** (3%) and bis-(dichloromethyl)mesitylene **4a** (ca. 1%). Vacuum distillation of the residue furnished 20.6 g (84%) of formylmesitylene **1a**, b.p. 108-111 °C (10 mm Hg), n_D^{20} 1.5534 (cf. Ref.[1]). Aldehydes **1b,c** were prepared similarly: formyldurene **1b** (96%), b.p. 130-132 °C (10 mm Hg), n_D^{20} 1,5540 (cf. Ref.[24]); 2,4-dimethylbenzaldehyde **1c** (95%), b.p.90-93 C°(11 mm Hg) (cf. Ref.[25]).

Substituted benzylidene dichlorides **2a-c** were obtained from aldehydes **1a-c** upon the action of PCl_5 in CH_2Cl_2 (stirring at room temperature for 1.5-2 h) with subsequent washing of the mixture with cold water and distillation: dichloromethylmesitylene **2a** (91%), m.p. 35-37°C (cf. Ref.[7]); dichloromethyldurene **2b** (95%), m.p. 105-106 °C (cf. Ref.[9]) and 2,4-dimethylbenzylidene dichloride **2c** (90%), b.p. 131-135°C (20 mm Hg), n_D^{20}1,5481 (cf. Ref.[9]).

Preparation of dialdehydes **5a-c**. 2,4,6-Trimethylisophthalic dialdehyde **5a**. A solution of dichloride **2a** (4.12 g, 0.02 mol) and DCME (4.66 g, 0.04 mol) in CH_2Cl_2 (60 ml) was added to a solution of $TiCl_4$ (9 ml, 0.08 mol) in CH_2Cl_2 (65 ml). The mixture was stirred for 15 min at room temperature and then poured onto crushed ice (200 g). The organic layer was separated, the aqueous one was extracted with chloroform (2 x 30 ml). Combined extract was washed with 1N HCl (2 x 200 ml). After evaporation of the solvent, 3-dichloromethyl-2,4,6-trimethylbenzaldehyde **3a** (unstable oil) was dissolved in ethanol (50 ml) acidified with hydrochloric acid, boiled for 1 h, poured into water and extracted with chloroform (2 x 50 ml). After removal of the solvent and recrystallization from hexane 2.85 g of dialdehyde **5a** (80%) was isolated, m.p. 87-89° C (cf. Ref.[1]). Dialdehydes **5b** and **5c** were prepared by similar procedures but with isobutanol as the solvent at the hydrolysis step : 2,3,5,6-tetramethylterephthalic dialdehyde **5b**, m.p. 179-182 °C (after recrystallisation from aqueous methanol and additional purification on silica with chloroform as eluent), yield 75.5% (cf. Ref.[21]); 4,6-dimethylisophthalic dialdehyde 5c, b.p. 155-157 °C (10 mm Hg), m.p. 104-106 °C (from hexane-benzene, 1:1), yield 68%, (cf. Ref.[14]), The yields of isolated dialdehydes **5a-c** based on the starting hydrocarbons are 61, 69, and 58%, respectively.

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