FACTORS CONTROLLING THE REGIOSELECTIVITY OF THE ADDITION OF DIMETHYL PHOSPHITE TO DIBENZYLIDENE DERIVATIVES OF KETONES

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In a continuation of our studies on the regioselectivity of the addition of dimethyl phosphite (DMP) to α -enones [1-3], in the present work we studied the reaction of DMP with dibenzylidene derivatives of acetone (I), cyclohexanone (II), and cyclopentanone (III) in the presence of bases. In the absence of catalysts, the reactions of (I) and (II) proceed on heating according to 1,4-addition scheme with the formation of γ -ketophosphonates (IVa) and (IVb) [4].

It was found that under the conditions of basic catalysis, the dibenzylidene derivatives of ketones react with DMP similarly to chalcone [2]: in the presence of sodium methoxide, the reaction proceeds with the formation of monoadducts (IVa, b, c) (see scheme),



while in the presence of amines there is no reaction. In analogy with monobenzylidene derivatives of acetone, cyclohexanone, and cyclopentanone [2], we assumed that the monoadducts (IVa, b, c) will add a second molecule

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of DMP at both the 1,2 and 1,4 positions of the conjugated system, with the formation of bisadducts (V) and (VI), respectively. However, in the presence of diethyl- and triethylamine the reaction did not take place, while in the presence of MeONa, it proceeded with the formation of 1,4-bisadducts (VIa, b, c) only. This behavior of monoadducts (IVa, b, c) can be explained by steric hindrance to the approach of the nucleophile to the C = O group, exerted by the dimethylphosphono-substituted benzyl group present at the β position. An examination of the Stuart-Briegleb models of the monoadducts confirms this supposition.

The structure of the bisadducts was established by elementary analysis and IR spectra.

For bisadducts (VIb) and (VIc), the formation of isomers with cis and trans disposition of the phosphonosubstituted benzyl groups is, in principle, possible, but the cis-diaxial conformation is, apparently, excluded because of the considerable 1,3-repulsion of the benzylphosphonic groups.



According to the data of the PMR spectrum, a cis-diequatorial disposition of the substituents in the ring was found for adduct (VIb). In the spectrum there are two doublets of the methoxyl protons at δ 3.32 and 3.0 ppm (12H, ${}^{3}J_{PH} = 10.8$ Hz), whose nonequivalency in pairs is due to the presence of an asymmetric α -C atom. The multiplet at δ 1.64 ppm corresponds to the methylenic protons of the ring. The signals of the methine protons of the ring are overlapped by the signals of the methoxyl groups, and their analysis is difficult. In the 3.60 ppm region, there is a quadruplet of methine protons of the benzyl groups. When double heteronuclear resonance is used, in this region the spectrum is reduced to a doublet at δ 3.61 (2H, J_{HH} = 10 Hz). The presence of one doublet indicates a cis-diequatorial, and not a trans-equatorially axial disposition of the benzyl-phosphonic substituents.

The regionselectivity of the addition of DMP to the α -enones can be considered from the point of view of the perturbation theory [5], as in [6, 7]. According to this theory, the addition of the nucleophile to the C = O group is a charge controlled process, while the addition to a conjugated system is an orbitally controlled re-action.

Data on the calculation of the charge on the carbonyl carbon atom (q_2) and the HCO energy (E_{HCO}) , and also the C_4 coefficients of HCO of certain α -enones [7] studied in the reaction with DMP, are listed in Table 1.

Although in the literature there are no data on the calculation of charge q_2 and E_{HCO} (C_4 coefficients) for monobenzylidene derivatives of cyclopentanone and cyclohexanone, and also for the dibenzylidene derivatives, nevertheless, on the basis of the calculated data [7], we can assume that these parameters of the first group of ketones shall be similar to the parameters of benzalacetone, cyclohexenone and cyclopentenone, and the parameters of the dibenzylidene derivatives – to the parameters of chalcone. This group should also include 2-benzaltetralone.

It follows from Table 1 that the charge on the carbonyl carbon atom decreases on transition from cyclohexenone and ethylideneacetone to chalcone, while E_{HCO} and the C_4 coefficients decrease in the same sequence. Consequently, the ability to undergo a charge controlled process of the 1,2-addition should decrease,

| æ-Enone | Hückel method | | | Ab initio | | | |
|-----------------|------------------|------------------|-------|------------------|--------|-------|--|
| | EHCO, units β | q ₂ * | C. | E _{HCO} | q2 † | C. | |
| o | -0,400 | +0,43 | 0,670 | 0,232 | +0,196 | 0,663 | |
| | -0,400 | +0,43 | 0,670 | 0,229 | +0,188 | 0,648 | |
| MeCCH=CHMe | -0,400 | +0,43 | 0,670 | 0,231 | +0,196 | 0,653 | |
| MeCCH=CHPh 0 | -0,226 | +0,38 | 0,563 | 0,185 | +0,190 | 0,475 | |
| PhCCH=CHPh 0 | -0,132 | +0,30 | 0,513 | | | | |

TABLE 1

 π Charge.

 $\dagger(\sigma + \pi)$ charge.

and the role of the orbital interaction leading to the 1,4-adducts, should increase in the same sequence.

The results obtained by us during the reaction of DMP with α -enones agree with the prediction of the perturbation theory. The reaction at the C = O group of the monobenzylidene derivatives of acetone, cyclopentanone, cyclohexanone, and also ethylideneacetone and cyclohexenone is kinetically more preferred than that at the conjugated system [1-3]. In the presence of diethyl- and triethylamine all these ketones form 1,2-adducts only. The ratio of the reaction products in the presence of MeONa depends on the amount of the catalyst. Thus, in the case of a small amount of MeONa, the formation of α -hydroxyphosphonates is preferred, while with the increase in the amount of the alcoholate, the yield of γ -ketophosphonates increases. This is explained by the fact that an increase in the amount of the starting materials, facilitating thus the 1,4-addition, which is practically irreversible under these conditions. A similar role is played by the time and temperature. With their increase, the yield of the 1,4-adducts increases.

The behavior of ethylideneacetone in the reaction with DMP is interesting. In the presence of amines the reaction proceeds at the C = O group, but in contrast to benzalacetone, even a small amount of MeONa at ~20°C leads to the γ -ketophosphonate only [3]. Similarly, in the reaction with phosphonoacetic ester in THF in the presence of t-BuOK, only the product of 1,4-addition has been isolated [7]. This cannot be explained by the perturbation theory: benzalacetone with a smaller charge on the carbonyl atom and somewhat smaller HCO level than in the case of ethylideneacetone, in the presence of catalytic amounts of MeONa forms both 1,4- and 1,2-adducts with DMP. With phosphonoacetic acid ester, the formation of products in two directions is also observed [6, 7]. The difference in the behavior of ethylideneacetone and benzalacetone can be explained by the greater reactivity of the β -C atom in ethylideneacetone, due to the lower deconjugation effect [7, 8]. If in the transition state, the β -C atom of the α -enone changes the sp²-hybridization for sp³, the loss of the π energy will be greater for benzalacetone than for ethylideneacetone, and this can predominate over the orbital factors [7].

In the presence of two competing reactions – a reversible addition to the C = O group and practically irreversible conjugated addition, increase in the rate of the latter leads to a shift in the equilibrium of the 1,2-addition in the direction of the starting materials, and hence, in the direction of a thermodynamically controlled product. In the presence of amines, the isolation of α -hydroxyphosphonate from ethylideneacetone is due to the fact that they are more stable in the presence of amines than in the presence of alcoholates, and DMP cannot form γ -ketophosphonates in the presence of amines [3].

According to data in [7], cyclohexenone has the same quantum-chemical characteristics (q_2 , E_{HCO} , C_4) as ethylideneacetone, but in the presence of MeONa, it forms adducts with DMP at both the C = O group and the conjugated system. Phosphonoacetic acid ester gives products of 1,4-addition only [7]. According to calculated data [9], in cross-conjugated ketones, the electrophilicity of the carbonyl carbon atom and the β -carbon atom become similar. Although the data in Table 1 show that the role of the orbital interaction for chalcone, and probably, for other benzylidene ketones with an aromatic nucleus or a second benzylidene group in the α position to the C = O group, increases, and the contribution of the charge control decreases, compared with the benzylidene derivatives of alkyl ketones, when we consider the regioselectivity of the nucleophilic addition of DMP, we must take into account the role of the deconjugation effect. The formation of an intermediate anion (A) in the 1,2-addition process should be accompanied by a higher loss of the conjugation energy than during the formation of the anion (B) according to the scheme of conjugated addition

 $\begin{array}{ccc} :O^{\odot} & :O^{\odot} \\ Ph-C-CH=CH-Ph & Ph-C=CH-Ph \\ O=P(OMe)_2 & (A) & O=P(Me)_2 & (B) \end{array}$

EXPERIMENTAL

<u>Reaction of Dimethyl Phosphite with Dibenzalacetone.</u> To a mixture of 1.17 g of dibenzalacetone and 1.1 g of DMP in benzene, 10 drops of a saturated solution of MeONa in MeOH were added to an almost complete decoloration of the solution. After 3 h, the reaction mixture was washed with water, dried over MgSO₄, and evaporated. By chromatography on a column with silica gel, from the residue, 1,5-diphenyl-5-(dimethyl-phosphono)-1-penten-3-one (IVa) (eluent – diethyl ether) and bis(dimethylphosphone)benzylacetone (VIa) (eluent – acetone) were isolated. Yield of (IVa) 13.37%, mp 105-106.5°C (from cyclohexane). IR spectrum (ν , cm⁻¹): 1038, 1050, 1070 (POC), 1260 (P=O), 1630 (C=C), 1660 (C=O). Found: C 66.28; H 6.42; P 8.95%. C₁₉H₂₁O₄P. Calculated: C 66.28; H 6.14; P 9.00%.

Yield of (VIa) 31.15%, mp 97-98°C (from a benzene-petroleum ether mixture). IR spectrum (ν , cm⁻¹): 1035, 1060 (POC), 1253 (P=O), 1720 (C=O). Found: C 55.52; H 6.69; P 13.61%. C₂₁H₂₈O₇P₂. Calculated: C 55.5; H 6.21; P 13.64%.

Reaction of Dimethyl Phosphite with γ -Ketophosphonate (IVa). To a mixture of 0.2 g of γ -ketophosphonate (IVa) and 0.12 g of DMP in ether, 7 drops of a saturated solution of NaOH in absolute MeOH were gradually added. The composition of the reaction mixture during the dropping of the alkali was controlled by IR spectra. After washing with water, drying over MgSO₄ and chromatography on a column with silica gel, the bisadduct (VIa) was isolated from the reaction mixture in a 41.3% yield.

Reaction of Dimethyl Phosphite with 2,6-Dibenzalcyclohexanone. To a mixture of 1.37 g of 2,6-dibenzalcyclohexanone and 1.1 g of DMP in ether, 25 drops of a saturated solution of MeONa in MeOH were added. The unreacted initial ketone was removed by filtration. After 15 h (~20°C), the crystals of 2,6-bis(dimethylphosphono)benzylcyclohexanone (VIb) separated from the solution. IR spectrum (ν , cm⁻¹): 1030, 1060, 1072 (POC), 1245, 1250 (P=O), 1725 (C=O). Yield 16.5%, mp 169-171°C (from CCl₄). Found: C 58.48; H 6.66; P 12.08%. C₂₄H₃₂O₇P₂. Calculated: C 58.28; H 6.52; P 12.53%.

The mother liquor was washed with water, dried over MgSO₄, and evaporated in vacuo. Chromatography of the residue on silica gel with elution with a petroleum ether-ether (1:1) mixture gave 2-(dimethylphos-phono)benzyl-6-benzalcyclohexanone (IVb). When ground with petroleum ether, (IVb) was converted into a pow-der, mp 64-66°C. IR spectrum (ν , cm⁻¹): 1039, 1055 (POC), 1250 (P=O), 1608 (C=C), 1690 (C=O). $\delta^{31}P$ 30 ppm. Found: C 68.50; H 6.60; P 7.86%. C₂₂H₂₅O₄P. Calculated: C 68.73; H 6.55; P 8.06%.

Reaction of Dimethyl Phosphite with γ -Ketophosphonate (IVb). To a mixture of 0.34 g of (IVb) and 0.3 g of DMP in ether, 6 drops of a solution of MeONa in MeOH were added, and the mixture was left to stand for 24 h. The crystals of the bisadduct (VIb) were isolated in a yield of 23%.

Reaction of Dimethyl Phosphite with 2,5-Dibenzalcyclopentanone. To a mixture of 1.2 g of 2,5-dibenzalcyclopentanone and 0.75 g of DMP in benzene, 30 drops of a saturated solution of MeONa in MeOH were added. After the evolution of heat had ceased, the reaction mixture was washed with water and dried over MgSO₄, and benzene was partially evaporated in vacuo. Crystals of 2-(dimethylphosphono)benzyl-5-benzal-cyclopentanone (IVc) were isolated in a yield of 18.3%, mp 126-127.5°C (from cyclohexane). IR spectrum (ν , cm⁻¹): 1035, 1060 (P-O-C), 1255 (P=O), 1750 (C=O). Found: P 8.26%. C₂₁H₂₃O₄P. Calculated: P 8.36%.

The mother liquor left after the separation of (IVc) was evaporated in vacuo, and ether was added to the residue. Crystals of 2,5-bis(dimethylphosphono)benzylcyclopentanone (VIc) were isolated in a yield of 21.2%, mp 183-185°C (from CCl₄). IR spectrum (ν , cm⁻¹): 1023, 1052, 1070 (POC), 1258 (P=O), 1750 (C=O). Found: C 58.3; H 6.25; P 12.83%. C₂₃H₃₀O₇P₂. Calculated: C 57.91; H 6.29; P 12.90%. The same bisadduct (VIc) was isolated by the reaction of monoadduct (IVc) with DMP in the presence of MeONa.

CONCLUSIONS

1. Dibenzylidene derivatives of acetone, cyclohexanone, and cyclopentanone react with dimethyl phos-, phite in the presence of sodium methoxide by the 1,4-addition scheme, with the formation of mono- and bisadducts with a γ -ketophosphonate structure.

2. In contrast to the benzylidene derivatives of acetone, cyclohexanone, and cyclopentanone, because of steric hindrance by the phosphono-substituted benzyl group, the monoadducts do not form addition products with dimethyl phosphite at the carbonyl group.

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AMINOMETHYLATION OF PHOSPHINES BY

ALKOXYMETHYLAMINES AND DIAMINOMETHANES

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Most of the known methods for the synthesis of aminomethylphosphines (AMP) are essentially modifications of the Mannich reaction [1-4]. The simplest variant consists in the reaction of a secondary amine, formalin, and phosphine [3]. However, in our attempts to synthesize dimethylaminomethyldiisopropylphosphine (I) according to [3], the yield did not exceed 47%. The main difficulty was, apparently, that by carrying out the reaction in aqueous medium, it was not possible to exclude the extraction stage, at which the readily oxidizable aliphatic phosphine was lost. We therefore developed methods for aminomethylation of phosphines in a nonaqueous medium by the action of accessible and readily purified tetraalkyldiaminomethanes and alkoxymethylamines (briefly described in [5]). The former have already been used for the preparation of AMP under fairly drastic conditions [5]. The addition of the acid catalyst made it possible to appreciably lower the reaction temperature, and the yields of the products varied within 65-95% (Table 1).

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$$(Me_2N)_2CH_2 + HPRR' \xrightarrow{80^\circ} CF_{3}COOH (cat.) Me_2NCH_2PRR'$$

 $R = R' = i - Pr \quad (I); \quad R = i - Pr, \quad R' = PhCH_2 \quad (II);$ $R = t - Bu, \quad R' = PhCH_2 \quad (III); \quad R = t - Bu, \quad R' = Ph \quad (IV)$

Alkoxymethylamines have already been successfully used for the aminomethylation of aziridines [6]. The reactions with phosphines are known only for similar, but more active reagents, tetraalkyldiaminoalkoxymethanes [7].

| Com- pound | Formula | Yield,% | bp, °C (p, mm Hg) | M+, m/e |
|---|---|--|---|--|
| (I) (II) (III) (IV) (V) (VI) (VII) (VII) | $\begin{array}{l} Me_2NCH_2P(i-Pr)_2\\ Me_2NCH_2P(i-Pr)CH_2Ph\\ Me_2NCH_2P(i-Bu)CH_2Ph\\ Me_2NCH_2P(i-Bu)Ph\\ O(CH_2CH_2)_2NCH_2P(i-Pr)_2\\ O(CH_2CH_2)_2NCH_2P(i-Pr)CH_2Ph\\ O(CH_2CH_2)_2NCH_2P(i-Bu)Ph\\ MeOOCCH(CH_2)_3NCH_2P(i-Pr)_2 \\ C \end{array}$ | 81 87 95 65 86 79 65 94 | 69 (8) 101-103 (1,5) 120-121 (4) 130 (10) 87 (3) 135 (3) 158 (6) 100-104 (2) | 175 223 237 223 217 a b 245 |
| (IX) | MeOOCCH(CH ₂) ₃ NCH ₂ P(<i>i</i> -Pr)CH ₂ Ph d | 63 | 150-152(1) | e |
| (X) | MeOOCCH(CH ₂) ₃ NCH ₂ P(t-Bu)Ph f | 78 | 149-150(1,5) | g٠ |

| TABLE 1. | Properties | of A | minometl | nyl | phosp | hines |
|----------|------------|------|----------|-----|-------|-------|
|----------|------------|------|----------|-----|-------|-------|

a) M⁺ is absent, characteristic peaks at m/e 166 and 100.

b) M⁺ is absent, characteristic peaks at m/e 166, 100, and 57.

c) $\left[\alpha \right]_{546}^{20}$ -76.8° (C 9.45, MeOH).

d) [α]²⁰₅₄₆ -22.3° (C 0.5, MeOH).

e) M^+ is absent, characteristic peaks at m/e166, 141, and 91.

f) $[\alpha]_{546}^{20}$ -57° (C 1.9, MeOH).

g) M⁺ is absent, characteristic peaks at m/e 166, 141, 110, and 57.

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