STEREOCHEMISTRY AND REACTIVITY OF UNSATURATED COMPOUNDS COMMUNICATION 15. SYNTHESIS AND EPIMERIZATION OF 1-HALOMETHYL-4, 6-DIMETHYL-3-CYCLOHEXENES

 G. P. Kugatova-Shemyakina, * V. M. Andreev,
 UDC 541.63 +541.427

 and L. I. Rozhkova
 +542.91:547.592.2

In order to synthesize analogs of trans-1-substituted 4, 6-dimethyl-3-cyclohexenes containing a functional group that is separated from the ring by more than one methylene unit, we proposed to prepare trans-1-bromomethyl-4, 6-dimethyl-3-cyclohexene (I) and then enter it into the Grignard reaction with CO_2 , aldehydes or ethylene oxide. We assumed that bromide (I) can be synthesized quite smoothly from the trans-alcohol (II) [2] by reaction with PBr_3 [3, 4], by analogy with the related compound, namely cyclohexen-3-ylmethanol [5]. Actually, the treatment of alcohol (II) in absolute ether with PBr_3 went in accordance with the data given in [5] and led to the bromo derivative in 50% yield. However, the carboxylation of the organomagnesium compound, obtained from this bromide, unexpectedly gave a mixture of stereoisomeric dimethylcyclohexenylacetic acids (III, IV) in a ratio of 64:36. This was established by subjecting the corresponding methyl esters, which were obtained by treatment with diazomethane, \dagger to GLC. A subsequent study of the bromide employing GLC disclosed that it is not a pure compound, and instead represents a mixture of the trans- and cis-isomers (I, V) in a ratio of 60:40



In order to establish the configuration of the components of this mixture we synthesized the pure trans-bromide (I) by tosylating the trans-alcohol (II) and subsequent cleavage of the tosylate (VI) by heating with LiBr in acetone [6], i.e., under the conditions of the S_N^2 reaction [7]. The corresponding trans-iodide (VII) and trans-chloride (VIII) were obtained in a similar manner.

*Deceased.

[†]The synthesis of trans-4, 6-dimethylcyclohexen-3-ylacetic acid and its methyl ester was described by us in [1].

 \ddagger The halides obtained in this manner contained 5-14% of an unidentified impurity, probably an olefin, that could be easily removed by distillation. Attempts to use the methods given in [8-11] to synthesize the pure halides proved unsuccessful.

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Hal=Br (I), I (VII), C1 (VIII)

The configuration of the pure trans-bromide (I) was proved by its reduction with $LiAlH_4$ [12] to trans-1, 2, 4-trimethyl-4-cyclohexene (IX) [2, 13]. The configuration of the cis-bromide (V) was confirmed by the NMR spectra. The spectrum of the mixed bromides (I, V) coincided almost completely with the spectrum of the trans-bromide (I), except for an additional singlet at δ 5.18 ppm in the region of the vinyl protons, which was caused by the cis-epimer (V) impurity. A shift of the signal of the vinyl proton upfield (from 5.18 up to 5.31 ppm) is in all probability explained by the effect of the diamagnetic anisotropy of the bromomethyl grouping, which is possible only with an axial conformation of the latter.

The inversion of the configuration that was observed by us when preparing the bromide from the trans-alcolol (II) could occur as a result of the isomerization of both the starting and the end materials, or as the consequence of the simultaneous progress of both processes. In order to solve this problem we studied the stability of the trans-bromide (I) toward HBr. For this we imitated the reaction conditions by adding the phosphorus halide to a solution of the trans-bromide (I) in ether, containing an equivalent of absolute methanol, and obtained a mixture of the trans- and cis-bromides (I, V) in a ratio of 75:25. When the obtained mixture of bromides (I, V) was repeatedly treated in a similar manner the amount of the cis-isomer in it increased up to 40%. Subsequently it was ascertained that the trans-alcohol (II) also underwent acid isomerization, since on refluxing in ether in the presence of H_2SO_4 it undergoes epimerization to the extent of 26% in 2.5 h.

Epimerization during the synthesis of the bromide from alcohol (II) when treated with PBr_3 can be understood if the mechanism of the S_N1 reaction is examined. In harmony with the generally accepted concepts [14], the process proceeds with the formation of the phosphorous acid ester, which is then converted to the carbcation (X). Here it is possible to assume that the tertiary hydrogen atom at C_1 takes part in the stabilization of the carbcation, which leads to an inversion of the configuration of the bromomethyl group



The acid isomerization of trans-bromide (I) and trans-alcohol (II) apparently proceeds in a similar manner, with the involvement of the unbounded atom at C_1 . As a result, all of the examined processes apparently proceed through a common intermediate state (X), and the isomerization during the reaction of trans-alcohol (II) with PBr₃ probably represents their total result.

In synthesizing the pure trans-halides it was discovered that the latter are inclined to undergo thermal isomerization. This caused us to make a special study of the thermal isomerization of the indicated compounds, and also the trans-alcohol (II) (Table 1).

The thermal isomerization of trans-halides (I), (VII) and (VIII), the same as the acid isomerization of trans-bromide (I) and trans-alcohol (II), is most likely explained by the involvement of the unbounded group (H atom) in the stabilization of carbcation (X), which is formed in the ionization step. The thermal epimerization of trans-alcohol (II) probably proceeds in a similar manner. The high stability in the thermal isomerization of trans-chloride (VIII), when compared with the other halides, is evidently the consequence of its slow rate of ionization, which for primary chlorides, as is known [7], is 25-60 times slower than for the analogous bromides; the latter in turn are ionized a total of 1.5-4.5 times more slowly than the corresponding iodides.

Starting com- pound	т., °С	Ratio of trans- and cis-isomers			
		in the start- ing material	aft e r 1 h	aft er 2 h	aft er 4 h
VII I VIII VIII II	124 - 125 $124 - 125$ $124 - 125$ $190 - 200$ $118 - 125$ 125	98:2 400:0 400:0 100:0 100:0	56 ; 44 70 : 30 100 : 0 100 : 0	58 : 42 72 : 28 100 : 0 100 : 0	58 : 42 68 : 32 100 : 0 55 : 45 * 100 : 0 †

TABLE 1. Thermal Isomerization of 1-Substituted Derivatives of 4, 6-Dimethyl-3-cyclohexene

*After 5 h.

+ After 8 h.

The halides (I), (VII) and (VIII) synthesized by us proved unsuitable for use in the Grignard reaction. Thus, chloride (VIII) in general failed to react with magnesium, while bromide (I) gave the Grignard compound in low yield. The iodide (VIII), although it reacted actively with magnesium, predominantly formed the products of the Wurtz reaction. The addition of either ethylene oxide or acetaldehyde to the reaction mixture led to obtaining only traces of the alcohols (data of the IR spectra).

The obtained results on the thermal isomerization of trans-bromide (I) and trans-iodide (VIII) give the values of the corresponding equilibrium constants (2.33 and 1.33), and consequently, also the possibility of calculating the differences in the free energies between the trans- and cis-isomers of both halides. When calculated using the equation: $\Delta G^0 = -RT \ln K$, this difference is 0.67 for the bromide, and 0.22 kcal /M for the iodide.

EXPERIMENTAL METHOD

All of the obtained compounds were analyzed on a GCHF-18 chromatograph (German). The column had a length of 1 m and a diameter of 7 mm, and was filled with neopentyl glycol adipate (10%) deposited on Celite C-22. The analyses were run at 150°C (for the hydrocarbon at 70°), using He as the carrier gas. The halides were also analyzed on a column filled with dinonyl phthalate (10%) deposited on Chromosorb W, at 120°. The IR spectra were taken on a UR-20 spectrophotometer for the pure liquids. The NMR spectra were obtained on a Varian-100 instrument in CCl₄, using TMS as the internal standard.

Reaction of trans-1-Hydroxymethyl-4, 6-dimethyl-3-cyclohexene (II) with PBr₃. With stirring, to a solution of 6.9 of alcohol (II) in 50 ml of absolute ether was gradually added 4.75 g of PBr₃, the mixture was refluxed for 2.5 h, poured on ice, extracted with ether, washed with aqueous NaHCO₃ solution, then with water, and dried over Na₂SO₄. We obtained 5.0 g (50%) of mixed (60:4) bromides (I) and (VII), bp 86-90° (10 mm); n_D^{20} 1.5038. A solution of 8.0 g of this mixture of bromides in 30 ml of absolute ether was added in 20 min to 0.96 g of Mg, and the mixture was refluxed for 1.5 h, cooled to -5 to -7°, after which solid CO₂ was added in small portions until the mixture became thick, and then it was allowed to stand for 12 h. The reaction mixture was decomposed with dilute H₂SO₄ solution, extracted with ether, the extract was treated with NaHCO₃, and the aqueous layer was separated and acidified with HC1. We obtained 2.33 g (35%) of mixed (64:36) trans-cis-4, 6-dimethylcyclohexene-3-ylacetic acids (III, IV) with bp 115-119° (2.5 mm); $n_D^{23.5}$ 1.4790. Found: C 71.49; H 9.46%. C₁₀H₁₆O₂. Calculated: C 71.39; H 9.59%. In order to analyze by the GLC method, the obtained mixture of acids was treated with diazomethane.

trans-1-Bromomethyl-4, 6-dimethyl-3-cyclohexene (I). To 21.0 g of p-toluenesulfonyl chloride in 75 ml of absolute pyridine at 2-4°, in 35 min, was added a solution of 14.0 g of alcohol (II) in 75 ml of absolute ether, and the mixture was stirred at 0° for 3h, kept at room temperature for 12h, and then poured on ice, extracted with CHCl₃, and the extract was washed with HCl solution, then with water, and dried over Na₂SO₄. After evaporation of the solvent we obtained 27.6 g of the tosylate contaminated with the starting alcohol, which was removed by chromatographing on 100 ml of Al₂O₃ (II activity) (eluted with hexane). We obtained 21.6 g (74%) of tosylate (VI) as a pale yellow viscous oil. A mixture of 5.4 g of tosylate (VI) and 1.75 g of anhydrous LiBr in 20 ml of absolute acetone was heated in a glass ampul for 2.5 h at 120-125°. The precipitate of lithium tosylate was filtered, and the filtrate was diluted with water and then extracted with ether. We isolated 2.35 g (63%) of the trans-bromide (I), bp 85-87° (10 mm); n_D²⁰ 1.4995. Found:

Br 39.55%. $C_9H_{15}Br$. Calculated: Br 39.40%. The yield of bromide (I) drops to 15% when the lithium bromide is replaced by NaBr.

The carboxylation of the pure trans-bromide (I) gave the trans-acid (III), the methyl ester of which, when based on the GLC data, is free of the stereoisomeric compound.

trans-1-Iodomethyl-4, 6-dimethyl-3-cyclohexene (VII). Using the method described for the synthesis of trans-bromide (I), from 17.6 g of tosylate (VI) and 9.9 g of anhydrous NaI in 60 ml of absolute acetone was obtained 8.9 g (59%) of trans-iodide (VII), bp 103-105° (10 mm); n_D^{20} 1.5410. Based on the GLC data, the trans-iodide is contaminated with 2-4% of the cis-isomer. Found: C 43.55; H 6.13; I49.01%. C₉H₁₅I. Calculated: C 43.25; H 6.00; I 50.76%.

trans-1-Chloromethyl-4, 6-dimethyl-3-cyclohexene (VIII). A mixture of 7.0 g of tosylate (VI) and 1.1 g of anhydrous LiCl in 25 ml of absolute acetone was heated for 3.5 h at 120-125°. After the workup we obtained 2.1 g (55%) of trans-chloride (VIII), bp 68.70° (10 mm); n_D^{20} 1.4835. Found: C 67.86; H 8.90; Cl 22.22%. C₉H₁₅Cl. Calculated: C 68.13; H 9.53; Cl 22.34%. When the reaction is run for 2.5 h the yield of trans-chloride (VIII) decreases noticeably; substantial tarring is observed when the heating time is increased up to 5 h and the yield of (VIII) drops, in which connection the simultaneous formation of the cis-isomeric chloride occurs.

trans-1, 2, 4-Trimethyl-4-cyclohexene (IX). To a refluxing suspension of 2.2 g of LiAlH_4 in 15 ml of absolute THF was slowly added 1.5 g of trans-bromide (I), after which the mixture was refluxed for 1 h, and then the excess hydride was decomposed with 60% aqueous THF solution and the reaction mixture was poured over ice, to which 1 ml of H_2SO_4 had been added. Petroleum ether was used to extract (IX), which was identified by comparison with an authentic sample [2] employing GLC.

Isomerization of trans-1-Bromomethyl-4, 6-dimethyl-3-cyclohexene (I) under the Influence of Hydrogen Bromide. To 1.0g of trans-bromide (I) in 7 ml of absolute ether was added 0.16g of absolute methanol, and then 0.69g of PBr₃ was added. The mixture was refluxed for 3h. After workup we obtained a mixture (75:25) of the trans-cis-bromides (I, V).

When a mixture (75:25) of the trans-cis-bromides (I, V) is isomerized in a similar manner the amount of the cis-isomer in it increases up to 40%.

Thermal Isomerization of trans-Halides (I), (VII) and (VIII). For the isomerization we took 0.1 g of trans-bromide (I), trans-iodide (VII) and trans-chloride (VIII) and heated them in sealed samples at 120-125° for 1, 2 and 4h. In addition, the trans-chloride (VIII) was heated for 5h at 190-200°. The results of the GLC analysis of the isomerization products are given in Table 1.

Isomerization of trans-1-Hydroxymethyl-4, 6-dimethyl-3-cyclohexene (II). Thermal Isomerization. One gram of alcohol (II) was heated at 195-200° for 5h, after which it was converted to the tosylate, which was cleaved by heating with LiBr in acetone, as described above.* The obtained mixture of bromides (I, V) was analyzed by GLC (see Table 1).

Acid Isomerization. A solution of 1.0 g of alcohol (II) in 7.5 ml of absolute ether was refluxed with 0.2 ml of conc. H_2SO_4 for 2.5 h, after which the mixture was washed with water and the residue from the evaporation of the ether was converted through the tosylate to a mixture of the trans-cis-bromides (ratio 74:26).

The NMR spectra were taken by V. I. Sheichenko and were interpreted by T. M. Ivanova, to whom we express our sincere gratitude.

CONCLUSIONS

1. The pure trans-isomers of the 1-bromomethyl-, 1-iodomethyl- and 1-chloromethyl-4, 6-dimethyl-3-cyclohexenes were synthesized.

2. A study was made of the epimerization of the 1-halomethyl- and 1-hydroxymethyl-4, 6-dimethyl-3-cyclohexenes under the influence of temperature and acid catalysts.

 $\overline{}$ The primary alcohol (II) and its cis-isomer were not separated under the GLC conditions employed by us.

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