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RE-ESTERIFICATION, A NEW STEP IN THE ALDOL-TISHCHENKO REACTION

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Abstract. The second step of the aldol-Tishchenko reaction proceeds over 6 + 6 bicyclic activated complex leading initially to the formation of the secondary half-ester. The partial re-esterification of the secondary half-ester into the primary one can be looked upon as a new, third step in the reaction.

Key words: aldol condensation, aldol-Tishchenko reaction, re-esterification.

INTRODUCTION

The aldol-Tishchenko reaction (Scheme 1) is the aldol condensation of two aldehyde (**1**) molecules containing at least one α-H atom, followed by disproportionation, where the resulting aldol (**2**) is reduced by a third aldehyde molecule. The reaction yields regioisomers of 1,3-diol half-esters (**3a** and **3b**). One or two new chiral centres are introduced in the first step and the chirality does not change later.

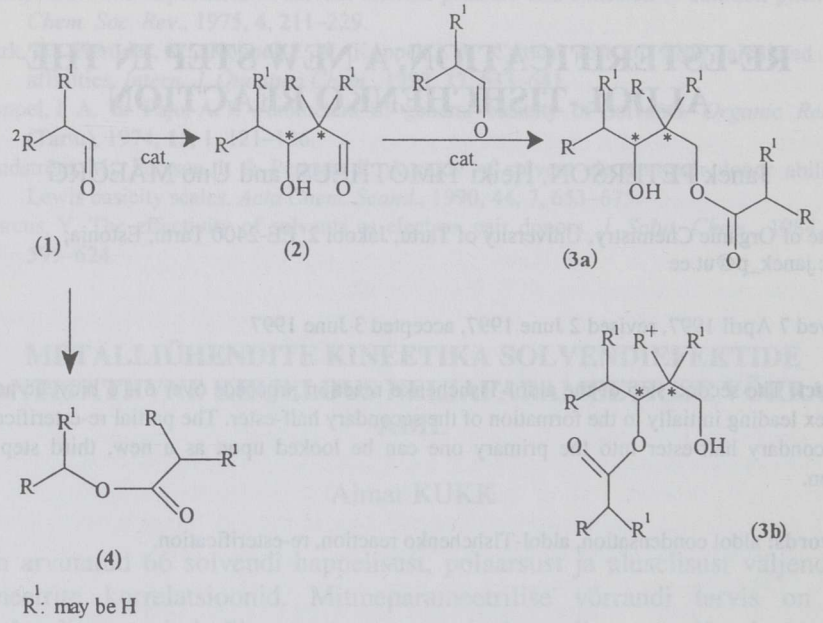
The aldol-Tishchenko reaction (one-pot synthesis) is advantageous if the initial aldehyde is inexpensive and easily available (two-thirds of the aldehyde form the carbon chain of the product, a third is spent on the reduction) [1]. Basic hydrolysis of 1,3-diol half-esters, sometimes carried out directly in the same reaction mixture [2], gives free 1,3-diols, which are widely used in industry [3] and as intermediates in the syntheses of several natural compounds and their analogues. The aldol-Tishchenko reaction was studied already at the end of the last century and at the beginning of this century in Austria [2, 4–6]. The later publications are rather sporadic; in recent years interest in this area has greatly increased.

Depending upon the conditions, the reaction may proceed in three competitive directions:

(1) aldol-Tishchenko reaction affords half-esters (**3a** and **3b**);

(2) elimination of water from (**6**) gives α,β-unsaturated aldehyde (**7**);

(3) Tishchenko reaction gives a simple ester (**4**).



Scheme 1. General scheme of the classical aldol-Tishchenko reaction.

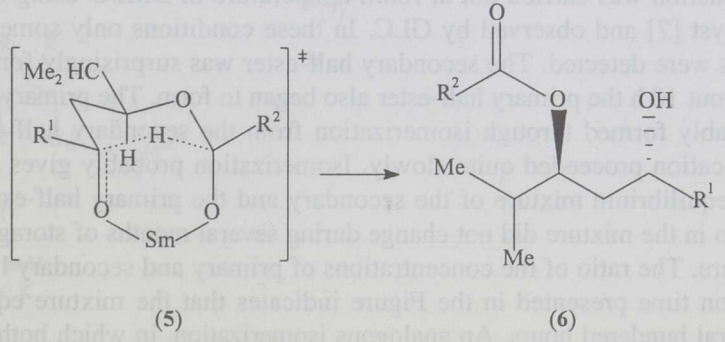
The probabilities of these directions are determined by the catalyst, solvent, and the structure of the aldehyde [1]. The formation of aldol (or α,β-unsaturated aldehyde) is known to be favoured by strong bases (alkali and alkaline earth metal hydroxides), while the formation of a simple ester via the Tishchenko reaction is favoured by weak bases (Al alcoholates). Therefore, the proper catalyst must be a base of medium strength [1, 3, 7–13]. According to most publications, the best catalysts are various phenolates in polar aprotic solvents (DMSO, DMF, HMPT) [1, 3, 4, 7–9]. On the other hand, anhydrous K_2CO_3 without a solvent is a satisfactory catalyst for Me_2CHCHO. Although the reaction is slow, the yield of the half-ester is high (87%) [5, 6].

If the cross (nonclassical) aldol-Tishchenko reaction is carried out between an unbranched aldehyde and Me_2CHCHO, the latter always reacts as the methylene component in the aldol condensation step and as the reducing agent in the Tishchenko reaction step [1].

RESULTS AND DISCUSSION

The mechanism of the aldol condensation, the first step of the reaction, is well documented [14–18]. The mechanism of the Tishchenko reaction has been studied considerably less thoroughly, although in general the mechanism (hydride ion transfer) has been known for a long time. It can be expected that the mechanism of the aldol-Tishchenko reaction differs from the simple Tishchenko reaction in two aspects: (1) in aldol there is a hydroxy group near the reaction centre, which may participate in the reaction; (2) the catalyst is a rather strong base, as it must catalyse also the aldol condensation. Aldehyde is always the donor of the hydride ion and aldol is the acceptor [9, 19]. Earlier publications [10–12, 19] suggest the aldol-Tishchenko reaction product to be a half-ester in which the primary alcoholic OH of the 1,3-diol is acylated (later in our text – primary half-ester). Later works refer to the product [7–9] as a mixture of regioisomers (primary and secondary half-ester) with the domination of the primary one. Burkhardt and co-workers found the secondary half-ester (yield 43%) to be the main product (initial aldehyde Me_2CHCHO, catalyst Ni enolate ($C_5H_5(Ph_3P)NiCH_2CO$-t-Bu)) [20]. The first serious discussion on the reaction mechanism is presented by Casnati and co-workers [8]. They suggest that aldol is reduced by the hemiacetal formed from aldehyde and catalyst (ArOMgBr). Consequently, the alcoholate of 1,3-diol and an aryl carboxylate are formed. The following acylation of the alcoholate of 1,3-diol gives a primary half-ester and a secondary half-ester.

Evans and Hoveyda [21] studied the Tishchenko reaction of optically pure isomers of β-hydroxyketones with different aldehydes using SmI_2 as a catalyst. They suppose that in this case the Tishchenko reaction proceeds over a bicyclic complex (**5**) including the metal cation. The aldehyde R^2CHO forms an alcoholate of hemiacetal with the OH group of the hydroxyketone. An intramolecular hydride ion transfer follows (Scheme 2) [21].



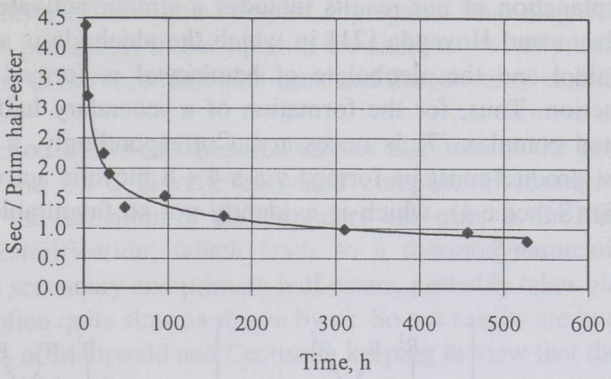
(5) (6)

Scheme 2. The supposed activated complex in the Tishchenko reduction of β-hydroxyketones [21].

The product is the half-ester (**6**) of 1,3-diol. The acyl group is situated at the oxygen of the diol that participates in the formation of the alcoholate of hemiacetal (in our case it is the secondary OH group of the diol). The proceeding of the reaction over such a bicyclic activated complex seems to be the only reasonable explanation of the anti-configuration of the reaction product (**6**). This reaction mechanism presented by Evans and Hoveyda can readily be used to explain the second step of the classical aldol-Tishchenko reaction (Tishchenko reduction) when simple basic catalysts are used. However, up to now it is not exactly known how primary and secondary half-esters are formed. In our opinion the fact of the formation the 6 + 6 bicyclic activated complex with subsequent re-esterification may be common for all events independent of the structure of the aldehyde and the catalyst [21, 22]. For a more detailed study of the formation of half-esters we carried out the aldol-Tishchenko reaction in simple (classical) conditions using only one aldehyde and simple catalysts as described by Pochini et al. [7]. In order to form only one chiral centre in the reaction, Me_2CHCHO was used as the initial aldehyde.

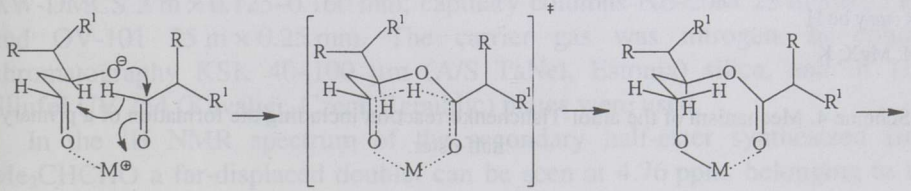
Both regioisomeric half-esters were separated by column chromatography on silica (the mobile phase was a mixture of hexane and ethyl acetate with a 5 : 1 ratio). The purity of the primary half-ester, determined by capillary GLC, was found to be excellent but the secondary half-ester was slightly contaminated with the primary half-ester. The structure of these compounds was determined by ^{1}H and ^{13}C NMR as well as by IR spectroscopy. Our finding that the secondary half-ester was contaminated with the primary one induced us to follow the reaction of the formation of the primary and the secondary half-ester. For that purpose we used capillary GLC and NMR spectroscopy. Data gathered from the pure isomers were used to interpret the spectra of the reaction mixture. In order to follow the formation of half-esters the doublet of protons at the chiral carbon atom was used as a diagnostic signal. This signal is situated at 3.25 ppm (J = 2.3 Hz) and 4.76 ppm (J = 2.3 Hz) in the spectra of primary and secondary half-esters, respectively.

The reaction was carried out at room temperature in DMSO using PhOMgBr as a catalyst [7] and observed by GLC. In these conditions only some traces of impurities were detected. The secondary half-ester was surprisingly formed first. Within about 10 h the primary half-ester also began to form. The primary half-ester was probably formed through isomerization from the secondary half-ester. The re-esterification proceeded quite slowly. Isomerization probably gives a thermodynamic equilibrium mixture of the secondary and the primary half-ester (2 : 3). Their ratio in the mixture did not change during several months of storage at room temperature. The ratio of the concentrations of primary and secondary half-esters vs. reaction time presented in the Figure indicates that the mixture equilibrates after several hundered hours. An analogous isomerization, in which both specially prepared pure regioisomeric half-esters of 1,3-diol turn into an equilibrium mixture containing two regioisomers, was described by Burkhardt et al. [20].

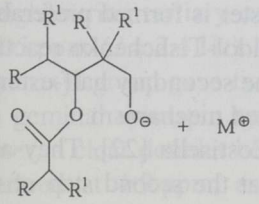


A plot of the ratio of the concentrations of half-esters (secondary/primary) vs. time.

The reaction that was then carried out under the conditions described by Kirchbaum [6] in neat Me_2CHCHO in the presence of anhydrous K_2CO_3 as a catalyst at 65 °C proceeded also relatively slowly but gave similar results. Probably the reaction mechanisms (Scheme 3) for both simple catalysts (K_2CO_3 and PhOMgBr) are similar. Such a mechanism of half-ester formation should also apply to unbranched aldehydes. This assumption, however, requires further study as the reaction is more complicated – $CH_3CH_2CH_2CHO$ yields aldol with two chiral centres and the number of isomers is bigger.



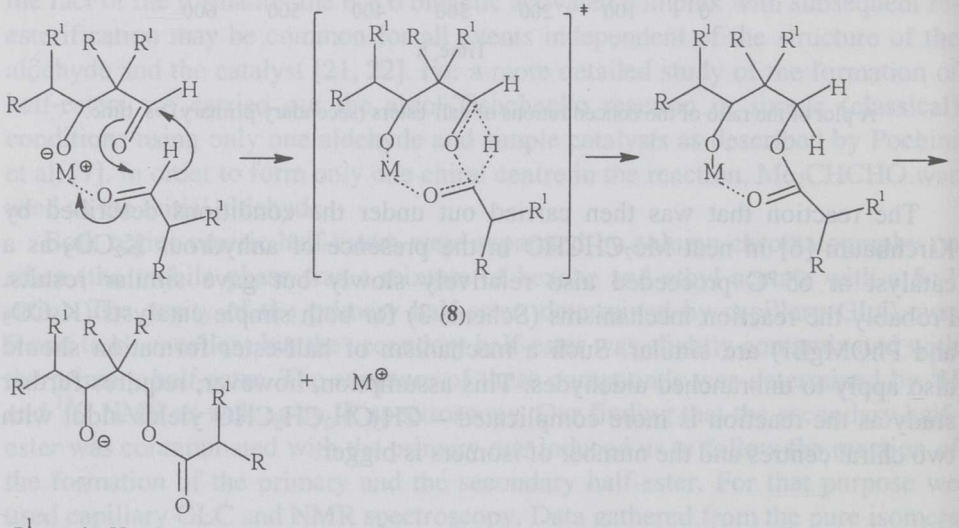
(7)



R^1: may be H
M: MgX; K

Scheme 3. Mechanism of the aldol-Tishchenko reaction including the formation of a secondary half-ester.

The best explanation of our results includes a similar activated complex as presented by Evans and Hoveyda [21] in which the aldehyde is attached to the OH group of aldol and the alcoholate of hemiacetal is formed in the aldol-Tishchenko reaction. Thus, for the formation of a secondary half-ester a 6 + 6 bicyclic activated complex (**7**) is necessary. Correspondingly, a primary half-ester as the first product must be formed via a 4 + 8 bicyclic activated complex intermediate (**8**) (Scheme 4), which is evidently not so favourable as the 6 + 6 one.



Scheme 4. Mechanism of the aldol-Tishchenko reaction including the formation of a primary half-ester.

This suggestion can explain why the secondary half-ester is formed preferably. Our results confirm that under classical conditions the aldol-Tishchenko reaction embodies also a third step, re-esterification reaction of the secondary half-ester to the primary one. It is in good agreement with the suggested mechanism.

Analogous results were obtained by Mahrwald and Costisella [22]. They also suppose, relying on the work of Evans and Hoveyda, that the second step of the aldol-Tishchenko reaction proceeds over a 6 + 6 bicyclic activated complex as a result of which a secondary half-ester is formed initially; it subsequently isomerizes partially into the primary half-ester during 24 h. In this case we are dealing with a nonclassical aldol-Tishchenko reaction. They used titanium ate complex ($BuTi(OiPr)_4Li$) as a catalyst but its exact structure was unknown. They supposed that the re-esterification takes place only if the titanium ate complexes are prepared

from lithium alkyles. If the same complex is prepared from magnesium alkyles, re-esterification is prevented. In our opinion the catalyst probably influences the rate of the formation of the secondary half-ester and the rate of re-esterification, but not its existence.

In this reaction the re-esterification step is also due to the proceeding of the reaction over the 6 + 6 bicyclic activated complex. Evidently, it is the only possibility for the formation of the secondary half-ester as the first product. The following re-esterification, which leads to a thermodynamically more stable mixture of the secondary and primary half-esters, probably takes place in all cases, although it is often quite slow as shown by us. So our results are in good agreement with the results of Mahrwald and Costisella keeping in view that they observed the reaction during 24 h only.

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ with an AC 200 P spectrometer (Spektrospin AG), ^1H NMR 200 MHz, ^{13}C NMR 50 MHz, using $SiMe_4$ as internal standard. IR spectra were recorded with INTERSPECTRUM PFS 2020, with KBr windows. For GLC Chrom 5 (Laboratorní Přístroje, Praha) and Tsvet 152 (Russia) instruments with FID and the following columns were used: packed columns (glass 2.5 m × 2 mm) Permabond Cyano Degs 80/100 mesh; 10% liquid crystal H-158 (4-(4-methoxycinnamoyloxy)-4'-methoxyazobenzene), Chromosorb W/HP 100/120 mesh; 5% Carbowax 20M, Chromaton N, AW-DMCS 3 m × 0.125–0.160 mm; capillary columns NB-20M 25 m × 0.25 mm and OV-101 25 m × 0.25 mm. The carrier gas was nitrogen. In column chromatography KSK 40–100 μm (A/S TaNel, Estonia) silica, and in TLC Silufol UV 254 (Kavalier, Czech Republic) plates were used.

In the ^1H NMR spectrum of the secondary half-ester synthesized from Me_2CHCHO a far-displaced doublet can be seen at 4.76 ppm, belonging to the proton at the secondary carbon atom and split (J = 2.3 Hz) by the proton at the neighbouring tertiary carbon which itself could be detected as five doublets at 2.05 ppm (J = 2.4 Hz). The two protons at the primary carbon bonded to the hydroxyl group gave two doublets (J = 11.9 Hz, with midpoint at 3.15 ppm) due to geminal spin-spin splitting caused by diastereotopism. For the primary half-ester, a clear doublet belonging to the protons at the tertiary carbon was visible, centred at 1.9 ppm, as well as two doublets (J = 10.9 Hz) of diastereotopic protons displaced by the influence of the ester group, centred at 4 ppm. For the ester group a hydrogen septet (J = 7.0 Hz) of a proton at the tertiary carbon split by two methyl groups was easily identifiable. The ^{13}C NMR spectrum has the following identifiable primary (δ 177.2, 79.4, 71.4, 39.4, 34.2, 28.7, 23.5, 22.03, 20.5, 19.05, 16.7) and secondary (δ 178.1, 79.8, 70.03, 40.1, 34.6, 28.3, 22.9, 22.3, 20.5, 19.06, 16.7) half-ester signals.

In the IR spectra of the half-esters the following peaks are of importance: a wide OH_{Str} maximum (3400–3500 cm^{-1}), a split, intensive $C{=}O_{Str}$ at 1700 cm^{-1}, and two $C{-}O_{Str}$ maximums between 1100 and 1300 cm^{-1}. The IR spectrum also shows regioisomers with a characteristic area on the spectrum, namely the split, intensive $C{=}O_{Str}$ maximum at 1700 cm^{-1}, regardless of whether a straight or branched chain aldehyde is used for the synthesis.

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ÜMBERESTERDUMINE KUI UUS ETAPP ALDOOL-TIŠTŠENKO REAKTSIOONIS

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Aldool-Tištšenko reaktsiooni teine etapp kulgeb 6 + 6 bitsüklilise aktiveeritud kompleksi kaudu ning selle tulemusel moodustub esimesena sekundaarne poolester. Sekundaarse poolestri ümberesterdumist primaarseks võib aga vaadelda kui uut, kolmandat etappi aldool-Tištšenko reaktsioonis.