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Tandem aldol-transfer–Tischtschenko reaction of aldehydes and β-hydroxyketones catalyzed by trimethylaluminum

Ilkka Simpura* and Vesa Nevalainen

Department of Chemistry, PO Box 55 (A.I. Virtasen aukio 1), University of Helsinki, FIN-00014 Helsinki, Finland

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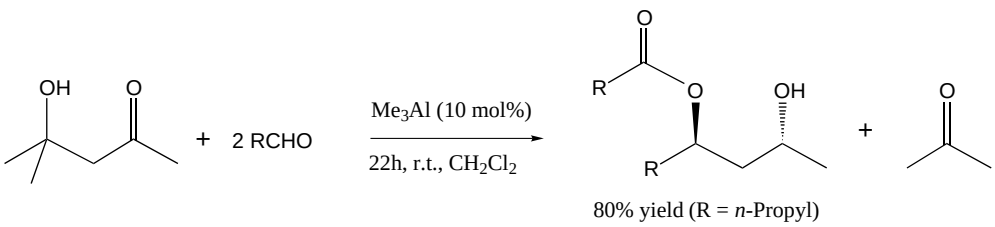
Abstract—A novel tandem aldol-transfer–Tischtschenko reaction has been developed. It provides a simple one-step synthetic route to diolmonoesters from β-hydroxyketones and aldehydes. The reaction is catalyzed by trimethylaluminum.

Nucleophile-transfer reactions possess great potential for organic transformations.[1–6] They are analogous to hydride-transfer reactions (hydride as a nucleophile) found on the basis of pioneering work by Meerwein, Ponndorf, Verley and Oppennauer[1] in the beginning of the 20th century. During recent years, several publications considering new transfer-reactions of nucleophiles other than hydrides have appeared. Inoue et al. have described the use of aluminum and titanium based promotors (stoichiometric amounts) for HCN transfer from acetonecyanohydrin to aldehydes.[2] They also report the use of lanthanoid alkoxides for the same reaction in catalytic amounts.[3] Maruoka et al. have published an alkenyl-transfer reaction (to aldehydes) mediated by an aluminum-*o*,*o*′-biphenyldioxy species[4] and zirconium alkoxides.[5] Analogous allyl-transfer reactions have recently been reported by Nokami.[6]

The Tischtschenko reaction offers an efficient way to synthesize esters directly from aldehydes through a reduction–oxidation reaction sequence.[7] This reaction, which is usually carried out using aluminum alkoxides as a catalyst, has been studied in detail by several groups.[8] The intramolecular Tischtschenko reaction has been found to be a simple, mild and *anti*-stereoselective method for the reduction of the carbonyl group of β-hydroxycarbonyl compounds.[9]

Recently we have described a novel aldol-transfer reaction by which one half of a self-aldol adduct of a ketone is transferred to an aldehyde (the other half is released as free ketone).[10] In order to explore the utility of the aldol-transfer reaction we developed the coupled aldol-transfer–Tischtschenko reaction shown in Scheme 1. This technique allows direct conversion of the intermediate products of the aldol-transfer reaction (**A**, Scheme 2) to the corresponding monoacylated diol of *anti*-stereochemistry (**B**, Scheme 2). Various aldehydes together with 4-hydroxy-4-methyl-2-pentanone were used as a test system. The results are summarized in Table 1.[11]

In order to choose conditions for the reactions summarized in Table 1, a basic assumption was that it should be possible to achieve a high aldehyde to monoacylated diol conversion efficiency at room temperature with a low amount of catalyst. Therefore, five experiments (entries 1–5, Table 1, conversion of butanal to 2-



Scheme 1. Tandem aldol-transfer–Tischtschenko reaction.

* Corresponding author.

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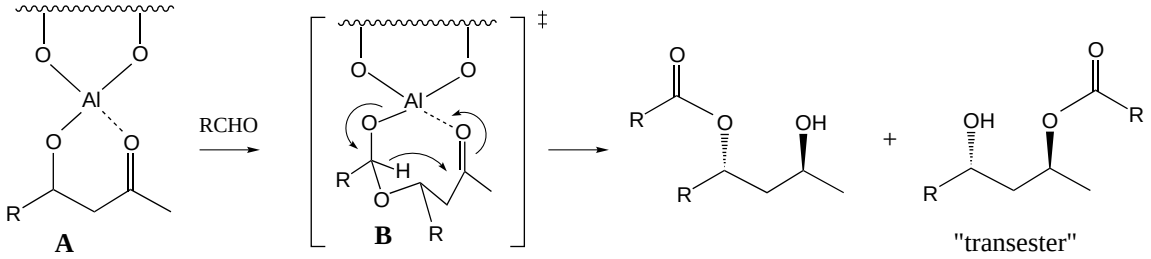

Scheme 2. Possible transition state for the formation of the monoacylated diol from the preformed aldol and aldehyde.

Table 1. The catalytic tandem aldol-transfer–Tischtschenko reaction of aldehydes

Entry	R	Aldehyde (equiv.)[a]	Me_3Al mol%[a]	Rxn time (h)	Yield (%)[a,b]
1	1-Propyl	3	5	22	35
2	1-Propyl	2	5	22	48
3	1-Propyl	2	10	22	56[c]
4	1-Propyl	3	10	22	80[d,e]
5	1-Propyl	2	1	138	Trace
6	Methyl	3	10	22	68[f]
7	Ethyl	3	10	22	73[g]
8	1-Heptyl	3	10	22	79[e]
9	2-Propyl	3	10	22	59[e]
10	2-Pentyl	3	10	22	81
11	*c*-Hexyl	3	10	22	74[c]
12	1-(1-Bromo)heptyl	3	10	22	0[h]

[a] Yield of ester relative to 4-hydroxy-4-methyl-2-pentanone.
[b] Isolated by flash chromatography.
[c] Transester formed in small amounts.
[d] Ester–transester in ca. 5:1 ratio.
[e] Only the *anti*-diastereomer of the corresponding diol was observed (^1H NMR and ^{13}C NMR).
[f] Isolated by distillation.
[g] Ester–transester in ca. 3:2 ratio.
[h] Not detectable.

hydroxy-4-heptylbutanoate) with different reaction times were conducted. The amount of catalyst was varied in the range of 1–10 mol% (entries 1, 4 and 5, Table 1). The results indicated that in order to reach high conversion 10 mol% of Me_3Al is needed. The excess aldehyde accelerates the formation of monoacylated diol (entries 3 and 4, Table 1). In every reaction, small amounts of the corresponding ester (i.e. butylbutyrate) and aldol adduct (i.e. 4-hydroxy-heptan-2-one) are formed as side-products.

A plausible reaction mechanism is based on a two-step reaction: at first an enolate of acetone is transferred to the aldehyde via an aldol-transfer reaction to give intermediate **A** (Scheme 2).[10] In the next step adduct **A** reacts with the second equivalent of aldehyde potentially forming a hemiacetal adduct **B** (Scheme 2). The intramolecular hydride-transfer reaction taking place in **B** reduces the carbonyl group of the ketone moiety.

The reaction (Scheme 1) was studied with eight aliphatic aldehydes as summarized in Table 1 (entries 4 and 6–12). All of these aldehydes gave good yields. The lowest yield was observed in the case of isobutyric aldehyde (59%) and acetaldehyde (68%) (entries 6 and 9, Table 1). The yield when acetaldehyde was used as a substrate (entry 6) cannot be compared with the yields of other aldehydes because the product was isolated by distillation (instead of flash chromatography). Interestingly α-bromo-octanal (entry 12, Table 1) appeared to be inert under these conditions. The lack of reactivity is potentially due to either steric hindrance or increased acidity of the α-hydrogen of the aldehyde precursor.

The yield of diolmonoester increases with the lengthening of the carbon chain in the case of linear aldehydes (entries 4, 6, 7 and 11, Table 1) except in the case of octanal which gave a slightly lower yield than butanal.

Two reaction products were hydrolyzed to the corresponding diols in order to determine the relative stereochemistry (entries 4 and 9, Table 1). Only the *anti*-diastereomer was observed in both cases when NMR spectra of diols were compared with the literature values.[12]

Herein, we have introduced a novel tandem aldol-transfer–Tischtschenko reaction for the one-pot synthesis of diolmonoesters from β-hydroxyketones and aldehydes using diacetonealcohol as a model compound. The simplicity and generality of the reaction makes it an attractive alternative for existing methods. Further studies on the utilization of the aldol-transfer technology[10] are in progress.

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11. Typical procedure for the tandem aldol-transfer–Tischtschenko reaction is as follows: trimethylaluminum in toluene (0.2 mmol, 0.1 ml) was added at room temperature under argon to dry CH_2Cl_2 (1 ml). To the solution was simultaneously added butanal (6 mmol, 0.54 ml, 3 equiv.) and 4-hydroxy-4-methyl-2-pentanone (2 mmol, 0.25 ml, 1 equiv.) by syringe. After stirring for 22 hours, the reaction mixture was poured into aqueous HCl solution (0.5 M, 5 ml) and extracted with diethylether (3×10 ml). The combined extracts were dried over $MgSO_4$. Evaporation of the solvent and purification of the residual oil by flash chromatography gave 2-hydroxy-4-heptylbutanoate (324 mg, 1.6 mmol) as colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$, 20°C, $CHCl_3$, 7.27 ppm): δ 5.10-4.97 (m, 1H, CH), 3.65–3.56 (m, 1H, CH), 2.28 (t, $J=7.5$ Hz, 2H, CH_2), 1.7–1.2 (m, 8H, $4CH_2$), 1.13 (d, $J=6.2$ Hz, 3H, CH_3), 0.96 (t, $J=7.3$ Hz, 3H, CH_3) 0.87 (t, $J=7.1$ Hz, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 174.5, 71.2, 63.2, 44.6, 36.9, 36.3, 22.8, 18.7, 18.5, 13.8, 13.6.
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