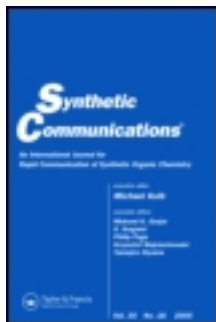


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Sosale Chandrasekhar^a & Malempati Srimannarayana^a

^a Department of Organic Chemistry, Indian Institute of Science, Bangalore, India

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New Approaches to the Cannizzaro and Tishchenko Reactions

Sosale Chandrasekhar and Malempati Srimannarayana
Department of Organic Chemistry, Indian Institute of Science,
Bangalore, India

Abstract: It is demonstrated that the titled reactions are best carried out at high concentrations, as indicated by mechanistic considerations: the observed high reaction orders and the possibility that the Cannizzaro reaction is driven by the hydrophobic effect, which effects proximity between the two molecules of the aldehyde reactant. The present studies have led to improved conditions, simplified workup, and excellent yields of products. The Tishchenko reaction converted benzaldehyde to benzyl benzoate with catalytic NaOMe/tetrahydrofuran in good yield, which is apparently unprecedented for this product of high commercial value.

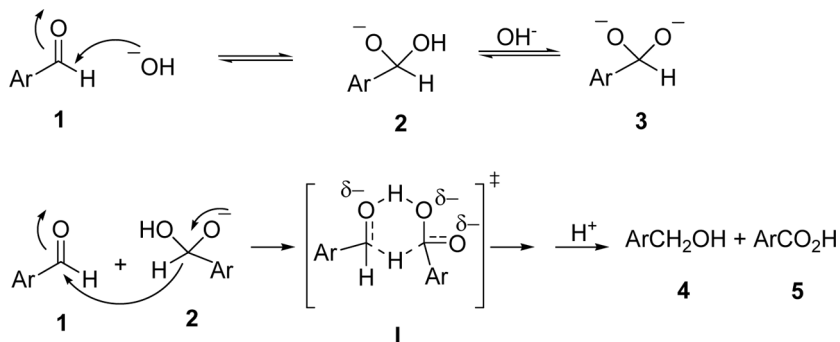
Keywords: Benzaldehyde, Cannizzaro, hydrophobic, oxidation, reduction, Tishchenko

The Cannizzaro reaction is not only one of the oldest reactions in organic chemistry but also remains of much synthetic and mechanistic importance even today.^[1–3] The reaction is an interesting redox process that generally occurs in aqueous base and converts aromatic or nonenolisable aldehydes (**1**, Scheme 1) to a mixture of the corresponding benzyl alcohol (**4**) and benzoic acid (**5**).

The Cannizzaro reaction is generally believed to occur via the initial addition of hydroxide ion to the aldehyde **1**, with the resulting tetrahedral intermediate **2** transferring a hydride ion to another molecule of **1** in a

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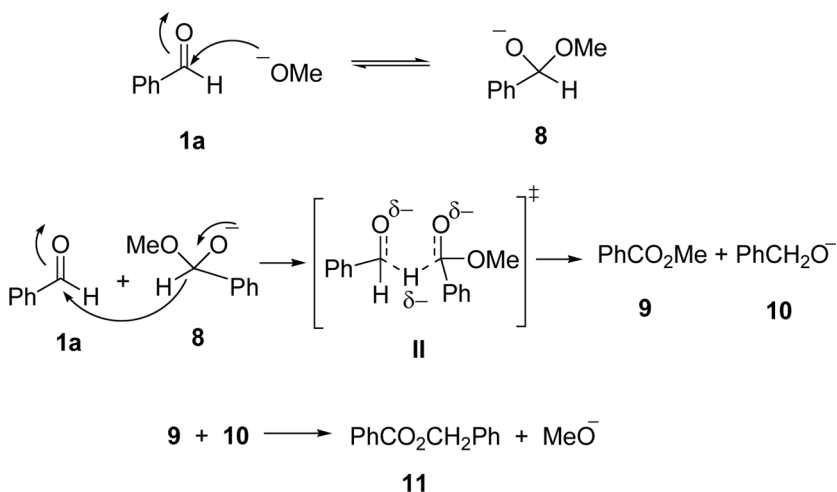
Address correspondence to Sosale Chandrasekhar, Department of Organic Chemistry, Indian Institute of Science, CV Raman Avenue, Malleswaram, Bangalore 560012, India. E-mail: sosale@orgchem.iisc.ernet.in



Scheme 1. Cannizzaro reaction of an aromatic aldehyde **1** forming the corresponding benzyl alcohol (**4**) and benzoic acid (**3**) products via transition state **I**.

key in termolecular step. At strong base concentrations, dianion **3** is formed and reacts analogously. The overall reaction is thus second order in the aldehyde and either first or second order in hydroxide depending on its concentration.

The Tishchenko reaction is an interesting variant of the Cannizzaro reaction, in which an alkoxide ion nucleophile adds initially to a benzaldehyde (**1**), to produce finally the corresponding alkyl benzoate (**9**, Scheme 2).^[2,4,5]



Scheme 2. Tishchenko reaction of benzaldehyde **1a** catalyzed by sodium methoxide in THF, forming benzyl benzoate (**11**).

The objective of this study was the development of improved procedures for these reactions, based on mechanistic considerations as discussed. (The classical procedures generally require either long reaction times or relatively high temperatures, and it would be desirable to moderate these conditions.)

In the case of the Cannizzaro reaction, the high reaction orders mentioned previously, and the fact that the saturation concentration of the aldehyde substrate in water would be constant at a given temperature, indicate that a minimal quantity of water needs be employed. Also, the need for an aqueous medium possibly indicates the hydrophobic association of two molecules of the aldehyde.

We have found that the Cannizzaro reaction of several aromatic aldehydes (**1**) may be conveniently effected with 4 molar equivalents of potassium hydroxide, employed as a saturated aqueous solution, within 2 h at room temperature (Table 1). Previous procedures involved overnight reaction and a difficult workup because of the emulsification of the reaction mixture.^[3] Under our conditions, the reaction was particularly rapid in the case of the activated nitro-substituted benzaldehydes. (In the case of electron-donating substituents, the yields were poor, but this is a general problem with the Cannizzaro reaction.^[1-3])

As a mechanistic aside, we have also attempted to evidence the hydrophobic driving force for the Cannizzaro reaction. We observed that the reaction with benzaldehyde is almost completely suppressed at high ionic strengths of the aqueous medium. This is most likely the result of the vastly decreased solubility of benzaldehyde in the aqueous medium, from where it is "salted out" by the sodium chloride added to increase the ionic strength. The reported ineffectiveness of phase-transfer catalysis is understandable in this context,^[6] as the reaction occurs in the aqueous phase. This is also supported by the report that the reaction is highly inefficient in nonaqueous media.^[7]

Table 1. Percentage yields of the benzyl alcohol and benzoic acid products in the Cannizzaro reaction of various benzaldehydes (cf. Scheme 1)

Item	Reactant ArCHO (1)	Yield (%) of ArCH ₂ OH (4)	Yield (%) of ArCO ₂ H (5)
1	Benzaldehyde (1a)	75 (4a)	80 (5a)
2	3-Nitrobenzaldehyde (1b)	92 (4b)	93 (5b)
3	4-Nitrobenzaldehyde (1c)	91 (4c)	90 (5c)
4	4-Methoxybenzaldehyde (1d)	85 (4d)	90 (5d)
5	4-Methylbenzaldehyde (1e)	93 (4e)	93 (5e)
6	2-Chlorobenzaldehyde (1f)	85 (4f)	91 (5f)

Table 2. Products formed in the Tishchenko reaction of aromatic aldehydes (**1**) in THF at 25°C under various conditions (cf. Scheme 2)

Item	Reactant	Reagent	Time (h)	Products	Yield (%)
1	Benzaldehyde (1a)	NaOMe	16	Benzyl benzoate (11)	70
2	Benzaldehyde (1a)	PhCH ₂ ONa	16	Benzyl benzoate (11)	18
3	1c^a	NaOMe	18	Mixture	<10
4	1d^a	NaOMe	14	Mixture	<10
5	1e^a	NaOMe	10	None	—

^aCompare with Table 1.

We have found that the Tishchenko reaction may be carried out with benzaldehyde (**1a**) and sodium methoxide in catalytic amounts, again at high concentrations in tetrahydrofuran (THF) solution. These conditions led to the formation of benzyl benzoate (**11**) in excellent yields (Table 2), presumably via the mechanism in Scheme 2. (This is analogous to Scheme 1, with hydride transfer occurring from the tetrahedral intermediate **8** via transition state **II**.) The initially formed methyl benzoate (**9**) and benzyl alcoholate (**10**) react further to form benzyl benzoate (**11**), thus regenerating the methoxide ion.

The yield of benzyl benzoate is much less if benzyl alcoholate anion (**10**) is employed (Table 2, item 2), possibly a steric effect of the bulkier benzyl alcoholate anion. The reaction also essentially failed with substituted benzaldehydes (Table 2, items 3–5). (The reaction was also decelerated at high pressures, presumably because of a decrease in the diffusion of the reactive species.)

In conclusion, improved experimental procedures for the Cannizzaro reaction of aromatic aldehydes have been developed. These involve shorter reaction times, minimal use of water, and a simplified workup. The Tishchenko reaction of benzaldehyde has also been carried out under considerably milder conditions than before.

EXPERIMENTAL

General Comments

The following instruments were used: Jasco Fourier-transform-infrared (FT-IR) 410 and Jeol JNM-LA 300 FT NMR. IR spectra were recorded on thin films, and ¹H NMR spectra were measured at 300 MHz in CDCl₃ solution with tetramethylsilane (TMS) as internal standard. Evaporation of solvent was performed in a rotary evaporator under reduced pressure.

General Procedures

Cannizzaro Reaction

The aromatic aldehyde (1.0 mmol) was added to a saturated solution of potassium hydroxide (KOH, 4.0 mmol), and the mixture was stirred at room temperature for 1–2 h. The thick slurry was treated with water (10 ml), and the resulting mixture was extracted with CH_2Cl_2 (20 ml). The extracts were washed with water and dried (MgSO_4), and the solvent was distilled off to obtain the crude benzyl alcohol product. The aqueous part was acidified with 3 N HCl, extracted with CH_2Cl_2 , and worked up as before to obtain the benzoic acid product. The crude products were purified by chromatography or recrystallization, and the products were identified spectrally, typically as follows: 4-Methoxybenzyl alcohol **4d**: ν_{max} 3357 cm^{-1} ; δ_{H} 3.80 (s, 3H), 4.61 (s, 2H), 6.88 (d, J 15 Hz, 2H), 7.27 (d, J 15 Hz, 2H). 3-Nitrobenzoic acid **5b**: ν_{max} 3444, 3095, 1706 cm^{-1} ; δ_{H} 7.73 (m, 1H), 8.48 (m, 2H), 8.96 (s, 1H).

Tishchenko Reaction

Benzaldehyde (1.0 mmol) was added to a solution of NaOMe (0.1 mmol) in dry THF (3.0 ml), and the mixture was stirred at 25°C for 16 h. The thick slurry was treated with water (1 ml), and the resulting mixture was extracted with ethyl acetate (5 ml). The extracts were dried (Na_2SO_4), and the solvent was distilled off in vacuo to obtain the crude benzyl benzoate product. This was purified by column chromatography (SiO_2) and identified spectrally. Benzyl benzoate (**11**): ν_{max} 1718 cm^{-1} ; δ_{H} 5.36 (s, 2H), 7.40 (m, 6H), 7.56 (m, 2H), 8.08 (m, 2H).

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