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Transformations of acetophenone and its derivatives in supercritical fluid isopropanol/CO_2 in a continuous flow reactor in the presence of alumina

V.P. Sivcev[c], K.P. Volcho[b], N.F. Salakhutdinov[b], V.I. Anikeev[a,*]

[a] *Boreskov Institute of Catalysis, Siberian Branch of the Russian Academy of Sciences, Prosp. Akad. Lavrent'eva 5, Novosibirsk 630090, Russian Federation*
[b] *Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Prosp. Akad. Lavrent'eva 9, Novosibirsk 630090, Russian Federation*
[c] *Novosibirsk State University, Pirogova st. 2, Novosibirsk 630090, Russian Federation*

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ABSTRACT

Acetophenone and its derivatives undergo various transformations in binary supercritical solvent isopropanol/CO_2 in a flow reactor in the presence of granulated Al_2O_3. Depending on the reaction temperature, respective secondary alcohols, or isopropyl ethers, or substituted styrenes are formed at contact times of ~4 min. Selectivity for the reaction products attains 96% at high conversion of initial compounds. It was shown that the nature of a substituent in ketone aromatic ring exerts primary effect both on the conversion of initial compounds and on stability of intermediates under reaction conditions, and thus affects the end product distribution.

1. Introduction

The use of continuous flow reactors in fine organic chemistry enables ready variation of the reaction parameters (temperature, pressure, flow rate, contact time, etc.), process safety, feasible upscaling, etc. [1–4]. Combination of the flow reactors with heterogeneous catalysts and supercritical fluids provides significant system enhancement [5,6].

As shown in our recent studies [7,8], a system comprised of a continuous flow reactor, supercritical solvent isopropanol/CO_2 and Al_2O_3 catalyst provided efficient Meerwein–Ponndorf–Verley (MPV) reduction of aliphatic and aromatic aldehydes to respective alcohols at short contact times and temperatures below 473 K. In these reactions, isopropanol was the reducing agent; it converted to acetone. The CO_2 additive to isopropanol allows to perform the process under supercritical conditions in the overall range of the used temperatures and pressures and to improve the reaction conversion and selectivity [7]. It should be noted that no reduction of aliphatic ketone pinocamphone was observed under the specified conditions [7,8]. At the same time, reduction of ketones into secondary alcohols is one of the most important reactions in fine organic chemistry and pharmaceutically industry in particular [9]. In contrast to aldehydes, reduction of ketones produces quite labile secondary alcohols. As a result, at high temperatures and in the presence of heterogeneous catalyst, subsequent transformations become highly probable, that imposes essential limitations on the selection of the reaction conditions.

The aim of the present work was to find reaction conditions for selective transformation of acetophenone **1a** and its derivatives into valuable products in a continuous flow reactor in supercritical fluid.

2. Experimental

Commercially available (Aldrich) acetophenone, 4-fluoroacetophenone, 4-chloroacetophenone, 4-bromoacetophenone, 4-methylacetophenone, 4-methoxyacetophenone, 4-nitroacetophenone and benzophenone of purity better than 99% were used in the present experiments. The used isopropyl alcohol contained no less than 99.8 wt.% of the main substance and no more than 0.05 wt.% of water. CO_2 was a stated purity of 99.9 vol.% and contained no more than 0.02 vol.% water. The reactor was loaded with Al_2O_3 (Macherey-Nagel, pH 7 ± 0.5, free BET surface area ~130 m^2/g) of 50–200 μm particle size.

Experimental studies were performed in the laboratory-scale set-up described earlier [7], using a tubular flow-type reactor (6.0 mm × 0.8 mm, length 3.0 m) loaded with 42 cm^3 (39.1 g) of alumina. The initial mixture was fed to the reactor as two streams. The first stream – supercritical CO_2 – was delivered by syringe pump to a mixer mounted at the reactor inlet, through a heat exchanger

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* Corresponding author.
E-mail address: anik@catalysis.nsk.su (V.I. Anikeev).

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where it was heated to the reaction temperature. The liquid CO_2 flow rate was 5.0 ml/min. The second stream – 1% solution of compound in isopropanol – was fed to the same mixer by piston pump at a flow rate of 3.0 ml/min.

The products of reaction were cooled at the reactor outlet, separated into gas and liquid phases, and analyzed.

In order to determine the reaction conditions (temperature and pressure) providing a homogeneous state of reaction mixture in the reactor, thermodynamic calculations were used to construct a phase diagram for the initial composition of the mixture, and the critical values were found. The calculations were based on techniques developed earlier using the RKS equation of state [10]. The critical values $T_{cr} = 396.0$ K and $P_{cr} = 14.5$ MPa were found to the mixture CO_2/isopropanol in molar ratio 4/1. Since the total part of CO_2 and isopropanol in the initial mixture exceeds 0.95 and remains virtually constant in the course of reaction, one can suggest that position of the critical point will change only slightly during the reduction.

It is known that critical values for CO_2 are $T_{cr} = 304.2$ K and $P_{cr} = 7.38$ MPa, isopropanol – $T_{cr} = 508.2$ K and $P_{cr} = 5.3$ MPa. The experimental temperature and pressure intervals were selected as $T = 455–620$ K and $P = 17.2–18.2$ MPa in the result of above calculations.

The authors would like to notice that the advantages of CO_2 (system CO_2/isopropanol) are well proved in the literature for a large class of reactions. The use of supercritical CO_2 as a component of the two-component solvent allowed to reduce significantly the critical temperature of a solvent, i.e., enabled the reaction carrying out in supercritical region at a temperature below the critical temperature of the second component.

The reaction mixture residence time τ was ~5.3 min at 8.0 ml/min total flow rate and was calculated as a ratio of catalyst volume V_{cat} (cm^3) to the inlet volume consumption of liquid mixture Q (cm^3/min). The temperature and pressure intervals were $T = 455–620$ K and $P = 17.2–18.2$ MPa.

Composition of the reaction products in the liquid phase was determined by gas chromatography–mass spectrometry (GC–MS) using an Agilent 7890A gas chromatograph equipped with a quadrupole mass spectrometer Agilent 5975C as a detector. Quartz column HP-5MS (copolymer 5%-diphenyl–95%-dimethylsiloxane) of length 30 m, internal diameter 0.25 mm and stationary phase film thickness 0.25 μm was used for the analysis. The standard deviation for chromatographic analysis is not more than 3%.

Qualitative analysis was performed by comparing retention indices of components and their complete mass spectra with the corresponding data for pure compounds if any and with the data of the NIST library, the Wiley7 library of mass-spectrometric data. In experiments with acetophenone, the percentage composition of the mixture was calculated using internal standard and correction coefficients. In other cases, the percentage composition of mixtures was calculated from the surface areas of chromatographic peaks using no correction coefficients.

To identify the structure of several compounds not found in the libraries of mass-spectrometric data, we performed preparative separation of the substances form the reaction mixtures. The structure was determined by comparing the obtained ^{1}H NMR (300 MHz, $CDCl_3$) spectra with available literature data.

2.1. *Compounds **2a** and **3a***

The solvent and styrene **4a** were removed in a rotary evaporator from the combined reaction mixtures obtained after acetophenone **1a** reduction at 455–555 K. The residue (1.25 g) was separated in silica gel (9 g) column using hexane/ethyl acetate gradient (0–100%) elution. The obtained products were 1-phenylethanol **2a** (0.803 g) and (1-isopropoxyethyl)benzene **3a** (0.087 g).

Compound **2a**. ^{1}H NMR spectrum, δ, ppm: 7.38–7.23 m (5H), 4.87 qd ($J_q = 6.4$ Hz, $J_d = 3.0$ Hz, 1H), 2.0 s (1H), 1.48 d ($J = 6.7$ Hz, 3H). The ^{1}H NMR spectrum of compound **2a** coincided with respective spectrum reported in the literature [11].

Compound **3a**. ^{1}H NMR spectrum, δ, ppm: 7.35–7.21 m (5H), 4.52 q ($J = 6.5$ Hz, 1H), 3.48 septet ($J = 6.2$ Hz, 1H), 1.40 d ($J = 6.5$ Hz, 3H), 1.14 d ($J = 6.1$ Hz, 3H), 1.09 ($J = 6.3$ Hz, 3H). The ^{1}H NMR spectrum of compound **3a** coincided with respective spectrum reported in the literature [12].

2.2. *Compounds **5g**, **7** and **11***

The solvent was removed in a rotary evaporator from the reaction mixtures obtained after 4-nitroacetophenone **1g** reduction at 570 K. The residue (0.056 g) was separated in NEt_3-deactivated silica gel (4 g) column using hexane/ethyl acetate gradient (0–100%) eluent containing 1% NEt_3. The obtained products were 0.016 g of 14-ethylaniline **5g**, 0.006 g of 1-(4-aminophenyl)ethanone **7** and 0.014 g of 4-ethyl-N-isopropylaniline **11**.

Compound **5g**. ^{1}H NMR spectrum, δ, ppm: 6.98 d ($J = 8.3$ Hz, 2H), 6.61 d ($J = 8.3$ Hz, 2H), 3.75–3.22 s (2H), 2.52 q ($J = 7.7$ Hz, 2H), 1.17 t ($J = 7.6$ Hz, 3H). ^{1}H NMR spectrum of compound **5g** coincided with respective spectrum reported in the literature [13].

Compound **7**. ^{1}H NMR spectrum, δ, ppm: 7.01 d ($J = 8.6$ Hz, 2H), 6.55 d ($J = 8.4$ Hz, 2H), 2.80 s (3H). ^{1}H NMR spectrum of compound **7** coincided with respective spectrum reported in the literature [14].

Compound **11**. ^{1}H NMR spectrum, δ, ppm: 6.98 d ($J = 8.4$ Hz, 2H), 6.52 d ($J = 8.4$ Hz, 2H), 3.58 septet ($J = 6.3$ Hz, 1H), 2.51 q ($J = 7.6$ Hz, 2H), 1.21–1.14 m (9H). Detected $[M]^+$ 163.1355. $C_{11}H_{17}N$. Calculated M 163.1356.

2.3. *Compounds **13**, **14** and **15***

The reaction mixture after reduction of benzophenone **12** at 570 K was filtered; the obtained sediment was (isopropoxymethylene)dibenzene **14** (0.018 g). The mother liquor was boiled out in the rotary evaporator. The product mixture (0.028 g) consisted of diphenylmethane **13** and (oxybis(methanetriyl))tetrabenzene **15** in ratio 1:0.23 (according to ^{1}H NMR data).

Compound **13**. ^{1}H NMR spectrum, δ, ppm: 7.40–6.97 m (10H), 3.99 s (2H). ^{1}H NMR spectrum of compound **13** coincided with respective spectrum reported in the literature [15].

Compound **14**. ^{1}H NMR spectrum, δ, ppm: 7.21–6.96 m (10H), 4.76 s (1H), 4.01 septet ($J = 6.1$ Hz, 1H), 1.20 d ($J = 6.0$ Hz, 6H). ^{1}H NMR spectrum of compound **14** coincided with respective spectrum reported in the literature [16].

Compound **15**. ^{1}H NMR spectrum, δ, ppm: 7.40–6.97 m (10H), 5.49 s (2H). ^{1}H NMR spectrum of compound **15** coincided with respective spectrum reported in the literature [17].

3. Results and discussion

For experimental studies of MPV reaction in supercritical isopropanol/CO_2 mixture in the presence of heterogeneous catalyst alumina, acetophenone **1a** (Scheme 1) was selected as the first substrate. Earlier, the authors of [18] attempted to perform noncatalytic reduction of acetophenone **1a** in supercritical isopropanol in continuous flow reactor, but the reaction showed low selectivity and low acetophenone **1a** conversion.

The reaction was run at temperatures of 455–620 K. The reaction mixtures were analyzed by GC–MS using internal standard and correction coefficients.

The effect of the supercritical CO_2 concentration (which can be varied by changing its flow rate) on the product distribution was not studied because authors in early work [19] showed, that