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Dedicated to Professor Valer Fărcăşan
at his 85th anniversary

HYDROAMINATION OF 1,3-CYCLOHEXADIENE IN WATER – HEPTANE LIQUID-LIQUID TWO-PHASE CATALYTIC SYSTEM

J. BÓDIS[1,2], T. E. MÜLLER[2] and J. A. LERCHER[2]

[1] *Babes-Bolyai University, Department of Organic Chemistry, str. Arany Janos nr. 11, 400028 Cluj, Romania. E-mail: jbodis@chem.ubbcluj.ro*
[2] *Institut für Technische Chemie, Technische Universität München, Lichtenbergstr. 4, D-85747, Garching bei München, Germany*

ABSTRACT. The direct addition of substituted aromatic amines to 1,3-cyclohexadiene was efficiently catalyzed in a liquid - liquid two phase system comprised of a polar catalyst of $Zn(CF_3SO_3)_2$ in water and the substrate and reactant mixture in n-heptane. The successful replacement of 1-ethyl-3-methyl-imidazolium trifluoromethanesulfonate with water, a greener and cheaper polar solvent than any ionic liquid (IL), for hydroamination reactions of cyclohexadiene with aromatic amines, was demonstrated.

Keywords: Hydroamination, 1,3-Cyclohexadiene, Amines, Catalysis, Lewis and Brönsted acids, Water

INTRODUCTION

The direct reaction of unsaturated compounds (alkenes or alkynes) with ammonia or primary/secondary amines (hydroamination) is an atom-economical route for the synthesis of nitrogen containing organic compounds [1]. The resulting amines or imines are of great importance for the chemical and pharmaceutical industry. While the new amines are potential drug candidates, the pharmaceutical companies have a serious deficit concerning their amine libraries [2]. Intensive explorative research has been made worldwide in the last years in order to develop efficient hydroamination processes [3]. Unfortunately, a real breakthrough did not occur in this area and only one process, the synthesis of *t*-butylamine from ammonia and isobutene in the presence of a zeolite catalyst has been commercialized [4]. None of other catalysts (homogeneous or heterogeneous) developed and tested until now reached sufficient activity for commercial applications [5].

Since the rate of the hydroamination reactions is directly dependent on the amount of catalyst employed, one of the most efficient strategies to achieve higher reaction rates is the use of a high concentration of catalysts, coupled with an efficient separation. This can be realized in solid-gas, solid-liquid or liquid-liquid heterogeneous systems. The possibility of catalyzing hydroamination reactions with Zn^{2+} ion exchanged zeolites has been demonstrated for the addition of methylamine to propyne (solid-gas system) [6] and for the cyclization of 6-aminohex-1-yne (solid-liquid system) [7,8].

The first hydroamination reaction in a liquid-liquid two-phase system has been realized for the cyclization of *o*-ethynylanilines to indoles with palladium(II)-salts in CH_2Cl_2 and aqueous HCl [9].

The challenge of the recent studies was to develop a new liquid-liquid two-phase system using green solvents, which would allow to perform hydroamination reactions in a more general manner. The selection of the solvent pair faces several boundary conditions: (i) most transitional metal catalysts for hydroamination reactions are cationic (*e.g.*, Rh^+, Pd^{2+}, Cu^+, Zn^{2+}) [10-12], and therefore, to dissolve the corresponding salts, a polar solvent is required, (ii) to achieve high reaction rates, the metal ion should be only weakly coordinated to the solvent, and (iii) the catalyst bearing liquid phase has to be immiscible with an appropriate apolar organic solvent in which the reactants and product should have high solubility. For the intramolecular hydroamination of 6-aminohex-1-yne, an ionic liquid (IL), 1-ethyl-3-methylimidazolium trifluoromethanesulfonate was chosen as polar phase (solvent for the catalyst precursor, $Zn(CF_3SO_3)_2$) and *n*-heptane as apolar phase (solvent for the starting materials and products) [5]. Based on the promising results (good conversions and yields, fast reaction, no leaching of the catalyst, possibility of continuous operation), the liquid-liquid two-phase catalytic procedure was extended to intermolecular hydroamination reactions [13-15], as well (see Fig.1).

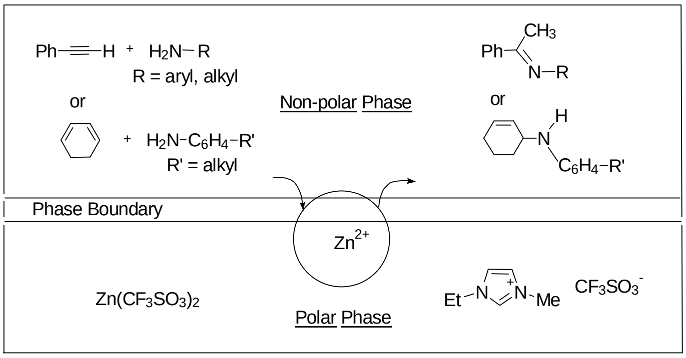
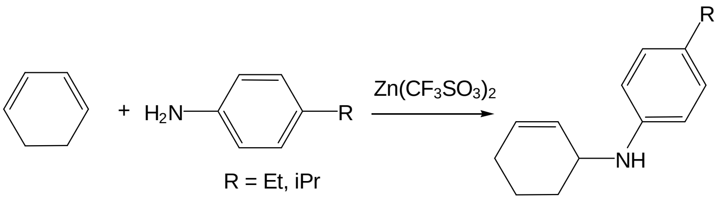


Fig. 1. Schematic model of liquid-liquid two-phase catalytic intermolecular hydroamination reactions.

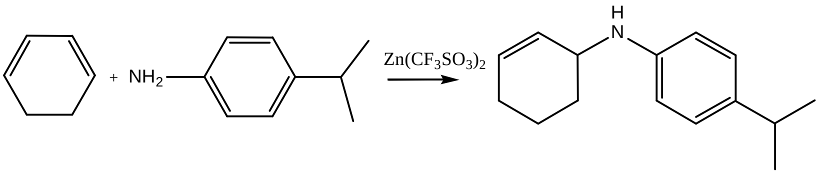
The present contribution is focused on liquid-liquid, water-heptane two-phase catalytic intermolecular hydroamination reactions of an alkene-type substrate (hydroamination of 1,3-cyclohexadiene, see Eq. 1).

 (1)

RESULTS AND DISCUSSION

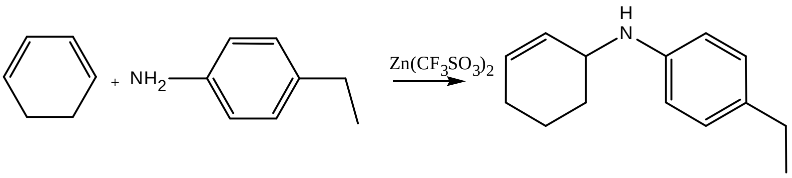
To test the scope and suitability of two-phase catalysis by using water as polar solvent, the hydroamination reaction of 1,3-cyclohexadiene with phenylamine, 4-ethyl-phenylamine, 4-isopropyl-phenylamine and 4-fluoro-phenylamine were explored. The reactions were performed in the batch mode stirring the reaction mixture sufficiently fast (1000 rpm) to obtain a fine emulsion of the polar water phase in heptane. In this case, a large surface area was achieved, enabling a relatively fast mass transfer across the phase boundary.

The reaction between 1,3-cyclohexadiene and 4-isopropyl-phenylamine provided cyclohex-2-enyl-(4-isopropyl-phenyl)-amine as the major product (Eq. 2).



(2)

4-ethyl-phenylamine is giving cyclohex-2-enyl-(4-ethyl-phenyl)-amine (Eq. 3), but phenylamine and 4-fluoro-phenylamine did not react with cyclohexadiene.



(3)

For both reactions, the concentration of the starting materials in the apolar phase decreased rapidly within the first minutes of the reaction (see the concentration-time diagrams for the hydroamination reaction of 1,3-cyclohexadiene with 4-isopropyl-phenylamine on Fig. 2). The formation of the major product follows first order kinetics, k_{init} = 0.000652 min^{-1}, TOF = 3.9 h^{-1}, (TOF = turnover frequency). 42% yield is reached after 25 hrs reaction time. At longer reaction times, the reactants were consumed at a lower rate. Only a few amount of the dimer of 1,3-cyclohexadiene is formed as a secondary product, no other products were identified in the reaction mixture.

We estimated the partitioning of each component between the heptane phase and a solution of $Zn(CF_3SO_3)_2$ in water. The starting materials, 1,3-cyclohexadiene and both 4-isopropyl-phenylamine and 4-ethyl-phenylamine were considerably more soluble in heptane than in water (solubility close to 0) at a temperature range of 25 - 98°C (Eq. 4, *React* stands for 1,3 cyclohexadiene and for the amines used).

$$K_{eq}^{React} = \frac{c^{React}(H_2O)}{c^{React}(Heptane)} = 0 \qquad (4)$$

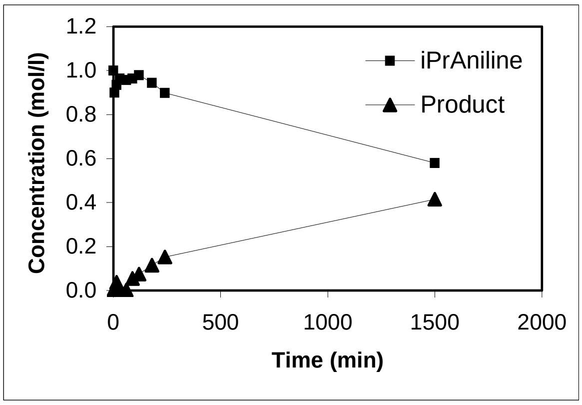


Fig. 2. Concentration *versus* time diagram for the hydroamination reaction between cyclohexadiene and 4-isopropyl-phenylamine (stoichiometic ratio) catalysed by $Zn(CF_3SO_3)_2$ in water-heptane liquid-liquid two-phase system.

The same behavior was found for the main products of the reactions, they were found also to be present only in the heptane phase (Eq. 5).

$$K_{eq}^{Product} = \frac{c^{Product}(H_2O)}{c^{Product}(Heptane)} = 0 \qquad (5)$$

Based on the observation that homogeneous hydroamination reactions could be accelerated by addition of a Brønsted acid, trifluoromethanesulfonic acid was added to the reaction mixture of 1,3-cyclohexadiene and 4-isopropyl-phenylamine. The same product, cyclohex-2-enyl-(4-isopropyl-phenyl)-amine was formed with almost the same reaction rate. Similarly, the rate of reaction was very close, when trifluoromethanesulfonic acid was employed as the only catalyst. This indicates that the two-phase reaction of 1,3-cyclohexadiene proceeds almost the same when the catalyst $Zn(CF_3SO_3)_2$ is employed under neutral or acidic conditions or CF_3SO_3H alone is used as catalyst. Thus, the reaction seems to be most likely Brønsted acid catalyzed, being different from the reaction of phenylacetylene with aromatic amines in ionic liquid-heptane two-phase system, where the results revealed a Lewis acid catalysis [13-16].

The new reaction system employed in this study is very close to the ideal synthesis [17] (environmentally acceptable, resource efficient, available materials, one step, safe, simple, high yield).

CONCLUSIONS

It has been demonstrated that the addition of aromatic amines (with alkyl groups on the benzene ring) to 1,3-cyclohexadiene can be efficiently catalyzed with $Zn(CF_3SO_3)_2$ or with CF_3SO_3H in a liquid-liquid water-heptane two-phase system. The major advantage is that after the reaction the catalyst remains quantitatively in water, which can be easily separated from the organic phase. The product is obtained after removal of heptane in a high quality.

Water as a green (ecological) and cheap solvent is able to substitute the highly expensive and less greener 1-ethyl-3-ethylimidazolium trifluoromethanesulfonate ($EtMeIm^+TfO^-$) ionic liquid found recently a good catalyst bearing solvent for two-phase catalytic intermolecular hydroamination [13-15]. The new reaction system employed in this study is very close to the ideal synthesis.

EXPERIMENTAL

Materials and Methods

n-heptane (99%) was obtained dry from Aldrich. 1,3-cyclohexadiene (97%, Aldrich) and the amines (phenylamine, 4-ethyl-phenylamine, 4-isopropyl-phenylamine and 4-fluoro-phenylamine) were obtained in high purity (98-99%) from Aldrich and used as received. Zinc trifluoro-methanesulfonate ($Zn(CF_3SO_3)_2$, 98%, Aldrich) and trifluoro-methanesulfonic acid (CF_3SO_3H, 99%, Aldrich) were employed as catalysts without further purification.

Physical and Analytical Methods

^{1}H- and ^{13}C{^{1}H}- NMR spectra were recorded on a Bruker GX 360 NMR instrument and referenced in ppm relative to the solvent shift [18] or tetramethylsilane. GC-analyses were performed on a HP 5890A gas chromatograph with FID detector and a HP 5890 series II gas chromatograph with HP 5971 mass selective detector HP 5730A. Both gas chromatographs were equipped with a crosslinked 5% diphenyl- 95 % dimethyl-polysiloxane column (30 m, Restek GmbH, Rtx-5 Amine). Infrared spectra were obtained on a Perkin Elmer 2000 FT-IR spectrometer as thin film of the neat compound. Elemental analyses were performed by the Microanalytical Laboratory of the TU München.

Preparation and kinetic measurements

The kinetic experiments were performed in the batch mode in magnetically stirred custom built 60 cm^3 autoclaves at 180-200 ºC and 6-10 bar. In a typical experiment, the reactor was charged with $Zn(CF_3SO_3)_2$ (0.07 g, 0.2 mmol) and distilled water (0.5 cm^3, home made) under nitrogen. After the catalyst had dissolved in water (several minutes) n-heptane (15 cm^3) and amine (20 mmol) were introduced. The mixture was stirred at 1000 rpm and the reactor heated to the reaction temperature. 1,3-cyclohexadiene was then introduced with a HPLC pump. Samples were taken for GC and MS analyses. The final reaction mixture was separated, the water phase was washed with n-heptane and the unified organic phase concentrated in a rotating evaporator. The liquid product was purified by distillation in a partial vacuum.

Cyclohex-2-enyl-(4-isopropyl-phenyl)-amine.
Yield: 1.72 g, 40%.
B.p. 105-107°C (0.3 mbar).
Found: C, 84.2; H, 9.9; N, 6.4%.
Calc. for $C_{15}H_{21}N$: C, 83.7; H, 9.8; N, 6.5%.
^{13}C{^{1}H}-NMR (CD_3COCD_3): 166.2 (s, *C*N), 151.3 (s, C^iPr), 145.0 (s, Ph), 141.2 (s, Ph), 131.9 (s, Ph), 129.8 (s, Ph), 128.7 (s, Ph), 128.3 (s, Ph), 120.9 (d, Ph), 35.0 (s, CH), 25.2 (s, 2 CH_3), 18.0 (s, $\mathit{C}H_3CN$) ppm.

^{1}H-NMR (CD_3COCD_3): 6.93 (dtd, 2H, Ph), 6.54 (dd, 2H, Ph), 5.89 (mt, 1H, C=C*H*), 5.64 (mq, 1H, *H*C=C), 4.26 (b, 1H, N*H*), 3.47 (m, 1H, NC*H*), 2.75 (sept, 1H, CH), 2.0 - 1.3 (m, not resolved, 6H, 3 CH_2), 1.19 (d, 6H, 2 CH_3) ppm.
IR (neat): 3448 (m), 3365 (m), 3017 (s), 2956 (vs), 2929 (vs), 2864 (s), 1622 (vs), 1502 (vs), 1458 (m), 1429 (w), 1381 (w), 1361 (w), 1279 (s), 1156 (w), 1046 (w), 994 (w), 886 (m) cm^{-1}.
m/z (FAB) 215 (M^+), 200 (M^+-CH_3).

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