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Synthesis of primary amines from the renewable compound citronellal via biphasic reductive amination

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ABSTRACT

The reductive amination of the natural product citronellal with ammonia is presented as a new and atom economic way to its primary amine derivatives. The aqueous ammonia phase contains the homogeneous catalytic system $[Rh(cod)Cl]_2$/TPPTS in a biphasic solvent system, whereas the starting material and the products remain in the apolar solvent phase. This concept supresses side reactions effectively, achieving a high yield of primary amines of up to 87%. Systematic investigations demonstrate that the cleavage of the secondary imine as an undesired by-product is necessary in achieving high selectivites, which can be controlled by the reaction conditions. Surfactants, ionic liquids or native cyclodextrins and their derivates prove to be useful phase transfer agents for optimising the interaction between the organic and the aqueous phase. The use of the ionic liquid [DecMIM]Br and the cyclodextrin derivative methyl-β-cyclodextrin provided especially fast and accurate phase separation.

1. Introduction

Citronellal (3,7-dimethyloct-6-en-1-al) is a monoterpenoid that contains an aldehyde function. As a natural resource, it is well known as a flavoring agent and insect repellent. Citronellal exists in the form of two possible enantiomers: the (*R*)-isomer is typically found in citronella [1] while the (*S*)-isomer appears mainly in the essential oil of kaffir lime [2] (Fig. 1).

In addition to that, citronellal as a racemate is among many essential oils that are derived from the fruits and leaves of citrus plants. Essential oils can be extracted from these plants by means of steam distillation. Apart from the natural way of producing citronellal, it can be synthesised from the monoterpene β-pinene. β-Pinene itself is in large part the turpentine oil from conifers. After pyrolysis to β-myrcene, amination, isomerisation and hydrolysis, citronellal is produced as a racemate ($1.000\,t\,a^{-1}$) [3a,b]. Alternative synthesis routes include the dehydrogenation of citronellol [4] or the selective hydrogenation of citral [5a–c]. Citronellal is used for the production of isopulegol and menthol, as well as vitamins A and E at an industrial scale [6]. A review describes well-established synthesis routes based on citronellal.[7]

The reductive amination is a tandem reaction that consists of a condensation and a hydrogenation step (Scheme 1). Reductive aminations are possible with ketones, aldehydes, and even alcohols as starting materials. They react with an amine substrate in a condensation reaction, which results in an aldimine, imine or enamine in the initial step. In the second step, the intermediate is hydrogenated catalytically under the same reaction conditions, which results in primary, secondary or tertiary amines depending on which amine is used.

Reductive aminations of aldehydes with ammonia were first described in a general sense in relation to the Borch-reduction [8]. Bhattacharyya et al. investigated the reductive amination in two steps including the combination of ammonia with titanium(IV) isopropoxide and a consecutive reduction with sodium borohydride [9]. With benzaldehyde as substrate, a 77% yield of the primary amine was achieved. Later, Timmer et al. developed an alternative process using sodium cyanohydridoborate in combination with ammonium acetate and ammonia [10]. The best yield was reached in the reduction of n-nonanal to its analogous primary amine at 98%. Late transition metals have also been used for the reductive amination of aldehydes, mainly in combination with the model substrate benzaldehyde [11–13]. Beller et al. transformed benzaldehyde to benzylamine with a 96% yield by raising the reaction temperature to 135 °C [12]. A catalytic system consisting of a rhodium precursor and water-soluble phosphine ligand was used in a biphasic solvent system. Liu et al. described an iridium-catalysed alternative

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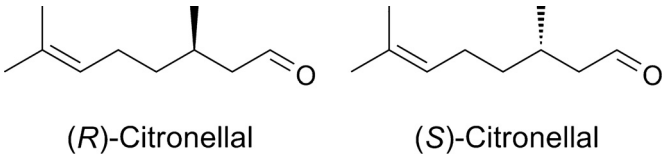
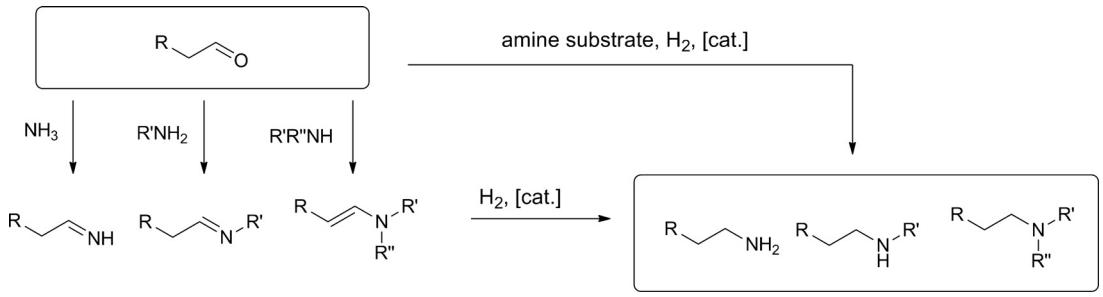


Fig. 1. The two natural isomers of citronellal.



Scheme 1. Reaction scheme of the reductive amination of an aldehyde with different amine substrates.

that required an additional reducing agent (triethylsilane) to produce a 40% yield of benzylamine [13]. Heterogeneous alternatives have been described by Peters et al., [14] Bayer AG [15] and OXEA [16]. Articles reviewing reductive amination in a general sense have been written by Hartwig et al. [17] and Maschmeyer et al. [18]. Implementation on an industrial scale is known from the heterogeneously catalysed reductive amination of alcohols using ammonia. It results in a product mixture of primary, secondary, and tertiary amines. [19]

To the best of our knowledge, the functionalisation of citronellal with ammonia leading directly to primary amines has not been described until now. The main product, citronellyl amine, was synthesised from the analogous oxime, [20] amide [21] and from geranylnitrile [22]. Published examples of the transition metal catalysed reductive amination of aldehydes with ammonia demonstrated the need to suppress side reactions in order to achieve high primary amine yield. The use of an efficient working biphasic solvent system is an alternative to the subsequent cleavage of secondary amines [23]. Aqueous biphasic reaction systems like the one used in this reaction often require phase transfer agents to reduce transport limitations. Important examples include the use of surfactants, [24] cyclodextrins [25] or ionic liquids [26], predominantly known for their use in hydroformylation and hydrogenation reactions. We compared these potential means of reductive amination of citronellal with ammonia in order to identify an optimal catalytic system that provides ample opportunities for catalyst separation.

2. Experimental

2.1. Typical synthetic procedure

All reactants, catalysts and solvents were commercially available and were used without further purification. In a typical experiment Chloro(1,5-cyclooctadiene) rhodium(I) (0.03 mmol 14.8 mg), triphenylphosphine trisulfonate (TPPTS, aq. saturated, 0.12 mmol, 68.2 mg) and hexadecyltrimethylammonium chloride (CTAC, aq. 25%, 0.031 mol, 60.7 mg) were dissolved in an aqueous ammonia solution (28%, 216.0 mmol, 13.14 g NH_3). Nexy, toluene (5.0 ml, 4.3 g) and citronellal (6.0 mmol, 925.5 mg) were added to the solution, which was sonicated for 5 min. The solution was transferred to an evacuated stainless steel autoclave with a volume of 70 ml (Parr Instrument Company). The autoclave was pressurised at 60 bar of H_2, mechanically stirred with 800 rpm and heated up to 130 °C. At the end of the reaction time, the autoclave was allowed to cool to room temperature, the pressure was released, the two layers were separated using a separating funnel, and the solution was analysed by gas chromatography.

2.2. Characterisation

Citronellyl amine **4** (see Scheme 2) is known from the synthesis of the analogous oxime. Analytical data is in accordance with published data [22].

MS (70 eV, EI): m/z (%): 155 (M^+, 1%), 138 (2), 123 (6), 112 (3), 109 (3), 95 (17), 81 (29), 70 (100), 55 (52).

For the characterisation of amine **5**, a mixture of amines **4** and **5** was hydrogenated, which resulted in compound **5** exclusively.

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 0.86 ppm (d, ^{3}J(H,H) = 6.6 Hz, 6H, 2 x -CH_3), 0.89 (d, ^{3}J(H,H) = 6.6 Hz, 3H, CH_3), 1.15 (m, 6H, 3 x -CH_2), 1.37 (m, 2H, -CH_2), 1.58 (m, 2H, 2 x -CH-) 2.80 (m, 2H, -CH_2), 3.68 (m, 2H, NH_2).

^{13}C NMR (125.77 MHz, $CDCl_3$): δ = 19.92, 22.87, 22.95, 25.00, 28.31, 29.85, 37.70, 39.58, 40.33, 41.58.

MS (70 eV, EI): m/z (%): 157 (M^+, 6), 140 (11), 125 (4), 114 (43), 100 (26), 84 (21), 70 (80), 55 (100)

The observed side products are identified by comparing the analytical data with the pure substance (citronellol **2**) or by mass spectrometry.

Citronellol **2**

MS (70 eV, EI): m/z (%): 156 (M^+, 1), 138 (2), 123 (9), 109 (7), 95 (31), 81 (50), 69 (100), 55 (92).

3,7-Dimethyloct-6-en-1-imine **3**

MS (70 eV, EI): m/z (%): 154 (M^+, 1%), 139 (3), 121 (12), 111 (8), 95 (33), 93 (13), 91 (11), 84 (16), 79 (27), 77 (22), 69 (100), 67 (74), 65 (19), 63 (7), 55 (90), 83 (74), 51 (28).

(E)-N-(3,7-dimethyloct-6-en-1-ylidene)-3,7-dimethyloct-6-en-1-amine **6**

MS (70 eV, EI): m/z (%): 291 (M^+, 1%), 276 (7), 248 (41), 234 (8), 222 (11), 208 (49), 194 (5), 180 (6), 166 (100), 152 (15), 138 (9), 124 (26), 110 (16), 98 (28), 84 (43), 69 (69), 55 (42).

Bis(3,7-dimethyloct-6-en-1-yl) amine **7**

MS (70 eV, EI): m/z (%): 293 (M^+, 2%), 278 (5), 250 (1), 236 (2), 224 (2), 208 (100), 168 (25), 152 (4), 138 (2), 126 (24), 112 (7), 98 (18), 93 (2), 81 (18), 69 (100), 65 (4), 55 (57), 51 (2).

(E)-N,N-Bis(3,7-dimethyloct-6-en-1-yl)-3,7-dimethylocta-1,6-diene-1-amine **8**

MS (70 eV, EI): 346 (2), 180 (2), 152 (2), 124 (2), 109 (4), 95 (6), 82 (12), 77 (2), 69 (100), 55 (57), 51 (1).