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Review

Heterogeneous Catalysis as an Efficient Tool for Selective Hydrogenation of Oximes to Amines and Hydroxylamines

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Abstract: The synthesis of many biologically active compounds is not complete without transforming the carbonyl group into an amino group, carried out by the reaction of nucleophilic substitution with hydroxylamine at the carbonyl carbon atom and further reduction of the C–N and N–O bonds. This method eliminates nitrating agents that exhibit oxidizing properties and may cause undesirable effects on other structural fragments of complex molecules. Selective hydrogenation of oximes over heterogeneous catalysts is still one of the most useful and challenging reactions in synthetic organic chemistry to obtain amines and hydroxylamines since the 1920s when the Adam's catalyst was first used for this reaction. In this review, we focused on the application of heterogeneous catalysts for the hydrogenation of oximes in relation to the methods applied for pharmaceutical synthesis.

Keywords: aldoximes; ketoximes; hydrogenation; heterogeneous catalysts; amines; hydroxylamines

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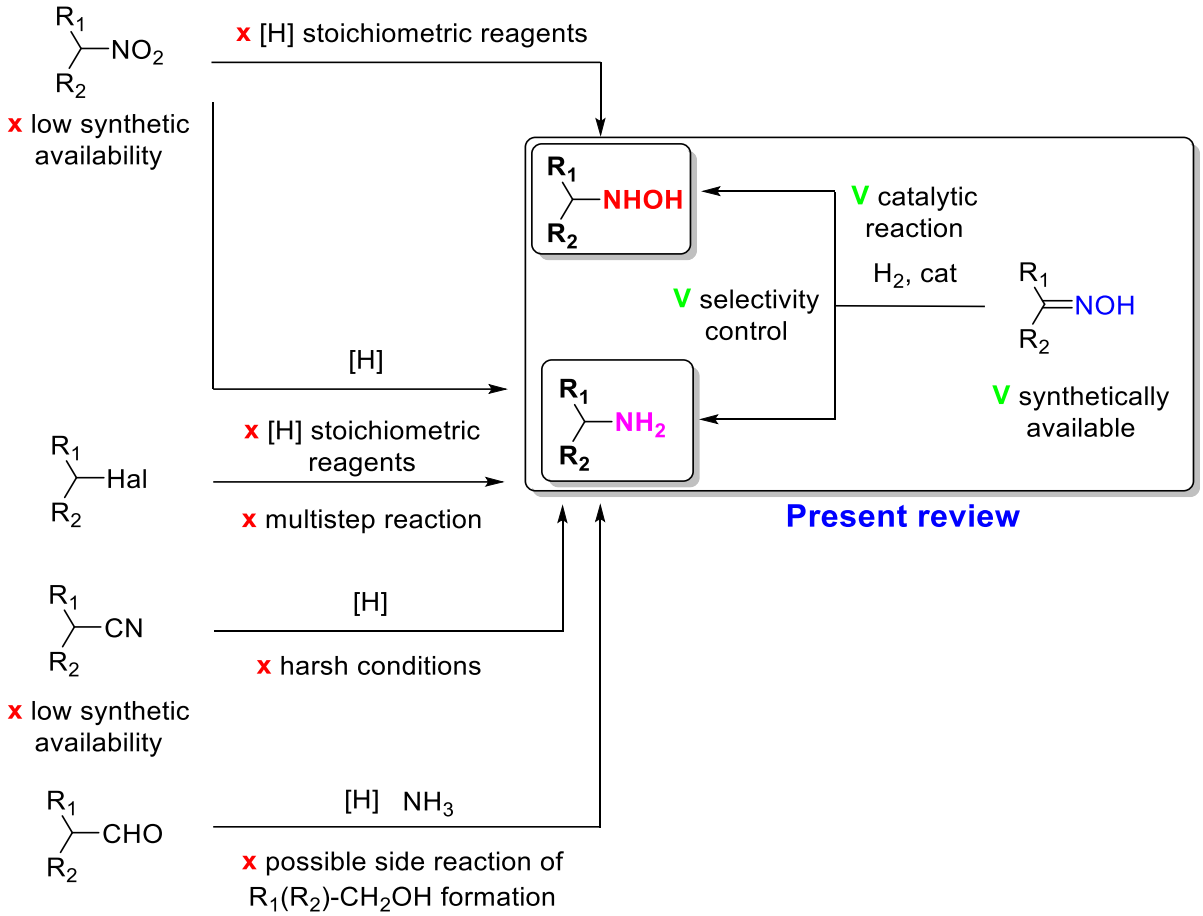
1. Introduction

Amines and hydroxylamines are valuable for basic and fine organic product synthesis. The common way of amine synthesis implies the reduction of nitro compounds, nitriles, and imines (Scheme 1). However, there are a lot of restrictions and difficulties, i.e., nitro compounds, excluding aromatic ones, as well as nitriles are not available reagents. Moreover, their reduction usually requires stoichiometric reagents or severe reaction conditions, which can lead to problems relating to selectivity and product separation/purification [1]. The reaction of aldehydes can also provide the synthesis of primary amines with ammonia, but the side reactions, such as aldehyde reduction and secondary amine formation, are usually observed. The synthesis of hydroxylamines is an even more challenging task. A stoichiometric reduction of nitro compounds with Zn/NH_4Cl is used to obtain hydroxylamines [2].

On the other hand, heterogeneous catalytic hydrogenation of oximes is the simplest way to obtain amines or hydroxylamines [3]. The main advantages of this methodology are the use of easily available oximes and a benign reducing agent—hydrogen—as well as the possibility to control the selectivity to amine or hydroxylamine formation (Scheme 1). Oximes are obtained by reacting a carbonyl compound with hydroxylamine hydrochloride (Scheme 1). Therefore, this reaction allows for the synthesis of a wide range of oximes with a different structure, the catalytic hydrogenation of which leads to a variety of amines or hydroxylamines. This is one of the most applied steps in drug synthesis. Thus, in the present review, we want to fully systemize the reported data on the heterogeneous hydrogenation of oximes, discuss some mechanistic aspects of the reaction, and show examples of the application of heterogeneous catalytic oximes' hydrogenation in pharmaceutical synthesis.

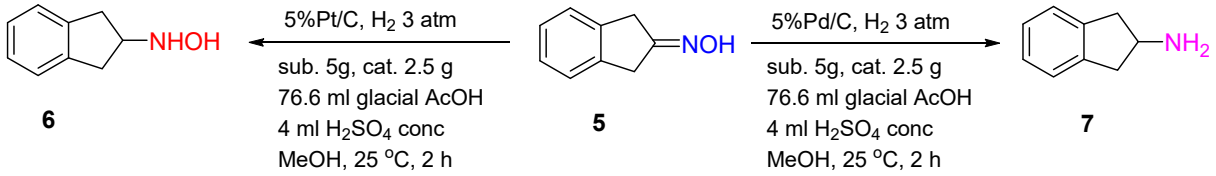


Scheme 1. Synthetic routes for the synthesis of amines and hydroxylamines.

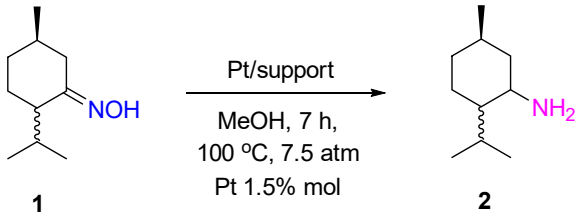
2. Hydrogenation of Ketoximes to Amines

2.1. Noble Metal Catalysts

The hydrogenation of ketoximes over Pt- or Pd-based catalysts is actively applied in pharmaceutical production, which is usually based on multistep organic synthesis processes, as an efficient tool to convert ketones to the corresponding amine products through the oxime formation step. In the very first work on selective oxime hydrogenation reported by Vavon et al., PtO_2 (Adam's catalyst) was shown to be an active and selective catalyst for the synthesis of N-hydroxy/alkoxy derivatives of amphetamines from aryl-acetone oximes at room temperature and a hydrogen pressure of 3 atm in the presence of an equivalent amount of HCl [4]. PtO_2 was applied in the hydrogenation of terpenoid oximes, such as carvone oxime, fenchone oxime, and camphor oxime [5]. Recently, Pt supported on TiO_2, ZrO_2, Al_2O_3, and MgO was also used for hydrogenation of monoterpenoid oximes (menthone oxime **1** and carvone oxime **3**, Scheme 2) to the corresponding amines [6]. Menthylamine **2** can be obtained with a 90% yield over Pt/Al_2O_3 catalysts after 7 h of the reaction at 100 °C and a hydrogen pressure of 7.5 atm in MeOH (Figure 1). The Pt supported on TiO_2, ZrO_2, and MgO was less selective, and the process led mostly to ketone formation. The same trend was observed in carvone oxime hydrogenation: Pt/TiO_2 and Pt/MgO catalyzed the deoximation reaction that proceeded most likely via the hydrolysis of the substrate molecule with the participation of hydroxyl groups of the support. However, all reducible groups in the carvone molecule were hydrogenated over Pt/Al_2O_3 with the formation of 5-isopropyl-2-methylcyclohexanamine **4** with a yield of up to 60% (Figure 2).



Scheme 2. Hydrogenation of 2-indanone oxime over Pt/C or Pd/C catalysts.



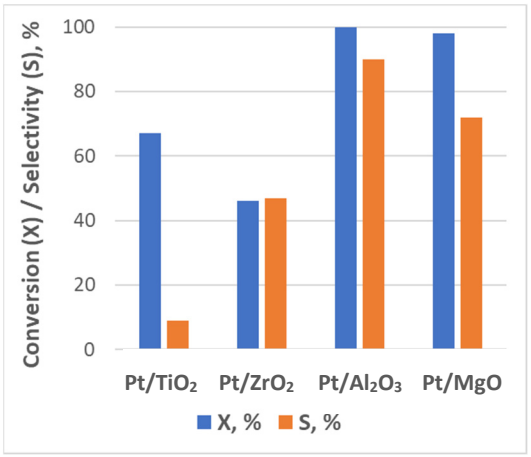
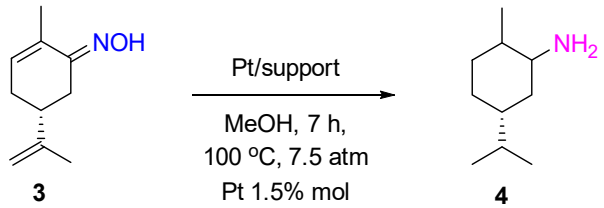


Figure 1. Hydrogenation of menthone oxime over Pt-supported catalysts.



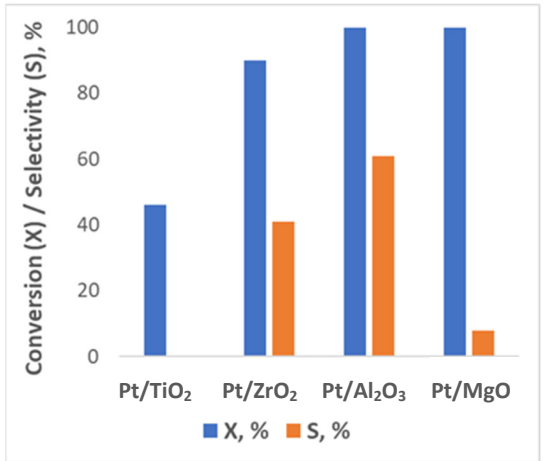
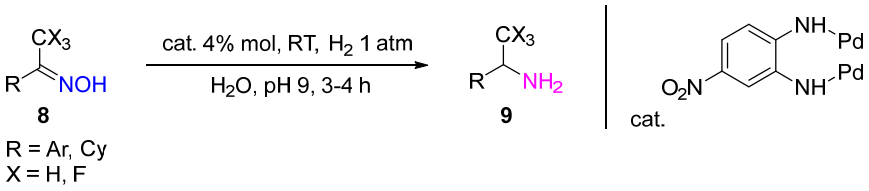


Figure 2. Hydrogenation of carvone oxime over Pt-supported catalysts.

The Pd/C catalyst was shown to provide 2-indanone oxime **5** hydrogenation to 2-aminoindane **7** with a yield of 94% in the presence of glacial AcOH and H_2SO_4 (conc.) after 2 h of the reaction at 20–25 °C and 3 atm of the hydrogen pressure. Interestingly, using 5%Pt/C under the same conditions led to hydroxylamine **6** formation with a yield of 54% (Scheme 2) [7].

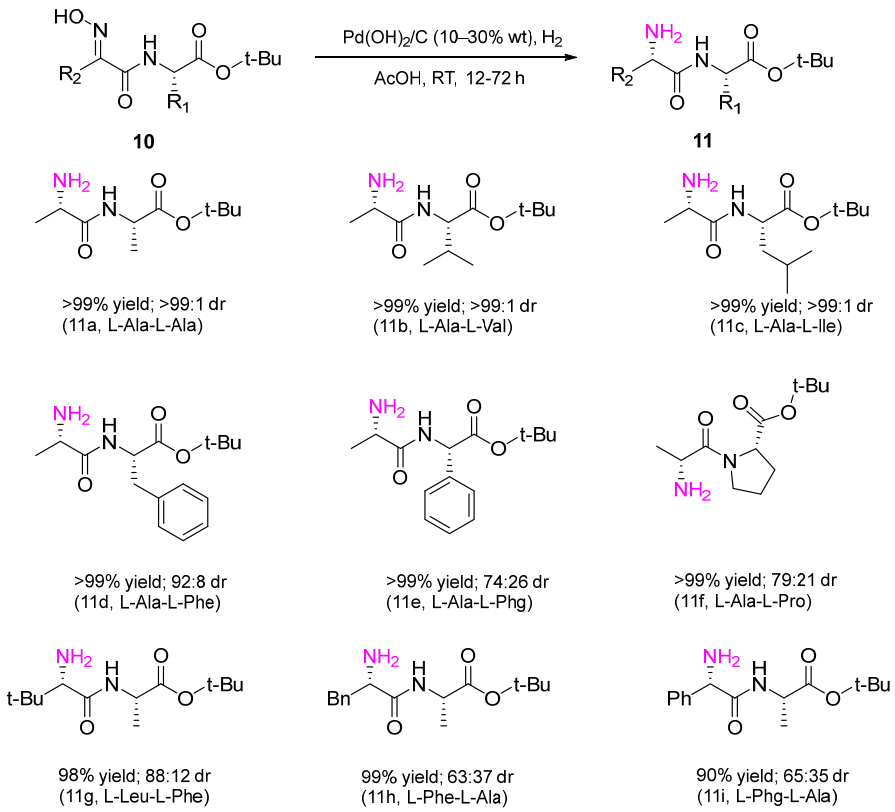
The differences in the mechanism of oxime hydrogenation over Pd and Pt catalysts can explain the differences in the hydrogenation products. The studies of Rosen and Green showed that Pd catalyzed N-O bond reduction, while Pt catalyzed the reduction of a C=N bond in the protonated 2-indanone oxime.

Pd-containing complexes can also be used as heterogeneous catalysts. Thus, the Pd complex with a 4-nitrobenzene-1,2-diamine ligand provided selective hydrogenation of oximes **8** in water under H_2 atmospheric pressure and RT with a quantitative yield of corresponding amines (Scheme 3) [8]. The catalyst can be easily isolated from the reaction product and used again without additional treatment.



Scheme 3. Hydrogenation of ketoximes over Pd complex with a 4-nitrobenzene-1,2-diamine ligand.

In the recent work, a heterogeneous Pd catalyst, $Pd(OH)_2/C$, was used in diastereoselective hydrogenation of amides **10** to obtain dipeptides **11** of different structures with a new chiral center with high diastereoselectivity in excellent yields (Scheme 4) [9].



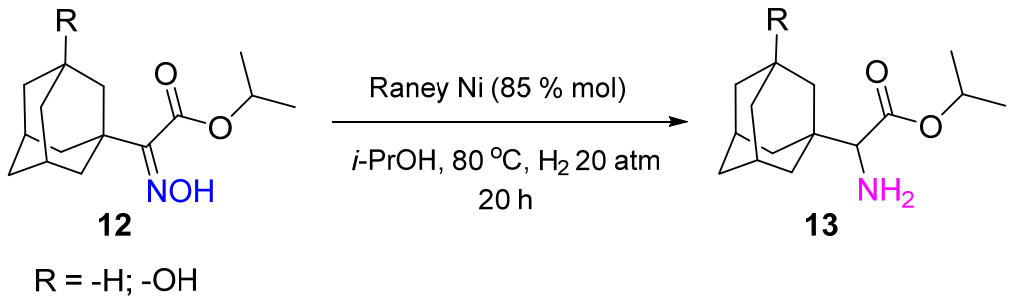
Scheme 4. Diastereomeric hydrogenation of amides bearing an oxime group to dipeptides over a $Pd(OH)_2/C$ catalyst; dr–diastereomeric ratio.

The reaction was performed in AcOH at RT and H_2 atmospheric pressure. The method has significant synthetic value. Due to the high specificity of peptides compared to small molecule drugs, they are considered promising pharmaceuticals for the treatment of cancer and tuberculosis and for antimicrobial therapy.

Enantioselective hydrogenation of oximes was also reported on Pd and Pt catalysts [10–12], but enantiomeric excess (*ee*) was not enough for the practical implementation of this approach in pharmaceutical synthesis in contrast to homogeneous hydrogenation of oximes by metal complexes with chiral ligands [13,14]. For instance, 5%Pd/Al_2O_3 modified with natural chiral amino alcohol (1R,2S)-(−)-Ephedrine was applied for enantioselective hydrogenation of pyruvic acid oxime to alanine at 30 °C in ethanol under H_2 pressure of 10 atm [10]. The yield of target alanine did not exceed 15%, with *ee* of *S*-alanine being only 26%.

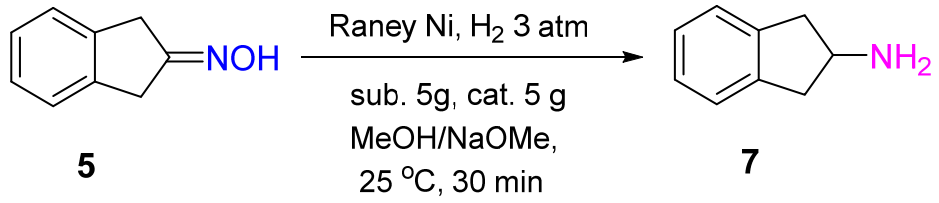
2.2. Non-Noble-Metal Catalysts

Non-noble metal catalysts based on Co and Ni are effectively applied in oxime hydrogenation. Raney Ni was used to synthesize 1-adamantyl-glycine derivatives **13**, which are known to possess high antiviral activity to influenza virus A [15]. The synthesis was realized by hydrogenation of corresponding oxime **12** at 80 °C and H_2 pressure of 20 atm in 20 h (Scheme 5).



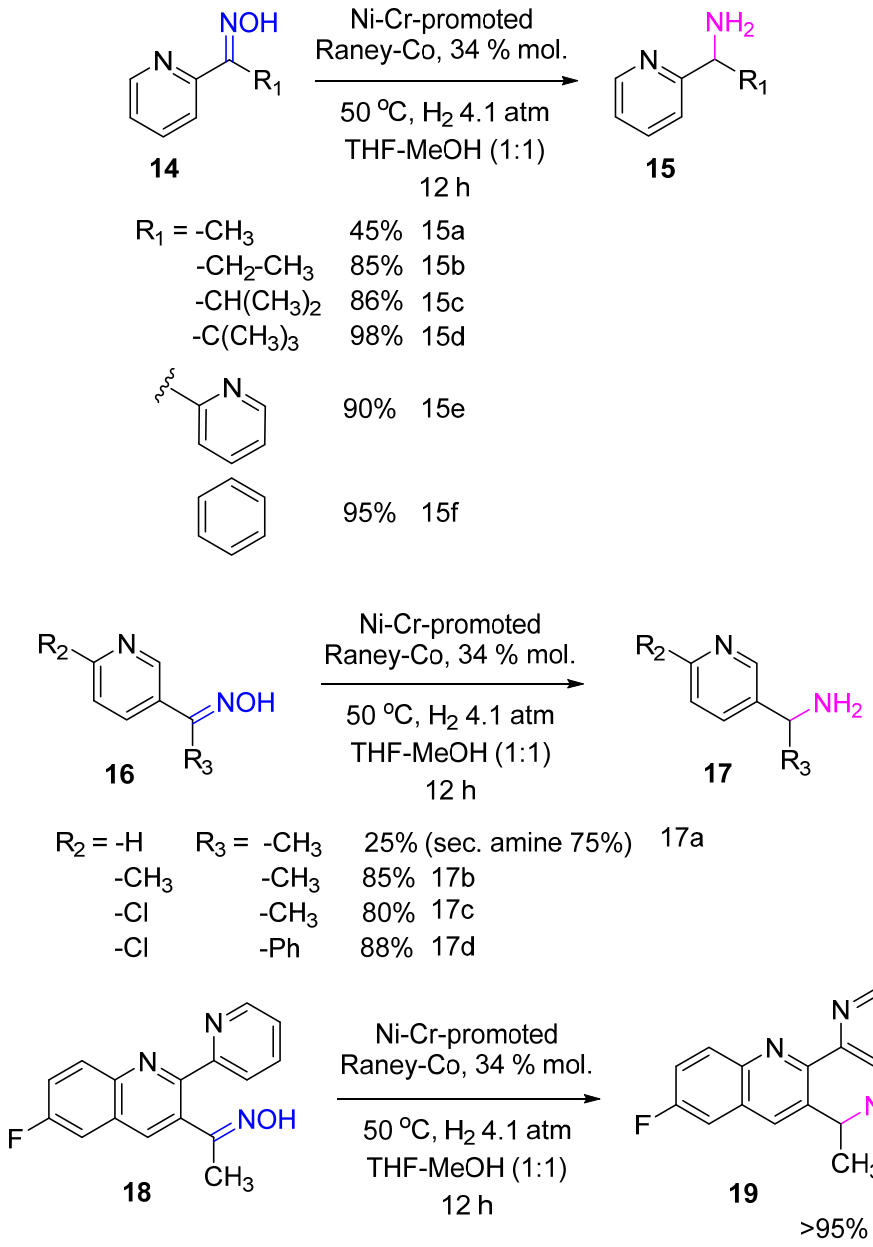
Scheme 5. Synthesis of 1-adamantyl-glycine derivatives by hydrogenation of a corresponding oxime over Raney Ni.

Under mild reaction conditions, Raney Ni showed high catalytic activity in the hydrogenation of 2-indanone oxime **5** with the yield of corresponding amine **7** of 91%. In contrast to Pt and Pd catalysts, to obtain the high yield of amine over Raney Ni, basic conditions were required (Scheme 6) [7].



Scheme 6. Hydrogenation of 2-indanone oxime to 2-aminoindan over Raney Ni.

Baucom et al. used Ni–Cr-promoted Raney-Co for the hydrogenation of ketoximes as a synthetic step in transforming heteroaromatic ketones to the corresponding amines, an advanced intermediate of a kinase inhibitor [11]. Ketoximes **14**, **16**, **18** were hydrogenated to the primary amines **15**, **17**, **19** with yields of 85–99%, and only for less sterically hindered substrates (14a, 16a), the competitive formation of secondary amines was a problem (Scheme 7).

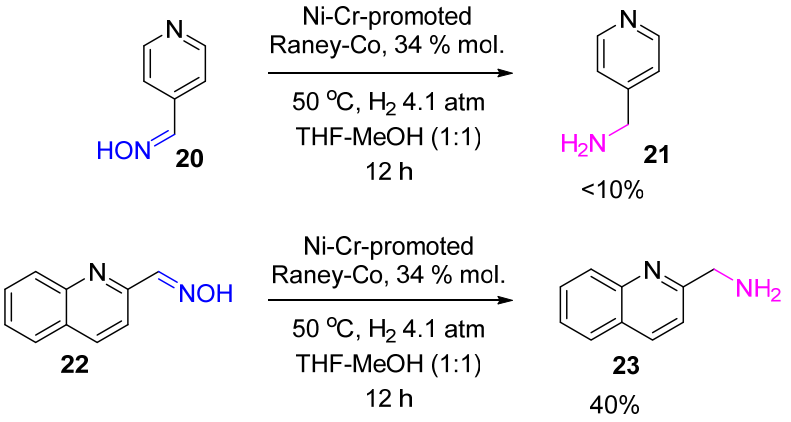


Scheme 7. Hydrogenation of heteroaromatic ketoximes to amines over Ni–Cr-promoted Raney-Co.

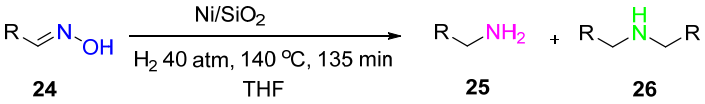
3. Hydrogenation of Aldoximes to Amines

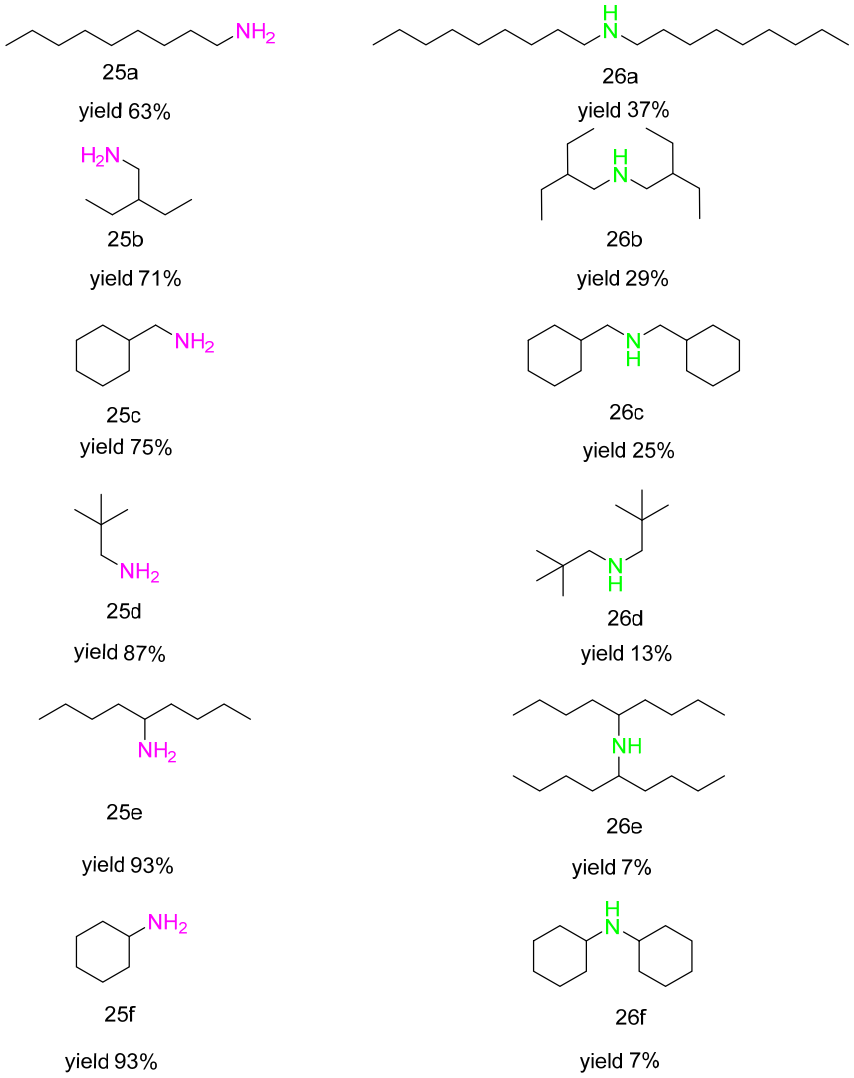
Reduction of aldoximes with H_2 over heterogeneous catalysts is usually accompanied by a side reaction of secondary amine formation due to the high steric accessibility of the oxime carbon atom. Thus, hydrogenation of heteroaromatic aldoximes **20**, **22** on the above-mentioned Ni–Cr-promoted Raney-Co proceeded unselectively with the yield of corresponding primary amines **21**, **23** not exceeding 40% (Scheme 8) [16].

Gebauer-Henke with co-authors showed the same selectivity trend when studying hydrogenation of alkyl aldoximes **24** over Ni/SiO_2 catalysts (Ni 46.6% wt., Cr 9.9% wt.) (Scheme 9) [17]. It was also observed that the selectivity to the primary amine **25** increased with the increasing steric demand of the substituent. In contrast to aldoximes, hydrogenation of ketoximes proceeded with a considerably higher selectivity to the primary amines. This fact proves that steric hindrance at the oxime carbon atom is one of the critical factors for the high selectivity of primary amines in hydrogenation.



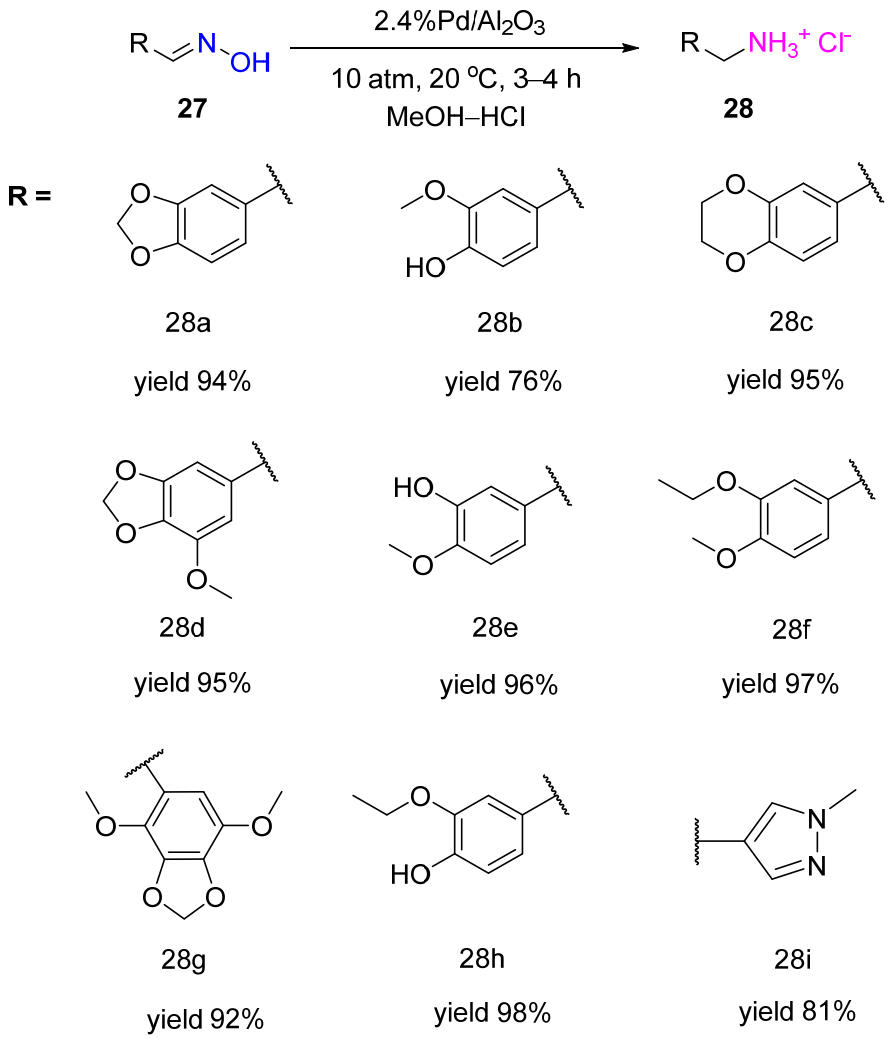
Scheme 8. Hydrogenation of heteroaromatic aldoximes to amines over Ni–Cr-promoted Raney-Co.





Scheme 9. Hydrogenation of aliphatic aldoximes to amines over Ni/SiO_2.

Nothwithstanding, the selective hydrogenation of aldoximes can be afforded in acidic media. Ignatov et al. showed that Pd supported on high-porosity foamed ceramic material containing 6% γ-Al_2O_3 appeared to be an active, selective, and recyclable catalyst for hydrogenation of benzaldoximes **27** to the corresponding primary amines **28** at RT and hydrogen pressure of 20 atm in a methanolic solution of HCl (3.6% *v*/*v* HCl) (Scheme 10) [18]. The obtained benzylamine derivatives can be used as synthons for the preparation of anticancer drugs and psychotropic substances for the treatment of mental disorders. The deposition of Pd on alumina-containing porous ceramic material enabled more than 20 recycles of the obtained catalyst.



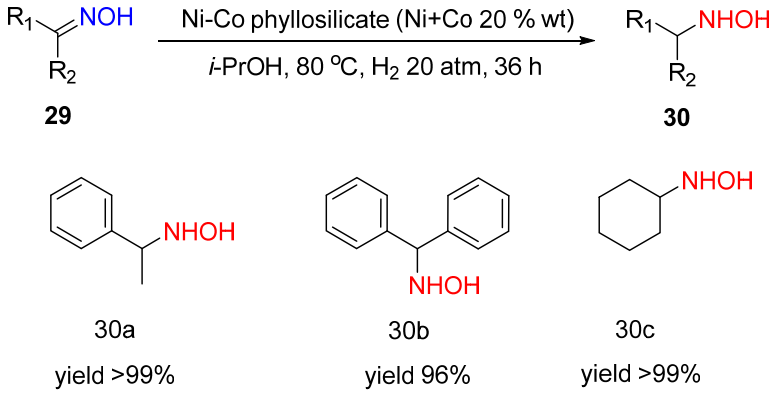
Scheme 10. Hydrogenation of aromatic aldoximes to amines over Pd/Al_2O_3.

4. Hydrogenation of Oximes to Hydroxylamines

Hydroxylamines are valuable compounds for both pharmaceutical and agrochemical synthesis. The most prominent way to obtain hydroxylamines is oxime hydrogenation. However, it is a challenging task because hydrogenation of a weak N-O bond is more thermodynamically favorable than hydrogenation of a C=N bond. Only a few examples exist in the literature on oxime hydrogenation to hydroxylamines [3].

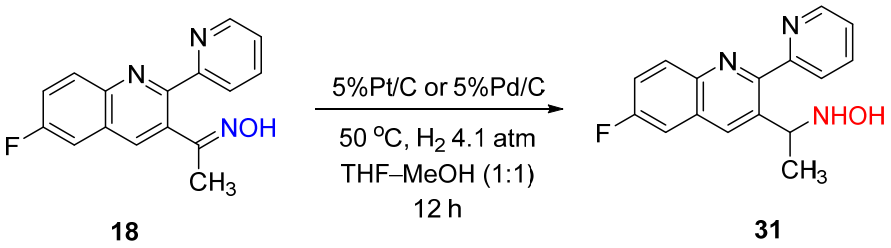
The Ni-Co phyllosilicate (Ni:Co = 1:1) was shown to provide selective hydrogenation of oximes **29** to hydroxylamines **30** with the yields 96–99% at 80 °C and an H_2 pressure of 20 atm in 36 h (Scheme 11) [19]. The reaction can be performed without acid additives. At the same time, the catalyst is not stable, and it loses the activity from cycle to cycle because of the Co surface oxidation and poisoning of the active sites by products. However, the

reason for the observed unusual selectivity in oxime hydrogenation to hydroxylamine was not discussed.



Scheme 11. Hydrogenation of ketoximes to hydroxylamines over Ni-Co phyllosilicate.

As we mentioned above, Rosen and Green noticed the change in the selectivity from amine to hydroxylamine when Pt/C was used instead of Pd/C for 2-indanone oxime hydrogenation (Scheme 2) [7]. In contrast, Baucom et al. reported that Pd/C or Pt/C catalysts led to the formation of hydroxylamine in the case of hydrogenation of ketoxime **18** (Scheme 12) [16].



Scheme 12. Example of ketoxime hydrogenation to hydroxylamine over Pd/C or Pt/C catalysts.

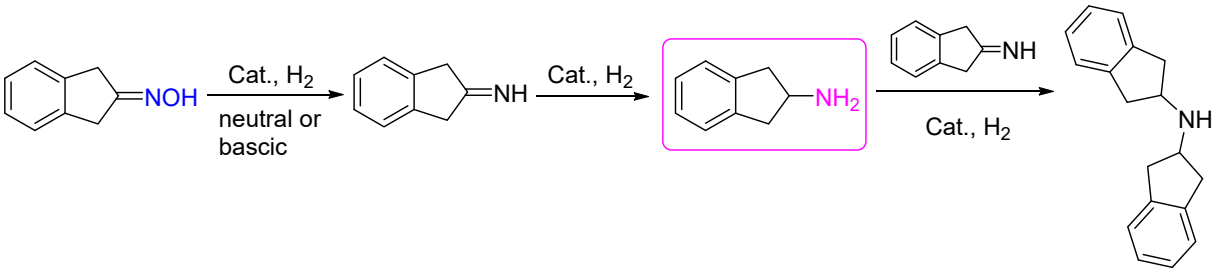
The last example is the already mentioned work of Vavon et al., where it was shown that hydrogenation of aryl-acetone oximes on PtO_2 in the presence of an equimolar amount of HCl led to N-hydroxy/alkoxy derivatives of amphetamines [4]. The variety of hydroxylamines obtained by this method and its limitations were recently reviewed and thoroughly discussed by Mas-Roselló and Cramer [3].

5. General Mechanisms of Hydrogenation of Oximes

The selectivity of hydrogenation of oximes can be tuned by different factors, i.e., the structure of oxime (aldoxime or ketoxime), the catalyst used, and the additives (acid or base). Here, we want to briefly address all these factors and discuss the mechanistic insights of the reaction.

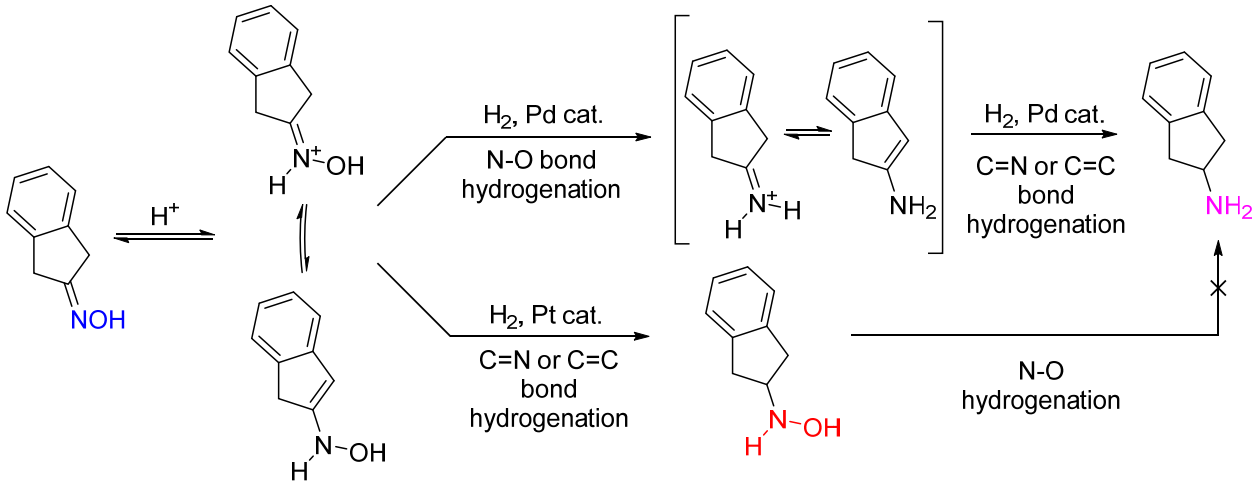
5.1. Hydrogenation of Oximes to Amines and Hydroxylamines

Rosen and Green, in their intensive study of the mechanism of 2-indanone oxime hydrogenation over Pd, Pt, and Ni catalysts, revealed that there are two possible reaction sequences: the first one is realized in neutral or basic reaction conditions, the second one takes place in acidic media (mineral acid catalyzed reduction) [7]. Under the basic or neutral conditions, hydrogenation presumably proceeds via N-O bond hydrogenolysis with the formation of intermediate imine, which can be hydrogenated to amine or may react with formed amine to give the secondary amine (Scheme 13).



Scheme 13. Reaction pathway of 2-indanone oxime hydrogenation in neutral or basic conditions.

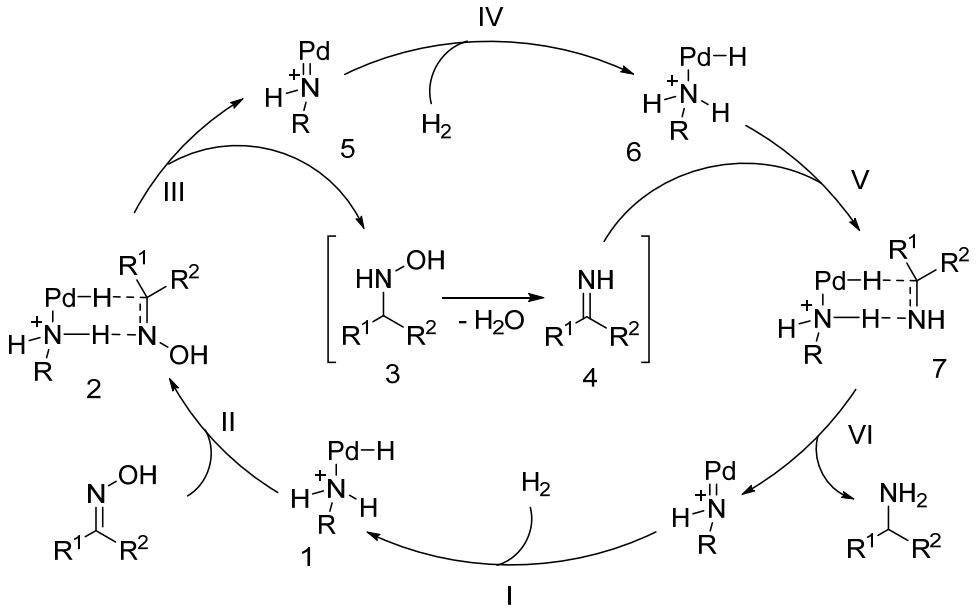
In the presence of mineral acid, the first step of the reaction is oxime protonation (Scheme 14) [7,20]. The elimination of a C1 hydrogen atom led to an isomer of 2-(hydroxylamino)indene. The authors believed that this isomer was a key intermediate in 2-aminoindanone oxime hydrogenation. Thus, the hydrogenation of protonated oxime or 2-(hydroxylamino)indene on Pt/C proceeded via the C=N or C=C bond correspondingly to give hydroxylamine. Interestingly, further hydrogenation of hydroxylamine to amine did not proceed on Pt/C, and proceeded very slowly on Pd/C. At the same time, oxime hydrogenation on Pd/C rapidly led to amine formation. Therefore, the authors believed that Pd-catalyzed oxime hydrogenation proceeded first via the N-O bond reduction and then through the reduction of the C=N or C=C bond of the intermediate structures. Mineral acid is usually added in an equimolar amount, and amine or hydroxylamine is obtained as an easily recovering salt.



Scheme 14. Reaction pathway of 2-indanone oxime hydrogenation in acidic conditions over Pd/C or Pt/C catalysts.

Liu et al. demonstrated the mechanism of ketoximes hydrogenation over a Pd-containing metal-complex catalyst (Pd-L), wherein the reaction started with the protonation of a nitrogen atom of a ligand (Scheme 15) [8]. In the first step, the H_2 molecule is adsorbed on the Pd-L catalyst, and then the H-atoms protonate the N-atom of the ligand to form an intermediate **1**. Then, the protonated amine group in the ligand is coordinated with the nitrogen atom of the oxime molecule with the formation of intermediate **2**. After that, the H atom is transferred from the Pd atom to the C1 atom of oxime, and the H atom from the protonated amine of the ligand is transferred to the N-atom of oxime, thus forming hydroxylamine **3** and releases the catalyst **5**. After that, hydroxylamine is transformed to imine **4**, which then meets the intermediate **6**. After the coordination steps of oxime and its protonation, an amine molecule is released, and the catalyst is restored. Here one can see that both hydroxylamine and imine are intermediates, and H_2 plays the role of a

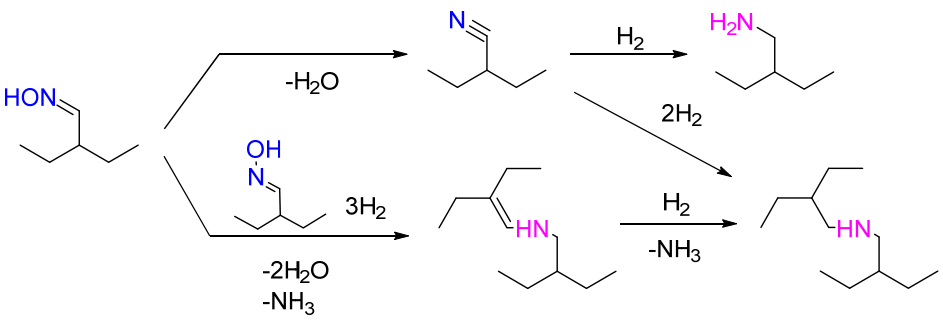
protonation agent. The unusual role of H_2 and the Pd heterogeneous complex makes it possible to provide the reaction under ambient conditions with yields > 99%.



Scheme 15. Reaction pathway of ketoxime hydrogenation over a Pd-containing metal-complex catalyst (Pd-L), in which the reaction started with the protonation of the nitrogen atom of a ligand.

5.2. Hydrogenation of Aldoximes

Heterogeneous hydrogenation of aldoximes, as it has been shown above, proceeds with a lower selectivity to primary amines than hydrogenation of ketoximes because of the high steric accessibility of the oxime carbon atom. Gebauer-Henke et al. proposed a general scheme of alkyl aldoximes hydrogenation according to the experimental data obtained for 2-ethyl-butyraldoxime hydrogenation (Scheme 16) [17]. They observed the formation of nitrile, Schiff base, and secondary amine together with the primary amine. According to the authors, nitrile is formed by the dehydration of oxime, and then nitrile hydrogenation leads to the primary amine. The parallel concurrent reaction is the formation of the Schiff base, which proceeds via reductive condensation of two oxime molecules, releasing two water and one ammonia molecule. The subsequent hydrogenation of the Schiff base produces the secondary amine. At the same time, the hydrogenation of a nitrile molecule can also lead to the formation of the secondary amine due to the nucleophilic attack of the C-atom in the intermediate imine by the amine molecule. The authors showed that the ammonia addition suppressed the formation of the Schiff base and secondary amine, thus increasing the selectivity of the primary amine formation up to 99%.

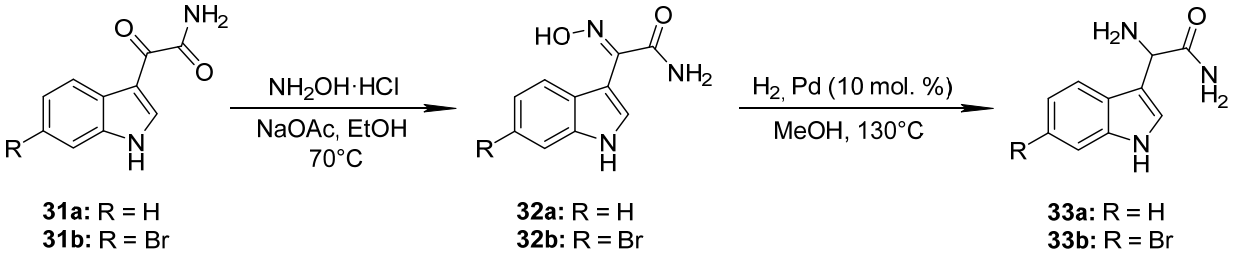


Scheme 16. Reaction pathway of 2-ethyl-butyraldoxime hydrogenation.

6. Hydrogenation of Oximes in Pharmaceutical Synthesis

Oxime hydrogenation appears to be an advantageous tool in drug synthesis. Mild reaction conditions allow one to insert an amino group into any molecule without introducing protective groups. The use of non-oxidizing reagents excludes the occurrence of side reactions and thus expands the approach to the molecules with a complex structure.

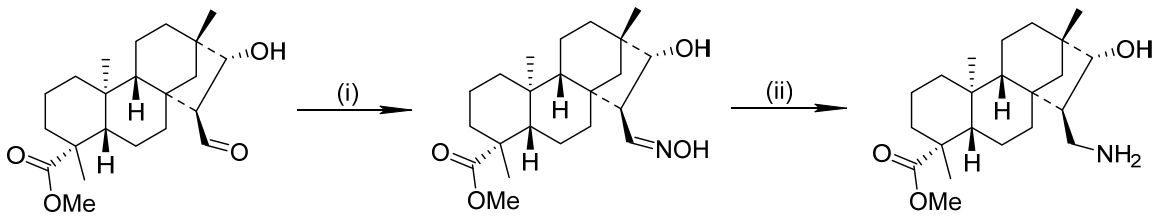
Bisindole alkaloids, isolated from deep-water marine sponges, were found to show promising anti-inflammatory, cytotoxic, antifungal and antimicrobial properties. The members of the bisindole alkaloid family, dragmacidines and hamacanthines, can be approached via cyclocondensation of indole derivatives [21,22]. A newly discovered total synthesis of these subunit molecules includes keto amide treatment with hydroxylamine, followed by oxime hydrogenation on a Pd/C catalyst, finally yielding an amino acetamide derivative (Scheme 17).



Scheme 17. The second and third steps of the 1-(indol-3′-yl)-1,2-diaminoethane synthesis.

A similar pathway was implemented in the synthesis of indane derivatives. Haadsma-Svensson et al. reported a novel synthesis scheme of *N*-substituted 2-aminoindanes, selective dopamine D_3 antagonists and thus potential antipsychotic agents [23]. Other examples include indane-ureido-thioisobutyric acids—a novel class of PPAR agonists with favorable hypolipidemic activity. In 2007, Matthews et al. performed 5-methoxyindan-1,2-dione oxime reduction to the corresponding aminoindane via catalytic hydrogenation with a 33% yield [24].

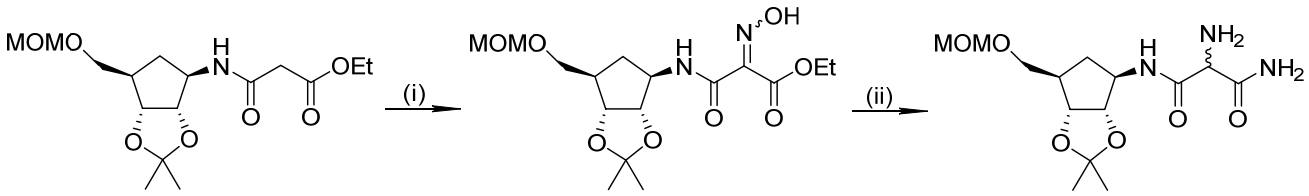
Polycyclic compounds are also of great interest to the pharmaceutical industry. Tetracyclic diterpenoids, a group of C_{20} skeleton molecules, possess essential pharmacological properties. Recently, isosteviol derivatives have become the focus of attention due to their biological activities, including antibacterial, anticancer and cardioprotective properties. Ozsvár et al. discovered new synthetic routes to is steviol-based 1,3-aminoalcohols [25]. These products were obtained via the oximation of an aldehyde precursor and then oxime hydrogenation catalyzed by Raney Ni (Scheme 18). Identical hydrogenation conditions were applied to oxime pyrazole derivative in synthesizing danusertib—an Aurora kinase inhibitor with significant therapeutic potential against various cancers [26].



Scheme 18. A part of stereoselective synthesis of the key intermediate from commercially available stevioside. (i) NH_2OH-HCl (2 eq.), EtOH, 12 h, reflux, 76%; (ii) Raney Ni, H_2 (10 atm), THF, 12 h, 25 °C, 83%.

Azoles are another large class of valuable compounds with a broad spectrum of action and bioavailability. Azole-based pharmaceuticals are extensively used as antifungal, antiviral and antibiotic agents. 1,3-oxazoles were obtained by cyclization of α-amido-β-ketoesters, previously synthesized via subsequent methyl acetoacetate oximation and reduction [27].

To synthesize diverse trisubstituted imidazoles, Laufer and Liedtke converted heteroaryl-substituted ethanones into the corresponding α-oximino derivatives with further reduction under regioselective conditions [28]. In 2013, Nair and Zhang reported the synthesis of carbocyclic bredinin analogue with RNA antiviral activity. The malonamide side chain was successfully modified in three steps using aqueous sodium nitrite, methanolic ammonia and 10% platinum on carbon with a 77% purified product yield (Scheme 19) [29].



Scheme 19. Malonamide chain modification in the synthesis of a carbocyclic analog of bredinin. (i) 1. $NaNO_2$, CH_3CO_2H, THF, r.t., 40 h, 46%; 2. NH_3, CH_3OH, 0 °C, 12 h, 99.1%; (ii) H_2, 10% Pt/C, CH_3OH, r.t., 0.5 h, 77%.

7. Conclusions

Heterogeneous catalytic hydrogenation of oximes is an efficient tool for synthesizing amines and hydroxylamines. The reaction can proceed under mild conditions, even at room temperature. The catalysts with noble (Pt, Pd) and non-noble metals (Ni, Co) are actively used in this process, and we showed real examples, when the step of oxime hydrogenation was applied to introduce an amine group in the structure of a drug molecule. However, a selectivity problem arises when hydrogenation of aldoxymes to the target amine product is carried out because of secondary amine formation.

The synthesis of barely accessible hydroxylamines by oxime hydrogenation is still a challenging task. There are only a few examples of selective heterogeneous hydrogenation of oximes to hydroxylamines. Moreover, there are no general ideas as to why one can obtain hydroxylamine instead of amine, even under identical conditions and using the same catalyst.

Therefore, the deep study of the reaction mechanism and the influence of the catalyst's properties on the activity and selectivity in oximes hydrogenation is highly needed and has not yet been reported. The comprehensive study of structure–property relationship of known catalysts or novel catalytic systems by modern physicochemical methods, such as XPS, XRD, EPR, TEM, SEM, etc., together with analytical instruments for the characterization of reaction intermediates will take the heterogeneous hydrogenation catalysis to the next level.

There is also significant room for improvement in catalyst design for heterogeneous enantioselective hydrogenation of oximes, which would open new opportunities in pharmaceutical synthesis.

We hope that this minireview will be useful for the researchers from both catalysis and organic chemistry communities and will inspire studies in the field of heterogeneous oxime hydrogenation to obtain a deeper understanding of the role of catalyst properties on the reaction mechanism that will aid in the development of novel efficient and selective catalytic systems.

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