Russian Chemical Reviews **68** (1) 55 – 72 (1999) © 1999 Russian Academy of Sciences and Turpion Ltd

UDC 547.233

Reductive amination of oxygen-containing organic compounds

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Abstract. The data dealing with reductive amination of oxygen-containing organic compounds of different classes are systematised. New data on the amination agents and the catalysts used are presented. The dependence of the reactivity of reagents on their structures is considered. The bibliography includes 249 references.

I. Introduction

Reductive amination or hydroamination is widely used for the synthesis of amines. This method is based on the reaction between oxygen- and nitrogen-containing compounds on the surface of a catalyst under a hydrogen atmosphere or in solution in the presence of hydrogen donors.

In the literature, this reaction is often referred to as 'reductive alkylation', which does not reflect exactly its chemical essence.

It has been shown in numerous studies that during the reaction with oxygen-containing compounds in the presence of hydrogen donors, some nitrogen-containing compounds, namely, nitro and nitroso compounds, nitriles and oximes, are first reduced to amines, and then the latter react with oxygen-containing compounds. Thus, this reaction occurs successfully when an amino group is present; therefore, it is more correct to call this reaction 'reductive amination' or 'hydroamination' rather than 'reductive alkylation'.

This review deals with reductive amination reactions involving hydrogen or hydrogen donors; the reaction conditions and the catalysts used are discussed.

II. Reductive amination of carbonyl compounds with ammonia and amines

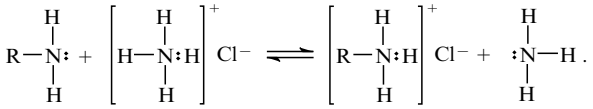
The ability of ammonia and amines to form imines with aldehydes and ketones and the fact that imines can be reduced relatively easily to the corresponding amines permitted the synthesis of amines by direct amination of carbonyl-containing compounds with ammonia or amines. Hydrogen (in the presence of a catalyst) or formic acid and its derivatives are used most often as the reducing agents in this process. This reaction is widely employed to prepare amines from various aldehydes and ketones.

Mignonac [1, 2] was the first to carry out the reductive amination of aldehydes and ketones with ammonia. Mixtures of the corresponding primary, secondary and tertiary amines were obtained from aliphatic aldehydes and ammonia in the presence of nickel catalysts.

In the first stage of the reaction, ammonia adds to the carbonyl compound (Scheme 1, pathway *a*); this is followed by the reduction of either the product of nucleophilic addition itself, α-amino alcohol **1** (pathway *d*), or the product of its dehydration, imine 2 (pathways *b* and *c*).[3] In some cases, the imines formed in the condensation of carbonyl compounds with ammonia can be isolated, whereas the α-amino alcohol **1** could not be isolated.[4]

As the primary amine is accumulated in the reaction mixture, it enters into reaction with the initial carbonyl compound similarly to ammonia (Scheme 1, pathway *e*). The imine **3**, which is formed upon dehydration of the condensation product, is converted into secondary amine (pathways *f* and *g*). In addition, primary amine can react with the imine **2** to give addition product **4**, the reduction of which also gives a secondary amine (pathways *h*–*j*). Secondary amines also can enter into this type of reactions (pathways *k*–*n*); this gives tertiary amines. Thus, the process occurs as a set of consecutive and parallel reactions yielding a mixture of primary, secondary and tertiary amines.

To suppress the formation of secondary and tertiary amines, the reductive amination of carbonyl compounds is carried out in the presence of ammonium salts.[5] Under these conditions, only primary amines are formed. Apparently, an excess of ammonium salts shifts equilibrium towards primary amines; in addition, the formation of secondary amines is suppressed because primary amines lose their nucleophilic properties upon transformation into alkylammonium ions

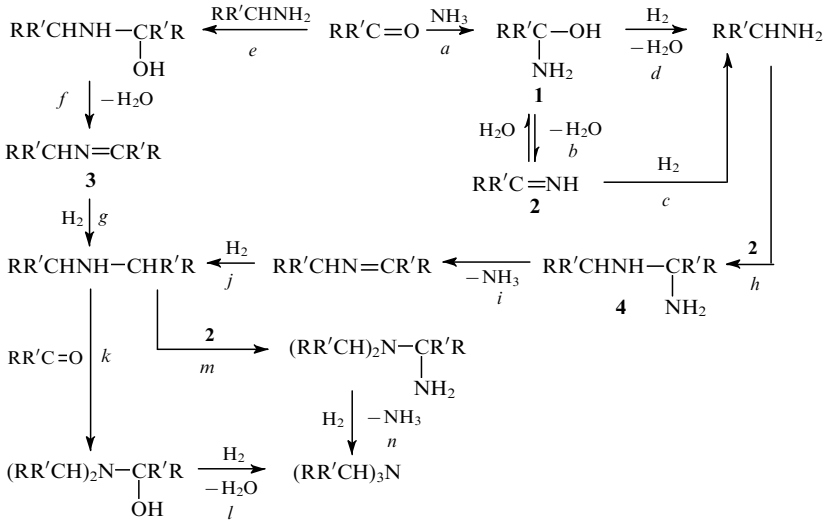


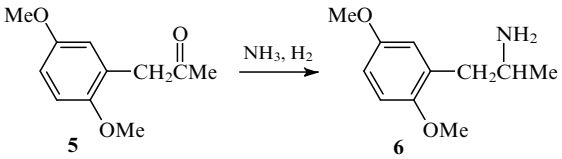
For example, the introduction of ammonium chloride into the reaction mixture during hydroamination of 1-(2,5-dimethoxyphenyl)propan-2-one **5** with ammonia in methanol in the presence of Raney nickel permitted the synthesis of 2-amino-1-(2,5-dimethoxyphenyl)propane **6** in 95% yield.[6]

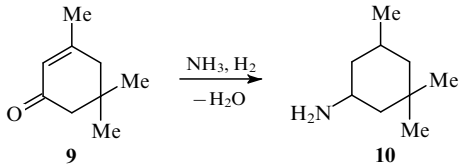
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Received 2 July 1998
Uspekhi Khimii **68** (1) 61 – 79 (1999); translated by Z P Bobkova

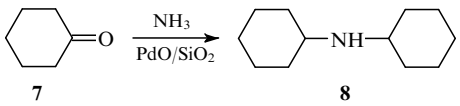
Scheme 1







Most often, hydroamination of carbonyl-containing compounds with ammonia is carried out in the presence of nickel catalysts.[7–9] When metallic rhenium and rhodium supported on alumina are used as the catalysts, the total yield of primary and secondary amines reaches 93%–95%.[10] In order to direct the process at the formation of secondary amines, catalysts are often modified by various oxides. Thus the reaction of cyclohexanone **7** with ammonia catalysed by the 0.35% PdO/SiO_2 catalyst modified by Ag, Mn, K, Na and Al oxides gives dicyclohexylamine **8** in 97% yield.[11]

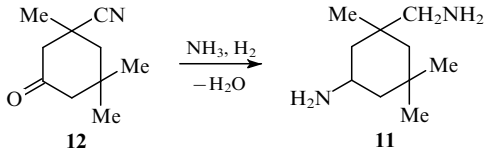


Synthesis of 2,2-disubstituted 1,5-diaminopentane derivatives by the reaction of the corresponding aldehydes containing a terminal nitrile group with excess ammonia over acid catalysts has been reported.[12,13] The imino nitrile formed in the first stage is hydrogenated over catalysts based on Co, Ni, Ru and other noble metals at 60–150 °C and 5–15 MPa. The yields of diamines amount to 50%–72%.

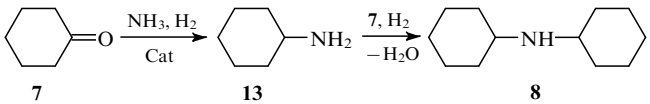
The use of reduced promoted fused iron catalysts (RPFIC) in various reactions, most of all, in reductive amination of carbonyl-containing compounds, has been described in a review.[14] Among other reactions, the reductive amination of octan-2-one with ammonia has been studied in detail.[15–18] The kinetic isotope effect observed after replacement of H_2 by D_2 made it possible to propose a stepwise mechanism of reductive amination of carbonyl compounds, the addition of hydrogen to ketimine being the rate-determining step.

Hydroamination of 3,5,5-trimethylcyclohex-2-enone (isophorone, **9**) with ammonia in the presence of a copper–zinc–aluminium catalyst (SNM-1) and RPFIC at 160–230 °C has been reported.[19,20] The yield of 3,3,5-trimethylcyclohexylamine **10** reaches 90%–95%.

3-Aminomethyl-3,5,5-trimethylcyclohexylamine **11** is prepared by reductive amination of 1,3,3-trimethyl-5-oxocyclohexanecarbonitrile **12** with ammonia with simultaneous reduction of the cyano group at 50–150 °C on Raney nickel or cobalt using anhydrous Ni, Co, Y, and La halides as co-catalysts. The yield of the amine **11** was 83%.[21]

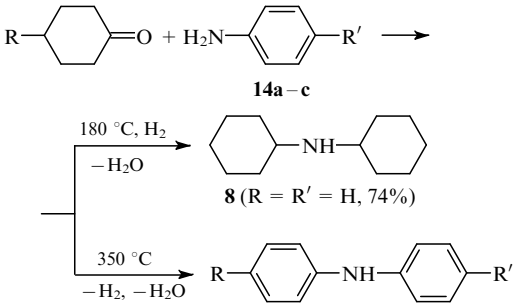


Transformation of aldehydes and ammonia into secondary amines was attained [22] by using a three-component catalyst based on Cu, a metal of the series Cr, Mn, Fe and Zn and a platinum group metal (Pt, Pd, Ru, Rh). The predominant formation of either primary or secondary amines from ketones and ammonia can depend significantly on the procedure used to prepare the catalysts and on the catalyst composition, all other factors being the same. Study of hydroamination of cyclohexanone **7** with ammonia in the presence of various catalysts has demonstrated [23] that in the presence of a nickel catalyst, the primary amine, cyclohexylamine **13**, is formed predominantly, whereas the use of colloidal platinum results in the secondary amine **8** being formed as the major product.



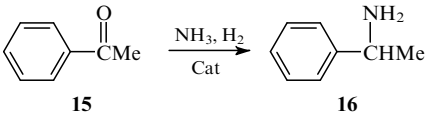
However, later,[24] it was found that in the presence of platinated silica gel, the ketone **7** is readily converted into the primary amine **13** rather than into the secondary amine **8**, as noted in the study [23] cited above. Thus, depending on the method for the preparation of the platinum catalyst, either secondary or primary amines can be synthesised. Hydroamination of alicyclic ketones with aromatic amines in the presence of catalysts containing Ru, Rh, Pd or Ni supported on γ-Al_2O_3 yields, depending on the temperature conditions, either cycloaliphatic or aromatic secon-

dary amines. For example, at 180 °C and p_{H_2} = 5 MPa,[25] dicyclohexylamine was obtained from cyclohexanone **7** and aniline **14a** over a nickel catalyst, whereas the reaction between the same compounds or their *para*-substituted derivatives at temperatures of dehydration of alicyclic compounds (above 300 °C) gives[26] only the corresponding diarylamines.

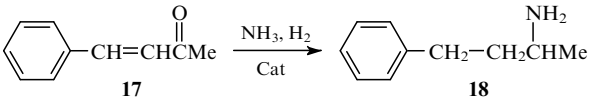


R, R′ = H (**a**), Hal (**b**), Alk (**c**).

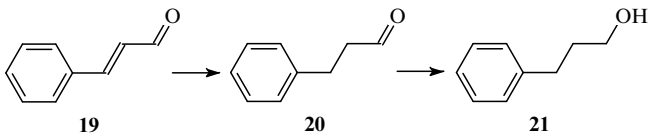
The reductive amination of arylaliphatic aldehydes and ketones with ammonia results in the formation of primary aliphatic-aromatic amines.[9,27,28] The reaction is complicated by the reduction of the corresponding carbonyl compounds to hydrocarbons. The yield of the amination products is influenced by the location of the carbonyl group with respect to the aromatic ring of the initial aldehyde or ketone. The yields of amines produced from aromatic aldehydes or alkyl aryl ketones are much lower than the yields of amines formed upon hydroamination of ketones in which the carbonyl group is removed from the aromatic nucleus. Thus over a nickel catalyst at 150 °C and 8 MPa, acetophenone is converted into 1-phenylethylamine **16** in 50% yield.[28]



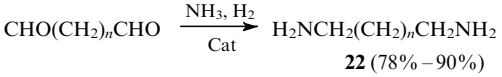
Under the same conditions, benzylideneacetone **17** gives 2-amino-4-phenylbutane in 84% yield.[29]



In this case, it should be borne in mind that the reaction starts with hydrogenation of the alkene double bond. This eliminates the conjugation between the carbonyl group and the aromatic nucleus. Thus it has been shown[30] that hydrogenation of 3-phenylacrolein **19** at 80 °C and p_{H_2} = 2 MPa gives initially aldehyde **20** and then alcohol **21**.

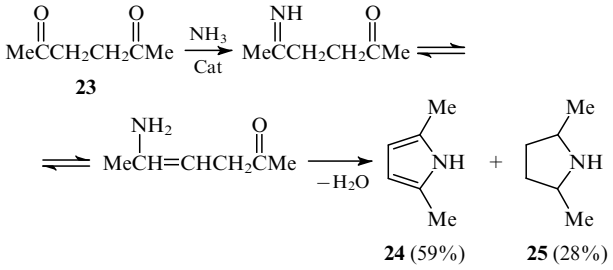


A method has been proposed[31,32] for the synthesis of diamines **22** from aliphatic dialdehydes containing four to ten carbon atoms; according to this method, they are treated with excess ammonia and hydrogen in the presence of Ni, Co, Pd or Ru catalysts at 40 – 150° C and a pressure of 10 MPa.

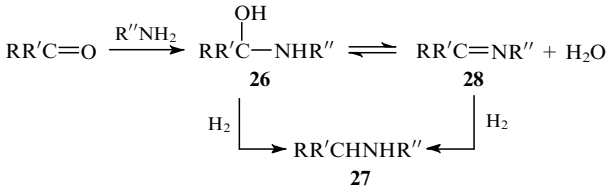


n = 4 – 10.

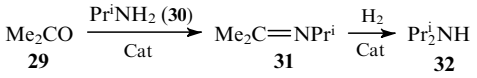
In order to prevent the formation of secondary amines and possible intramolecular cyclisation giving a heterocyclic derivative, excess ammonia is used (the ammonia : aldehyde molar ratio is 5 : 1). Conversely, an excess of the initial dicarbonyl compound is favourable for the formation of heterocyclic systems. Thus the reaction of acetonylacetone **23** with ammonia [the diketone : ammonia molar ratio is (2 – 3) : 1] in the presence of Raney nickel at p_{H_2} = 15 MPa resulted in the synthesis of a mixture of 2,5-dimethylpyrrole **24** and 2,5-dimethylpyrrolidine **25**, *i.e.* amination and cyclisation were accompanied by hydrogenation of the pyrrole ring.[33] Esters of 4-oxo acids behave in a similar way.



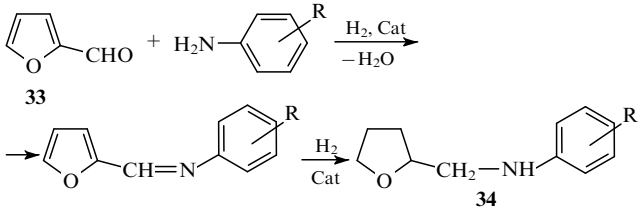
Hydroamination with primary amines, like hydroamination with ammonia, involves evidently the intermediate formation of addition product **26**, which is either hydrogenated to amine **27** or is converted initially into imine **28** and then into the amine.[34]



A kinetic study of the catalytic reductive amination of acetone **29** with isopropylamine **30** in aqueous alcohol over a platinum catalyst at 29 °C has demonstrated[35] that the reaction consists of two steps: the formation of imine **31** and its subsequent hydrogenation, giving rise to diisopropylamine **32**.

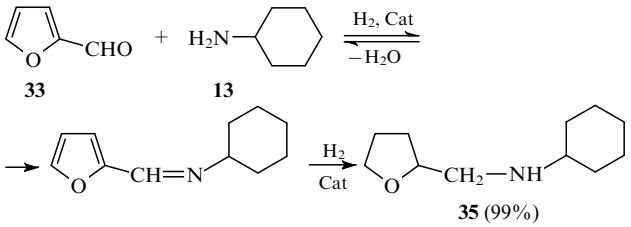


This pathway to secondary amines, which includes the formation of imines, has also been confirmed in studies dealing with hydroamination of furfural **33** with aromatic amines. It was shown that the reaction over palladium catalysts includes the initial formation of the corresponding imines, which are then hydrogenated, in particular, in the furan ring.[36 – 38] The yields of substituted *N*-(2-tetrahydrofurylmethyl)anilines **34** vary from 10% (for *o*-bromoaniline) to 85% (for aniline). When palladium immobilised in the polymeric matrix of the AB-17-8 or AN-1 anion exchanger is used, the yield of *N*-(2-tetrahydrofurylmethyl)aniline reaches 100%.



R = H, *m*-Me, *p*-Me, *o*-Me, *m*-Hal, *p*-Hal, *o*-Hal.

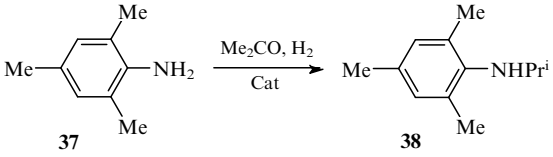
The reductive amination of furfural **33** with cyclohexylamine over the same catalysts at 20 – 60 °C and p_{H_2} = 0.98 – 1.03 MPa in a solvent (an alcohol or a hydrocarbon) affords *N*-(2-tetrahydrofurylmethyl)cyclohexylamine **35** in a high yield.



33 **13** **35** (99%)

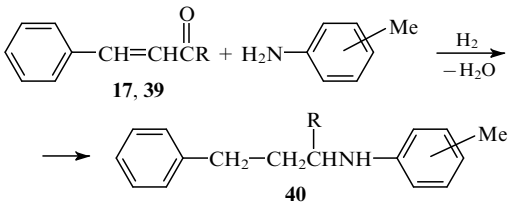
Palladium catalysts immobilised in an anion-exchanger polymeric matrix are inferior to Pd/C regarding the rate of formation of the amine **35** but are superior regarding the selectivity and the service stability. The rate of reductive amination of the aldehyde **33** was found[39] to be directly proportional to the dielectric constant of the solvent.

N,*N*-Diethylaminophenols are prepared[40] in high yields by reductive amination of acetaldehyde with *o*-, *m*- and *p*-aminophenols at 150 °C and p_{H_2} = 2 MPa in the presence of Pt, Pd or Ni catalysts in the medium of an aliphatic alcohol (MeOH, EtOH, Pr^nOH). For example, in the case of *m*-aminophenol, the yield of *N*,*N*-diethyl-*m*-aminophenol was 98.4%. In a study of reductive amination of aliphatic ketones with primary amines, it has been found[41–43] that the product yield is substantially influenced by steric factors caused by the structures of both the ketone and the initial amine. Steric restrictions were considered[44] to be the only reason for the fact that the yields of amines upon the hydroamination of ketones with cyclohexylamine **13** decrease in the sequence acetone > methyl ethyl ketone > diethyl ketone. When ethanolamine is used instead of cyclohexylamine, steric hindrance markedly diminishes, and the yields of hydroamination products obtained from acetone and diethyl ketone **36** become almost identical. Study of the influence of steric factors on the reductive amination of acetone with aniline and 2,4,6-trimethylaniline **37**[45] has shown that the sterically hindered amine **37** is converted into secondary amine, *N*-isopropyl-2,4,6-trimethylaniline **38**, in 36% yield (when aniline is used, the yield of the corresponding secondary amine increases to 98%).



37 **38**

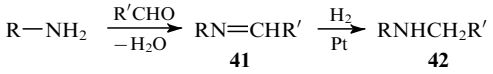
The yield of the product of reductive amination of benzylideneacetone **17** and benzylideneacetophenone **39** with toluidines[46] varies as a function of the position of the methyl substituent in the aromatic amine. The yields of secondary amines **40** in the hydroamination of the ketone **17** were 14.0, 35.0 and 52.4% for *o*-, *m*- and *p*-toluidine, respectively. Meanwhile, it was found that the yields of secondary amines formed from aliphatic amines increase with an increase in the basicity of the amine used.



17, **39** **40**

R = Me (**17**), Ph (**39**).

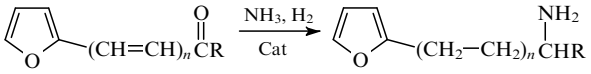
Secondary amines of the aliphatic series have been prepared in two stages from primary amines and aldehydes.[47] In the first stage, imines were synthesised; after isolation, they were hydrogenated over a platinum catalyst in anhydrous EtOH. The total yields of the imines **41** and the amines **42** were 40% – 63%.[48]



41 **42**

R = R′ = Et, Pr^n, Pr^i, Bu^n, Bu^i.

Reductive amination of carbonyl compounds of the furan series has been studied only occasionally. Reductive amination of unsaturated ketones **43** with ammonia has been reported.[49–51] The reaction was carried out in methanol saturated with ammonia over skeletal nickel – aluminium catalyst and under a hydrogen pressure of 12 – 14 MPa.[52]

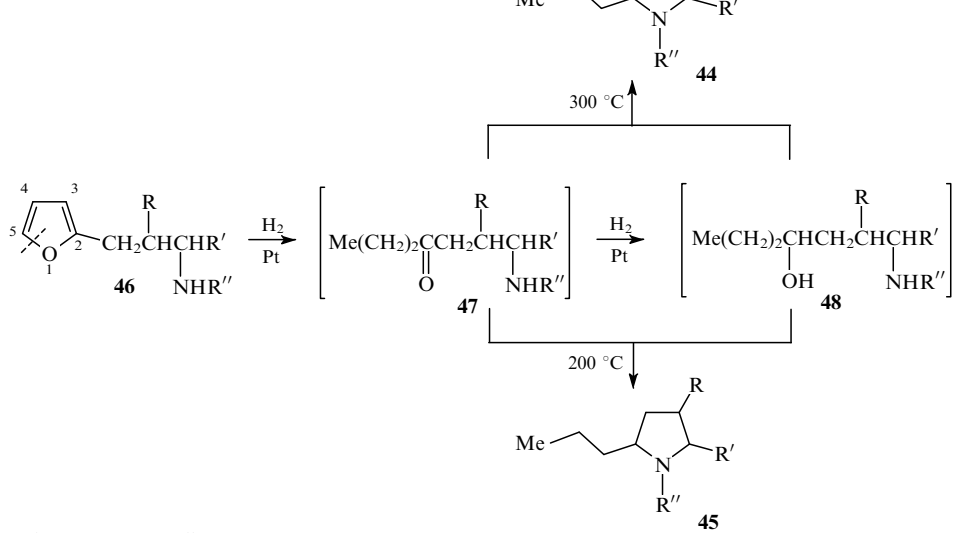


43

n = 1, 2; R = Alk.

The synthesis of pyrrole (**44**) and pyrrolidine (**45**) homologues from furan derivatives **46**, containing an amino group in the alkyl substituent, over platinum catalysts should be regarded as a peculiar intramolecular reductive amination reaction (Scheme 2). The reaction consists of two stages: hydrogenolysis of the furan ring at the O(1) – C(5) bond to give amino ketones **47** and amino alcohols **48** and their intramolecular hydroamination leading to the formation of a heterocycle.[53–55] Selective hydrogenolysis at the O(1) – C(5) bond is possible only with platinum catalysts

Scheme 2

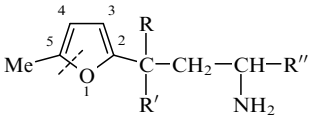


44 **46** **47** **48** **45**

R = R′ = H, Me, Et; R″ = H, Me.

(Pt/C, Pt/asbestos); in this case, the mixture of reaction products contains pyrrolidines and pyrroles with a propyl radical at the 5-position. Pyrrolidine homologues are formed at 200–220 °C, their yields being 85%–90%, whereas pyrrole homologues are produced at 300 °C in ~85% yield. The yields of *N*-methyl-substituted pyrrolidines and pyrroles are somewhat lower (70% and 73%–75%). High-boiling nitrogen-containing compounds (2%–3%) and the recovered amine (~23%) were also detected in the product mixture.[55]

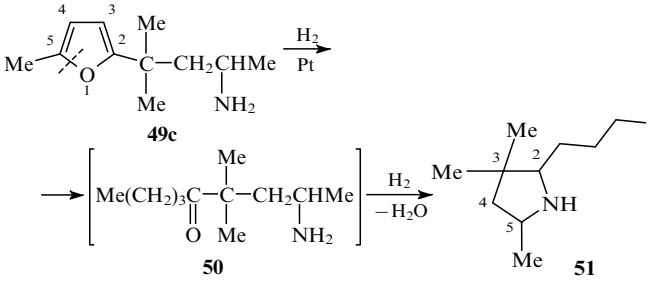
The structure of the pyrrolidines and pyrroles formed is determined by the structure of the aminoalkyl side chain.[54,55] The influence of the structure of alkyl and aminoalkyl groups in the molecules of the furan derivatives **49** on the course of hydrogenolysis and the formation of pyrrole and pyrrolidine trialkyl derivatives was studied.[55]



49a–c

R = R′ = R″ = H (**a**); R = Me, R′ = R″ = H (**b**); R = R′ = R″ = Me (**c**).

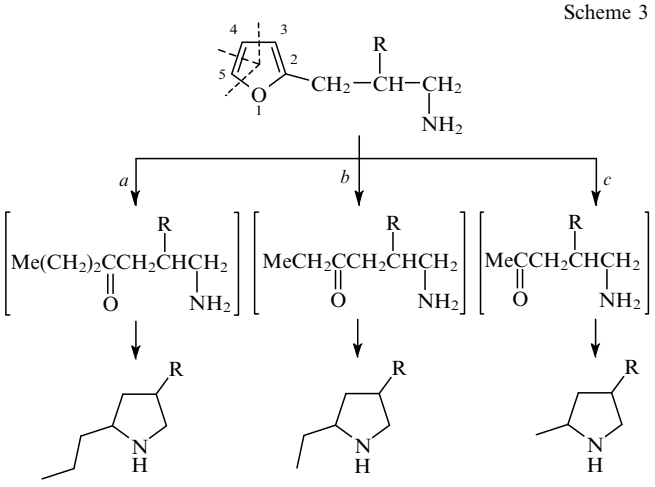
When the substituents R and R′ at the carbon atom attached directly to the furan ring in **49** are methyl groups, hydrogenolysis of the furan ring is more selective, due to the shielding effect, and involves the O(1)–C(5) bond. In addition, in the presence of these substituents, the formation of the pyrrole ring is impossible. As a result, catalytic hydrogenation of 2-(3-amino-1,1-dimethylbutyl)-5-methylfuran **49c** over platinum catalysts at 250 °C resulted in the synthesis of 2-n-butyl-3,3,5-trimethylpyrrolidine **51**.[56]



49c **50** **51**

Whereas the reaction on platinum catalysts gives only one series of pyrrolidine homologues owing to the selective rupture of the C(5)–O(1) bond at 200–220 °C, in the presence of skeletal nickel–aluminium catalysts, three series of pyrrolidine homologues containing methyl, ethyl or n-propyl groups at the 2-position can be obtained (Scheme 3).[57]

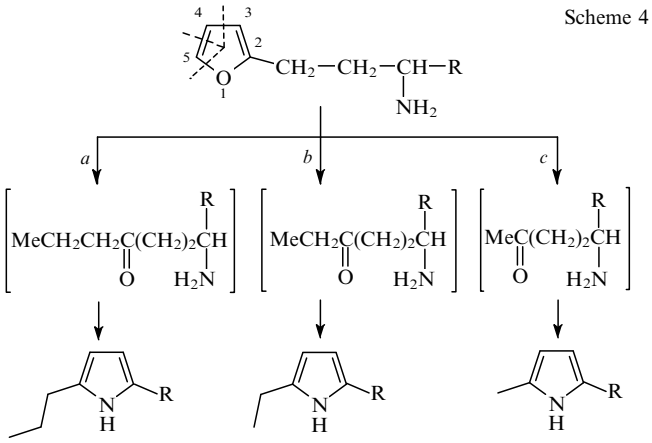
Scheme 3



(*a*) rupture of the O(1)–C(5) bond; (*b*) rupture of the O(1)–C(5) and C(4)–C(5) bonds; (*c*) rupture of the O(1)–C(5) and C(3)–C(4) bonds.

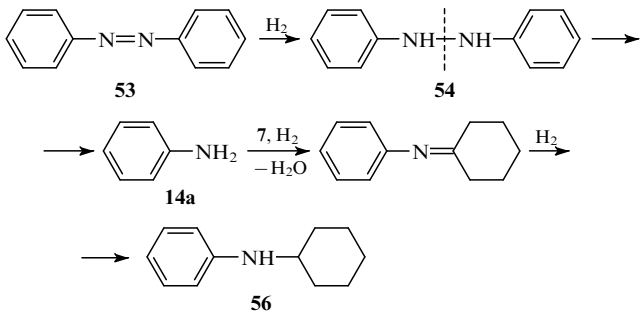
The yield of pyrrolidines in the hydrogenolysis products was, on the average, 70%–75% based on the consumed amine. The pyrrolidines formed contained 35% of 2-methyl-4-R-pyrrolidines, 20% of 2-ethyl-4-R-pyrrolidines and 45% of 2-n-propyl-4-R-pyrrolidines. The formation of a particular pyrrolidine homologue depends substantially on the reaction temperature. For example, when the temperature is raised to 270 °C, the proportion of 2-methyl-4-R-pyrrolidines increases to approximately 50%–60%; however, the overall content of pyrrolidines in the reaction products diminishes to 30%–40%. The synthesis of pyrrole homologues over skeletal nickel–aluminium catalyst is carried out at 300 °C;[58] in this case, the mixture of pyrroles contains 30% of 2-methyl-5-R-pyrroles, 25% of 2-ethyl-5-R-pyrroles and 45% of 2-n-propyl-5-R-pyrroles (Scheme 4).

Scheme 4



(*a*) rupture of the O(1)–C(5) bonds; (*b*) rupture of the O(1)–C(5) and C(4)–C(5) bonds; (*c*) rupture of the O(1)–C(5) and C(3)–C(4) bonds.

Hydroamination of cyclohexanone **7** and cyclopentanone **52** was performed [59] using azobenzene **53**, 1,2-diphenylhydrazine **54** and cyclohexanone phenylhydrazone **55**. It is known that hydrazines are able to undergo hydrogenolysis over nickel–alumina or copper–alumina catalysts at 250 °C to give primary amines.[60] It was found that in all cases, hydrogenolysis of the N–N bond and the formation of secondary cycloalkylamines (in 18% to 75% yields) is a typical reaction pathway. Since the N = N bond in azobenzene **53** is relatively stable, it can undergo hydrogenolyis only after saturation; therefore, the use of the hydrazine **54** results in higher yields of the reductive amination products; for example, the yields of *N*-cyclohexylaniline **56** obtained upon hydroamination of cyclohexanone with azobenzene and 1,2-diphenylhydrazine are 45% and 75%, respectively.



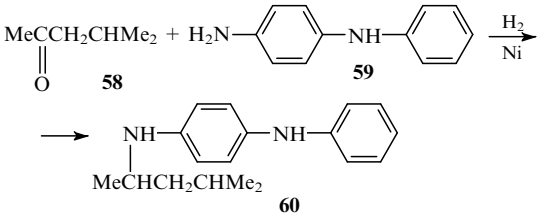
53 **54** **14a** **56**

Several studies,[14,61–70] 'generically' related to hydroamination, deserve special attention. They describe the synthesis of various amines in the presence of RPFIC in the Fischer–Tropsch synthesis. These catalysts are used to prepare various hydrocarbons and oxygen-containing organic compounds from CO and H_2.[71,72] The use of the modified Fischer–Tropsch reaction for the synthesis of oxygen-containing compounds and their reductive amination with ammonia, alkylamines and piperidine **57** have led to the development of a number of one-step proce-

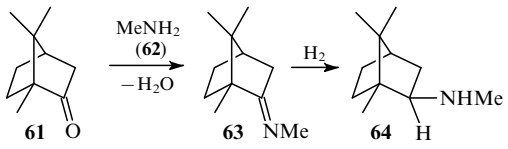
dures for the synthesis of various amines. Thus hydrogenation of CO at 169–195 °C, 10–12 MPa and at an H_2 : CO ratio of (2–6) : 1 in the presence of $HNMe_2$ (1 vol. %–10 vol. %) over RPFIC gives rise to dimethylalkylamines.[70] The yield of liquid amines reaches 73%. The use of piperidine and RPFIC in the modified Fischer–Tropsch synthesis permitted the preparation of *N*-alkylpiperidines with alkyl substituents consisting of one to fifteen C atoms at the nitrogen atom (the selectivity of the reaction with respect to amines reaches 97%).[64–69] The highest activity was found for RPFIC containing V_2O_5, Al_2O_3 or Cr_2O_3 and CuO.[68] Two pathways to *N*-alkyldimethylamines are possible: (1) hydroamination of a surface oxygen-containing intermediate, precursor of an aldehyde, ketone or alcohol; (2) direct hydroamination of alkanals or alkyl methyl ketones, primary components of the Fischer–Tropsch synthesis.

Synthesis of alkylamines from CO, H_2 and N_2 in the presence of RPFIC has been carried out. The process included two alternating reactions performed in one catalytic area: first NH_3 was obtained from H_2 and N_2 and then it was used to aminate the oxygen-containing or olefinic products of the Fischer–Tropsch synthesis, formed after the introduction of CO. Primary terminal C_4–C_9 amines were the major reaction products.[73,74]

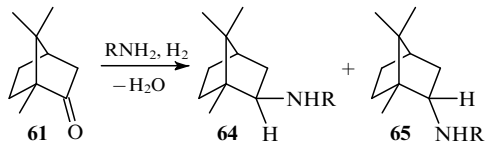
Reductive amination of aldehydes and ketones is usually carried out at high (up to 50 MPa) pressures of hydrogen.[75] Various solvents have been used in this process, MeOH, EtOH, Pr^iOH, Bu^tOH, THF and cyclohexanol.[76–78] Nickel or cobalt catalysts[34,77,79–81] and platinum group metals (Pt, Pd) supported on activated carbon[79,82–85] are used most often. Some metals (Ni, Pt, Ru, Rh) supported on an active material, for example, on alumina or kieselguhr, are also employed.[77,86–88] Catalysts based on copper and chromium oxide mixtures have been patented.[89] Rhenium and palladium sulfides (Re_2S_7, PdS) as well as Fe, Co, Ni, W and Mo sulfides supported on alumina proved to be highly active catalysts of reductive amination.[90,91] In some studies, catalysts modified with sulfur or other organic or inorganic sulfur-containing compounds have been considered. Thus reductive amination of 4-methylpentan-2-one **58** with *N*-phenyl-1,4-phenylenediamine **59** over nickel supported on kieselguhr (63% Ni) at 165 °C and a hydrogen pressure of 5.2–7.0 MPa gave *N*-phenyl-*N′*-(1,3-dimethylbutyl)-1,4-phenylenediamine **60** in 58% yield. The addition of Bu^t_2S increased the yield of the diamine **60** to 97%.[88]



Sulfoxides, thiols and sulfur-containing heterocycles have also been used to modify the catalysts.[92] The influence of the nature of the catalyst on the yield of the final product can be followed in relation to the reductive amination of camphor **61** with methylamine **62**. Thus when Raney nickel is used as the catalyst, *N*-methylbornan-2-imine **63** (yield 82.8%) is formed predominantly, whereas the reaction over 5% Pd/C yields a mixture of the imine **63** and *N*-methylbornan-2-ylamine **64** (30.4% and 65.7%, respectively).



If platinum oxide is used as the catalyst, the yield of the amine **64** reaches 92.7%.[82] High stereoselectivity of RPFIC, unusual for metallic heterogeneous catalysts, has been noted.[93–95] Thus the degree of transformation of *d,l*-camphor into *endo*- (**65**) and *exo*-bornan-2-ylamines (**64**) during hydroamination reaches 92%, the *endo* to *exo* ratio being (1.4–1.8) : 1. Apparently, this stereoselectivity is due to the 'imine–enamine' tautomerisation occurring on the acid–base sites of the catalyst.



R = H, Alk.

Highly effective and selective catalysts for hydroamination of aldehydes and ketones with ammonia, amines and nitro compounds have been developed. These catalysts, which make it possible to conduct this reaction under mild conditions (20–60 °C, and p_{H_2} = 0.1 MPa), are Pd, Pt, Rh, Co, Fe, Ni and Cu complexes with dimethyl- and dibenzylglyoximes and with polymeric macroligands such as polyacrylic acid, polyethyleneimine, copolymers, anion exchangers, cation exchangers, *etc*.[96–106] The rate of hydroamination in the presence of these catalysts depends appreciably on the nature of the polymeric matrix. The major contribution to the activity is made by the rigidity of those sections of the macromolecule which bear the active metal sites. The activity and selectivity of these catalysts can be controlled by changing the 'local rigidity;' this can be attained by increasing the temperature, by using a different solvent or exchangeable ion, by varying the particle size of the support, by irradiating the polymeric matrix or by introducing microadditives of another solvent.[99,106]

III. Reductive amination of alcohols with ammonia and amines

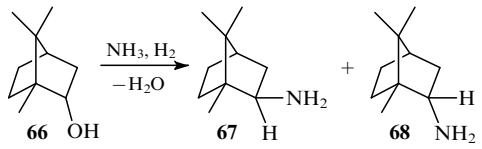
The reaction of ammonia with alcohols results in the formation of mixtures of primary, secondary and tertiary amines. In the vast majority of cases, alcohols react with ammonia or amines only in the presence of catalysts. Heterogeneous acidic catalysts have found wide application in industry. In the presence of these catalysts, the process is carried out in the gas phase at 350–450 °C. Their influence consists in the activation of the C–OH bond due to adsorption of the alcohol on the catalyst acid sites.

The reactions between ammonia and alcohols are carried out using dehydrating catalysts (copper, nickel and cobalt on alumina, fused iron, copper chromites)[107–111] and hydrogen. In this case, the reaction follows a mechanism other than the acid–base one. First, the alcohol is dehydrogenated to give aldehyde, and then the aldehyde condenses with ammonia, and the imine thus formed undergoes hydrogenation coupled with dehydration.

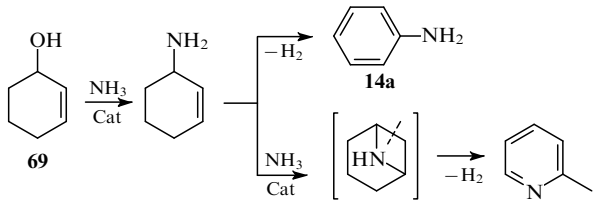
$$RCH_2OH \xrightarrow[-H_2]{} RCHO \xrightarrow[-H_2O]{NH_3} RCH{=}NH \xrightarrow[Cat]{H_2}$$

$$\longrightarrow RCH_2NH_2 \xrightarrow[-NH_3]{RCH=NH} (RCH_2)_2NH \xrightarrow[-NH_3]{RCH=NH} (RCH_2)_3N$$

The mechanism of dehydration of alcohols followed by amination has been comprehensively studied by Bashkirov *et al*.[112–117] Secondary and tertiary amines are formed upon the reactions of primary and secondary amines with aldimines. RPFIC modified with various oxides have been successfully used in reactions with amines. For example, hydroamination of a number of alcohols (2-ethylhexan-1-ol, octan-1-ol, octan-2-ol, heptan-4-ol) with dimethylamine at 210–240 °C gave the corresponding *N*,*N*-dimethylalkylamines in ~80% yields. The highest yield of tertiary amine was observed in the presence of RPFIC promoted by 10% Al_2O_3 + 1% CuO.[118] The same catalyst was used in the reductive amination of borneols **66** with ammonia, which afforded bornylamines **67** and **68**, mostly as *endo*-isomers.[119]



Copper-containing catalysts exhibit high activity in the amination of various alcohols with ammonia and amines. When bifunctional catalysts, Cu/Al_2O_3 or Ni/Al_2O_3, were used in hydroamination of alicyclic alcohols, the yields of primary amines reached 80%. To suppress cyclisation and isomerisation, lithium and potassium hydroxides were introduced into the alumina.[120] Hydroamination of cyclohex-2-enol **69** in the presence of Cu/Al_2O_3, Ni/Al_2O_3 and Pt/Al_2O_3 has been studied.[121] In the case of the copper catalysts, cyclohexylamine is mostly formed (yield 65%), whereas the reaction carried out at 310 °C over active dehydrating Pt and Ni catalysts containing 10%, 15% and 20% of the metal gives aniline. In the presence of copper and nickel catalysts at 310 °C, pyridine bases are formed, mostly 2-methylpyridine (60%–62% of the total amount of pyridine bases). Presumably, in the latter case, the reaction passes through the formation of an unstable bicyclic compound resulting from insertion of the nitrogen atom of the amino group into the ring with the simultaneous rupture of the carbon–carbon bond.



When alkanols are hydroaminated with dimethylamine, 2-ethylhexylamine and cyclohexylamine over the industrial copper–zinc–aluminium oxide-type catalyst (SNM-1) and over RPFIC,[122–125] the highest yields of non-symmetrical secondary and tertiary amines (up to 90%) are attained at 175–195 °C and at an amine : alcohol molar ratio of 0.2. Secondary amines containing an alkyl radical (C_{10}–C_{22}) are prepared by hydroamination of alcohols with primary amines at $p_{H_2} = 0.3$–0.5 MPa in the presence of the Ni or Ni–Cu catalyst containing some K_2CO_3; the yields of non-symmetrical secondary alkylamines can be as high as 85%.

$$RNH_2 + R'OH \xrightarrow[Ni,\ K_2CO_3]{H_2} RNHR' + RNR'_2$$

$R = C_{10}H_{21}$–$C_{22}H_{45}$, $R' = CH_3$–C_8H_{17}.

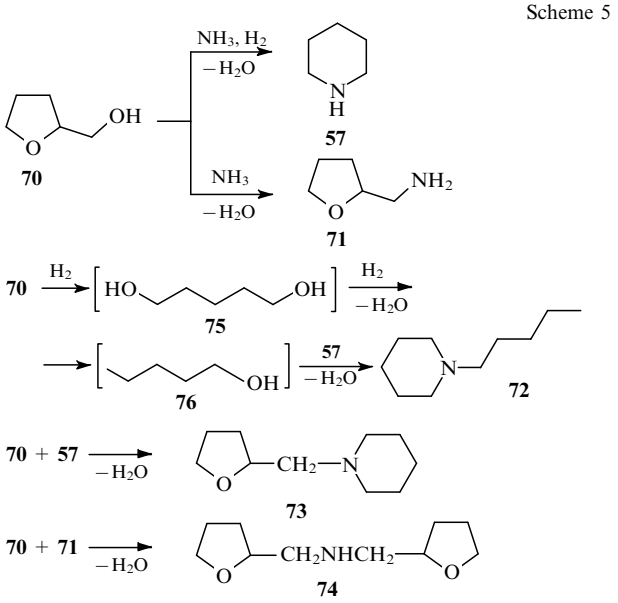
When K_2CO_3 is not added, the content of secondary amine in the amination products is 17%, and the content of tertiary amine is 45%.[126]

To increase the yield of amines, nickel catalysts are modified with various additives. Thus the activity of nickel oxides prepared by various methods and their mechanical mixtures with titanium dioxide, quartz and Aerosil has been studied in the vapour-phase amination of n-butanol in the presence of hydrogen under atmospheric pressure.[127] Synergism of nickel–titanium and nickel–silicon binary oxide catalysts in this reaction was found. It is noteworthy that in some cases, in order to attain higher yields of amines, two-stage synthetic procedures are used, which include a separate a stage of dehydration of alcohols to aldehydes.[111]

Non-symmetrical dialkylamines are prepared in 75%–90% yields [112] by the reaction of a primary amine with an alcohol in the presence of a catalyst containing copper chromite at 180–210 °C and $p_{H_2} = 4.0$–12.0 MPa. When copper catalysts are used, the reaction between ethanol and ammonia at $p_{H_2} = 15.0$ MPa affords triethylamine (yield 90%).[128]

Unlike hydroamination of primary and secondary aliphatic alcohols with ammonia, which mainly yields primary amines, hydroamination of tetrtahydrofurfuryl alcohol **70** gives rise to a heterocyclic compound, piperidine **57**. This reaction, which is of interest from the practical viewpoint, has been studied in detail.[129–135] Scheme 5 shows the possible pathways to the main products (**57**, **71**–**74**) formed from the alcohol **70**, ammonia and hydrogen. It was found that, irrespective of the catalyst used, the reaction products contain piperidine, tetrahydrofurfurylamine **71**, *N*-(n-pentyl)piperidine **72**, *N*-(tetrahydrofurfuryl)piperidine **73** and bis(tetrahydrofurfuryl)amine **74**.

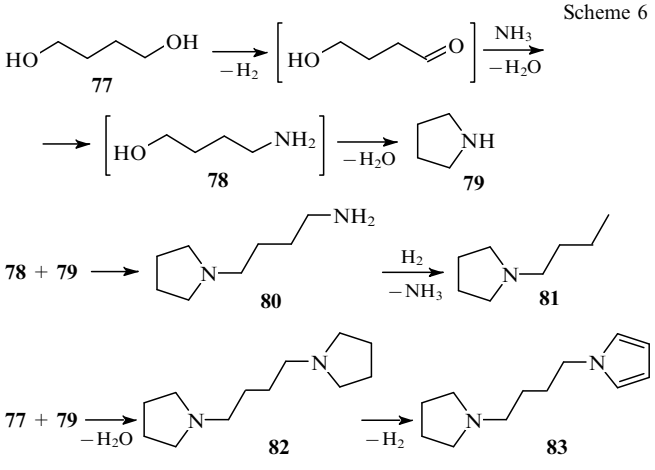
Scheme 5



When this reaction is carried out in the presence of the SNM-1 catalyst, the yield of the amine **71** reaches 62% at a virtually complete conversion of tetrahydrofurfuryl alcohol. When Co- and Ni-based catalysts are used, the formation of piperidine is the predominant reaction route (its yield reaches 51%). The compounds **73** and **74** result from intermolecular amination of the alcohol **70** with piperidine and with the amine **71**, respectively. The presence of *N*-(n-pentyl)piperidine **72** among the reaction products was explained [135] by hydrogenolysis of the alcohol **70** at the intracyclic C–O bond with the intermediate formation of pentane-1,5-diol **75**, its partial hydrodeoxygenation to n-pentan-1-ol **76** and subsequent interaction of the alcohol **76** with piperidine.

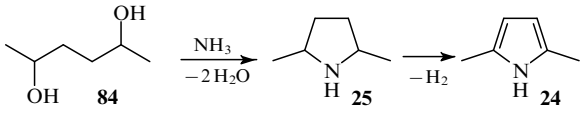
Nitrogen-containing five-, six- and seven-membered heterocyclic compounds have been prepared by hydroamination of the corresponding diols with ammonia over the industrial SNM-1 catalysts and RPFIC.[136–139] The formation of the heterocycle in the reaction of butane-1,4-diol **77** with a mixture of NH_3 and H_2 (Scheme 6) occurs in two stages. First, the initial diol **77** is aminated to give 4-aminobutan-1-ol **78**, and then this product undergoes intramolecular amination (cyclisation) to give pyrrolidine **79**.

Scheme 6

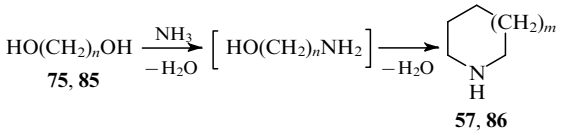


The yield of the compound **79** on the SNM-1 catalyst at 220 °C reaches 85.5%.[139] The appearance of *N*-4-aminobutylpyrrolidine **80** in the product mixture can be interpreted as being due to the reaction between 4-aminobutan-1-ol **78** and pyrrolidine. Partial hydrodeazotisation of the compound **80** affords *N*-(n-butyl)pyrrolidine **81**. 1,4-Dipyrrolidinobutane **82** is formed upon exhaustive amination of butanediol with pyrrolidine. The highest yield of the compound **82** (22.5%) was attained with RPFIC. Dehydrogenation of one heterocycle in the molecule of **82** gives rise to *N*-(4-pyrrolidinobutyl)pyrrole **83**.

The reaction of hexane-2,5-diol **84** with a mixture of NH_3 and H_2 is highly selective. The yield of 2,5-dimethylpyrrolidine **25** over RPFIC at 200 °C amounts to 93%.[139] The subsequent dehydrogenation of pyrrolidine **25** yields 2,5-dimethylpyrrole **24**.



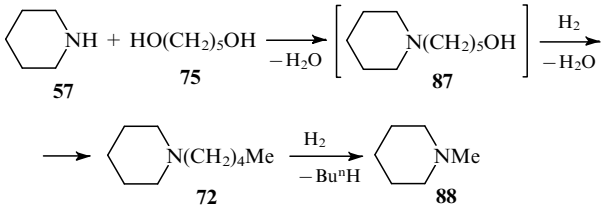
Hydroamination of pentane-1,5-diol **75** and hexane-1,6-diol **85** with ammonia follows a similar route, resulting in the formation of piperidine **57** and perhydroazepine **86**, respectively.



n = 5 (**75**), 6 (**85**); *m* = 1 (**57**), 2 (**86**).

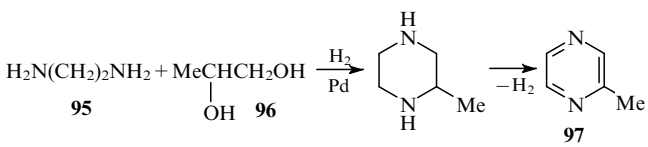
The main pathways of the catalytic transformations of the diol **75** during its interaction with NH_3 and H_2 can be illustrated by Scheme 7. The presence of *N*-(n-pentyl)piperidine **72** in the reaction products is due to the alkylation of piperidine **57** with the diol **75** involving the intermediate formation of *N*-(5-hydroxypentyl)piperidine **87** and its subsequent hydrodeoxygenation. Hydrogenolysis of the C–C bond in the alkyl substituent of the compound **72** accompanied by elimination of an n-butane molecule gives rise to *N*-methylpiperidine **88**.

Scheme 7

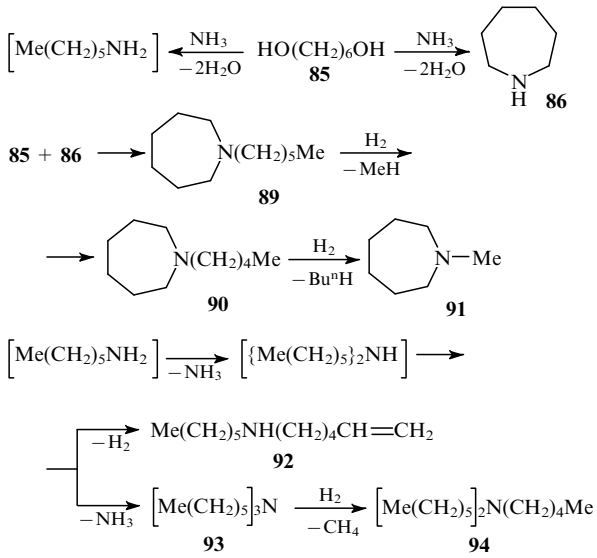


A typical feature of the transformation of the diol **85**[139] (Scheme 8) is relatively high yields of *N*-alkyl-substituted perhydroazepines **89**–**91** and secondary and tertiary alkylamines **92**–**94**. For example, when the diol **85** is hydroaminated over the SNM-1 catalyst at 180°C, the total contents of perhydroazepines **89** and **91** in the reaction products reaches 22%.

Piperazine and 1-alkyl- and 1,4-dialkyl-piperazines have been synthesised by hydroamination of diethanolamine or *N*-alkyldiethanolamines in the presence of RPFIC.[140] Cyclisation of ethylenediamine **95** with propane-1,2-diol **96** giving 2-methylpyrazine **97** over a catalyst containing 1% of Pd supported on a mixture of zinc and chromium oxides (Zn : Cr = 3 : 1) has been studied.[141] The highest selectivity of this process is observed at 38°C.

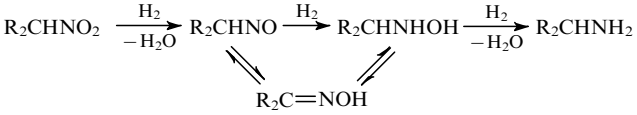


Scheme 8



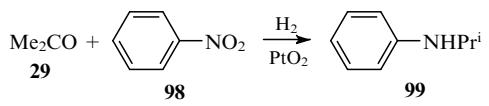
IV. Reductive amination of aldehydes and ketones with nitro compounds and pyridine bases

Reduction of nitro compounds, which is carried out in a variety of ways (catalytic hydrogenation; reduction with iron in the presence of hydrochloric acid, with metal sulfides, zinc or iron in a strongly alkaline medium, lithium aluminium hydride and hydrazine; and electrochemical reduction) is among the methods used most widely for the synthesis of amines. These reactions occur *via* several intermediate stages; for most of the reducing agents listed above, they include the formation of nitroso compounds and hydroxylamines.



Catalytic hydrogenation has found wide application in industry. Most often, it is used to convert aromatic nitro compounds into the corresponding amines.[142, 143]

The ability of nitro compounds to be reduced to amines under the conditions of reductive amination has permitted the use of this ample class of nitrogen-containing organic compounds for direct amination of aldehydes and ketones. This reaction was first performed by Emerson.[144] A mixture of acetone **29** and nitrobenzene **98** was reduced by hydrogen in an autoclave over platinum oxide; the yield of *N*-isopropylaniline **99** reached 59%.[144–147]



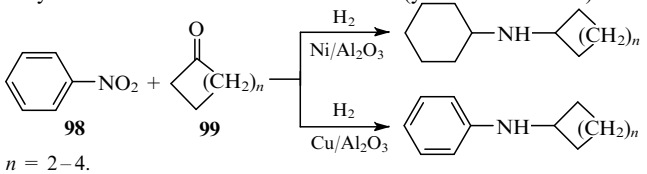
Subsequently this reaction has been widely used to synthesise secondary amines. Hydroamination by nitro compounds is normally carried out in autoclaves over platinum catalysts under a pressure of hydrogen.[86,148] Thus reductive amination of acetone by 4-nitrodiphenylamine at 120 °C and p_{H_2} = 2.0–2.5 MPa on the Pt/C catalyst gave *N*-phenyl-*N*′-isopropyl-*p*-phenylenediamine in 95% yield.[149] To increase the yield of secondary amines the catalysts are modified by various additives. For example, the reaction catalysed by platinum supported on carbon containing phosphorous acid gives amines in preparative yields.[78] Other acids or acidic compounds — H_3BO_3, organic acids or anhydrides, CO_2

— are also used as modifying agents. Acidic additives form salts with primary amines and thus prevent side reactions.

Apart from platinum, nickel catalysts are also widely used in this reaction. The use of a catalyst containing 63% of Ni supported on kieselguhr permits preparation of secondary amines from nitro compounds and ketones in yields of up to 57%. Modification of this catalyst by sulfur-containing compounds (sulfides, disulfides, sulfoxides, thiols) made it possible to increase the yields of amines to 75%.[87] Hydroamination carried out with aromatic nitro compounds is accompanied in some cases by hydrogenation of the aromatic ring.[150,151] To prevent this process, mixtures of ketones with aromatic nitro compounds are reduced over various catalysts containing Pt, Pd, Ni, Rh, Os, Sr or Co on silica or alumina in the presence of SO_2.[150] The same can be attained by using metal sulfides. Amines can be obtained in preparative yields by conducting the reaction at 250 °C at a pressure of hydrogen of up to 10.0 MPa in the presence of cobalt, nickel or molybdenum selenide or telluride as the catalyst.[152]

Palladium-containing anion exchangers are efficient catalysts of hydroamination of aldehydes and ketones by nitro compounds (mostly, aromatic ones).[99,106] A study of the influence of the substrate structure on the rates of hydroamination of oxygen-containing compounds by nitro compounds of the aromatic series has shown that the reaction rate decreases following an increase in the magnitude of the Hammett constant.[153]

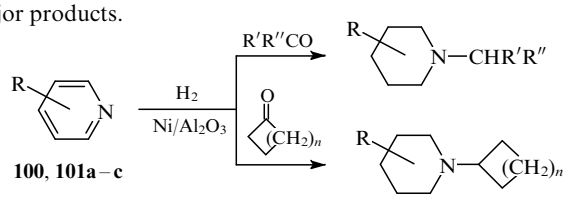
Several studies [151, 154–156] have been devoted to hydroamination of alicyclic and heterocyclic ketones by nitro compounds of aliphatic and aromatic series over nickel– and copper–alumina catalysts. It was found [151] that hydroamination of alicyclic ketones **99** with nitrobenzene at 250 °C and at p_{H_2} = 2.0 MPa over nickel catalysts gives rise to *N*-cycloalkylcyclohexylamines in yields of up to 82%. In the presence of copper catalysts, *N*-cycloalkylanilines are formed in this reaction (yields 40%–80%).



98 **99**

n = 2–4.

The capability of pyridine and its alkyl-substituted derivatives to be reduced to piperidines permits the use of these nitrogen-containing heterocycles in the reductive amination of ketones. Thus reductive amination of aliphatic and alicyclic ketones with pyridine and its monomethyl derivatives over nickel catalysts under a pressure of hydrogen has been studied.[157,158] The reactions of pyridine **100** and α-, β- and γ-picolines **101a–c** with ketones afford the corresponding *N*-substituted piperidines as the major products.

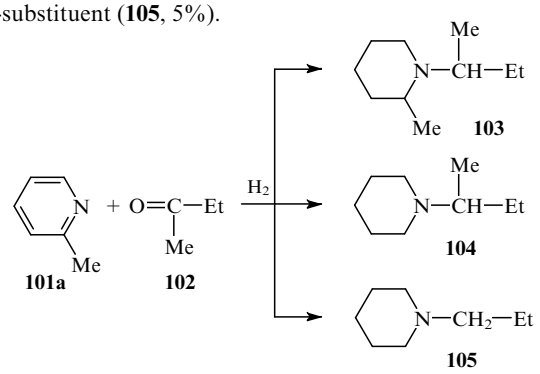


100, **101a–c**

R = H (**100**), 2-Me (**101a**), 3-Me (**101b**), 4-Me (**101c**);
R′ = Me, Et, Bu^t; R″ = Me, Et; n = 2, 3.

It was assumed [157,158] that this reaction can follow two pathways. One of them includes simultaneous reduction of the ketone to the corresponding secondary alcohol and hydrogenation of pyridine **100** to piperidine **57**. The subsequent interaction of the alcohol with piperidine accompanied by dehydration affords *N*-substituted piperidine derivatives. In the second pathway, pyridine is reduced to piperidine and the latter reacts directly with the ketone, without its intermediate transformation into the alcohol. This pathway, like the first one, affords *N*-substituted piperidine as the final product.

The use of α-picoline as the aminating agent demonstrated that the methyl group located in the vicinity of nitrogen has a substantial influence on the reaction route. For example, hydroamination of methyl ethyl ketone **102** with this compound, in addition to the expected product **103** (yield 4%), gave the products resulting from elimination of the methyl group from the pyridine ring (**104**, 9%) and elimination of the methyl group from the *N*-substituent (**105**, 5%).



101a **102**

The course of hydroamination of aliphatic ketones with pyridine bases depends substantially on the ketone structure. Thus the highest yield of the final reaction products is achieved when pyridine is made to react with alkyl methyl ketones; for example, the yield of *N*-butan-2-ylpiperidine in the reaction with methyl ethyl ketone amounts to 50%. When pyridine reacts with diethyl ketone **36** and propyl ethyl ketone **106**, the yields of the target reaction products sharply decrease (32%, for the ketone **36**) due to the substantial steric hindrance created by the two alkyl radicals attached to the carbonyl group. *tert*-Butyl methyl ketone does not enter into hydroamination at all.[158] The optimum conditions for the synthesis of *N*-alkylpiperidines are the following: temperature 220–230 °C, p_{H_2} = 2.0 MPa; v = 0.3 h^{-1}, catalyst — 20% Ni/Al_2O_3.[158]

V. Reductive amination of aldehydes, ketones and alcohols with nitriles and oximes

1. Nitriles and oximes as aminating agents

Owing to the progress in the chemistry of nitrogen-containing organic compounds achieved in recent years, nitriles can be considered to be readily available starting compounds for the synthesis of diverse and valuable organic products.

Methods of catalytic ammonolysis occupy a special place in the synthesis of nitriles. They include, first of all, oxidative ammonolysis of saturated and unsaturated hydrocarbons, methylbenzenes, naphthalene and pyridine. Linear hydrocarbons, for example, butane and butenes, can be converted by ammonolysis into saturated and unsaturated mono- and dinitriles.[159–167] Thus oxidative ammonolysis of butadiene gives rise to a mixture of nitriles of fumaric and maleic acids (total yield 67%).[168] Oxidative ammonolysis of toluene, xylenes, mesitylene or dimethylnaphthalenes can be used to synthesise nitriles of the corresponding mono-, di-, and tri-carboxylic acids, their yields being 70%–95%.[169,170] Halotoluenes, toluidines and cresols can also be introduced into ammonolysis; this gives rise to the corresponding benzonitrile. Methylpyridines are converted into the nitriles of pyridinecarboxylic acids in 70%–95% yields.[171–175]

At present, ammonolysis is employed in industry to produce acrylonitrile, benzonitrile and nitriles of methacrylic, terephthalic, and nicotinic acids. These processes have been patented and considered in several reviews (see, for example, Refs 176–179).

Thus, the development of this line of research has extended substantially the range of raw materials used for the production of diverse amines.

Hydrogenation of carbonitriles has been studied in detail, because the products of their reduction are important for practical purposes. Nitriles are converted into primary amines upon the

addition of two hydrogen molecules. However, the first molecule is added faster than the second one. Therefore, the reduction intermediately gives aldimines, which are converted into primary amines during subsequent hydrogenation. In some cases aldimines can be isolated in a pure state. The general pattern of hydrogenation of nitriles can be written as follows:

$$RC{\equiv}N \xrightarrow[Cat]{H_2} RCH{=}NH \xrightarrow[Cat]{H_2} RCH_2NH_2.$$

Aldimines are highly reactive and are able to react with the resulting primary amines; this gives rise to secondary and tertiary amines. Therefore, hydrogenation of nitriles can yield different products, depending on the reaction conditions.[180]

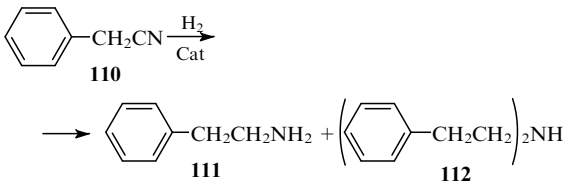
Catalytic reduction of nitriles with molecular hydrogen is the most interesting process. A fairly broad range of catalysts have found practical application in the nitrile hydrogenation — monometallic (Pt, Pd, Ni, Co, *etc*.) and bimetallic (Ni–Co, Co–Cr, *etc*.) catalysts; bifunctional metallic catalysts supported on various materials (Al_2O_3, TiO_2, SiO_2, MgO) modified with various additives (acids, alkalis); and metals (Pt, Pd, Ni, Co) immobilised on polymers. For example, synthesis of 3-amino-5-aminomethyl-2-methyl-4-methoxymethylpyridine by coupled hydrogenation and dehalogenation of 6-chloro-2-methyl-4-methoxymethyl-3-nitropyridine-5-carbonitrile over palladium-containing anion exchanger AB-17-8 has been described.[181] The yield of the target product (20–60 °C, p_{H_2} = 0.98–1.03 MPa, EtOH as the solvent) reaches 99%. The catalyst proposed for this reaction proved to be much more stable and active than Pd/C.

Data on the liquid-phase hydrogenation of hexanenitrile to amines have been reported.[182] Reduced metals (Ni, Co, Ru, Pd, Pt, Os, Cu) on γ-Al_2O_3 were used as the catalysts in this reaction. In terms of their activity in hydrogenation, the studied catalysts can be arranged in the sequence Ru > Ni > Os > Co > Pd > Pt > Cu; the selectivities of these catalysts were also dissimilar. Thus the cobalt catalyst exhibited the highest selectivity (91%) with respect to primary amine (hexylamine). The highest selectivity with respect to secondary amine was found for Ru and Pt catalysts (81%–89%). In the presence of the Pd catalyst, the yields of di- and tri-hexylamines are 65.4% and 34.6%, respectively. Hydrogenation of hexanenitrile over the industrial nickel–chromium catalyst at 120–140 °C and p_{H_2} = 5.0 MPa gave a mixture of amines containing 64% of the secondary amine and 36% of the primary and tertiary amines (the total yield). By varying the reaction temperature, the pressure of hydrogen and the chemical composition of the catalyst, the ratio of the reaction products can be controlled. Thus at 145 °C and p_{H_2} = 0.35–0.50 MPa, 100% conversion of acetonitrile was attained; the reaction products were found to contain 3.1% of primary amines, 45.4% of secondary amines and 51.5% of tertiary amines. At higher temperatures, the yield of secondary amines increases.[180] The use of Pd, Pt and Ru catalysts supported on lithium aluminium spinel in this reaction permits the preparation of an amine mixture containing 99.7% of tertiary amine.[183]

Numerous studies dealing with hydrogenation of acetonitrile **107** and acrylonitrile **108** over a series of copper and copper–nickel catalysts with various metal contents (5% Cu; 8% Cu + 2% Ni; 15% Cu + 2% Ni, *etc*.) have been carried out. Gumbrin was used as the support. Some catalyst specimens were modified with NaOH (3%). Hydrogenation was carried out at 100–200 °C under atmospheric pressure. The reduction of the nitriles **107** and **108** affords mixtures of the corresponding primary, secondary and tertiary amines. The copper–nickel catalyst (8% Cu + 2% Ni) annealed at 900 °C proved to be the most active towards hydrogenation of acrylonitrile; the total yield of amines on this catalyst was 69.7%. The modification of the Cu–Ni catalyst with alkali increases its stability.[184] The nitrile **108** was converted into dipropylamine in two stages with a high yield.[185] In the first stage, acrylonitrile was hydrogenated to propionitrile **109** in the presence of a catalyst containing Pd, Bi and K on silica gel, and in the second stage, the resulting propionitrile was converted into dipropylamine using 50%–56% Ni supported on kieselguhr at p_{H_2} = 0.1–2.0 MPa and 140–200 °C.

$$\underset{\mathbf{108}}{CH_2{=}CHCN} \xrightarrow{H_2} \underset{\mathbf{109}}{CH_2CH_2CN} \xrightarrow{H_2} (CH_3CH_2CH_2)_2NH$$

To increase the yield of primary amines, hydrogenation is carried out in the presence of ammonia. The role of ammonia or alkali is to retard the reaction of aldimines with amines and deamination.[186–188] The addition of ammonia markedly increases the yields of higher primary amines (C_8–C_{24}) produced in the hydrogenation of the corresponding individual nitriles or their mixtures.[189–191] The introduction of LiOH, NaOH, KOH or Na_2CO_3 (0.1 mass %–2.0 mass % relative to the catalyst) leads to higher yields of primary amines. Thus hydrogenation of phenylacetonitrile **110** over Raney nickel gave 2-phenylethylamine **111** in 51.2% yield, the yield of the corresponding secondary amine **112** being 37.5%. When 2.0 mass % NaOH was introduced into the catalyst, the yield of the primary amine became 92.5%–95.5%.[192, 193]

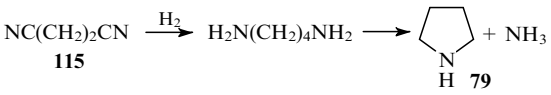


Since benzylamine **113** is a valuable compound for fine organic synthesis, a large number of studies dealing with catalytic hydrogenation of benzonitrile have been carried out. Hydrogenation of benzonitrile in dioxane in the presence of ammonia at 70–80 °C has been studied.[194] Nickel supported on kieselguhr was used as the catalyst. The benzene ring was not hydrogenated under these conditions; the yield of benzylamine was 76%–79% and the selectivity was 82.5%. Interesting results have been obtained in a study of hydrogenation of benzonitrile on the Pt/C, Pd/C and Ru/C catalysts.[195] The reaction rate was found to increase on increasing the pressure of hydrogen; however, the yield of toluene also increased (from 0.3%–3.0% to 8%–9%).

Hydrogenation of nitriles and dinitriles in methanol or cyclohexane[196] is carried out on cobalt catalysts supported on Fe, Co, Mn or Cr metal powders at 80–120 °C and p_{H_2} = 25.0–35.0 MPa in the presence of ammonia. The yields of the corresponding primary amines were 90%–95%. It was noted that the service life of metal-supported catalysts is longer than those of catalysts supported on oxides.

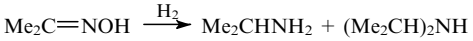
Dinitriles of the aliphatic and aromatic series are hydrogenated under the same conditions as mononitriles. For example, octamethylenediamine (yield 91%) is prepared by catalytic reduction of the dinitrile of the corresponding acid in the presence of a ruthenium catalyst in an inert solvent containing an additive of NH_3, at p_{H_2} = 3.0 MPa.[197] By varying the reaction conditions, the reduction of dinitriles can be terminated at the stage of formation of amino nitrile as the major reaction product. Thus the dinitriles $CN(CH_2)_nCN$ (where n = 1–10) can be converted on a rhodium catalyst into the corresponding amino nitriles, formed in high yields.[198, 199] Data on the conditions and the mechanism of this reaction and various factors that influence its course have been described systematically.[200] The mechanisms of the formation of primary, secondary and tertiary amines were described in detail. In terms of their activity in this reaction, known catalysts can be arranged in the following sequence: Pt > Pd > Ni > Co > Fe > Cu. The reduction of aliphatic dinitriles containing CN groups at the 1,2-, 1,3- and 1,4-positions, in addition to the corresponding diamines, yields five-, six- and seven-membered saturated heterocyclic compounds, resulting from intramolecular heterocyclisa-

tion. For example, succinodinitrile **115** is converted into pyrrolidine **79**.



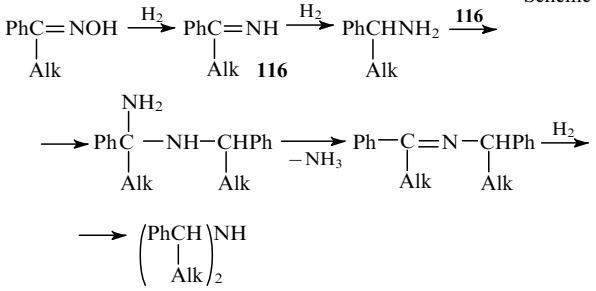
Data on the hydrogenation of nitriles in the presence of homogeneous or heterogeneous catalysts in the liquid phase have been described systematically.[201] The reaction mechanisms and the pathways to side products were considered. The effects of the solvent, temperature, the pressure of hydrogen and the nature of the catalyst on the course of this reaction carried out over heterogeneous catalysts were studied.

Oximes are also hydrogenated using nickel catalysts. Thus hydrogenation of acetone oxime gives a mixture of amines in which the secondary amine predominates.[202]

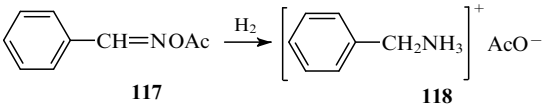


Hydrogenation of a number of alkylaromatic oximes has been studied.[203] It was found that the formation of primary amines is preceded by the intermediate formation of imines **116**; in some cases, they can be isolated from the reaction mixture (Scheme 9). The reaction products contain primary, secondary and tertiary amines.[204–207] Secondary amines result from interaction of the imine **116** with primary amines. They can also arise upon deamination of primary amines in the presence of a catalyst.[208]

Scheme 9



Rosenmund *et al.*[209] were the first to use an oxime acetate for preventing the formation of a secondary amine. Hydrogenation of the benzaldehyde oxime acetate **117** gave a primary amine (formed as acetate **118**) in 91% yield.



Primary amines are also prepared by hydrogenation of oximes in acetic anhydride. Thus hydrogenation of benzaldehyde oxime under these conditions resulted in the synthesis of *N*-benzylacetamide; hydrogenation of acetone oxime gave *N*-(1-phenylethyl)acetamide.[204] Free amines are obtained by hydrolysis of these amides. Good yields of primary amines, formed as hydrochlorides, are attained when oximes are hydrogenated on a palladium catalyst in anhydrous ethanol with three equivalents of HCl.[210] Hydrogenation of oximes in the presence of ammonia,[211] which increases the yield of primary amines, has found a wider practical application.

In the case of catalytic hydrogenation of oximes, nickel, cobalt and rhodium supported on alumina are used most often as the catalysts.[204] In the reduction of oximes of α,β-unsaturated ketones, platinum dioxide is used as the catalyst and MeOH is used as the solvent.[205] The solvent has a substantial influence on the composition of the products of oxime reduction in the liquid phase. For example, when a more polar solvent was used, aziridine was obtained from benzylideneacetone oxime, in addition to the corresponding amine.[212] Study of hydrogenation of cyclohexanone oxime in various solvents in the presence of Pt, Pd, Rh and Ru supported on finely dispersed carbon made it possible to elucidate the influence of the solvent and the catalyst on the reaction rate and the product composition. The reaction does not occur in dioxane; the reaction in methanol proceeds in the presence of the rhodium catalyst, while in acetic acid, it proceeds over a platinum catalyst. When the reaction is carried out in water, cyclohexanol is produced as the major product.[212]

Apart from the platinum Group metals listed above, cobalt is also used to catalyse hydrogenation of oximes. In some cases Raney cobalt is more active than the nickel catalyst.[213] Alumina is usually employed as the support.[204, 214]

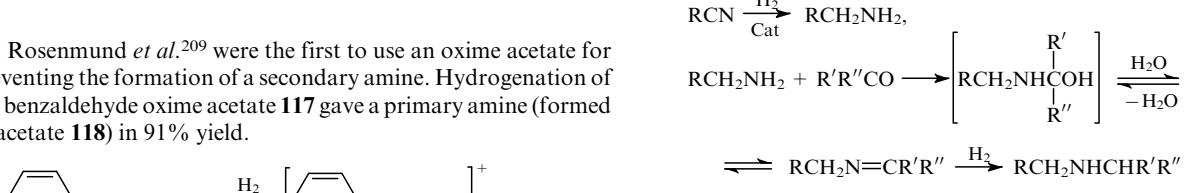
When oximes are reduced over copper catalysts, together with amines, side products are formed, in particular, the Beckmann rearrangement product, the corresponding ketones, aldehydes, nitriles and imines.[215]

Apart from molecular hydrogen, the hydrazine–Raney nickel system is also widely used as the reducing agent in the hydrogenation of oximes.[208, 216] This system permits easy and selective reduction of oximes to primary amines.

2. Reductive amination of oxygen-containing compounds with nitriles and oximes

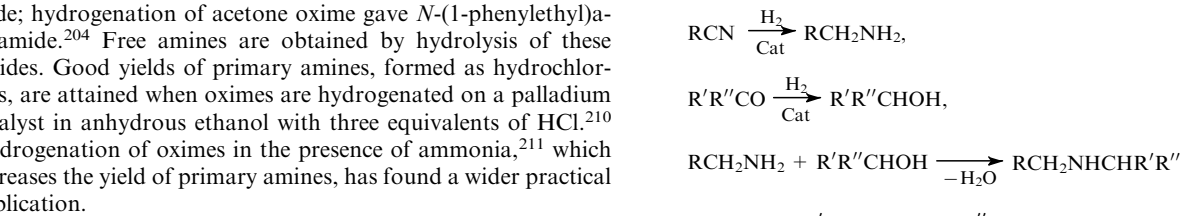
Significant progress in the development of new methods for the synthesis of amines was associated with the use in the reductive amination of nitriles and oximes, which had not been used previously as direct aminating agents. Hydroamination of oxygen-containing compounds with nitriles extends still further the potential of this reaction.

The ability of nitriles to be reduced to amines under the conditions of catalytic hydrogenation made it possible to aminate various ketones and aldehydes in one stage.[217–221] The reaction is carried out in the vapour phase over a heterogeneous catalyst in a flow-type setup operating under a pressure of hydrogen. The process of hydroamination of oxygen-containing compounds with nitriles includes several successive coupled reactions resulting in the formation of secondary amines. In the carbonyl compound–nitrile–hydrogen system, this reactions occurs in accordance with the following scheme:[218, 219]



R, R′ = H, Alk, Ar; R″ = Alk, Ar.

Under the reaction conditions, carbonyl compounds are partly reduced to the corresponding alcohols. The possibility of hydroamination of alcohols with nitriles, as shown below, also cannot be ruled out.

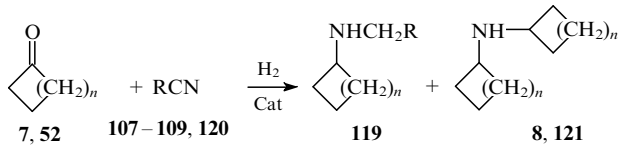


R = H, Alk, Ar; R′ = H, Alk, Ar; R″ = Alk, Ar.

The reaction pathway depends on the structures of the reactants and on the rate of each particular stage. The above reactions might also occur simultaneously.

Hydroamination of cyclic ketones by aliphatic nitriles under a pressure of hydrogen has been studied.[218, 219] Nickel–alumina and copper–alumina catalysts with a metal content of 15%–20%, both non-modified and modified by the addition of Li, Na

and K, were used. The main reaction pathway is the formation of alicyclic secondary amines **119**.

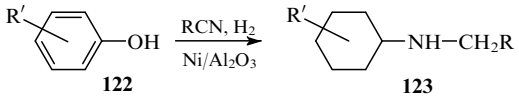


7, **52** **107**–**109**, **120** **119** **8**, **121**

R = Me (**107**), CH=CH$_2$ (**108**), Et (**109**), Pr^n (**120**); n = 3 (**7**, **8**), 2 (**52**, **121**).

The yields of the corresponding amines **119** with the 15% Cu/Al_2O_3 catalyst at 240 °C and p_{H_2} = 1.5 MPa reaches 75%. The introduction of alkaline additives (Li, Na, K) in the copper–alumina catalyst increases the total yield of amines by 5%–12%. The di(cycloalkyl)amines **8** and **121** are formed as side products. It was assumed [218] that the main reason for the formation of the amines **8** and **121** is the low stability of *N*-alkylcycloalkylamines **119** under the conditions employed. In fact, when *N*-ethylcyclohexylamine is passed over the catalyst under the conditions of hydroamination, it partly decomposes to give a mixture of cyclohexylamine **13** and dicyclohexylamine **8** (up to 30%). Study of the reductive amination of the alicyclic ketones **7** and **52** with aceto- (**107**), acrylo- (**108**), propio- (**109**) and butyro-nitriles (**120**) showed that the yield of *N*-alkylcycloalkylamines **119** decreases following an increase in the number of the carbon atoms in the nitrile molecule.

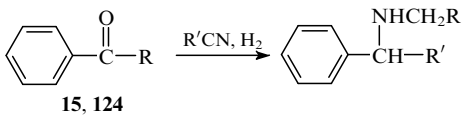
N-Alkylcyclohexylamines **123** have been prepared in good yields (up to 73%) by hydroamination of phenols **122** with nitriles on nickel–alumina catalysts. In this case, amination is accompanied by hydrogenation of the aromatic ring.[222]



122 **123**

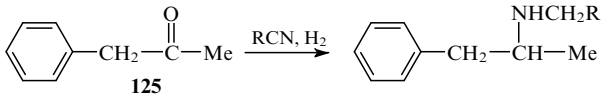
R = Me, Et, Pr; R′ = H, *o*-Me, *m*-Me, *p*-Me.

In order to synthesise aromatic amines which contain the amino group in the side chain and form a number of important biologically active compounds, hydroamination of acetophenone **15**, benzophenone **124** and benzyl methyl ketone **125** with nitriles has been carried out.[223] In the presence of copper–alumina catalysts, the highest yields (31%–72%) of secondary amines were attained with 20% Cu/Al_2O_3 at 220 °C, p_{H_2} = 1.5–2.0 MPa. The reactivity of ketones in the amination by nitriles decreases in the order **125** > **15** > **124**.[223] The conjugated system of bonds present in acetophenone results in a lower positive charge on the carbonyl carbon atom; this accounts for the decrease in the reactivity of the ketone **15**. In the case of hydroamination of benzophenone with acetonitrile, the yield of *N*-ethylbenzhydrylamine is influenced not only by conjugation but also by steric factors. Ethylbenzene and diphenylmethane were isolated as side products upon hydroamination of aceto- and benzophenone. Virtually no propylbenzene is formed on hydroamination of benzyl methyl ketone.



15, **124**

R = Me, Ph; R′ = Me, Et, Pr^n.



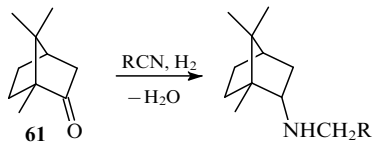
125

R = Me, Et, Pr^n.

Unsaturated ketones, aliphatic nitriles, phenylacetonitrile, aliphatic and alicyclic ketones, benzonitrile and aldehydes have been used successfully for the synthesis of aliphatic-aromatic amines [219, 223–227] (Table 1). *N*-Alkylbornan-2-ylamines were synthesized in 45%–55% yields by hydroamination of camphor **61** by aliphatic nitriles.[228]

Table 1. Synthesis of aliphatic-aromatic secondary amines by hydroamination of ketones and aldehydes with nitriles

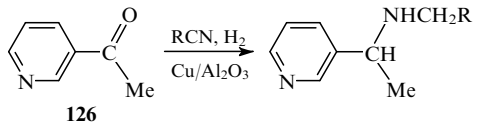
Ketone, aldehyde	Nitrile	Catalyst	The resulting amine	Yield (%)	Ref.
T = 220 °C, p_{H_2} = 1.5 MPa, v = 0.25 h^{-1}					
Acetophenone	acetonitrile	15% Cu/Al_2O_3 + 2% LiOH	*N*-ethyl-α-phenylethylamine	58	223
Benzophenone	"	15% Cu/Al_2O_3 + 2% LiOH	*N*-ethylbenzhydrylamine	28	223
Benzyl methyl ketone	"	20% Cu/Al_2O_3	*N*-ethyl-α-methyl-β-phenylethylamine	72	223
Benzylidenacetone	"	36% Cu/MgO	*N*-ethyl-1-methyl-3-phenylpropylamine	65	224
Acetone	benzonitrile	20% Cu/Al_2O_3	*N*-isopropylbenzylamine	58	219
Methyl ethyl ketone	"	20% Cu/Al_2O_3	*N*-(butan-2-yl)benzylamine	42	219
Diethyl ketone	"	20% Cu/Al_2O_3	*N*-(pentan-3-yl)benzylamine	46	219
Cyclopentanone	"	20% Cu/Al_2O_3	*N*-cyclopentylbenzylamine	36	219
Cyclohexanone	"	20% Cu/Al_2O_3	*N*-cyclohexylbenzylamine	54	219
T = 230 °C, p_{H_2} = 1.5 MPa, v = 0.20 h^{-1}					
Benzylidenacetone	acrylonitrile	36% Cu/MgO	*N*-propyl-1-methyl-3-phenylpropylamine	70	224, 225
	butyronitrile	36% Cu/MgO	*N*-butyl-1-methyl-3-phenylpropylamine	75	224, 225
	isobutyronitrile	15% Cu/Al_2O_3 + 6% LiOH	*N*-isobutyl-1-methyl-3-phenylpropylamine	60	224, 225
	benzonitrile	36% Cu/MgO	*N*-benzyl-1-methyl-3-phenylpropylamine	70	224, 225
p-Methoxybenzylidenacetone	acetonitrile	15% Cu/Al_2O_3 + 6% LiOH	*N*-ethyl-1-methyl-3-(*p*-methoxyphenyl)-propylamine	60	224
1-Phenylpent-1-en-3-one	"	15% Cu/Al_2O_3 + 6% LiOH	*N*-ethyl-3-phenyl-1-ethylpropylamine	60	224
T = 220 °C, p_{H_2} = 1.0 MPa, v = 0.30 h^{-1}					
Acetone	phenylacetonitrile	20% Cu/MgO	*N*-isopropyl-2-phenylethylamine	61	226
Diethyl ketone	"	20% Cu/Al_2O_3	*N*-(pentan-3-yl)-2-phenylethylamine	36	226
Methyl propyl ketone	"	20% Cu/MgO	*N*-(pentan-2-yl)-2-phenylethylamine	50	226
Cyclohexanone	"	20% Cu/MgO	*N*-cyclohexyl-2-phenylethylamine	52	226



R = Me, Et, Pr^n.

Systematic study of the reductive amination of carbonyl-containing compounds and secondary alcohols of the terpene series resulted in the development of preparative and selective methods for the synthesis of both unsaturated and completely hydrogenated amines with diverse structures (aliphatic; mono- bi- and tricyclic; containing three-, four, five- and six-membered rings) [229–239] (Table 2).

A series of 3-(1-alkylaminoethyl)- and 3-(arylmethylaminoethyl)-pyridines have been synthesised in 50%–65% yields by hydroamination of 3-acetylpyridine **126** with aliphatic and aromatic nitriles.[240]



126

R = Me, Et, Pr^n, Ar.

Hydroamination of an α,β-unsaturated heterocyclic ketone — 4-(2-furyl)but-3-en-2-one **127** — which has an additional reaction site, the oxygen atom of the furan ring, has been studied. This process can follow several alternative pathways depending on the catalyst used (Scheme 10). In the presence of a copper–magnesium catalyst, the reaction stops at the stage of formation of a secondary amine of the furan series, namely, 2-(3-alkylaminobutyl)furan **128** (yield 45%–48%); the use of copper–alumina catalyst results in hydrogenolysis of the furan ring at the O(1)–C(5) bond and cyclisation of the intermediate amino ketone. In this case, *N*-alkyl-2-methyl-5-propylpyrrolidine **129** is the main product (yield 42%–46%).[241] In addition, the reaction products contain a small amount of pyrrole derivatives **130** (5%), which result from the direct replacement of the oxygen atom of the furan ring by an amino group accompanied by hydrogenation of the carbonyl group and the double bond in the side chain.

Scheme 10

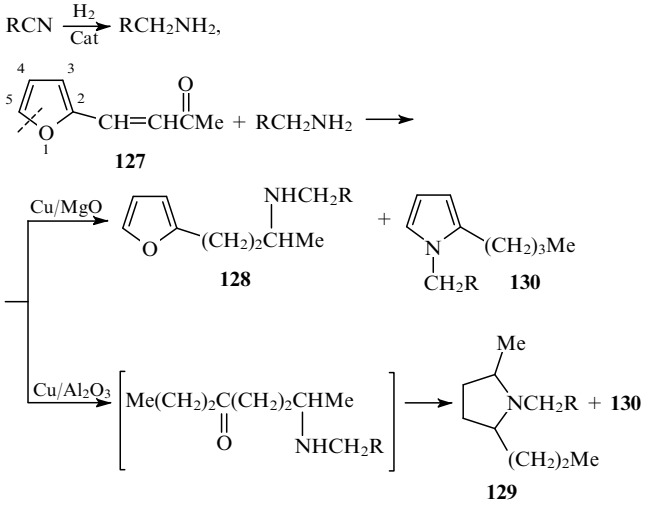
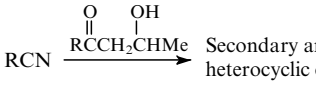


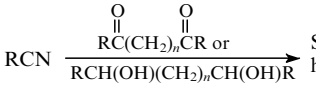
Table 2. Reductive amination of carbonyl-containing compounds and alcohols of the terpene series.

Ketone, alcohol	Nitrile, oxime	Catalyst	The resulting amine	Yield (%)	Ref.
T = 220 °C, p_{H_2} = 1.5 MPa, v = 0.25 h^{-1}					
L-Camphor	acetonitrile	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-ethylbornylamines (*exo*- and *endo*-isomers)	60 [a]	229
1,3,3-Trimethylbicyclo-[2.2.1]heptan-2-one	"	15% Cu/Al_2O_3 + (2–6)% LiOH	the same	80	230
(+)-*S*-Carvone	"	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-ethylcarvo-, isocarvo-, neocarvo- and neoisocarvomenthylamines	60–70 [a]	231
Acetone	(+)-*S*-carvone oxime	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-isopropyl-5-isopropyl-2-methyl-cyclohexylamine	60	232
L-Menthol	acetonitrile	15% Cu/Al_2O_3 + (2–6)% LiOH; 36% Cu/MgO	*N*-ethylmenthyl-, neomenthyl-, isomenthyl- and neoisomenthylamines	70 [a]	233, 234
cis-3,7,7-Trimethylbicyclo-[4.1.0]heptan-2-ol	"	15% Cu/Al_2O_3 + (2–6)% LiOH; 36% Cu/MgO	*N*-ethyl-5-isopropyl-2-methylcyclo-hexylamine	60	235
Hexahydropseudoionone	benzonitrile	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-benzyl-1,5,9-trimethyldecylamine	85	236
1-Ethylbicyclo[2.2.1]-heptan-2-one	acetonitrile	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-ethyl-1-ethylbicyclo[2.2.1]hept-2-yl-amines (*exo*- and *endo*-isomers)	69 [a]	237
T = 250 °C, p_{H_2} = 1.5 MPa, v = 0.25 h^{-1}					
Isocamphanone, isocamphanol	acetonitrile	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-ethylisocamphylamines	80	238
Isofenchol	propionitrile	15% Cu/Al_2O_3 + 6% LiOH	*N*-propylisofenchylamine	60	238
1-Ethyltricyclo-[2.2.1.$0^{2,6}$]heptan-3-one	acetonitrile	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-ethyl-1-ethyltricyclo[2.2.1.$0^{2,6}$]-hept-3-ylamine	75	238
Citronellal	propionitrile	15% Cu/Al_2O_3 + (2–6)% LiOH	*N*-propyl-3,7-dimethyloctylamine, *N*-propyl-3,7-dimethyloct-6-enylamine	35 30	238
T = 240–260 °C, p_{H_2} = 1.5 MPa, v = 0.20 h^{-1}					
2-Acetylbicyclo-[2.2.1]hept-5-ene	acetonitrile	36% Cu/MgO	2-(α-ethylaminoethyl)bicyclo-[2.2.1]heptane	70	239

[a] The total yield is given.

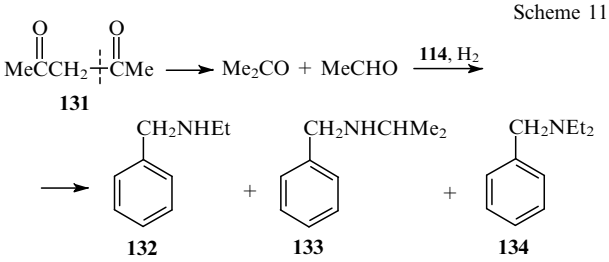
Several studies have been devoted to the interaction of nitriles with bifunctional oxygen-containing compounds in which both reaction sites can be involved in hydroamination. In particular, reactions of hydroxy ketones, diketones and diols were investigated.[242–244]



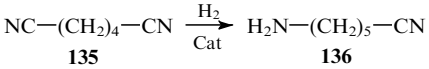


α-Diketones and α-glycols react with nitriles according to similar patterns. Thus the reaction of diacetyl with nitriles yields the same products as the reaction of ethylene glycol, namely, mono- and diamines.[243, 244] Acetylacetone (β-diketone) **131** is unstable under the reaction conditions, products of its decomposition being involved in reductive amination. The reaction of the diketone **131** and benzonitrile **114** over the 15% Cu/MgO catalyst at 240 °C and p_{H_2} = 1.5 MPa gives rise to *N*-ethylbenzylamine **132** (yield 29%), *N*-isopropylbenzylamine **133** (yield 19%) and *N*,*N*-diethylbenzylamine (yield 18%) (Scheme 11).

Scheme 11

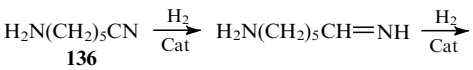


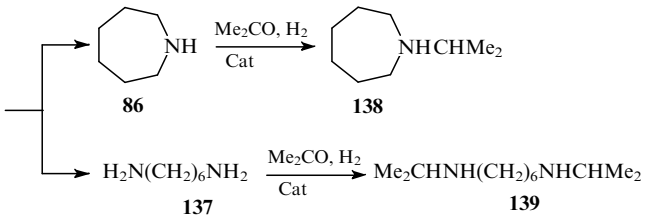
Reactions of dinitriles with carbonyl compounds have been studied. It was found[221] that hydroamination of acetone and butanal with adiponitrile **135** can follow two pathways, one yielding a heterocycle and one yielding aliphatic amines. The nitrile groups in the adiponitrile molecule behave under the hydrogenation conditions as if they possessed different reactivities. This fact has been explained by the formation of unstable cyclic systems.[245] A pseudo-ring forms upon interaction of nitrogen of one nitrile group with the hydrogen located at the α-position relative to the second nitrile group. Therefore, reductive amination occurs as preferential reduction of one nitrile group rather than simultaneous reduction of both of them and yields 6-aminohexanenitrile **136**.



The amino nitrile **136** can undergo two types of transformation. The first of them is hydrogenation of the second CN group to give hexamethylenediamine **137** and subsequent hydroamination of a carbonyl compound, for example, acetone **29**. The second route includes hydrogenation of the amino nitrile **136** accompanied by cyclisation and gives rise to perhydroazepine **86**.

The crucial factor which determines the reaction route is temperature. Thus at 190 °C, the yields of *N*-isopropylperhydroazepine **138** and *N*,*N*′-diisopropylhexamethylenediamine **139** are 25% and 84%, respectively, whereas at 240 °C they are 22% and 3%.

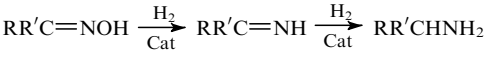




The good results attained in hydroamination of oxygen-containing compounds, together with the theoretical fundamentals and the published data concerning reduction of oximes to primary amines under conditions similar to those used in hydroamination, permitted oximes to be employed for the first time for reductive amination of various ketones and aldehydes.[246–249] Analysis of the ability of oximes to be reduced over heterogeneous catalysts led to the conclusion that, in addition to the traditional catalysts used to reduce oximes to primary amines (platinum Group metals and nickel), copper catalysts are also active in this process.

Hydroamination of carbonyl compounds with various oximes includes several consecutive coupled reactions, resembling those involved in hydroamination of carbonyl compounds with nitriles. The necessity of a high degree of coupling between separate stages becomes evident if one examines the processes occurring in the 'oxime–carbonyl compound–hydrogen' ternary systems over a heterogeneous catalyst. Initially, the oxime is reduced on the hydrogenating sites of the catalyst to give a primary amine (Scheme 12).[247, 248]

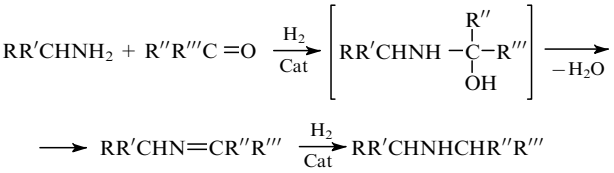
Scheme 12



R = Alk, Ar; R′ = H, Alk, Ar.

The resulting primary amine can participate in many thermodynamically allowed reactions. Within the scope of our review, condensation of the primary amine with the carbonyl compound is of interest (Scheme 13).[247, 248]

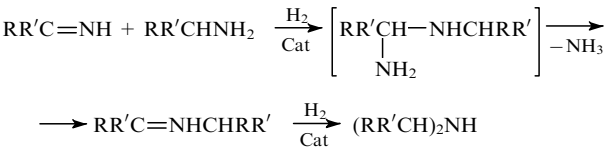
Scheme 13



R, R″ = Alk, Ar; R′, R‴ = H, Alk, Ar.

The reaction of the primary amine with the imine, resulting from incomplete reduction of the oxime, is a competing process (Scheme 14).[247, 248]

Scheme 14



Thus, when there is no coupling between the formation of primary amine and its condensation with the carbonyl compound (see Schemes 12 and 13), the overall process can be substantially influenced by the reaction of the primary amine with the nitrogen analogue of the carbonyl compound, *i.e.* imine (see Scheme 14). The formation of symmetrical secondary amines markedly decreases the selectivity of the main reaction.[247, 248]

The attainment of coupling depends appreciably on the catalyst. The carbonyl compound should be activated towards condensation (see Scheme 13) to an extent that its reactivity in

Table 3. Reductive amination of ketones, aldehydes and alcohols with oximes.

Ketone, aldehyde, alcohol	Oxime	Catalyst	The resulting amine	Yield (%)	Ref.
T = 210 °C, p_{H_2} = 1.5 MPa, v = 0.25 h^{-1}					
Pentan-2-one	cyclohexanone	36% Cu/MgO	*N*-(pentan-2-yl)cyclohexylamine	41	246
	cyclopentanone	36% Cu/MgO	*N*-(pental-2-yl)cyclopentylamine	52	246
Cyclohexanone	cyclohexanone	36% Cu/MgO	dicyclohexylamine	62	246
Acetaldehyde	"	15% Cu/Al_2O_3 + 6% LiOH	*N*-ethylcyclohexylamine	55	247
Propanal	"	15% Cu/MgO	*N*-propylcyclohexylamine	67	247
Butanal	cyclopentanone	15% Cu/MgO	*N*-butylcyclopentylamine	74	247
2-Methylpropanal	"	15% Cu/MgO	*N*-isobutylcyclopentylamine	55	247
T = 210 °C, p_{H_2} = 1.0 MPa, v = 0.30 h^{-1}					
Acetaldehyde	benzaldehyde	36% Cu/ZnO	*N*-ethylbenzylamine	44	248
Propanal	"	15% Cu/Al_2O_3	*N*-propylbenzylamine	46	248
Pentanal	"	36% Cu/MgO	*N*-pentylbenzylamine	60	248
3-Methylbutanal	"	36% Cu/MgO	*N*-(pentan-2-yl)benzylamine	48	248
T = 240 °C, p_{H_2} = 1.5 MPa, v = 0.25 h^{-1}					
Cyclohexylmethanol	3-methylbutanal	15% Cu/Al_2O_3 + 6% LiOH	*N*-(pentan-2-yl)cyclohexylmethylamine	46	249
	"	36% Cu/ZnO	"	45	249

relation to the nucleophile be higher than that of the imine. This activation occurs on the acid sites of the catalyst.[248] The condensation proceeds *via* intermediate formation of the addition product, which is converted into imine upon dehydration. This stage is followed by hydrogenation of the C=N double bond on the hydrogenating sites of the catalyst and by the formation of a secondary amine, which is the final reaction product. The data on the methods of synthesis of secondary amines from oximes, ketones, aldehydes and alcohols are presented in Table 3.

VI. Conclusion

The data considered in the review convincingly demonstrate the substantial progress achieved in the development of catalytic methods for the synthesis of amines based on reductive amination of various oxygen-containing organic compounds. The most significant achievements are the use of nitriles and oximes, which had not been used previously for these purposes, as aminating agents; elaboration and use of complex catalysts for reductive amination, which allow the processes to be conducted under mild conditions with high selectivity; and the use of reduced promoted fused iron catalysts in the synthesis of nitrogen-containing heterocycles.

The assimilation of new reactions of oxidative ammonolysis and oxo synthesis made it possible to synthesise numerous nitriles, carbonyl compounds and oximes, needed for the production of amines of various structures and compositions. Thus, there are strong grounds for believing that in the near future, the reaction in question would become one of the most significant methods for the preparation of amines.

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