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Journal of Catalysis 234 (2005) 161–171
JOURNAL OF CATALYSIS
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Structure-selectivity relationship in the chemoselective hydrogenation of unsaturated nitriles

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Received 6 April 2005; revised 9 June 2005; accepted 13 June 2005

Available online 19 July 2005

Abstract

Several unsaturated nitriles of various structures (cinnamonitrile, cyclohex-1-enyl-acetonitrile, acrylonitrile, 3,3-dimethyl-acrylonitrile, geranylnitrile, and 2- and 3-pentenenitrile) with different substituents at the double bond were hydrogenated over Cr-doped Raney cobalt and nickel and over their undoped equivalents. The substitution and the position of the double bond relative to the nitrile group are crucial in determining the chemoselectivity for the unsaturated amine. The double bond is not hydrogenated when it is sterically hindered or if it is too far from the nitrile group (cyclohex-1-enyl-acetonitrile, double bond at C-6 in geranylnitrile). In conjugated systems, such as acrylonitrile or 2-pentenylnitrile, the activated double bond is hydrogenated before the nitrile. An additional methyl substituent at the double bond enhances the selectivity for unsaturated amines and, thus, 3,3-dimethyl-acrylonitrile and geranylnitrile were hydrogenated with selectivity up to 40%. The highest selectivities for unsaturated amines (up to 90%) were reached during the hydrogenation of nonconjugated systems, such as cyclohex-1-enyl-acetonitrile and 3-pentenylnitrile.

Keywords: Chemoselective hydrogenation; Unsaturated nitriles; Cr-doped Raney cobalt; Raney nickel; Unsaturated amines; Structure–reactivity; Structure–selectivity relationship

1. Introduction

Chemoselective hydrogenation is an important tool in the fine chemicals industry. The molecules to be hydrogenated often contain several reducible groups, and, in many cases, only one of them has to be reduced. As an example, the hydrogenation of unsaturated carbonyl compounds can be mentioned. This type of chemoselective hydrogenation has been studied intensively [1,2], and molecules such as cinnamaldehyde, citral, benzalacetone, and ketoisophoron were hydrogenated as test molecules. The unsaturated alcohols are usually the desired products because of their application in the fine chemicals industry. The catalysts generally used in this reaction are doped noble metals (mainly Pt and Ru) supported on various supports. Much effort has been devoted to improving the selectivity for C=O group hydrogenation, and the positive effect of promoting the noble metal catalysts with other metals (e.g., Sn, Fe, Ge, Ga, etc.) has been confirmed.

We have focused on a very similar but unexplored system, the hydrogenation of unsaturated nitriles. In this case, two unsaturated groups are present in the molecule (C=C and C≡N). In general, three types of products can be obtained during the hydrogenation of an unsaturated nitrile: a saturated nitrile (hydrogenation of the C=C bond), an unsaturated amine (hydrogenation of the C≡N bond), and a saturated amine (hydrogenation of both bonds). The unsaturated amines are the most desired products because of their use as intermediates in the specialty and fine chemicals industry [3,4]. Selective hydrogenation of C≡N groups in the presence of C=C bonds is still an unsolved problem, particularly when the groups are conjugated or in close proximity [5–8]. From a thermodynamics point of view, the hydrogena-

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0021-9517/$ – see front matter
doi:10.1016/j.jcat.2005.06.011

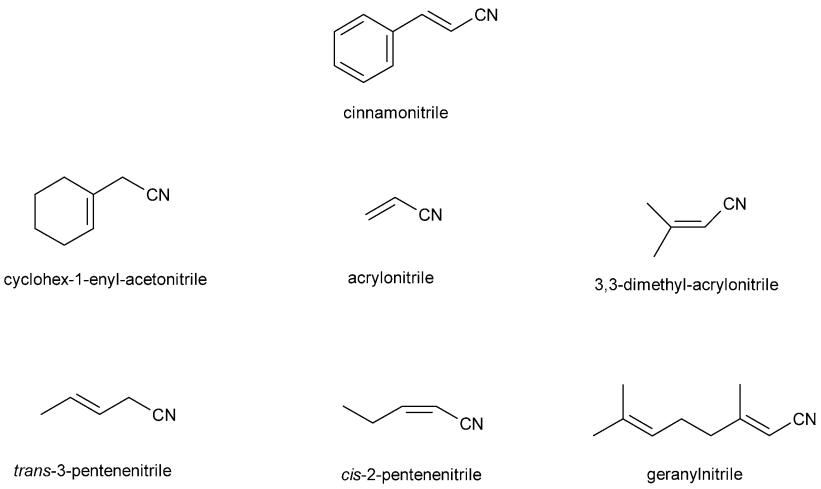

Fig. 1. Structures of hydrogenated unsaturated nitriles.

tion of the double bond is preferred in comparison with the nitrile group and, therefore, the saturated nitriles are usually the main products [6–8]. Dallons et al. proved that the rate of cyclohexene hydrogenation is much faster than that of propionitrile hydrogenation under the same reaction conditions. However, during the competitive hydrogenation of propionitrile and cyclohexene, propionitrile reacts preferentially [6]. This effect was confirmed in the competitive hydrogenation of cyclohexene and propylamine. The slower hydrogenation of the C=C bond is explained by the higher adsorption strength of the nitrile and the amine groups on the catalytic surface. The nitrile group, which adsorbs more strongly, blocks the active sites on the surface of the catalyst, and, at the same time, it is hydrogenated to the amine. The amine remains adsorbed on the surface with a lower adsorption strength than the nitrile, but still much more strongly than the double bond. Thus, the active sites on the surface of the catalyst are blocked and the hydrogenation of the C=C bond is slowed down.

However, the hydrogenation of the C=C bond is slower only in the case of the intermolecular competition (two monofunctional molecules) or when the double bond is sterically hindered [9] or far from the nitrile group (hydrogenation of long-chain unsaturated nitriles, e.g., oleonitrile) [10,11]. The situation is more complicated in the case of intramolecular competition (bifunctional molecules). Several bifunctional molecules (acrylonitrile, 3-butenenitrile, crotononitrile, and cinnamonitrile) have been hydrogenated over silica-supported nickel and Raney nickel catalysts, but the formation of unsaturated amines was not observed [6–8]. The molecules are probably adsorbed on the surface via the nitrile group, and the double bond is then hydrogenated preferentially by an internal transfer of hydrogen [7]. It has been shown recently that, with the proper catalytic system, the chemoselective hydrogenation of the nitrile group in the presence of a double bond is possible [12]. It was found that several factors play a crucial role in the selectivity: the type of catalyst, the catalyst promoters, the presence of ammonia, and the type of solvent. The reaction conditions, such as temperature, pressure of hydrogen, and substrate-to-catalyst ratio, did not influence the selectivity to a great extent. All of these parameters were optimized during the hydrogenation of cinnamonitrile. Under the optimized conditions, a selectivity of up to 80% to 3-phenyl-allylamine at a conversion above 90% was obtained with a Cr-doped Raney cobalt catalyst [12].

This paper focuses on the next most important factor influencing the selectivity: the molecular structure of the substrate. We investigated the influence of the substitution and position of the double bond relative to the nitrile group on the selectivity for unsaturated amines. Seven different substrates (see Fig. 1) were chosen for hydrogenation tests. Considering the position of the double bond, three different groups of substrates were compared. In five cases the double bond was in conjugation with the nitrile group (α,β-unsaturated nitriles), in two cases (cyclohex-1-enyl-acetonitrile and 3-pentenenitrile) the double bond was just one carbon atom away from the nitrile group (β,γ-unsaturated nitriles), and in one case (geranylnitrile) the molecule also had a double bond at position 6 (ε,ϕ-unsaturated nitrile). Conjugation itself, of course, is not the only factor to play a role in the determination of selectivity. Steric hindrance by substitution of the double bond by various substituents will also have an important influence on the selectivity. Thus, we compared the effects of different substituents (methyl, ethyl, *iso*-hexenyl, and phenyl in 3,3-dimethyl-acrylonitrile, *cis*-2-pentenenitrile, geranylnitrile, and cinnamonitrile, respectively). We also tested cyclohex-1-enyl-acetonitrile, where the double bond is part of a cyclohexene ring. All of the experiments were carried out under the same optimized reaction conditions (as found during the cinnamonitrile hydrogenation). All of the substrates were hydrogenated over four different catalysts: Raney nickel, Raney cobalt, and their Cr-doped equivalents. Therefore, we can discuss not only the influence of the molecular structure, but also the effect of different catalysts on the hydrogenation of all of the tested sub-

strates. This contribution describes the structure–selectivity and the structure–reactivity relationships and explores the scope and limitations of chemoselective hydrogenation of various unsaturated nitriles.

2. Experimental

2.1. General remarks

Apparatuses: Agilent GC (HP6890 equipped with autosampler and semipolar chromatographic column (DB-17, 30 m × 0.32 mm × 0.5 μm from J&W Scientific), Agilent GC-MS (HP6890 MSD equipped with HP-5MS column, 30 m × 0.25 mm × 0.25 μm from Agilent), and Bruker NMR (300 & 500 MHz) with autosampler.

2.2. Chemicals

Cinnamonitrile (97% *trans*-), cyclohex-1-enylacetonitrile, valeronitrile, *n*-amylamine, *iso*-amylamine, geranylnitrile (mixture of *cis*- and *trans*-isomers) (all Acros Organics); hydrocinnamonitrile and 3-phenyl-propylamine (Fluka); *trans*-3-pentenenitrile, *cis*-2-pentenenitrile, geranylamine (Aldrich); and 3,3-dimethylacrylonitrile (Merck) were available commercially. 3-Phenyl-allylamine, 2-cyclohex-1-enyl-ethylamine, *trans*-3-pentenylamine, and 3-methyl-2-butenylamine were prepared from the corresponding nitriles by reduction with $LiAlH_4$. We also attempted to prepare *cis*-2-pentenylamine by reducing *cis*-2-pentenenitrile with $LiAlH_4$ or $NaBH_4$, but the reaction provided only higher amines and polymers. A mixture of *cis*- and *trans*-2-pentenenitriles and *trans*-3-pentenenitrile (38:44:18) was prepared by isomerization of pure *cis*-2-pentenenitrile with DBN (1,5-diazabicyclo[4,3,0]non-5-ene). All of the compounds were characterized by GC with an appropriate analytical standard, by GC-MS and/or NMR.

2.3. Catalysts

Four different catalysts were used for the hydrogenations: Raney nickel (RaNi), Raney cobalt (RaCo), and Raney nickel (RaNi/Cr) and Raney cobalt (RaCo/Cr), both doped with chromium (1–5%). The catalysts were commercial samples supplied by Doducco (RaNi, Raney nickel-Actimet M) and Grace Davison (RaCo, Raney 2700; RaNi/Cr, Raney 2400, and RaCo/Cr, Raney 2724). Raney catalysts were supplied and stored under water and were weighed according to manufacturers' instructions. The water was usually removed from the container, as was a first layer of decanted catalyst, and an appropriate amount of catalyst suspension, containing approximately 50% water, was taken for weighing. The 5% palladium on charcoal (Fluka) was used to prepare some of the reaction intermediates.

2.4. Hydrogenation procedure

Hydrogenation reactions were performed in the liquid phase in a 60-ml stainless-steel autoclave (Premex) equipped with a sampling tube and magnetic gas-inducing impeller. The catalyst (usually 250 mg wet catalyst) and solvent (27 ml 30 wt% NH_3 in MeOH) were put into the reactor, and an appropriate amount of substrate (23 mmol) was added. The autoclave was closed, and the air was displaced first with nitrogen (three times) and then with hydrogen (three times). The autoclave was pressurized with hydrogen to the desired value (80 bar), and a leak test was carried out (10 min). The reaction was started at room temperature with a magnetic stirrer (ca. 1100 rpm). After saturation of the liquid phase with hydrogen (1.5 min), the reactor was heated to the reaction temperature (usually 12 min from 25 to 100 °C). The samples were withdrawn periodically until there was no observable consumption of hydrogen. Then the reaction was stopped, the pressure was released, and the hydrogen was displaced by nitrogen. The withdrawn samples and the product were filtered to remove the catalyst before the analytical measurements.

2.5. Analytics

The samples of the reaction mixture, withdrawn during the reaction, were analyzed by gas chromatography. For the products of cinnamonitrile hydrogenation a less polar column HP-5MS (J&W Scientific) was used, and the products were separated under the following analytical conditions: carrier gas, helium 100 kPa; temperatures, inj. 250 °C, det. 280 °C; oven temperature program, 100 °C (2 min), 10 °C/min to 200 °C, 30 °C/min to 280 °C (10 min). The products were characterized by comparison of their retention times with corresponding analytical standards. Some of the samples were also analyzed by NMR and GC-MS in order to compare the results obtained by independent methods. The samples of the reaction mixtures, withdrawn during the reactions with all of the other substrates, were analyzed with a more polar column, DB-17 (J&W Scientific), and under milder chromatographic conditions: carrier gas, helium 113.5 kPa; temperatures, inj. 250 °C, det. 280 °C; oven temperature program, 50 °C (5 min), 30 °C/min to 280 °C (10 min). The samples obtained during the hydrogenation of acrylonitrile were diluted in deuterated methanol and analyzed directly by NMR (Bruker, 300 MHz). The retention times, mass spectra, and NMR data for all of the substrates, reaction intermediates, and products are listed in Appendix A.

3. Results and discussion

We investigated the hydrogenation of cinnamonitrile, since this molecule was used as a model substrate in our

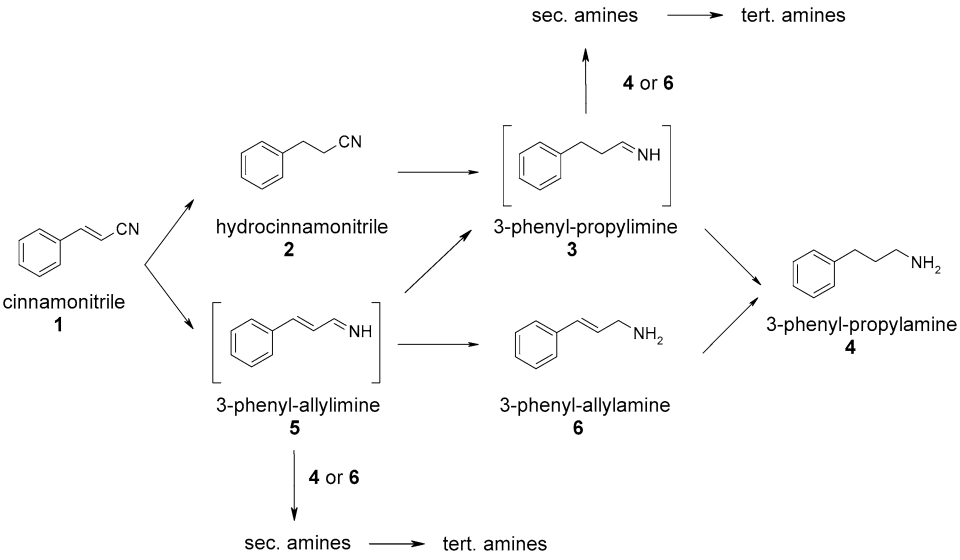

Fig. 2. Possible reaction pathways of cinnamonitrile hydrogenation.

previous study on the hydrogenation of α,β-unsaturated nitriles [12]. Cinnamonitrile has an activated, but not very sterically hindered double bond, which is in conjugation with the nitrile as well as with the phenyl group. The hydrogenation of cinnamonitrile **1** can proceed along two major pathways, shown in Fig. 2. In the more frequently observed route, the C=C bond of cinnamonitrile is reduced first to give hydrocinnamonitrile **2**, which is transformed via the saturated imine **3** to the final product, 3-phenyl-propylamine **4**. Alternatively, H_2 can add to the nitrile to form the unsaturated conjugated imine **5**, which can either react to **3** or to the desired 3-phenyl-allylamine **6**. Consecutive hydrogenation of **6** leads again to the fully hydrogenated **4**. Furthermore, the two imine intermediates **3** and **5** can react with the already formed **4** or **6** to form various secondary amines (which in turn can react even further to give tertiary amines). However, under the optimized conditions, which were described in detail in our previous publication [12], the formation of secondary and tertiary amines is suppressed and their concentration does not exceed 5 wt%. The imines **3** and **5** are very reactive intermediates and were not observed in the reaction mixture. Therefore, the imine intermediates are omitted in the following reaction schemes. In some of the reactions, by-products formed, but their content was usually below 1 to 2 wt% (unless otherwise mentioned).

The results of the cinnamonitrile hydrogenation with Cr-doped and undoped Raney cobalt and Raney nickel catalysts are listed in Table 1. The concentration of unsaturated amine in the first column represents the highest concentration of unsaturated amine (**6** in case of cinnamonitrile hydrogenation) reached during the reaction. This maximum concentration was reached at the conversion shown in the second column. The selectivity for the unsaturated amine was defined as SEL_{unsat} = % unsaturated amine/(% unsaturated amine + % saturated nitrile + % saturated amine) and was also calculated at the maximum concentration of the unsaturated amine. The activity of the catalyst is presented as the reaction rate at 50% conversion of the substrate. During cinnamonitrile hydrogenation, the highest concentration of unsaturated amine (61%) and the highest selectivity (0.70) were obtained with the chromium-doped Raney cobalt catalyst. The modification of Raney cobalt with chromium influences not only the selectivity for unsaturated amine, but also the activity of the catalyst. The reaction rate increased three times after the modification of Raney cobalt with chromium. A much lower increase in the reaction rate was observed with Raney nickel. After the modification, the rate increased by only 10%. However, the activity of undoped Raney nickel was already higher than that of undoped Raney cobalt. The selectivities of both nickel catalysts were also somewhat higher than the selectivity of pure Raney cobalt. On the other hand, the highest concentrations of unsaturated amine were reached at lower conversions of cinnamonitrile. An opposite effect of the chromium modification on the selectivity over cobalt and nickel catalysts was found. Whereas the addition of chromium increases the selectivity of cobalt, the addition of chromium to nickel results in a selectivity decrease.

The second molecule we examined was cyclohex-1-enyl-acetonitrile. The double bond is more sterically hindered, since it is part of a cyclohexene ring and is not conjugated with the nitrile group. This molecule was hydrogenated with skeletal catalysts in liquid ammonia by Poepel and Gaube [9]. We were interested in comparing their results with those obtained under our standard reaction conditions with chromium-doped catalysts. The reaction scheme of cyclohex-1-enyl-acetonitrile hydrogenation (see Fig. 3) is more complicated, since cyclohex-1-enyl-acetonitrile **7** undergoes isomerization to cyclohexylidene-acetonitrile **8** under basic conditions and at higher temperature. Both isomers can further react with one molecule of hydrogen, and the C=C bond can be hydrogenated to the saturated nitrile, cyclohexyl-acetonitrile **9**. If we suppose a prior reaction

Table 1
Results of hydrogenation experiments

Substrate	Catalyst	Unsaturated amine (%)	Conversion[a] (%)	SEL_{unsat}[b]	$Rate_{50\%}$ (mmol/(min g_{cat}))
Cinnamonitrile	RaCo/Cr	61	95	0.70	5.2
	RaCo	34	94	0.41	1.7
	RaNi/Cr	37	90	0.44	4.6
	RaNi	42	78	0.58	4.2
1-Cyclohexenyl-acetonitrile	RaCo/Cr	86	100	0.87	3.4
	RaCo	82	100	0.82	1.6
	RaNi/Cr	78	100	0.79	1.1
	RaNi	70	95	0.76	0.7
trans-3-Pentenenitrile	RaCo/Cr	57	96	0.61	5.9
	RaCo	42	98	0.43	2.3
	RaNi/Cr	34	81	0.44	3.6
	RaNi	46	92	0.52	2.4
cis-2-Pentenenitrile	RaCo/Cr[d]	2/68[c]	95	0.03/0.74[c]	14.1
	RaCo	3/66[c]	100	0.03/0.73[c]	5.7
	RaNi/Cr[e]	0/89[c]	99	0.00/0.97[c]	23.8
	RaNi[e]	0/82[c]	99	0.00/0.95[c]	18.6
3,3-Dimethyl-acrylonitrile	RaCo/Cr	32	81	0.40	8.9
	RaCo	24	77	0.33	3.9
	RaNi/Cr	4	71	0.05	5.7
	RaNi	6	69	0.09	3.0
Geranylnitrile (3,7-dimethyl-2,6-octadienenitrile)	RaCo/Cr[d]	33	88	0.38	8.2
	RaCo	30	87	0.34	2.4
	RaNi/Cr	5	78	0.06	3.6
	RaNi	12	72	0.17	1.8

Reaction conditions: 23 mmol substrate, 250 mg wet catalyst, 27 ml 30 wt% NH_3 in MeOH, 100 °C, 8 MPa of hydrogen.
[a] At maximum concentration of unsaturated amine.
[b] SEL_{unsat} = % unsaturated amine/(% unsaturated amine + % saturated nitrile + % saturated amine) at the maximum concentration of unsaturated amine.
[c] Concentration and selectivity to saturated nitrile (valeronitrile).
[d] 1/2 amount of catalyst.
[e] 1/3 amount of catalyst; up to 10% of by-products formed.

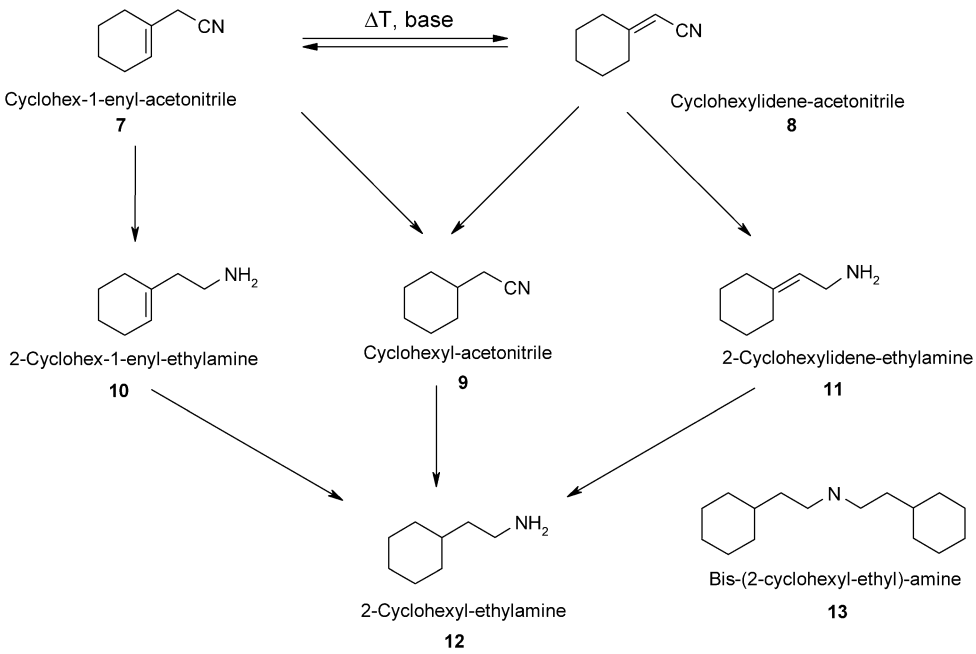

Fig. 3. Reaction scheme of hydrogenation of cyclohex-1-enyl-acetonitrile.

of the nitrile group, the unsaturated amines, 2-cyclohex-1-enyl-ethylamine **10** and 2-cyclohexylidene-ethylamine **11,** form from **7** and **8**, respectively. Further hydrogenation of all three intermediates **9**–**11** results in the same product, 2-cyclohexyl-ethylamine **12**.

Before we started to investigate the hydrogenation itself, the intermediates **9** and **10** were prepared as standard materials by hydrogenation over Pd/C and $LiAlH_4$, respectively. The hydrogenation of **7** to **9** proceeded with 62% selectivity ($SEL_{satnitrile} = \%\mathbf{9}/(\%\mathbf{7} + \%\mathbf{9} + \%\mathbf{10} + \%\mathbf{12} + \%\mathbf{13})$) over the Pd/C catalyst, and a significant amount of secondary amine **13**, bis-(2-cyclohexylethyl)-amine, was produced as a by-product (18%). Reduction of **7** to **10** was carried out with a standard procedure for the reduction with $LiAlH_4$ with 85% yield. We also tested the isomerization reaction of **7** to **8** in ammonia-saturated MeOH. It was found that it is much slower than the hydrogenation reactions (more than 20 times), and it explains why we did not observe the isomer **8** during the hydrogenations.

The results of the hydrogenation of **7** (Table 1) show that the selectivity for unsaturated amine **10** was very high over all of the catalysts (0.76–0.87). It is in good agreement with the results obtained by Poepel and Gaube [9]. The high selectivity is probably the result of steric hindrance and the isolation of the C=C bond. The highest reaction rate was obtained with the RaCo/Cr catalyst followed by the undoped Raney cobalt. The activity of both nickel catalysts was lower than that of Raney cobalt and much lower than in the case of cinnamonitrile hydrogenation. The activity of the Cr-doped Raney cobalt was somewhat lower, and the activity of pure Raney cobalt remained the same as during cinnamonitrile hydrogenation. The consecutive hydrogenation of the unsaturated amine **10** to the final product **12** was very slow, and the reaction almost stopped at the intermediate **10**. This confirms that the hydrogenation of a sterically hindered C=C bond is much more difficult.

It is known from the literature that in cases in which the double bond is far from the nitrile group, as in case of the hydrogenation of long-chain unsaturated nitriles (e.g., oleonitrile), it is easy to preserve the double bond during the hydrogenation and thus produce unsaturated amines [10,11]. Higher temperatures are required to hydrogenate the double bond and to obtain a saturated amine, and the hydrogenation of the C=C bond proceeds with a lower reaction rate than the hydrogenation of the C≡N bond. The active sites on the catalyst are probably all occupied by adsorbed nitrile groups and later, after the hydrogenation of the nitrile groups, by the amine groups. The hydrogenation of the double bond is slowed because the nitrile and amine adsorb more strongly than the C=C bond, and a higher temperature is therefore required to hydrogenate the double bond. However, this is valid only when the C=C bond is far from the nitrile group. Dallons et al. studied the hydrogenation of 2- and 3-butenenitriles over Raney nickel, but they did not observe the formation of the corresponding unsaturated nitriles [7]. They explained their results by the so-called second-order interactions and simultaneous adsorption and hydrogenation of the C=C and C≡N bonds. We already know from the hydrogenation of cinnamonitrile and cyclohex-1-enyl-acetonitrile that it is possible to preserve the double bond, even in positions 2 and 3. In these cases, of course, the double bond is more sterically hindered, substituted with a large substituent, and/or in conjugation (e.g., with the phenyl ring in case of cinnamonitrile). All of these factors may make the hydrogenation of the C=C bond more difficult, and the selectivity for unsaturated amine can increase.

We carried out the hydrogenation of 2- and 3-pentenenitriles, in which the double bond is not sterically hindered, to study the influence of the double-bond position (conjugation) on the chemoselectivity for unsaturated amine. Commercially available *trans*-3-pentenenitrile and *cis*-2-pentenenitriles were used. Hydrogenation of each of these substances can proceed by two different pathways (see Fig. 4). In the first pathway the nitrile group is selectively reduced and *trans*-3-pentenentitrile **14** and *cis*-2-pentenenitrile **15** provide the unsaturated amines **16** and **17**, respectively. In the second pathway, the double bond is reduced, and the two nitriles **14** and **15** give the same product, valeronitrile **18**. All three intermediates are further hydrogenated to the same product, pentylamine **19**. The hydrogenation of *trans*-3-pentenenitrile **14** proceeded mainly by the first pathway, and up to 57% of unsaturated amine **16** was obtained during the reaction (see Table 1). The reaction course of *trans*-3-pentenenitrile **14** hydrogenation over Cr-doped Raney cobalt

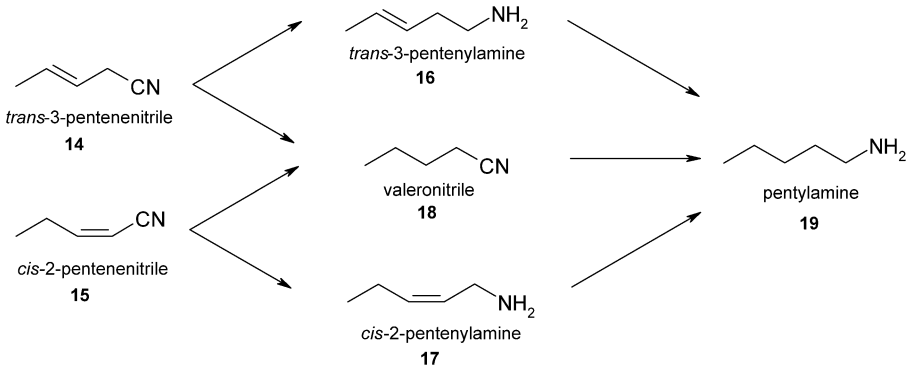

Fig. 4. Reaction pathways of *trans*-3- and *cis*-2-pentenenitrile hydrogenation.

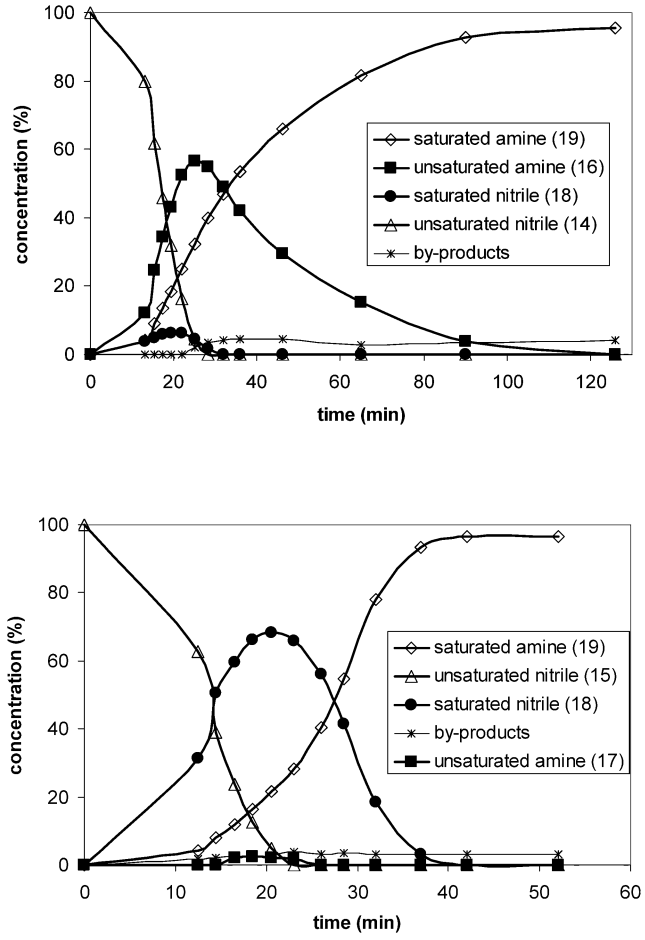

Fig. 5. Typical reaction profiles over Cr-doped Raney cobalt. (Top) Hydrogenation of *trans*-3-pentenenitrile; (bottom) hydrogenation of *cis*-2-pentenenitrile.

is shown in Fig. 5 (top). The *trans*-3-pentenenitrile **14** is hydrogenated very fast to the unsaturated amine **16**, which reacts further to the saturated product, pentylamine **19**. The hydrogenation of the unsaturated amine **16** to the saturated amine **19** is somehow slower than the hydrogenation of the unsaturated nitrile **14** to the unsaturated amine **16**. This is due to the stronger adsorption of the C≡N and the NH_2 groups in comparison with the C=C bond. The nitrile **14** is quickly hydrogenated to the unsaturated amine **16**, which reaches its maximum concentration at approximately 100% conversion of **14**. At this point, the catalyst surface is covered by the amine, and, therefore, the C=C bond hydrogenation is slow. The concentration profile of valeronitrile **18** remained almost flat, and its concentration did not exceed 6%. A short induction period at the beginning of the reaction is caused by starting the reaction at room temperature. It was found that this procedure provides the higher selectivities. The highest selectivity and the highest reaction rate were again reached with the Cr-doped Raney cobalt. The two undoped catalysts behaved similarly. The modification of nickel with chromium increased the reaction rate, but decreased the selectivity, as was observed before.

On the other hand, during the hydrogenation of *cis*-2-pentenenitrile **15**, the double bond was hydrogenated prior to the nitrile group and the main intermediate product was valeronitrile **18** (see Fig. 5 (bottom)). This was further hydrogenated to pentylamine **19**. The reaction rate of *cis*-2-pentenenitrile hydrogenation was very high, especially with the nickel catalysts (see Table 1), and the amount of the catalyst had to be reduced. Traces of the unsaturated amine **17** (<3%) were observed during the reactions carried out with RaCo and RaCo/Cr, and selectivity did not exceed 3%. Hydrogenation with both nickel catalysts proceeded exclusively via valeronitrile. Because of the low selectivity for the unsaturated amine **17**, Table 1 shows the maximum concentration reached and calculated selectivity in relation to valeronitrile. The reaction rate of the double bond hydrogenation (**15** to **18**) was the same as the reaction rate of the hydrogenation of the nitrile group (**18** to **19**). This means that the double bond of *cis*-2-pentenenitrile is hydrogenated while the molecule is adsorbed via the nitrile group. The consecutive reaction did not slow down as it did in the case of *trans*-3-pentenenitrile hydrogenation, since the surface was still covered by the nitrile, which is adsorbed with high adsorption strength.

An interesting phenomenon was observed during the hydrogenation over doped Raney cobalt and Raney nickel. Whereas the reaction rate of **15** to **18** was similar to further hydrogenation of **18** to **19** over Raney cobalt, the further reaction of **18** to **19** was much slower with Raney nickel. This finding corresponds well with the catalytic properties of these metals. Nickel is very active in the hydrogenation of C=C bonds and much less active in the hydrogenation of C≡N bonds, whereas cobalt has the opposite properties.

The opposite selectivity of *trans*-3-pentenenitrile and *cis*-2-pentenenitrile hydrogenation shows that the position of the double bond relative to the nitrile group plays a crucial role. In case of *cis*-2-pentenenitrile, the double bond is much more reactive due to the conjugation and activation by the nitrile group. The conjugated system of C=C and C≡N bonds of *cis*-2-pentenenitrile probably adsorbs at the surface at once, and the activated C=C bond is hydrogenated preferentially. In case of *trans*-3-pentenenitrile, the double bond is not in conjugation with the C≡N group, and, therefore, it is easier to preserve. The higher reactivity of a conjugated double bond is also demonstrated by the much higher reaction rate of *cis*-2-pentenenitrile hydrogenation (see Table 1). The reaction rate was especially high with nickel catalysts (almost 10 times higher than during *trans*-3-pentenenitrile hydrogenation), and it was necessary to reduce the catalyst to one-third of its original amount. The reaction rate of both cobalt catalysts was “only” twice as high as that of *trans*-3-pentenenitrile. Nevertheless, the reaction rate with the Cr-doped cobalt catalyst was so high that it was also necessary to reduce the amount of the catalyst. The other factor that probably contributes to the high reactivity of *cis*-2-pentenenitrile is the *cis*-geometry of the double bond. To verify this, we prepared a mixture of *cis*- and *trans*-2-pentenenitrile; the mixture was hydrogenated

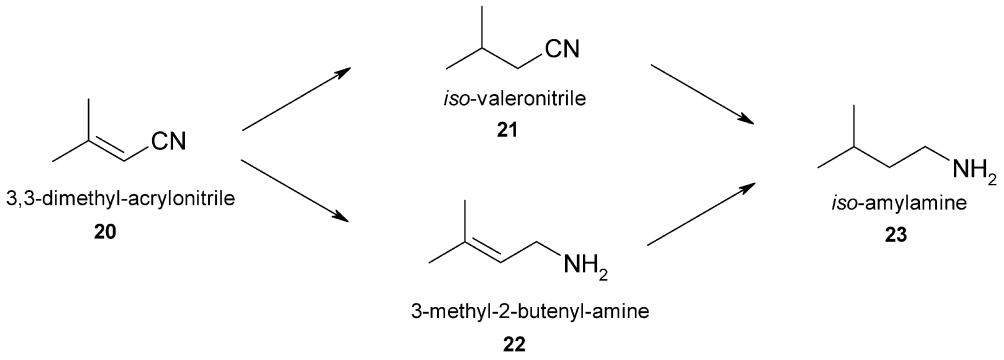

Fig. 6. Reaction scheme of 3,3-dimethyl-acrylonitrile hydrogenation.

under the same reaction conditions. The reaction rates of *cis*- and *trans*-2-pentenenitrile were identical. Nevertheless, a detailed analysis of the data showed that the selectivities of *cis*- and *trans*-2-pentenenitrile differed. The analysis of the data was based on the assumption that isomerization does not occur during the reaction and that the selectivity of the *cis*-isomer remains constant at the same level as during hydrogenation of the pure compound. The selectivity of the pure *cis*-isomer for unsaturated amine was not higher than 3%, and the calculated selectivity of the *trans*-isomer was almost 10%. These results are, however, semiquantitative, and to verify the difference it would be necessary to carry out the experiment with pure *trans*-2-pentenenitrile. We attempted to isolate pure *trans*-2-pentenenitrile from the mixture of the *cis*- and *trans*-isomers by rectification under reduced pressure, but it was unsuccessful because of the high reactivity and low stability of the *trans*-isomer. Nevertheless, we will explore this behavior in more depth in the future, because it might give important information about the adsorption mode and the nature of the active sites on the catalyst.

The above results prove that the position of the double bond relative to the nitrile group strongly influences the selectivity. It is much more difficult to preserve the double bond when it is in conjugation with the nitrile group (as in the case of 2-pentenenitrile, $S_{\text{unsat}} < 3\%$). On the other hand, the selectivity also depends to a large extent on the substitution of the double bond, as in the case of cinnamonitrile hydrogenation, where the selectivity reached 70% despite the conjugation with the nitrile group. In this case, the double bond is substituted not only with a large substituent (phenyl group), but by a substituent, which assists in preserving the double bond through additional conjugation.

To conduct an in-depth study of the influence of the double bond substitution on the selectivity for the unsaturated amine, we chose three additional substrates for the hydrogenation tests (acrylonitrile, 3,3-dimethyl-acrylonitrile, and geranylnitrile). Hydrogenation of acrylonitrile resulted in the formation of different by-products, since the activated terminal double bond readily reacted with the components of our reaction mixture (ammonia and methanol). The primary products were 3-amino-propionitrile (65%, addition of ammonia), 3-methoxy-propionitrile (20%, addition of methanol), and propionitrile (15%, reduction of double bond with hydrogen). No trace of allylamine was found with any of the four catalysts. All of the primary products were further hydrogenated to the corresponding amines, but this hydrogenation of the nitrile group was much slower than the addition reactions on the double bond. Moreover, the formation of heavier by-products (oligomers) was observed at longer reaction times. Substitution of the acrylonitrile double bond by two methyl groups deceased the reactivity; the addition of ammonia and methanol was not observed during the hydrogenation of 3,3-dimethyl-acrylonitrile **20** (see Fig. 6). The reaction can proceed by two pathways, leading to the formation of two different intermediates: *iso*-valeronitrile **21** and 3-methyl-2-butenyl-amine **22**. Both intermediates are further hydrogenated to the same product, *iso*-amylamine **23**. Table 1 lists the results of the 3,3-dimethyl-acrylonitrile hydrogenation. A moderately high selectivity was obtained with both cobalt catalysts. If we compare the results with those of *cis*-2-pentenenitrile, which has only an ethyl substituent at the double bond, it is obvious that the second methyl group in 3,3-dimethyl-acrylonitrile is responsible for the selectivity increase. The double bond is more sterically hindered in the case of the two alkyl substituents than in the case of *cis*-2-pentenenitrile, where only one substituent is present. Both nickel catalysts were much less selective than the cobalt catalysts, and the hydrogenation proceeded mainly via the *iso*-valeronitrile intermediate **21** to *iso*-amylamine **23**. The lower reaction rates of 3,3-dimethyl-acrylonitrile in comparison with *cis*-2-pentenenitrile provide further evidence of steric hindrance of the double bond by the second methyl group present in the molecule.

The last example is the hydrogenation of geranylnitrile **24** (see Fig. 7). Geranylnitrile contains two double bonds: one is in conjugation with the nitrile group, and the other is six carbon atoms away from the nitrile group. Both double bonds are further substituted by methyl groups at positions 3 and 7. Geranylnitrile is very similar to 3,3-dimethyl-acrylonitrile, the only difference being that one methyl group of 3,3-dimethyl-acrylonitrile is replaced by the larger *iso*-hexenyl group. This substitution introduces another geometry factor, namely the *cis*- and *trans*-geometry of the double bond at position 2. We hydrogenated a mixture of isomers (1:1),

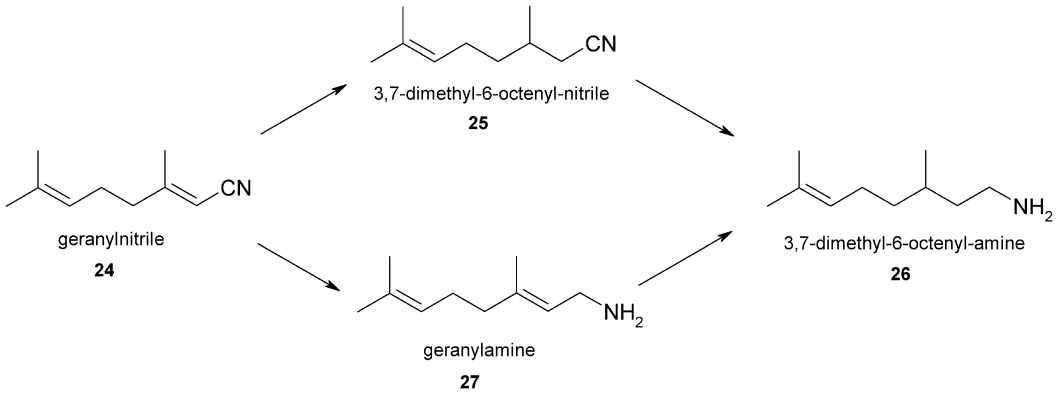

Fig. 7. Reaction scheme of geranylnitrile hydrogenation.

and the hydrogenation proceeded according to the reaction scheme in Fig. 7. During the hydrogenation over nickel catalysts, and especially over nickel doped with chromium, the conjugated double bond was hydrogenated prior to the nitrile with a high selectivity for 3,7-dimethyl-6-octene-nitrile **25**. Further hydrogenation of the nitrile group to 3,7-dimethyl-6-octenyl-amine **26** was somewhat slower. The opposite was true with the cobalt catalysts; the nitrile group of geranylnitrile **24** was hydrogenated first, and geranylamine **27** was formed as the main intermediate. The double bond at position 3 is hydrogenated in the next step and 3,7-dimethyl-6-octenyl-amine **26** is formed as the final product. Consecutive hydrogenation of **26** to the fully saturated product, 3,7-dimethyl-octylamine (not shown), was not observed under our reaction conditions. A higher reaction temperature is probably required to reduce the double bond at position 6. This is in good agreement with the observations that it is more difficult to reduce remote double bonds during the hydrogenation of unsaturated nitriles [11]. The selectivities obtained during geranylnitrile hydrogenation were very similar to those obtained with 3,3-dimethyl-acrylonitrile. Therefore, we conclude that the size of one of the substituents of the C=C bond hardly influences the selectivity, but the presence of the second substituent (e.g., methyl group in position 3) plays a crucial role in determining the chemoselectivity. The size of a substituent influences the reaction rate. This trend is obvious when the reaction rates of *cis*-2-pentenenitrile, 3,3-dimethyl-acrylonitrile, and geranylnitrile are compared (Table 1). In all of these cases the C=C bond is conjugated with the C≡N group, and only the substituents attached to the C=C bond vary. When there is only one substituent (*cis*-2-pentenenitrile) the reaction rate will reach the highest value. An additional methyl group attached to the C=C bond sterically hinders the double bond; the selectivity for the unsaturated amine increases, and the total reaction rate decreases at the same time (3,3-dimethyl-acrylonitrile). A further increase in the size of one of the substituents does not cause a significant change in the selectivity, but it does influence the reaction rate, which decreases further (geranylnitrile).

4. Conclusions

Structure–selectivity and structure–reactivity relationships in the chemoselective hydrogenation of unsaturated nitriles were studied to explore the scope and limitations of this type of hydrogenation. The molecular structure of the substrate is crucial in determining the selectivity for the unsaturated amine. One of the most important factors is the position of the double bond relative to the nitrile group. The highest selectivities are obtained when the double bond is not conjugated with the nitrile group; the further the C=C bond is from the C≡N group, the higher the selectivity. The second important factor is the substitution of the double bond. It is more difficult to hydrogenate a sterically hindered double bond, and the presence of more substituents at the C=C bond increases the selectivity for unsaturated amine. Another factor that influences the selectivity is the stabilization of the double bond by additional conjugation of the C=C bond with another unsaturated substituent (e.g., the phenyl group in cinnamonitrile). The molecular structure has a similar influence on the reaction rate, which also depends on the conjugation of the C=C bond with the C≡N bond and which decreases with a higher degree of substitution.

The comparison of Raney cobalt and nickel catalysts demonstrated the suitability of Raney cobalt, and especially Cr-doped Raney cobalt, in the chemoselective hydrogenation of unsaturated nitriles. Raney nickel catalysts have a higher activity in C=C bond hydrogenation and, therefore, a lower selectivity for unsaturated amines. Doping with chromium has a positive effect on the reaction rate with both the cobalt and the nickel catalysts. However, the effect on the selectivity for the unsaturated amine is different. This phenomenon is unclear and will be investigated further.

Acknowledgments

The authors thank Klaas van Gorp and Grace Davison for their kind supply of the Raney catalysts and Professor Roel Prins and Dr. Hans-Ulrich Blaser for carefully reading the manuscript.

Appendix A

GC, MS, and NMR data for the reaction components.

trans-Cinnamonitrile **1**: rt 8.5 min, ^{1}H NMR (300 MHz, CDCl3): 5.88 (d, =CH–C≡N, 1H), 7.35–7.47 (m, Ph–CH=, 6H). MS (EI) m/z (rel. intensity): 129(100), 102(40), 76(22), 63(18), 51(24).

Hydrocinnamonitrile **2**: rt 7.6 min, ^{1}H NMR (300 MHz, CDCl3): 2.61 (t, –CH_2–C≡N, 2H), 2.96 (t, Ph–CH_2–, 2H). MS (EI) m/z (rel. intensity): 131(83), 91(100), 77(18), 65(23), 51(13), 39(15).

3-Phenyl-propylamine **4**: rt 7.2 min, ^{1}H NMR (300 MHz, CDCl3): 1.19 (brs, –NH_2, 2H), 1.78 (m, –$CH_2CH_2NH_2$, 2H), 2.65 (t, –CH_2–NH_2, 2H), 2.72 (t, Ph–CH2–, 2H), 7.11–7.34 (m, Ph–, 5H). MS (EI) m/z (rel. intensity): 135(15), 118(100), 117(65), 91(61), 77(44), 65(53), 51(39), 42(19).

3-Phenyl-allylamine **6**: rt 8.3 min, ^{1}H NMR (300 MHz, CDCl3): 1.49 (brs, –NH_2, 2H), 3.48 (d, –CH_2–NH_2, 2H), 6.32 (dt, Ph–CH=CH–, ^{1}H), 6.51 (d, Ph–CH=CH–, ^{1}H), 7.18–7.41 (m, Ph–, 5H). MS (EI) m/z (rel. intensity): 133(100), 132(89), 115(67), 91(34), 77(21), 56(23), 51(17). Other by-products, usually <2%, not fully characterized, but probably including alkylated primary and secondary amines formed by the reaction with the solvent, rt 9.0–11.0 min; secondary amines such as bis-(3-phenyl-propyl)-amine, (3-phenyl-allyl)-(3-phenyl-propyl)-amine and bis-(3-phenyl-allyl)-amine), rt 16.0–20.0 min.

Cyclohex-1-enyl-acetonitrile **7**: rt 9.3 min, ^{1}H NMR (300 MHz, CDCl3): 1.43–1.77 (m, CH_2, 4H), 1.94–2.11 (m, CH_2, 4H), 3.00 (s, CH_2CN, 2H), 5.78 (t, >C=CH–, 1H), MS (EI) m/z (rel. intensity): 121(22), 81(100), 55(60), 53(29), 41(45), 39(40), 27(32).

Cyclohexylidene-acetonitrile **8**: rt 9.2 min, ^{1}H NMR (300 MHz, CDCl3): 1.53–1.67 (m, CH_2, 6H), 2.24 (t, CH_2C=, 2H), 2.48 (t, CH_2C=, 2H), 5.04 (s, CHCN, ^{1}H).

Cyclohexylacetonitrile **9**: rt 8.92 min, ^{1}H NMR (300 MHz, CDCl3): 1.07–1.38 (m, CH_2CH, 5H), 1.57–1.83 (m, CH_2, 6H), 2.24 (d, CH_2CN, 2H).

2-Cyclohex-1-enyl-ethylamine **10**: rt 8.56 min, ^{1}H NMR (300 MHz, CDCl3): 1.17–1.23 (brs, NH_2, 2H), 1.43–1.66 (m, CH_2, 4H), 1.89 (brs, CH_2, 2H), 1.98 (brs, CH_2, 2H), 2.06 (t, C$H_2CH_2NH_2$, 2H), 2.75 (t, CH_2NH_2, 2H), 5.46 (t, >C=CH–, ^{1}H).

2-Cyclohexyl-ethylamine **12**: rt 8.24 min, ^{1}H NMR (300 MHz, CDCl3): 1.03–1.32 (m, CH_2, 4H), 1.43–1.87 (m, CH + CH_2, 8H), 2.76 (t, CH_2NH_2, 2H).

trans-3-Pentenenitrile **14**: rt 5.52 min, ^{1}H NMR (500 MHz, CDCl3): 1.73 (dd, CH_3, 3H), 3.05 (d, CH_2, 2H), 5.38 (dq, =CHCH_2CN, ^{1}H), 5.79–5.86 (m, CH_3CH=, 1H), MS (EI) m/z (rel. intensity): 81(56), 80(14), 66(10), 54(100), 41(84), 39(56), 27(24).

cis-3-Pentenenitrile: rt 4.80 min, MS (EI) m/z (rel. intensity): 81(39), 66(11), 54(43), 41(100), 39(49), 28(26).

cis-2-Pentenenitrile **15**: rt 3.74 min, ^{1}H NMR (500 MHz, CDCl3): 1.06 (t, CH_3, 3H), 2.40 (dq, CH_2, 2H), 5.25 (d, =CHCN, ^{1}H), 6.45 (dt, CH_2CH=, 1H), MS (EI) m/z (rel. intensity): 81(45), 80(17), 66(16), 54(100), 41(46), 39(42), 28(30).

trans-2-Pentenenitrile: rt 5.30 min, ^{1}H NMR (500 MHz, CDCl3): 1.10 (t, CH_3–, 3H), 2.44 (dq, CH_2, 2H), 5.33 (d, =CHCN, ^{1}H), 6.79 (dt, CH_2CH=, 1H), MS (EI) m/z (rel. intensity): 81(74), 80(20), 66(42), 54(100), 41(67), 39(41), 28(26).

trans-Pent-3-enyl-amine **16**: rt 2.95 min, ^{1}H NMR (500 MHz, CDCl3): 1.43 (dd, CH_3, 3H), 2.03–2.27 (m, =CHCH_2, 2H), 2.81 (t, CH_2NH_2, 2H), 5.14–5.32 (m, =CHCH_2CN, ^{1}H), 5.33–5.61 (m, CH_3CH=, 1H), MS (EI) m/z (rel. intensity): 85(9), 67(11), 55(12), 41(17), 39(22), 30(100), 28(19).

cis-Pent-2-enyl-amine **17**: rt 3.04 min.

Valeronirile **18**: rt 5.09 min, MS (EI) m/z (rel. intensity): 82(14), 55(23), 54(70), 43(100), 41(82), 39(16), 27(34).

Pentylamine **19**: rt 2.56 min, MS (EI) m/z (rel. intensity): 87(17), 56(10), 55(11), 45(12), 41(16), 30(100), 27(16).

3,3-Dimethyl-acrylonitrile **20**: rt 5.00 min, ^{1}H NMR (300 MHz, CDCl3): 1.94 (d, CH_3, 3H), 2.06 (d, CH_3, 3H), 5.10–5.13 (m, CH, ^{1}H).

Iso-valeronitrile **21**: rt 3.58 min, ^{1}H NMR (300 MHz, CDCl3): 1.07 (d, CH_3, 6H), 2.00–2.10 (m, CH, ^{1}H), 2.25 (d, CH_2, 2H), MS (EI) m/z (rel. intensity): 82(13), 68(16), 52(11), 43(100), 41(74).

3-Methyl-2-butenyl-amine **22**: rt 3.11 min, ^{1}H NMR (300 MHz, CDCl3): 1.63 (d, CH_3, 3H), 1.68 (d, CH_3, 3H), 3.25 (d, CH_2, 2H), 5.26 (t, CH, ^{1}H), MS (EI) m/z (rel. intensity): 85(9), 84(15), 70(100), 57(12), 53(16), 43(22), 41(34), 39(19), 30(47), 28(33).

Iso-amylamine **23**: rt 2.15 min, ^{1}H NMR (300 MHz, CDCl3): 0.88 (d, CH_3, 3H), 0.91 (d, CH_3, 3H), 1.12 (brs, NH_2, 2H), 1.33 (q, C$H_2CH_2NH_2$, 2H), 1.58–1.68 (m, CH, ^{1}H), 2.70 (t, CH_2NH_2, 2H), MS (EI) m/z (rel. intensity): 87(11), 70(9), 55(13), 41(22), 30(100), 28(22), 27(20).

cis-Geranylnitrile **24**: rt 9.40 min, ^{1}H NMR (500 MHz, CDCl3): 1.60 (d, CH_3, 3H), 1.69 (d, CH_3, 3H), 1.90 (d, CH_3C=CHCN, 3H, $^4J = 1.1$ Hz), 2.13–2.21 (m, CH_2, 2H), 2.41 (t, CH_2, 2H), 5.05 (dt, CH–CH_2, ^{1}H), 5.09 (d, CH–CN, ^{1}H, $^4J = 1.0$ Hz), MS (EI) m/z (rel. intensity): 148(8), 134(14), 81(12), 69(100), 53(15), 41(53), 28(15).

trans-Geranylnitrile **24**: rt 9.28 min, ^{1}H NMR (500 MHz, CDCl3): 1.60 (d, CH3, 3H), 1.69 (d, CH_3, 3H), 2.04 (s, CH_3C=CHCN, 3H), 2.13–2.21 (m, CH_2, 2H), 2.41 (t, CH_2, 2H), 5.05 (dt, CH–CH_2, ^{1}H), 5.09 (s, CH–CN, ^{1}H), MS (EI) m/z (rel. intensity): 148(12), 134(22), 81(19), 69(100), 53(10), 41(59), 27(11).

3,7-Dimethyl-6-octenyl-nitrile **25**: rt 9.21 min, MS (EI) m/z (rel. intensity): 151(8), 150(16), 136(28), 122(14), 108(27), 94(25), 69(100), 55(29), 41(68), 27(12).

3,7-Dimethyl-6-octenyl-amine **26**: rt 8.80 min, MS (EI) m/z (rel. intensity): 155(10), 138(16), 123(23), 109(14), 95(32), 81(37), 70(100), 56(22), 41(39), 30(88).

cis-Geranylamine **27**: rt 9.09 min, MS (EI) m/z (rel. intensity): 153(8), 138(27), 121(32), 107(14), 93(47), 84(70), 70(95), 57(69), 41(100), 30(35).

trans-Geranylamine **27**: rt 8.96 min, MS (EI) m/z (rel. intensity): 153(9), 138(25), 121(31), 107(12), 96(69), 83(47), 70(92), 57(38), 41(100), 30(41).

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