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Synthesis of picolines and other aza-aromatics from arylamines by isomerization-rearrangement and from dinitriles by hydrogenation-cyclization reactions

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Abstract

New routes for the syntheses of α- and β-picoline and other valuable aza-aromatics with applications in the pharmaceutical and agricultural industry are described. Aniline and other arylamines, like toluidines, naphthylamines and *m*-phenylenediamine, all react to the corresponding *o*-methylsubstituted aza-aromatics when exposed to high NH_3 pressure and elevated temperature in the presence of acid catalysts. Zeolites show the best performance around 10 MPa and 600 K. The results can be explained if it is assumed that the reaction starts with addition of NH_3 to the arylamine, followed by ring opening to an enamino-imine intermediate through a reverse aldol reaction, ring closure and NH_3 elimination. The required high NH_3 pressure is explained by the need to add NH_3 to the aromatic ring, and the high temperature by the need to desorb NH_3 from the acid sites. β-Picoline was synthesized in a one-stage gas-phase process from 2-methylglutaronitrile, a by-product in the manufacture of adiponitrile, over silica-supported Pd and Pt catalysts. Initial reaction rates of both catalysts were extremely high and pore and film diffusion limitations were observed. Activity and selectivity of the Pd catalyst decreased with time on stream, because of intermolecular reactions of reaction intermediates. Therefore, a one-stage process is only viable when the conversion can be kept at 100%. Pt catalysts had a very high activity, but their selectivity was limited by hydrogenolysis reactions.

Keywords: α-Picoline synthesis; β-Picoline synthesis; Arylamine; Aniline; *m*-Phenylenediamine; Methylglutaronitrile

1. Introduction

Introduction of heteroatoms, such as N, S or O, into hydrocarbon molecules adds substantial value, and new routes for such reactions are of continuous interest to the chemical industry. There are two main classes of aromatic N-containing hydrocarbons, the arylamines and the aromatic N-heterocycles. The arylamines which are required industrially are exclusively obtained through synthesis, namely by nitration of aromatics to nitro-aromatics, followed by hydrogenation to arylamines [1,2]. Because of the lower demand for aromatic heterocycles than for arylamines, coal tar is still an important source for pyridine and methylpyridines (picolines). Rising demands for aromatic heterocycles have increased, however, the interest in synthetic routes, and processes in which aldehydes and ketones are condensed with NH_3 to pyridine and alkylated pyridines have been realized. When acetaldehyde, formaldehyde and ammonia are reacted in a fluid bed reactor over H-ZSM-5, the principal product is pyridine (40–50%) and β-picoline

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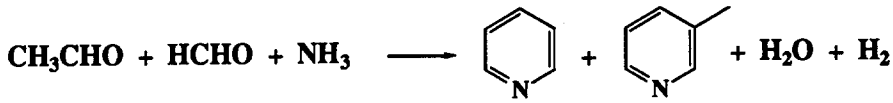
is obtained as a by-product in 20–30% yield [3–5]. Since pyridine is needed in much larger amounts than β-picoline, most β-picoline is obtained by this route (Scheme 1).

When acrolein is used as the starting material, the β-picoline yield increases to about 55%, while adding propionaldehyde further enhances its production [6–8] (Scheme 2).

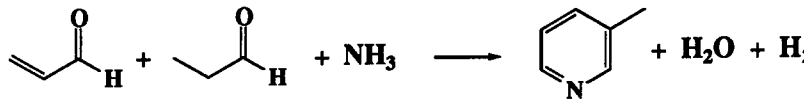
2-Methyl-5-ethylpyridine (MEP) and other 2- and 5-substituted- (methyl and ethyl) pyridines are obtained in the catalyzed reaction of acetaldehyde with ammonia [9] or of ethene and ammonia [10] (Scheme 3).

2-Methylpyridine (α-picoline) is synthesized by a base-catalyzed Michael addition of acetone and acrylonitrile, and subsequent cyclization and dehydrogenation of the resulting 1-cyano-4-pentanone to α-picoline (Scheme 4). 2,6-Dimethylpyridine (2,6-lutidine) is synthesized from acetone, methanol and NH_3 [1,2].

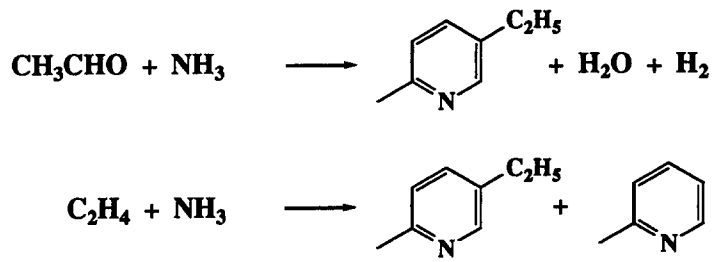
Pyridine derivatives are precursors for many chemical products of medicinal, agricultural and industrial importance. Pyridine itself is not only used as a solvent, but also as starting material for pharmaceuticals, herbicides, insecticides and fungicides. α-Picoline is a precursor for 2-vinylpyridine which is used for



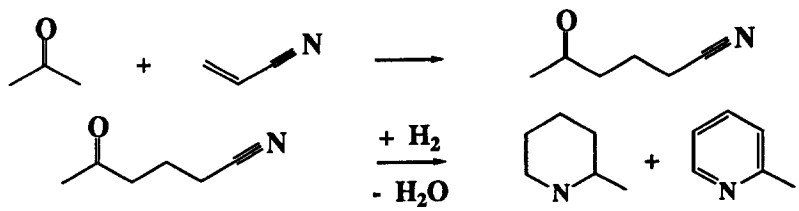
Scheme 1. Synthesis of pyridine and β-picoline.



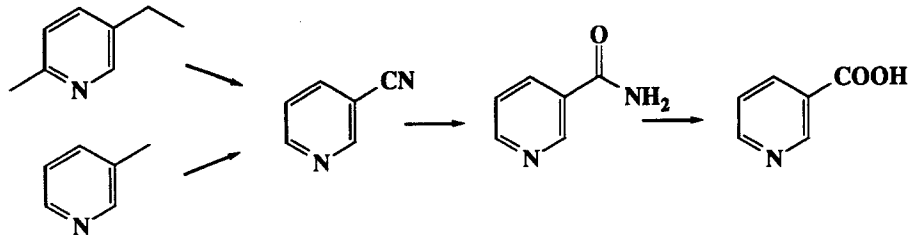
Scheme 2. Synthesis of β-picoline.



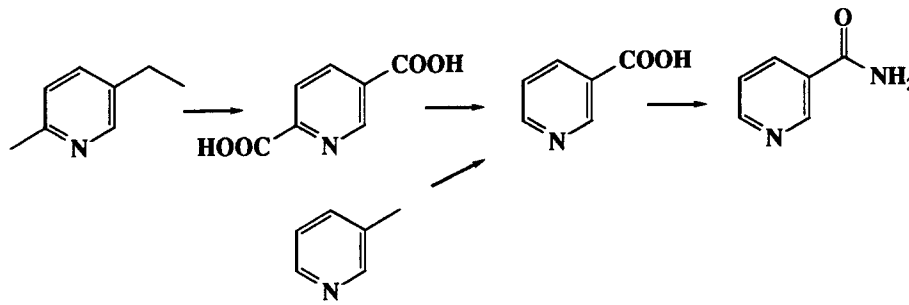
Scheme 3. Synthesis of 2-methyl-5-ethylpyridine.



Scheme 4. Synthesis of α-picoline.



Scheme 5. Ammoxidation routes for the synthesis of nicotinamide and nicotinic acid.



Scheme 6. Oxidation routes for the synthesis of nicotinic acid and nicotinamide.

the production of an adhesive for textile tire cord. The major use of γ-picoline is in the production of isonicotinic hydrazide, an antituberculosis agent. β-Picoline and 2-methyl-5-ethyl-pyridine are important intermediates in the production of two members of the vitamin B family, nicotinamide and nicotinic acid (also designated as vitamin B3). Nicotinamide is produced by two commercial routes. In the first route β-picoline or 2-methyl-5-ethylpyridine are ammoxidated (using oxides of vanadium and antimony as catalysts [11,12]) to nicotinonitrile, which is then submitted to alkaline hydrolysis (Scheme 5). The second route is the catalyzed oxidation of β-picoline or 2-methyl-5-ethylpyridine with nitric acid in the liquid phase to nicotinic acid [13], and treatment of the latter acid with a large excess of gaseous ammonia (Scheme 6).

All this demonstrates that there is a substantial need for the production of picolines; Table 1 gives an estimate of the worldwide production. In the following some novel routes to α- and β-picoline will be discussed which might in the future lead to new processes.

Table 1
Worldwide production of pyridine bases (estimation 1993 [14])

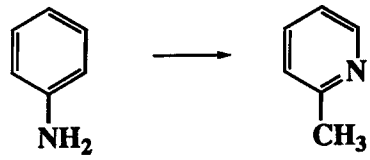
Product	Tons/year
Pyridine	26 000
α-Picoline	8 000
β-Picoline	9 000
γ-Picoline	1 500
MEP	8 000

MEP=2-methyl-5-ethylpyridine.

2. α-Picoline

2.1. *Isomerization of aniline to picoline and of m-phenylenediamine to aminopicoline*

About a decade ago a process for the conversion of phenol into aniline was patented by Mobil Oil [15]. At 783 K and a NH_3 pressure of about 1 MPa, a reasonable conversion to aniline was obtained over a H-ZSM-5 catalyst in a flow reactor. The two main by-products were diphenylamine, from the reaction of phenol with the aniline product, and 2-methylpyridine. It was suggested that the latter product was the result of a subsequent reaction of aniline. In a subsequent patent [16] the conversion of aniline to 2-methylpyridine was described (Scheme 7), which took



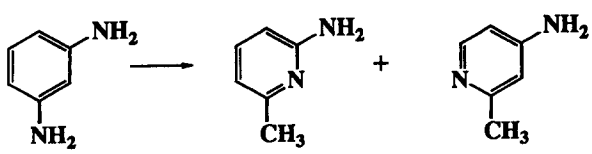
Scheme 7. Isomerization of aniline to α-picoline.

place under similar reaction conditions as the phenol to aniline reaction. A good selectivity (52%) was obtained at 783 K, 2.9 MPa NH_3 and a NH_3 to aniline molar ratio of 8, although the conversion was not very high (13%). By-products were acetonitrile and condensed aromatic heterocycles such as quinoline, indole and toluidine; the catalyst deactivated rapidly by coke formation.

In a patent by workers of the Bayer company [17], a similar isomerization reaction of an arylamine to an aromatic aza-heterocycle was described. They succeeded in transforming *m*-phenylenediamine into 2-amino-6-methylpyridine and 2-methyl-4-aminopyridine (Scheme 8) in a flow reactor at somewhat lower temperature (673 K), higher NH_3 pressure (19 MPa) and therefore higher NH_3 to arylamine ratio (60) than in the case of aniline. Conversion (74%) and selectivity (56% 2-amino-6-methylpyridine and 15% 2-methyl-4-aminopyridine) were substantially better than for aniline.

The isomerization of an arylamine to an N-containing aromatic heterocycle would in principle open a new route from aromatic hydrocarbons, via nitro-aromatics and arylamines, to pyridines and quinolines. We were therefore interested to find out the potential for this reaction, and have studied its scope, optimum conditions, as well as its mechanism [18,19].

Experiments in autoclaves demonstrated that a reasonably high temperature and ammonia pressure and an acid catalyst are required for the isomerization



Scheme 8. Isomerization of *m*-phenylenediamine to amino-methylpyridines.

reaction of arylamines to methyl-aza-aromatics, as suggested in [15–17]. The necessity of a high NH_3 pressure and temperature was investigated with *m*-phenylenediamine as educt, since its conversion and selectivity to amino-picolines are much higher than those observed for aniline to α-picoline. Results of pressure and temperature optimizations for a H-ZSM-5 catalyst showed that at 573 K the selectivity goes through a maximum of 90% around 10 MPa, and that at 6 MPa there is a temperature optimum around 600 K. Thus, after 4 h of reacting 2.5 g *m*-phenylenediamine with 0.5 g H-ZSM-5 at 593 K, 8 MPa and a NH_3/diamine ratio of 28 conversion was about 75% and selectivity to 2-amino-6-methylpyridine was 64 wt%. The P-T regime 7–12 MPa and 573–623 K therefore seems to be best suited for conversion of *m*-phenylenediamine.

That NH_3 is absolutely required for the transformation of arylamines into aza-aromatics was demonstrated by experiments with mixtures of NH_3 and N_2 at a total pressure of 10 MPa at 593 K. Conversion and selectivity decreased strongly below 6 MPa NH_3 pressure, and no 2-amino-6-methylpyridine was formed when no NH_3 was added to the reaction mixture. Use of other amines (pyridine and triethylamine) instead of ammonia did not produce any substituted pyridines. With trimethylamine 1% 2-amino-6-methylpyridine was observed, as well as a high conversion to alkylated *m*-phenylenediamines (as with triethylamine).

Also non-zeolitic solid acids transformed *m*-phenylenediamine into 2-amino-6-methylpyridine. An amorphous silica–alumina with a Si/Al ratio of 5 showed 19% conversion and 64 wt% selectivity under the same conditions as for the zeolitic catalysts, while NH_4Cl led to 74% conversion and 22 wt% selectivity. All four Lewis acids $AlCl_3$, $FeCl_3$, $SnCl_4$ and $ZnCl_2$ showed more or less the same conversion (75%) and selectivity (12–17 wt%), as well as a high selectivity (about 50 wt%) to small (C_2–C_4) N-containing molecules. Zeolites with one-dimensional pore systems (ZSM-12, ZSM-48, ZSM-23, Nu-10, MOR) as well as three-dimensional pore systems (Y, BETA, ZSM-5) catalyzed the transformation of arylamine to substituted pyridines. The one-dimensional zeolites showed the lowest selectivity with respect to pyridines, which suggests that either diffusional limitation in the pores plays a role, or that the reaction occurs solely on the

external surface. This might explain the high selectivity to condensed aromatics (quinoline, indole and their methylated derivates) for the zeolites with the narrowest pores. Quinoline and indole are most probably formed by ring closure of by-products formed by ortho-alkylation of *m*-phenylenediamine. Transmethylation, which needs much space for its bimolecular transition state [20], was especially strong for the ZSM-12 and ZSM-48 zeolites, as shown by the high selectivity for methylated *m*-phenylenediamine and demethylated products.

The zeolites with a three-dimensional pore structure had a higher selectivity for substituted pyridines than the one-dimensional ones. Although ZSM-5 has the narrowest pores of the three-dimensional zeolites studied, it had the highest selectivity. This suggests that the reaction takes place mainly inside the pores and that therefore transmethylation and the formation of condensed aromatics are suppressed. Passivation of the external surface area by reaction with triphenylsilyl chloride and subsequent calcination at 773 K indeed decreased the relative amounts of transmethylation and condensed aromatics. The concurrent decrease in conversion is probably due to the loss of active external surface area, as well as to blocking of pore mouths. The relatively low activity of catalysts other than ZSM-5 is ascribed to blocking of the pores of these catalysts by condensed aromatics formed in intermolecular side-reactions of the highly unsaturated intermediates.

The acid catalysis, in conjunction with the required high NH_3 pressure, explains why a relatively high reaction temperature is needed. At low temperature all acid sites are occupied by NH_3, and only at elevated temperature will enough NH_3 desorb and will acid sites become available for catalysis. Unfortunately, a high temperature also favors acid-catalyzed side reactions such as shifting of methyl groups and transmethylation. These lead to many side products and to separation problems. Initial experiments with less acid catalysts, which adsorb NH_3 less strongly and therefore do not require such high temperatures for NH_3 desorption, indeed gave promising results. The boron, gallium and iron equivalents of H-ZSM-5 were tested in autoclave experiments during 12 h with *m*-phenylenediamine. The results presented in Table 2 show that indeed higher conversions were reached than with H-ZSM-5 [21]. In contrast to the experiments with H-ZSM-5, with the B-, Ga- and Fe-MFI catalysts 2-methyl-4-aminopyridine was observed in addition to 2-amino-6-methylpyridine. The decrease in conversion with increasing temperature with the B-MFI catalyst suggests that this catalyst was not stable under reaction conditions. Experiments with the Fe-MFI catalyst showed that the 2,4 isomer yield decreased with increasing temperature, while that of the 2,6 isomer increased. This suggests that conditions may be found at which either this one or the other isomer can be made with high selectivity.

When synthesizing picoline from aniline, one needs aniline. Presently aniline is exclusively made by reduction of nitrobenzene, which in turn is made by nitration of benzene. As indicated above, an alternative route for the synthesis of aniline was studied by Mobil Comp., namely the amination of phenol. Since the main process for making phenol is the Hock process, in which benzene is alkylated with propene to cumene, which in turn is oxidized and transformed

Table 2
Results of the reactions of *m*-phenylenediamine over B-, Ga- and Fe-ZSM-5 [21]

Cat	Si/M	*T* (K)	P (MPa)	Conversion (%)	Selectivities (wt%)	
					2–6	2–4
B-MFI	26	525	5.3	51	41	13
		563	11.0	37	51	8
		583	11.0	23	72	1
Ga-MFI	24	483	11.3	11	6	19
		553	11.5	27	44	8
Fe-MFI	100	473	15.0	13	1	35
		568	12.5	44	66	1

2–6=2-amino-6-methylpyridine, 2–4=2-methyl-4-aminopyridine.

in phenol and acetone, in all cases benzene is the starting compound for making aniline. Therefore it would be advantageous to synthesize aniline from benzene directly in one step. In 1975 such a process was described in a patent [22]. Nickel–Zirconium oxides promoted with lanthanum oxide were claimed to function as 'cataloreactants' for the synthesis of aniline from benzene and ammonia in a flow reactor at 620 K and 30–48 MPa. It is clear from thermodynamics that a reaction from benzene and NH_3 to aniline and H_2 is impossible under such conditions, only coupling of this reaction with the hydrogenation of benzene to cyclohexane or of NiO to Ni will make it feasible. In the latter case the reaction is stoichiometric rather than catalytic, but can be made cyclic by reoxidation of the nickel. Unfortunately, our attempts to reproduce this reaction in autoclave experiments at 550–600 K and 10–20 MPa were not very successful [23]. Best results were indeed obtained with NiZrLa oxides, but conversion never exceeded 5% and the main product was cyclohexane. Some aniline, and even pyridine, was detected, however.

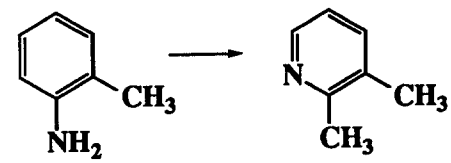
2.2. *Isomerization of other arylamines*

In order to find out whether the apparent N–ortho C exchange pattern in the transformation of aromatic amines to substituted pyridines also holds for other aromatic amines, we studied the reactions of *o*- and *p*-phenylenediamine, toluidines, naphthylamines and anthracylamines as well [19]. Experiments with *o*- and *p*-phenylenediamine under similar conditions as with *m*-phenylenediamine (600 K, 8 MPa NH_3, 0.5 g H-ZSM-5 and 2.5 g diamine, 5 h) showed reasonable to good conversions (28% for *o*-phenylenediamine and 92% for *p*-phenylenediamine), but almost no isomerization to methyl substituted pyridines.

Batch reactions of *o*-, *m*- and *p*-toluidine showed a low conversion, just a factor of 2 (*o*-toluidine) to 4 (*p*-toluidine) higher than that for aniline (Table 3). A large part of the conversion was, however, due to isomerization of one toluidine to the other two isomers, and to transmethylation to aniline and xylidines. The yield of substituted pyridines (lutidine and collidine) for *o*- and *p*-toluidine was therefore about as low as that for the aniline transformation. On the other hand, the selectivity for lutidines and collidines was much higher (44 wt%) for *m*-toluidine (Table 3). Thus, *m*-toluidine gives a much higher conversion to substituted pyridine than its ortho and para isomers, just like *m*-phenylenediamine gives a much higher conversion to amino-methylpyridines than *o*- and *p*-phenylenediamine.

Although the yields of substituted pyridines from the toluidines is low, they suffice to show that also in this case they are formed exclusively by an exchange of the N and ortho C atoms. For instance, the only substituted pyridines formed from *m*-toluidine are 2,4-lutidine and 2,6-lutidine, as well as 2,4,6-collidine as a result of subsequent transmethylation. The main pyridine-type product formed from *o*-toluidine, 2,3-lutidine, is a result of N–ortho C exchange as well (Scheme 9).

The pyridine-type products from *p*-toluidine (2,3-, 2,4-, 2,5- and 2,6-lutidine, as well as 2,4,6-collidine) look at first glance as a complex mixture. However, the strong isomerization of *p*-toluidine to *o*- and *m*-toluidine explains the subsequent formation of 2,3-lutidine,

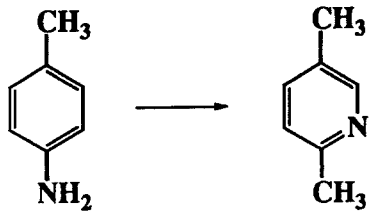


Scheme 9. Isomerization of *o*-toluidine to 2,3-lutidine.

Table 3
Results of the reactions of toluidines after 4 h at 600 K, 8 MPa and NH_3: toluidine=32 over H-ZSM-5 [19]

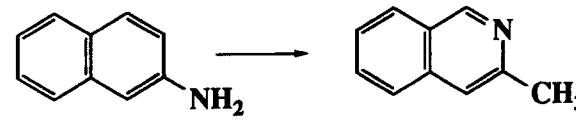
	Conversion (%)	Selectivities (wt%)					
		lut	coll	tol isom	anil, xyl	cond arom	Other
o-toluidine	10	5	0	13	19	32	31
m-toluidine	17	19	25	36	10	1	9
p-toluidine	20	4	2	61	29	1	3

lut=lutidine=dimethylpyridine, coll=collidine=trimethylpyridine, tol=toluidine=methylaniline, xyl=xylidine=dimethylaniline, anil=aniline, cond arom=condensed aromatics.



Scheme 10. Isomerization of *p*-toluidine to 2,5-lutidine.

Scheme 11. Isomerization of α-naphthylamine to 1-methylisoquinoline.



Scheme 12. Isomerization of β-naphthylamine to 3-methylisoquinoline.

and of 2,4- and 2,6-lutidine and 2,4,6-collidine, respectively, while 2,5-lutidine is the direct result of a N–ortho C isomerization of *p*-toluidine (Scheme 10).

Thus, all three toluidines lead to lutidines and 2,4,6-collidine by the exclusive interchange of the N and ortho C atoms in combination with isomerization of the toluidines. That the isomer distribution of the toluidines in the reaction of *p*-toluidine showed a higher content of *o*-toluidine than that of *m*-toluidine indicates that the isomerization has occurred inside the zeolite pores. This isomerization is known to occur via a 1,2 methyl-shift mechanism [24,25], which in case of *p*-toluidine should lead to more *m*-toluidine than *o*-toluidine. The much slower diffusion of *m*-toluidine as compared to *o*-toluidine out of the pores explains, however, why more *o*-toluidine is observed in the reaction mixture outside the zeolite. This example of disguised kinetics is analogous to that of the isomerization of xylenes, with the slower diffusion of *m*-xylene [26].

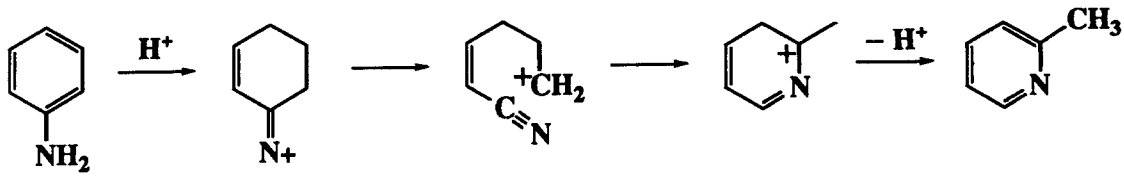
The aza-aromatic products of the reactions of α- and β-naphthylamine and of α- and β-amino-anthracene, presented in Table 4, are the result of N–ortho C interchange in combination with equilibration between α- and β-arylamine. Thus 1-methylisoquinoline is the direct product from α-naphthylamine (Scheme 11), and 3-methylisoquinoline is the direct product of β-naphthylamine (Scheme 12).

Isomerization of α- to β-naphthylamine explains why 3-methylisoquinoline is a by-product in the reaction of α-naphthylamine. Analogously, 1-methylisoquinoline is a by-product in the reaction of β-naphthylamine. It should be noted that almost no 2-methylquinoline was produced. Higher conversions were obtained with the 12-ring zeolite Beta than with the 10-ring zeolite ZSM-5, most probably due to diffusion limitations of the substituted naphthalenes in the 10-ring pores.

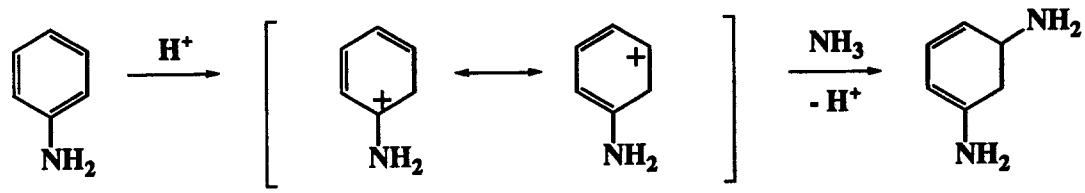
Table 4
Results of the reactions at 10 MPa of naphthylamines (NA), (NH_3: amine=18), and anthracylamines (AA), (NH_3: amine=14), over zeolite H-Beta

Amine	*T* (K)	Conversion (%)	Selectivities (wt%)				
			1-me-IQ	3-me-IQ	2-me-Q	isom	cond arom
α-NA	623	40	16	4	2	35	11
α-NA[a]	593	9	71			7	5
β-NA	623	50	2	7	1	45	18
α-AA	603	41	29[b]			0	
β-AA	603	17		17[c]		6	

1-me-IQ=1-methylisoquinoline, 3-me-IQ=3-methylisoquinoline, 2-me-Q=2-methylquinoline, isom=other arylamine isomer.
[a] Catalyst with passivated outer surface.
[b] 1-methyl-2-aza-anthracene.
[c] 2-aza-3-methylanthracene.



Scheme 13. Isomerization of aniline to α-picoline via an intramolecular Ritter reaction.



Scheme 14. Addition of ammonia to aniline.

2.3. *Mechanism of the arylamine rearrangement*

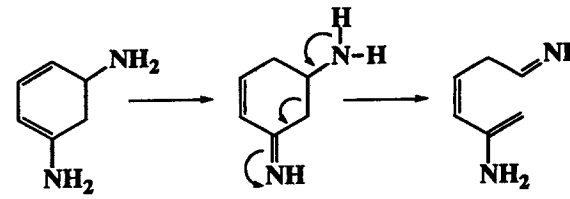
The only methyl-aza-aromatic products were those that can be thought of having been formed by an interchange of the N atom by a C atom from the ortho position of the benzene ring (Schemes 7 and 8). Chang and Perkins proposed that the reaction of aniline to α-picoline occurs via ring enlargement to an aza-7-ring, from which a carbon atom is extruded [15,27]. This reaction sequence might seem a plausible mechanism for the formation of α-picoline from aniline. However, the 7-ring mechanism is incapable of explaining why the toluidines, *m*-phenylenediamine, the naphthylamines and anthracylamines react exclusively via exchange of the N atom in the aromatic amine with a ring carbon atom in the ortho position. Assuming that carbon extrusion from the aza-7-ring takes place adjacent to the aza-atom, as suggested by the exclusive formation of α-picoline, the predicted products for *m*-toluidine are 2,3-, 2,4- and 2,5-lutidine, whereas 2,4- and 2,6-lutidine are observed. For *m*-phenylenediamine the predicted products are 2-methyl-3-amino-, 2-methyl-4-amino- and 2-methyl-5-aminopyridine, but 2-methyl-4-amino- and 2-amino-6-methylpyridine are observed. Also for the reaction of α-naphthylamine the wrong isomer, 3-methylisoquinoline instead of 1-methylisoquinoline (Table 4), is predicted. In addition to predicting the wrong reaction products, the 7-ring mechanism does not give an explanation for the need of the high NH_3 pressure either.

Another mechanism proposed by Chang and Perkins [27] is based on an intramolecular Ritter reaction, the reaction of a carbenium ion with the N atom of a cyano group (Scheme 13).

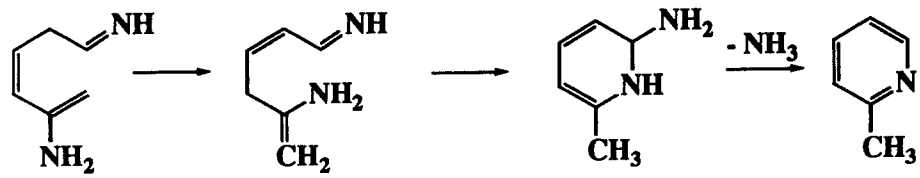
However, the necessity for a nitrenium ion, and the high strain in the intramolecular Ritter reaction step make this mechanism very unlikely. Also, the formation of nonlinear unsaturated nitriles is difficult to envisage in the pentasil-type zeolite, because of steric constraints in the transition state. In addition, the mechanism does not explain the need for a high NH_3 pressure and predicts the wrong products [19].

To explain all results it was necessary to assume that the aromaticity of the arylamine had to be broken by adding an ammonia molecule to the arylamine (Scheme 14).

This explains why a high NH_3 pressure is required and why the reaction runs better with naphthylamine than with aniline. Then ring opening occurs through a reverse aldol-type reaction (Scheme 15) and ring



Scheme 15. Ring opening through reverse aldol reaction.



Scheme 16. Ring closure after rearrangement.

closure may occur by addition of the original amino group to an imino group. Finally, the aza-aromatic is formed by elimination of NH_3 (Scheme 16).

2.4. *Outlook for the arylamine rearrangement*

The results obtained until now show that the levels of conversion and selectivity for the rearrangement of aniline to α-picoline and of toluidine to lutidine or collidine are limited; only the rearrangement of *m*-toluidine shows promise for further studies. The results for the rearrangements of *m*-phenylenediamine and naphthylamine give hope that further work (with flow instead of batch reactors, and with Fe- and Ga-ZSM-5 catalysts) may lead to efficient syntheses for amino-picolines and methylisoquinolines.

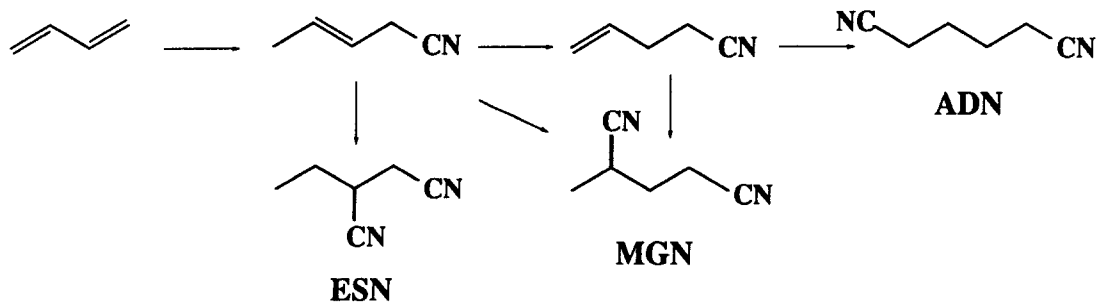
3. β-Picoline

3.1. *Processes from 2-methylglutaronitrile*

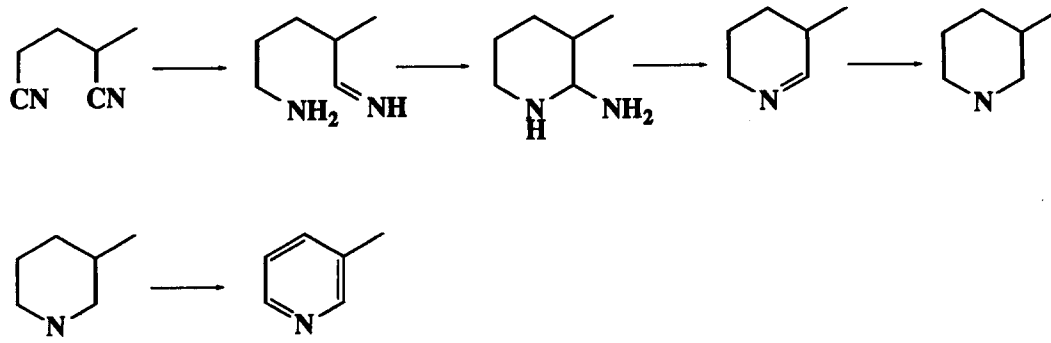
An alternative to the present commercial aldol condensation routes for the production of β-picoline described in Section 1 is the catalytic hydrogenation of 2-methylglutaronitrile (MGN), a by-product in the DuPont process for the manufacture of adiponitrile from butadiene (Scheme 17). The main use of adiponitrile (ADN) is in the production of hexamethylenediamine, a co-monomer for Nylon 6.6. Therefore ADN is produced worldwide on a very large scale (850 000 tons in 1993). The by-products of this process, mainly MGN and 2-ethylsuccinonitrile (ESN), find no industrial application and are burned as fuel. Due to the large scale of the ADN process, large amounts of MGN are available at low price.

β-Picoline can be obtained from MGN in two different ways. In a two-stage process MGN can be first hydrogenated and cyclized to 3-methylpiperidine, for instance over Raney-Ni at 400 K and 15 MPa in the presence of ammonia [28], or at a more elevated temperature and pressure over an iron catalyst [29] (cf., Scheme 18). The second step, the aromatization of 3-methylpiperidine to β-picoline, can be carried out over supported noble metal catalysts around 500 K [30–32], or with transition metal-oxide catalysts such as copper–chromium or molybdenum oxide at 900 K [33]. Two-stage processes involving the dehydrocyclization and aromatization of 2-methylpentane-1,5-diamine [30,33], obtained by the hydrogenation of MGN, were also described.

Although the thermodynamic conditions for the two steps are different, it should, in principle, be possible to combine them in a one-stage gas-phase process. The patent literature shows that MGN can indeed directly be converted into β-picoline, but that this process is



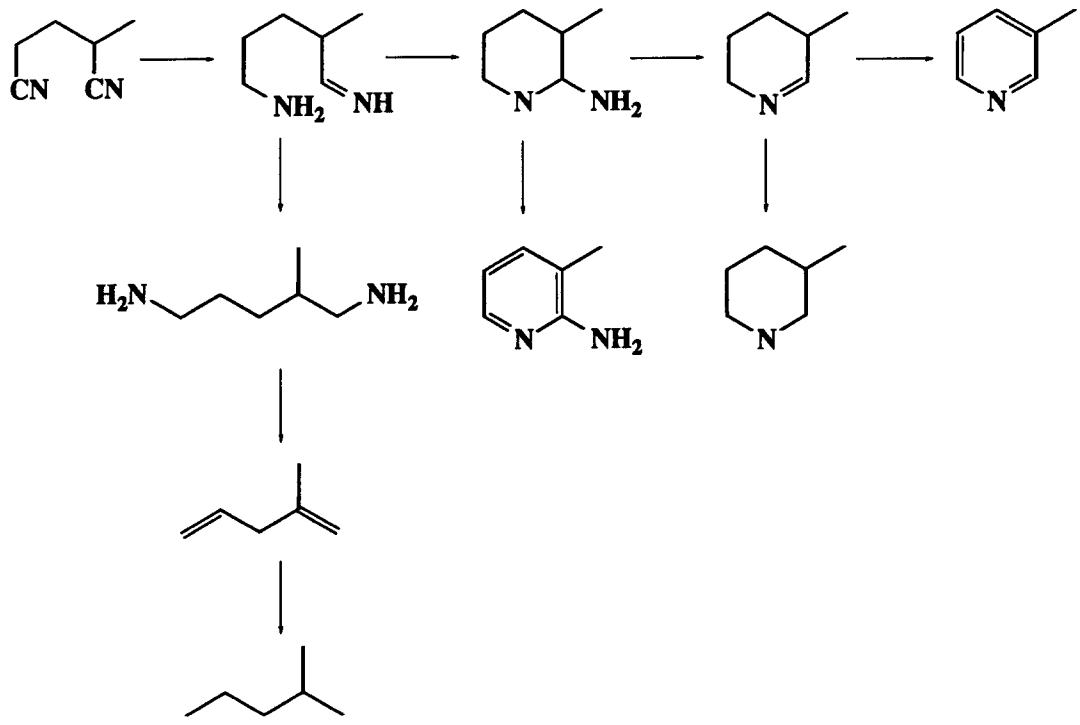
Scheme 17. Synthesis of adiponitrile from butadiene.



Scheme 18. Two-stage process for the synhesis of β-picoline from adiponitrile.

affected by several problems [34–38]. Incomplete MGN conversion was often observed, and in some cases a decrease of the activity and β-picoline yield with time on stream was reported [36]. Another drawback was the low selectivity to the desired end product, with the formation of many by-products [34]. This can be understood by looking at Scheme 19 which not only shows the main route from MGN to β-picoline, but also possible side reactions. It is understandable that achieving a high β-picoline selectivity might be a problem, because each of the intermediates shown (1-amino-4-methyl-pentylimine-5, 2-amino-3-methylpiperidine and 3-methyl-tetrahydropyridine) can form sideproducts (C_6-diamine and C_6-hydrocarbons, amino-picolines and methylpiperidine, respectively).

3-Methylpiperidine and aminopicolines can be recycled, and aminopicolines can find applications in the production of pesticides, herbicides, fungicides, cardiovascular and other pharmaceutical agents. The



Scheme 19. One-stage synthesis of β-picoline from MGN.

deaminated compounds are unusable, however, and represent an irreversible loss of reactants.

3.2. *One-step process from 2-methylglutaronitrile*

A one-step synthesis of β-picoline from MGN might lead to a simple process if the reported deactivation problems can be solved. To that end, we have investigated several supported metal catalysts and the effect of temperature, pressure, H_2/MGN ratio and space velocity on catalyst deactivation. The catalysts were prepared by pore volume impregnation as well as by ion exchange on several silica supports with surface areas ranging from 290 to 410 m^2/g. Metal loadings were in most cases about 450 μmol/g.cat [39–41].

Although widely used in nitrile hydrogenation [42,43], Ni and Ru did not exhibit any appreciable activity in the vapor phase hydrogenation of MGN

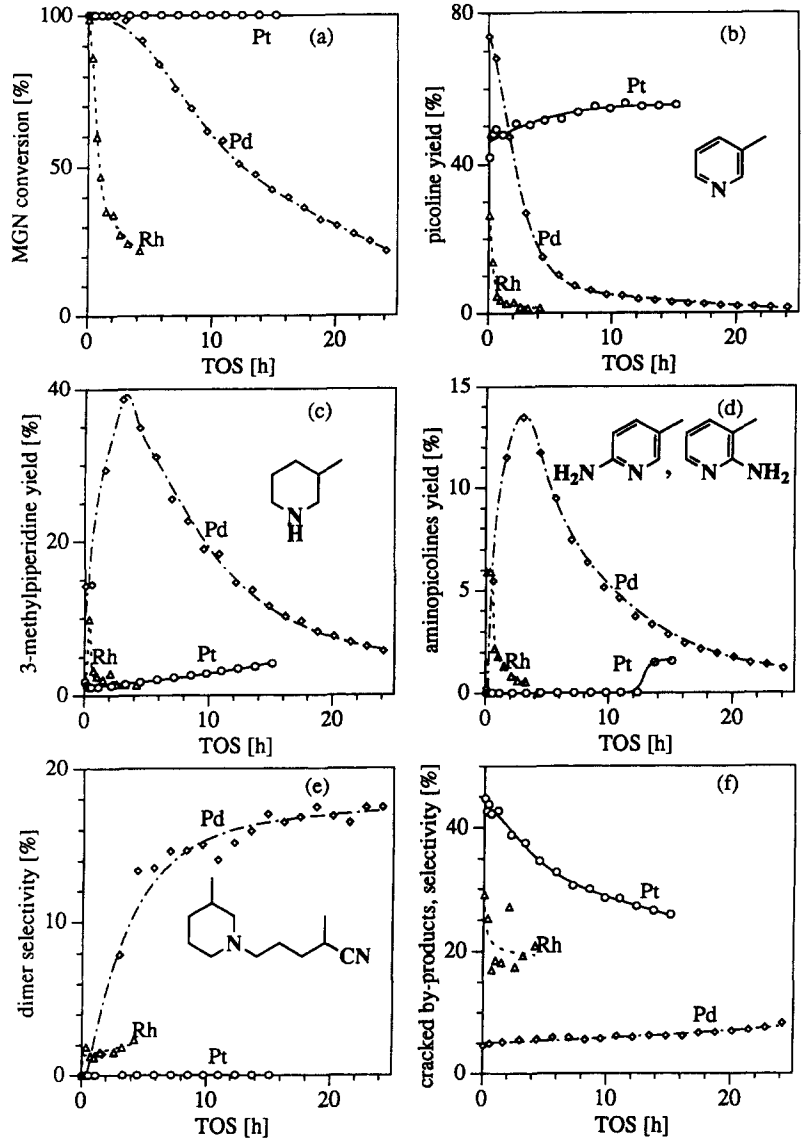
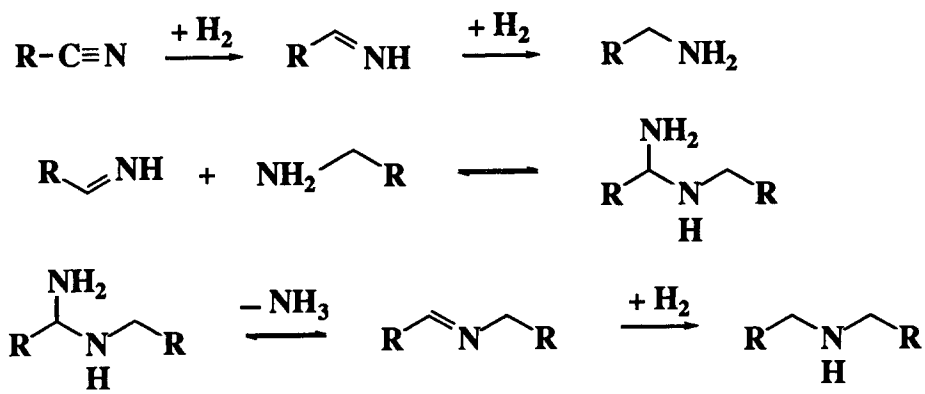


Fig. 1. Activities and selectivities of (◇) Pd/SiO_2, (△) Rh/SiO_2 and (○) Pt/SiO_2 catalysts in the hydrogenation of 2-methylglutaronitrile (MGN) at 573 K, 0.6 MPa, WHSV=40 h^{-1} and H_2/MGN=7 (reproduced with permission from Appl. Catal. 137 (1996) 187).

under our standard reaction conditions (573 K, 0.6 MPa, WHSV=40 g (MGN)/g(cat)·h, H_2/MGN=7). This is in accordance with the specific activity of Ni catalysts in liquid-phase nitrile hydrogenation which is much lower than that of Pd and Pt catalysts [44,45]. Pd, Rh and Pt supported on SiO_2 were active (Fig. 1), but exhibited different product distributions and rates of deactivation. Over the Pt/SiO_2 catalyst, MGN was completely converted and no deactivation could be observed up to 15 h on stream, whereas deactivation was important for the Pd/SiO_2 catalyst and dramatically fast for the Rh/SiO_2 catalyst, whose activity decreased 80% within 4 h from the reaction start (Fig. 1a). The highest β-picoline yield (75%) was obtained at reaction start over the Pd catalyst (Fig. 1b). Due to catalyst instability, however, this yield decreased to 10% within 6 h. The situation for the Rh catalyst was even more dramatic, starting with a value below 30% and decreasing to less than 5% within an hour. Over the Pt catalyst, on the contrary, the β-picoline yield increased smoothly from 45% to 55% during the first 15 h, so that 2 h after the reaction start the yield of the Pt catalyst was higher than that of the Pd catalyst. Without regeneration, it is thus possible to produce much larger amounts of β-picoline with the Pt catalyst than with the Pd catalyst. With a 40% peak value, Pd had the highest production of 3-methylpiperidine, whereas Rh was only active for a very short time, with a peak value of 10%. For Pt, the 3-methylpiperidine yield increased smoothly with time on stream, reaching about 4% after 15 h (Fig. 1c). Interestingly, no trace of aminopicolines was found in the product over the Pt catalyst, while their yield over Pd and Rh peaked at 13% and 6%, respectively (Fig. 1d).

To understand the different behaviors of the Rh, Pd and Pt catalysts, it is helpful to look at their behavior in the hydrogenation of mononitriles first. In the hydrogenation of mononitriles, the alkylamine product is formed via an alkylimine (Scheme 20). If relatively high concentrations of amine as well as imine are present, then an intermolecular reaction between amine and imine to an aminal can take place. At low ammonia concentration, the aminal deamminates to a dialkylimine, and this in turn can be hydrogenated to a dialkylamine. At high ammonia concentration, the deammination of the aminal is suppressed and it decomposes back into the amine and imine. As a consequence, in the hydrogenation of nitriles not only alkylamines, but also dialkylamines, and even trialkylamines are formed. The selectivity towards di- and trialkylamines depends on the rates of hydrogenation and on the adsorption strengths of reaction intermediates. It increases in the order Rh<Pd<Pt [44], the latter two metals showing a much higher activity for condensation reactions than for nitrile hydrogenation. The intermolecular amine–imine condensation, which via the aminal leads to di- and trialkylamines (Scheme 20), is also responsible for the intramolecular condensation to the 2-amino-3-methylpiperidine aminal which is the intermediate for the formation of 3-methylpiperidine, and thus for β-picoline (Schemes 18 and 19).

Although the initial activity of the Rh/SiO_2 catalyst was high, the yields towards the desired β-picoline, 3-methylpiperidine and 2-amino-3-methylpyridine pro-



Scheme 20. Hydrogenation of a mononitrile and formation of secondary amines.

ducts (Fig. 1b–d) were extremely limited, while the selectivity towards cracked by-products was comparatively high. Rylander and Steele observed that imines strongly adsorb on Rh catalysts in the liquid phase hydrogenation of aromatic nitriles at room temperature [46]. A high residence time of the imines on the Rh surface would favor hydrogenation and cracking reactions, producing lighter by-products, as well as some high molecular side reactions like imines trimerization, yielding heavy compounds which stay on the metallic surface and block catalytically active sites. Polymer-like compounds were clearly formed on Rh/SiO_2, since the spent catalyst formed a clump, glued together by a reddish resin.

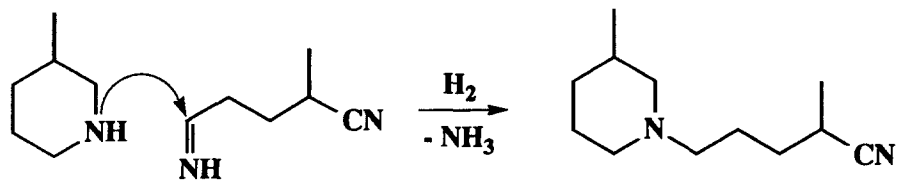
Intramolecular condensation reactions were more favored on Pd than on Rh, as indicated by the considerably higher selectivity towards cyclic compounds. Hydrogenolysis reactions, on the other hand, were clearly suppressed on Pd (Fig. 1f). The formation of relatively stable products by intramolecular condensation on the Pd surface decreased the coverage with incompletely reacted intermediates, thus preventing undesired intermolecular condensations (like trimerizations), hence lowering the rate of deactivation.

Besides the wanted products, such as β-picoline, 3-methylpiperidine and aminopicolines (Fig. 1b–d), many by-products were detected. GC/MS analysis showed that these by-products resulted from undesired hydrogenolysis (yielding compounds with low boiling points, such as 2-methylpentane, pentanenitrile and 2-methylpentanenitrile, cf., Scheme 19), as well as from condensations among reactive intermediates. Such condensations produce compounds with a high molecular weight, such as a dimer which was formed in substantial amounts by the reaction given in Scheme 21. Most high molecular by-products showed an MS signal at mass 112, corresponding to a fragment of an *N*-alkyl-3-methylpiperidine. This suggests that 3-methylpiperidine is the precursor of most unwanted by-products. In agreement with this conclusion, 1,5-bis(3-methylpiperidino)-2-methylpentane was observed in the hydrogenation of 2-methylglutaronitrile at 453 K and 5 MPa [47]. This 'trimer' originates most probably from a reaction analogous to that of the 'dimer' in Scheme 21, namely the addition of two piperidine molecules to 2-methylpentane-1,5-diimine, the half hydrogenated product of 2-methylglutaronitrile, removal of two ammonia molecules from the diaminal, followed by hydrogenation.

The Pt catalyst produced the largest amounts of low molecular compounds, their selectivity decreasing in the order Pt>Rh>Pd (Fig. 1f). Pt is known to be the better hydrogenation catalyst and thus it is not too surprising that a substantial part of the reactant was apparently totally hydrogenated to the diamine and subsequently hydrogenolyzed to hydrocarbons. The dimer was almost exclusively observed with the Pd catalyst. Over Rh its formation was much less important, whereas Pt yielded no heavy by-products at all (Fig. 1e). The hydrogenation capacity of the Pd catalyst was thus much lower than that of the Pt catalyst, and favored the accumulation and condensation of intermediates on the Pd surface. Rh assumed an intermediate character, yielding considerable amounts of cracked by-products when active, but simultaneously allowing the formation of the dimer.

3.3. *Deactivation on Pd catalysts*

Deactivation on Pd/SiO_2 was mainly due to reactions involving reactive intermediates produced during the hydrogenation of nitriles. For this reason MGN could not be hydrogenated in a differential way at low conversion, because this led to high concentrations of intermediates and therefore to a fast deactivation. The hydrogenation of α,ω-dinitriles is sensitive towards the structure of the substrate and to catalyst properties.



Scheme 21. Formation of 'the dimer' from intermediates.

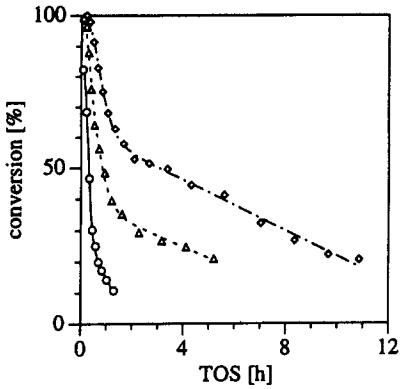


Fig. 2. Conversion of 2-methylglutaronitrile (MGN) at 573 K, 0.6 MPa, H_2/MGN=7 and WHSV=28 h^{-1} (◇), 40 h^{-1} (Δ) and 80 h^{-1} (○).

Increasing the metal dispersion and the metal loading led to better activity and stability, whereas the presence of basic dopants on the support dramatically decreased the performance of the catalyst, and alloying of the active metal atoms with an inactive phase led to a loss in activity, selectivity and stability [39–41].

Since deactivation could not be avoided at standard reaction conditions, the influence of operating parameters such as temperature, partial pressures and space velocity on the stability and selectivity of catalysts for the vapor phase hydrogenation of MGN were investigated.

The results obtained at 573 K, 0.6 MPa, H_2/MGN=7 and different WHSV-values are depicted in Fig. 2. The space velocity was varied by changing the amount of catalyst charged into the reactor. Although always complete at reaction start, the conversion of MGN (Fig. 2) decreased much faster when the space velocity was higher. As a consequence of the deactivation the β-picoline and 3-methylpiperidine yields decreased rapidly. However, he corresponding selectivities remained unaffected by the space velocity. The β-picoline selectivity was initially high (between 50% and 70%), but fell to about 20% within 1 h independent of the space velocity (Fig. 3a), whereas the 3-methylpiperidine selectivity was about constant with time (16%), independent of the space velocity. Also the aminopicolines selectivity was independent of the space velocity. It increased from 0% to 9% within 1.5 h and then decreased smoothly to 5% after 10 h. The dimer selectivity, on the other hand, showed a clear dependence on the space velocity (Fig. 3b). Within 1.5 h it reached a stable value of around 25% and 30% at WHSV values of 28 and 40 h^{-1}, respectively, while at 80 h^{-1} it reached 45% after 2 h and still showed a clear tendency to increase.

The fact that the initial conversion was always complete, independent of the space velocity (thus independent of the amount of catalyst), points to an extremely high MGN hydrogenation activity on the fresh catalyst, so that the first hydrogenation steps take place in a small part of the catalyst bed. Most intermolecular condensations presumably take place in the same reaction front, since they involve unsaturated intermediates like the iminonitrile resulting from a single hydrogenation step of MGN. Owing to their extremely high activity and to the high concentration

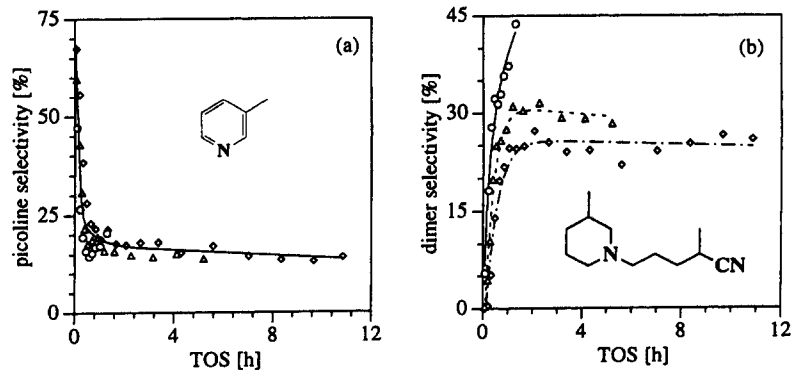


Fig. 3. Selectivities of β-picoline and the dimer in the hydrogenation of 2-methylglutaronitrile (MGN) at 573 K, 0.6 MPa, H_2/MGN=7 and WHSV=28 h^{-1} (◇), 40 h^{-1} (Δ) and 80 h^{-1} (○).

of reactive intermediates, the catalyst particles contained in this reaction front deactivate quickly, so that the reaction front moves downstream, leaving partly deactivated catalyst behind in the top part of the bed. After the initial fast deactivation, the hydrogenation activity slowly decreases with time on stream and catalysts with higher metal loading are more active. This can be explained by a fast deactivating front which migrates and reaches the end of the catalyst bed 1 or 2 h after the reaction start, leaving behind a catalyst bed in which MGN still reacts, but at a much lower rate than in the front. Intermediates (imines, dimers and amines) which travel faster than the deactivation front readsorb and react further to β-picoline or to cracked by-products in the part of the catalyst bed downstream of the front, as indicated by the decreasing of the dimer selectivity with increasing amounts of catalyst. Since the concentration of highly reactive intermediates is not very large, this part of the catalyst bed probably does not deactivate significantly. As long as the reaction front has not reached the end of the catalyst bed yet, a high β-picoline selectivity is maintained. As soon as the front has reached the end of the catalyst bed and the whole catalyst bed has significantly deactivated (1 or 2 h after the reaction start), the β-picoline selectivity drops to a value independent of the amount of catalyst. Simultaneously, the deactivation rate suddenly decreases, and a new, slow deactivation regime sets in. Thus, the deactivation in the front is especially detrimental for sensitive reactions like the aromatization to β-picoline which require large metal ensembles. When the front reaches the end of the catalyst bed these sensitive reactions almost stop, while the less sensitive (like hydrogenations) still take place, but at a much lower rate than in the front (Fig. 4).

Palladium thus showed promises as a catalyst for the one-stage gas-phase hydrogenation of MGN to β-picoline, but the deactivation was too fast for industrial applications. Either more drastic reaction conditions (such as a higher hydrogen partial pressure to avoid deactivation, and a higher temperature to prevent hydrogenation to 3-methylpiperidine and, consequently, high intermolecular condensation activity) and catalyst modifications (higher loadings and Pd–Pt alloys) have to be applied, or an operation mode with catalyst regeneration might be necessary. In the latter case, it seems doubtful that a process with swing reactors can compete against a two-stage process from MGN to β-picoline.

3.4. *Pt catalyst: Influence of operating conditions*

Supported platinum catalysts showed a stable operation, but also a marked production of hydrogenolyzed by-products. Therefore it was tried to find operation conditions where hydrogenolysis could be prevented. As expected from thermodynamics, increasing the temperature to 600 K enhanced the β-picoline yield at the expense of hydrogenation to 3-methylpiperidine. Other positive points were that the yield of hydrogenolyzed by-products decreased and that the MGN conversion remained 100%. At 623 K, however, the activity dropped to 70% within a few

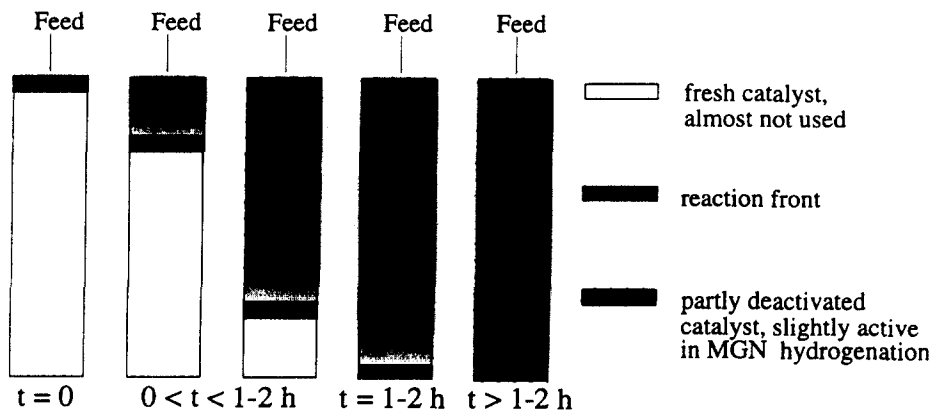
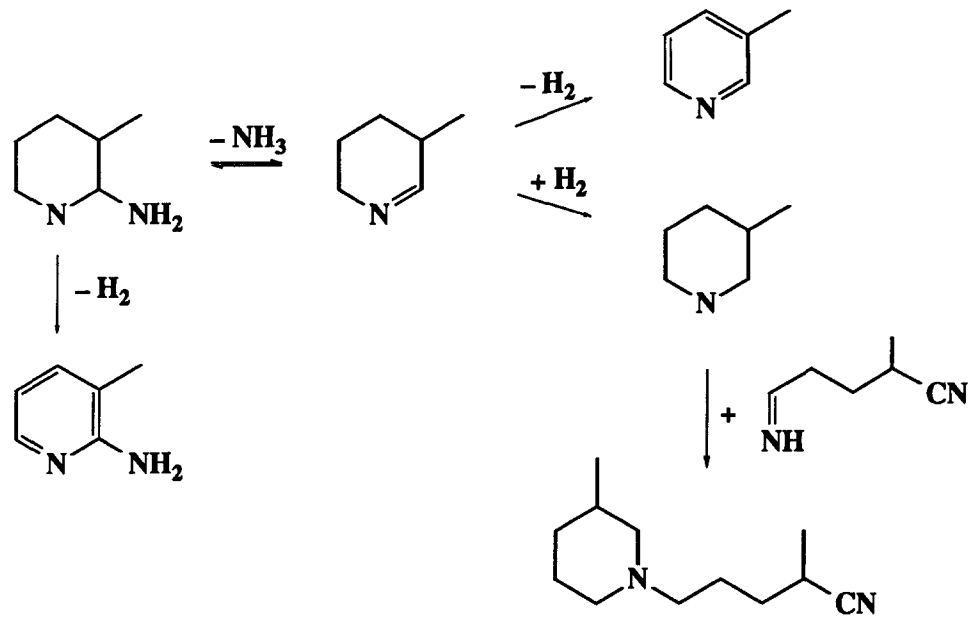


Fig. 4. Schematic representation of the deactivation of a Pd/SiO_2 catalyst bed in the hydrogenation of 2-methylglutaronitrile.



Scheme 22. Interdependence of products and by-products.

hours, the β-picoline yield decreased and the dimer selectivity increased. An operating temperature around 600 K therefore seems optimal. The losses due to hydrogenolysis over the Pt/SiO_2 catalyst could be reduced by choosing a lower operating pressure or H_2/MGN ratio, but this choice affected other reactions negatively. Thus, deactivation started within a couple of hours, the β-picoline yield decreased, and the 3-methylpiperidine and dimer yields increased.

The results of the experiments in which the temperature and pressure were varied point to serious problems with the last reaction steps in the formation of β-picoline (Scheme 22). For instance, during the initial deactivation phase at 0.3 MPa, a large change in product distribution from β-picoline to 3-methylpiperidine was observed. At this pressure much larger amounts of hydrogenated compounds are produced than at 0.6 MPa, and correspondingly much less aromatics are formed. This is opposite to what is expected on the basis of thermodynamics or kinetics. A higher hydrogen partial pressure most probably exerts a positive effect on those surface reactions which hinder the deposition of, or which remove, the residues, and also speeds up the reactions of the intermediates towards the stable final products. That aminopicolines are formed exclusively on the partially deactivated catalyst is probably due to the accumulation of their precursors caused by the slowing down of the reactions giving β-picoline and 3-methylpiperidine.

Lower pressures thus allow to obtain the desired decrease in hydrogenolysis activity, but at the expense of catalyst deactivation through deposition of residues which hinder the dehydrogenation of the β-picoline precursor and induce a dramatic selectivity shift towards 3-methylpiperidine, the dimer, aminopicolines and other undesired by-products. Experiments in which the hydrogen partial pressure was varied at constant MGN pressure confirmed that the improvements achieved by increasing the total pressure were mainly due to the increased hydrogen partial pressure, which protected the catalyst from deposition of residues, through the acceleration of the desired surface reactions of the intermediates, and probably also by an enhanced removal of the residues through their gasification.

Since the major problem with the supported platinum catalyst is the large production of hydrogenolyzed by-products, raising the space velocity, thus reducing the space time, should give better results. Therefore, two experiments were carried out, the first at standard reaction conditions (40 h^{-1}), while for the

second the space velocity was set equal to 100 h^{-1}. The yield of hydrogenolyzed by-products decreased indeed with increasing WHSV. Again, this improvement was accompanied by important drawbacks. At the higher space velocity, the conversion started to deviate from 100% after 10 h on stream. The worst consequence, however, was that the β-picoline yield quickly decreased from 50% to 35%, and then decreased almost linearly with time on stream, reaching 20% after 17 h, whereas at the lower WHSV it actually increased from 45% to 55% (Fig. 1b). At the same time there was a substantial increase of the 3-methylpiperidine yield, and of the formation of dimer and aminopicolines. These results were similar to those obtained by varying the pressure. Thus, whenever the catalyst was submitted to conditions where hydrogenolysis was suppressed, it deactivated faster and exhibited an important initial β-picoline yield decrease and strongly increased 3-methylpiperidine, dimer and aminopicolines yields.

Considering that increasing the space velocity corresponds to decreasing the space time, and that the amount of diluent does not have any influence on the catalyst performance, the product distribution obtained at the end of the catalyst bed at 100 h^{-1} corresponds to that after 40% of the catalyst bed at a space velocity of 40 h^{-1}. Therefore, the first 40% of the catalyst bed at 40 h^{-1} produce initially high amounts of β-picoline, but the selectivity shift towards 3-methylpiperidine and aminopicolines is very fast, although the conversion is still complete up to 10 h on stream. A couple of hours after the reaction start, large amounts of 3-methylpiperidine and small amounts of dimer and of aminopicolines are produced in the first part of the reactor, but at its end their yields have decreased substantially, and the yields of β-picoline and hydrogenolyzed by-products have increased. The experiments with varying space velocity showed that during the hydrogenation of MGN, products, by-products and intermediates are repeatedly adsorbed and desorbed, thus are subjected to further transformations until they leave the reactor. Therefore, 3-methylpiperidine produced upstream can be converted into β-picoline after readsorption on a dehydrogenation site. Nevertheless, all products and by-products tend, with increasing space time, to react to hydrogenolyzed by-products. This was confirmed by an experiment at WHSV=0.66 h^{-1} in which mainly 2-methylpentane and some other cracked by-products were obtained. Therefore, the space velocity has to be optimized. At too low values cracked products are favored, whereas at high values conversion tends to be below 100% and too high concentrations of intermediates like aminopicolines and 3-methylpiperidine are present. These lead to the intermolecular formation of dimers and thus to deactivation.

3.5. *One-stage versus two-stage process*

The described results make it clear that the coupling of all reactions from 2-methylglutaronitrile to β-picoline in an efficient one-stage process is extremely difficult, and it is therefore not surprising that a recently anounced new process for the synthesis of β-picoline from 2-methylglutaronitrile is based on a two-stage rather than a one-stage approach [47]. In this process, 2-methylglutaronitrile is first fully hydrogenated to 2-methylpentane-1,5-diamine, which is thereafter converted to 3-methylpiperidine over ZSM-5, followed by dehydrogenation over a Pd catalyst.

4. Conclusions

Two new routes for the synthesis of α- and β-picoline and related aza-aromatics were discussed. The rearrangement of arylamines to ortho-methyl-substituted pyridines shows, in principle, great promise. Nevertheless, the experimental as well as the mechanistic results show that the conditions necessary for such a rearrangement are quite rigorous. A high NH_3 pressure is needed to break the aromaticity of the phenyl ring, but this, at the same time, leads to a loss of catalytically active sites. At the high temperature required to desorb NH_3, several unwanted side reactions lower the selectivity to the desired product(s). Further research is needed to determine whether the rearrangements can be performed at lower temperature, but with other catalysts.

The synthesis of the valuable β-picoline from 2-methylglutaronitrile, a low value side product in the production of adiponitrile, already attracted attention in the past. The results described here demonstrate that this reaction is possible even in a single step process in which hydrogenation, cyclization and dehydrogena-

tion take place in one and the same reactor. Such a process would simplify the manufacture of β-picoline substantially. The disadvantage of the single stage process, however, is that oligomeric products may be formed. These lead to deactivation of the catalyst which, as the described results show, should be avoided at all costs. A single stage process, therefore, seems feasible only if the formation of the oligomeric products can be prevented to a large enough extent; even then, a (costly) swing process in which reactors alternate between reaction and regeneration, might be the only solution.

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