Journal of Molecular Catalysis A: Chemical 308 (2009) 182–185

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Liquid phase hydrodechlorination of some chlorinated aromatic nitrogen-containing heterocyclics

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ARTICLE INFO

Article history:
Received 16 March 2009
Received in revised form 16 April 2009
Accepted 17 April 2009
Available online 23 April 2009

Keywords:
Hydrodechlorination
Nitrogen heterocyclics
Palladium
Rhodium
Sol–gel

ABSTRACT

Several chlorinated pyridine, indole, quinoline and isoquinoline derivatives are hydrogenated at 80–140 °C in the presence of a silica sol–gel entrapped combined palladium–$[Rh(cod)Cl]_2$ catalyst to give ultimately chorine-free aromatic and/or hydroaromatic heterocyclic compounds. The process takes place stepwise. Except for the hydrogenation of 6-chloroquinoline, in which the hydrogenation of some aromatic double bonds precedes the elimination of the chlorine atom, the first step is always the hydrogenolysis of the halogen atom by which the parent aromatic heterocyclic compound is formed. Quinoline and isoquinoline derivatives form two isomeric tetrahydro compounds which are further hydrogenated to the decahydroquinolines and isoquinolines, respectively. The combined immobilized catalyst is leach-proof and recyclable. Its activity relies on a synergistic effect between the two different metallic nuclei.

1. Introduction

Many well-known pharmaceuticals of the 19th and 20th centuries are derivatives of chlorinated nitrogen heterocycles. Among them are, for example, the anti-histaminic chloropyridine derived chloropheniramines [1], the anti-inflammatory indole derived indomethacines [2], the anti-malarial chloroquine [3], and the analgesic gelafenine chloroquinolines [4], as well as the monoamine oxidase inhibiting chloroisoquinolines [5]. However, owing to public concerns about the hazardous influence of aromatic chlorocompounds towards the environment [6], a part of these drugs lost their popularity and were listed among compounds that should be destroyed. We have already shown [7,8] that one of the most efficient methods for dechlorination of aromatic carbocyclic environmental pollutants under mild conditions is based on Angelici's combined Pd–Rh catalyst [9] entrapped within a silica sol–gel support [10]. This catalyst proved also effective for denitrogenation of aromatic amines and nitro compounds in which the nitrogen is not part of the ring [11]. We have now found that this immobilized catalyst promotes the hydrodechlorination of chlorinated nitrogen heterocyclics without destroying their cyclic skeletons.

2. Experimental

2.1. Instruments

Infrared spectra were run on a Bruker model Vector 22 FTIR instrument. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 machine. Mass spectra were measured on a Hewlett-Packard model 4989 A mass spectrometer equipped with an HP gas chromatograph model 5890 series II. Gas chromatographic analyses were performed on a Hewlett-Packard model Agilent, using either a 15 m long capillary column packed with bonded and crosslinked (5% phenyl)methylpolysiloxane (HP-5) or a 30 m long column packed with Carbowax 20 M-poly(ethylene glycol) in fused silica (Supelco 25301-U). ICP-MS analyses were performed with a Perkin Elmer model ELAN DRC II instrument. The hydrogenation experiments were carried out either within a 100 ml glass lined Parr microreactor model 4592 equipped with a temperature controller model 4842, a mechanical stirrer and a sampling device, or within a 45 ml Parr pressure vessel model 4712 with a gage block no. 4316.

2.2. Chemicals

The various chlorinated substrates (**1–5**) and 2,2′-biquinoline, the reference compounds pyridine, 2-chloropyridine, piperidine, indole, quinoline, isoquinoline, 2,2′-biquinoline, 1,2,3,4- and 5,6,7,8-tetrahydroquinoline, *E*-decahydroquinoline, *E*-decahydroisoquinoline, 2,6-dimethoxypyridine, 5-methoxyindole, 2- and 6-methoxy quinoline, 1-methoxyisoquinoline were purchased either from Sigma–Aldrich or from ABCR. *E*- and *Z*-octahydroindole

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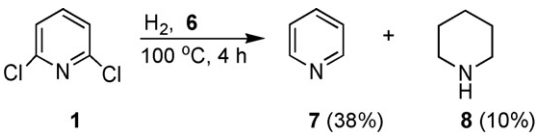
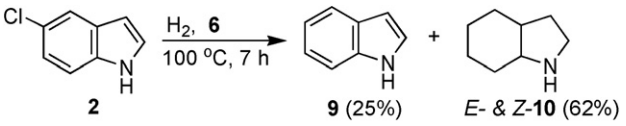
doi:10.1016/j.molcata.2009.04.008



Scheme 1.



Scheme 2.

[12,13], *Z*-decahydroquinoline [14], 6-chloro-1,2,3,3,4-tetrahydroquinoline [15], *Z*-decahydroisoquinoline [16], 1,2,3,4- and 5,6,7,8-tetrahydroisoquinoline [17,18] as well as the immobilized Pd–[Rh(cod)Cl]$_2$ catalyst [10] were prepared according to literature procedures.

2.3. General procedure for the hydrodechlorination experiments

Typically, a micro-reactor of 45 ml was charged with 0.65 g of sol–gel entrapped Pd–Rh catalyst **6**, that contained 0.08 mmol palladium in the form of nanoparticles and 0.015 mmol of [Rh(cod)Cl]$_2$ [7], 2.0 mmol of 2-chloroquinoline and (optional) 5 ml of either n-heptane or 1,2-dichloroethane. The reactor was sealed and flushed (3×) with N_2 and heated to the desired temperature. After temperature equilibration, the autoclave was pressurized to the required H_2 pressure (usually 27.6 bar), and stirring was operated at 500 rpm. Samples of 20 μl were withdrawn periodically, cooled to room temperature and neutralized with freshly prepared methanolic $NaOCH_3$ followed by filtration through a Millipore filter and subjected to gas chromatographic analysis. After the desired length of time the heating was stopped and the immobilized catalyst was filtered off. The filtrate was treated with excess methanolic $NaOCH_3$, filtered again and the solvent was evaporated. The residue was either separated by filtration through a short silica column or analyzed directly by gas chromatography. The NMR and mass spectra of the reaction mixture components were compared with those of authentic samples. The used catalyst was washed with water (15 ml), dried at 0.1 mm, washed and sonicated with CH_2Cl_2 (2× 15 ml) and dried again and then reused in a second run. ICP tests of the filtrate and of the washings revealed complete absence of palladium and rhodium compounds.

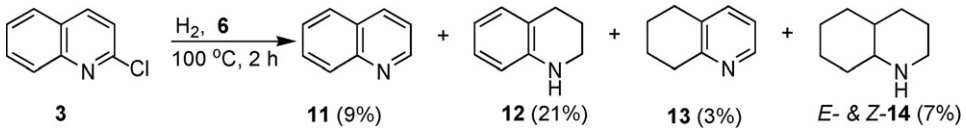
3. Results and discussion

Under the conditions described in Section 2.3, 2,6-dichloropyridine (**1**), 5-chloroindole (**2**), 2-chloroquinoline (**3**), 6-chloroquinoline (**4**) and 1-chloroisoquinoline (**5**) were hydrodechlorinated. The reactions were conducted in the presence of the silica sol–gel entrapped Pd–[Rh(cod)Cl]$_2$ catalyst (**6**) [10] either with or without a solvent between 80 and 140 °C. Except for one product of **4**, all other products were chlorine-free. Some representative partial hydrogenations at 100 °C are summarized in Schemes 1–5. The yields listed in these schemes are the average of at least two experiments (for each scheme) in which the products did not differ by more than ±3%. The missing percentages in the schemes reflect the amounts of recovered starting materials. Unlike the hydrodechlorination of carbocyclic chloroarenes [7,8], the liberated hydrogen chloride forms readily hydrochlorides with both the starting compounds and the products. Therefore, in order to enable facile product determination, the reaction mixtures were neutralized prior to the GC analyses. Attempts to carry out the neutralization with aqueous sodium hydroxide led to partial replacement of the chlorine atoms in the recovered starting materials by hydroxyl functions forming water-soluble compounds. The use of potassium carbonate was likewise, impractical since it usually produces the amine carbonates. Therefore, we used methanolic $NaOCH_3$ that yields aromatic methoxyl compounds, which are easily separable from the other components of the reaction mixtures and can be analyzed by GC, MS and NMR. The hydrodechlorination reactions shown in Schemes 1–5 were conducted in the absence of any solvent. (The yields listed in these schemes are the average of at least two experiments in each case that did not differ by more than ± 3%.) In the presence of a solvent (heptane and 1,2-dichloroethane) some reaction intermediates react differently and sometimes lead to the accumulation of different products. Most of our studies were performed in 1,2-dichloroethane. The latter is not affected at room temperature by methanolic sodium methoxide either during the neutralization or during the workup.

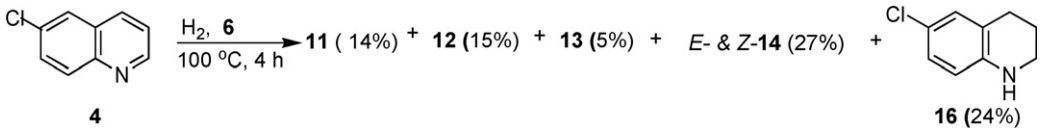
Between 80 and 140 °C the hydrodechlorinations outlines in Schemes 1–5 by the combined catalyst **6** takes place stepwise. Except in the hydrodechlorination of 6-chloroquinoline (**4**) the chlorine atom is eliminated in the first step. The chlorine-free parent heterocyclic compounds so formed, undergo further stepwise hydrogenation. At 100 °C 2,6-dichloropyridine (**1**) forms initially pyridine (**7**) which is cleanly converted into piperidine (**8**). Under these conditions monochloropyridine cannot be isolated. At 140 °C also the unsubstituted pyridine does not accumulate anymore. 5-Chloroindole (**2**) is transferred stepwise to indole (**9**) and to a mixture of *E*- and *Z*-octahydroindole (**10**). 2-Chloroquinoline (**3**) forms initially the chlorine-free parent compound **11**, which is further hydrogenated to 1,2,3,4- and 5,6,7,8-tetrahydroquinoline (**12** and **13**, respectively), probably via the various dihydroquinolines [18] and then further transferred to a mixture of *E*- and *Z*-decahydroquinoine (**14**). Unlike the hydrogenation of quinoline by a variety of other catalysts that form mainly **12** accompanied by only a small amount of **13** (see e.g., Refs. [18,19]) the reactions in the presence of the combined immobilized catalyst **6** lead to the generation and the transformation of significant quantities of **13** (see Fig. 1).

Catalyst **6** differs also from other supported ones by the ease that it promotes the transformation of the tetrahydroquinolines to the isomeric decahydroquinolines (**14**) under mild experimental conditions [19]. Although at 100 and 120 °C the formation of **14** is rather slow, at 140 °C full conversion of **3** into **14** is completed within 14 h (see Fig. 2).

Under these conditions the perhydroquinolines are accompanied by some biquinoline derivatives having molecular formulas of $C_{18}H_{16}N_2$ and $C_{18}H_{18}H_{20}N_2$ [20]. The formation of these dimers (which is negligible at 100 °C) proved to be reversible at higher temperatures and they disappear almost completely after prolonged heating under H_2. Thus, in fact they serve as additional



Scheme 3.



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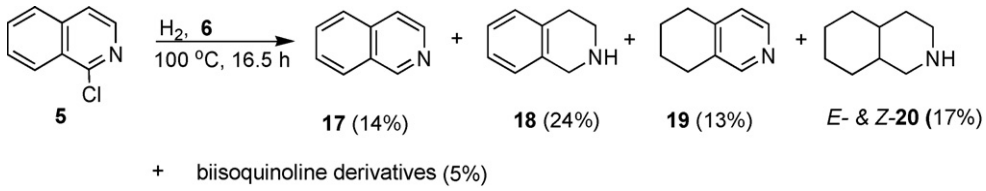

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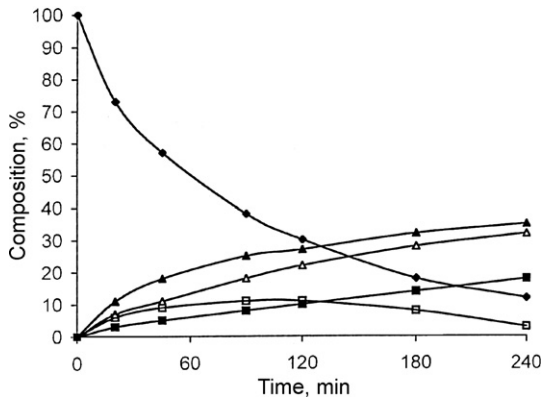

Fig. 1. Concentration time profile for the reactant and products in the catalytic hydrogenation of 2-chloroquinoline in the presence of 1,2-dichloroethane at 100 °C. (3, (♦); 11, (□); 12, (▲); 13, (△); 14, (■)).

intermediates in the production of **14** (cf. the reversible formation of aromatic and hydroaromatic amines in the presence of **6** [11]). The reversibility of biquinoline derivative was demonstrated also by an experiment in which commercial 2,2′-biquinoloine in $(CH_2Cl)_2$ was treated with H_2 in the presence of **6** for 30 h. The resulting reaction mixture contained, in addition to hydrogenated biquinolines 25% of **12**, 8% of **13** and 5% of the isomers of **14**. Although at 100 °C hardly any reduced biquinolines are formed, at 120 °C these compounds begin to accumulate after ∼1 h and their amount starts to diminish after ∼24 h. At 140 °C their formation

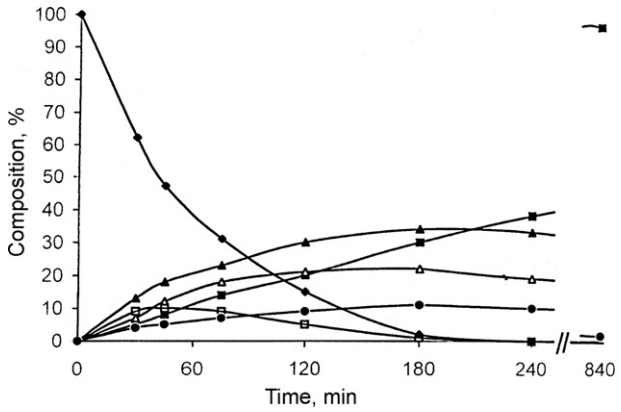

Fig. 2. Concentration time profile for the reactant and products in the catalytic hydrogenation of 2-chloroquinoline in the presence of 1,2-dichloroethane at 140 °C (1.5%, (♦); 11, (□); 12, (▲); 13, (△); 98.5%, (■); mixture of biquinoline derivatives, (●)).

begins right away but their decomposition is also fast. Under the conditions of Fig. 2, their amount rises to a maximum of 12% after 3 h, but it is reduced to 1.5% after 14 h.

The hydrogenation of 6-chloroquinoline (**4**) differs from that of **3** and the other chlorinated heterocycles studied, by the fact that a substantial amount of the chlorine containing 6-chloro-1,2,3,4-tetrahydroquinoline (**16**) is formed in the first isolable step. This compound is also a major product when **4** is hydrogenated by some other catalytic and non-catalytic methods (see e.g., Refs. [15,21–23]). After 4 h the reaction mixture consists of (in addition to 15% of **4** and 24% of **16**) 14% of **11**, 15% of **12**, 5% of **13** and 27% of the isomers of **14**. No biquinoline derivatives could be detected in this mixture. The hydrogenation of 1-chloroisoquinoline (**5**) proceeds rather slowly. After 4 h the isolable products were practically only 4% of isoquinoline (**17**) and 17% of 1,2,3,4-tetrahydroisoquinoline (**18**). However, after a prolonged heating (16.5 h) at 100 °C the product mixture consisted of 35% of **17**, 24% of **18**, as well as 13% of the 5,6,7,8-tetrahydroisoquinoline (**19**), 17% of the isomeric decahydroisoquinolines (**20**) and 5% of the transient dimmers having molecular masses of 260, 262 and 264. The latter was the major component of the bisoquinoline derivatives.

The immobilized Pd–$[Rh(cod)Cl]_2$ catalyst, **6**, has been suggested to operate by several mechanisms [24]. Notable are the reports by Angelici who suggested a spillover process [9], our own paper in which we disproved such a mechanism when the combined catalyst was entrapped within silica sol–gel [10], and the studies of Bianchini and his associates which proved that in the hydrogenation of benzene by a silica-supported Pd–Rh catalyst, both metals activate the substrates, and the Pd and Rh are linked to each other throughout the catalytic reaction [25]. Among these suggestions we found the one of Biachini and his group to fit best our observations. As in previous hydrodefunctionalization studies [8,11] we found the various hydrodechlorinations shown in Schemes 1–5 to be associated with synergism between the two different metal atoms. The reactions in the presence of **6** are not only faster than those in the presence of the immobilized Pd or $[Rh(cod)Cl]_2$ alone, but lead usually to a different product distribution. A representative example is demonstrated in the hydrogenations of 2-chloroquinoline in $(CH_2Cl)_2$ presented in Table 1.

ICP analyses indicated that the combined catalyst is perfectly leach-proof. We studied its recyclability at various temperatures in the hydrodehalogenation of 2-chloroquinoline (**3**) and found that even at 140 °C it does not lose any catalytic power for at least 5 runs. In a typical series of experiments at 140 °C we obtained (in the first 7 runs after 6 h) conversions of 51, 49, 55, 55, 52, 47 and 42%, respectively. Thereafter, the silica support deteriorated and the yield dropped sharply.

Table 1
Hydrogenation of 2-chloroquinoline (**3**) by **6** and by the different components of the sol–gel entrapped catalyst under comparable conditions[a].

Catalyst system	Metal in catalyst (mmol)		Percentage of **3** and products after 14 h (%)[b]					
	Pd	Rh	**3**	**11**	**12**	**13**	**14**	Dimers
Pd@sol–gel	0.095	–	74	17	9	–	–	–
$[Rh(cod)Cl]_2$@sol–gel	–	0.095	56	9	18	8	–	13
Pd–$[Rh(cod)Cl]_2$@sol–gel	0.080	0.015	–	–	35	23	41	1

[a] Reaction conditions: 2 mmol of **3** in 5 ml $(CH_2Cl)_2$; 100 °C; 27.6 bar H_2.
[b] The yields are average of at least two experiments that did not differ by more than ±3%. The missing percentages reflect on the unreacted starting compounds.

Since the hydrogenations of the chloroheterocyclic compounds are multi-step consecutive processes, complete kinetic studies are very complex. However, the analysis of the consumption of the starting substrates as function of time is straight forward. We measured the conversion of 2-chloroquinoline (**3**) and found that between 100 and 140 °C the reaction follows the first order rate law with corresponding k values at 100, 120 and 140 °C of 1.45×10^{-4}, 2.08×10^{-4} and $3.43 \times 10^{-4}\ s^{-1}$. These values were deduced from plots of $\ln(1-x)$ [x is the conversion of **3**] versus time. Trials to express our data in terms of either a zero or a second order rate law revealed that only the first order rate equation properly describes our observations. The data could be expressed as an Arrhenius plot which reveals an apparent activation energy E_a (hetero) = 6.55 kcal mol^{-1}. This value indicates that under our experimental conditions the hydrogenation of **3** is partially a diffusion controlled process [26].

4. Conclusions

The composite bimetallic sol–gel entrapped Pd–Rh catalyst **6** is demonstrated as an effective, selective and robust hydrogenation catalyst for detoxification of chlorinated nitrogen heterocycles such as, chloropyridine, chloroindole, chloroquinoline, and chloroisoquinoline. The process is stepwise in nature and typically the aromatic chlorine is removed first and the aromatic system is saturated in a consecutive step. The first step was shown to follow a first order rate law with activation energy of 6.55 kcal mol^{-1} suggesting the process is influenced by rate of the mass transfer. As the reaction mixture from which the immobilized catalyst had been removed by filtration proved inactive, it is assumed that the hydrodechorinations take place within the sol–gel particles and not in solution.

Acknowledgement

We gratefully acknowledge the support of this study by the Israel Science Foundation (ISF) through grant 296/06.

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