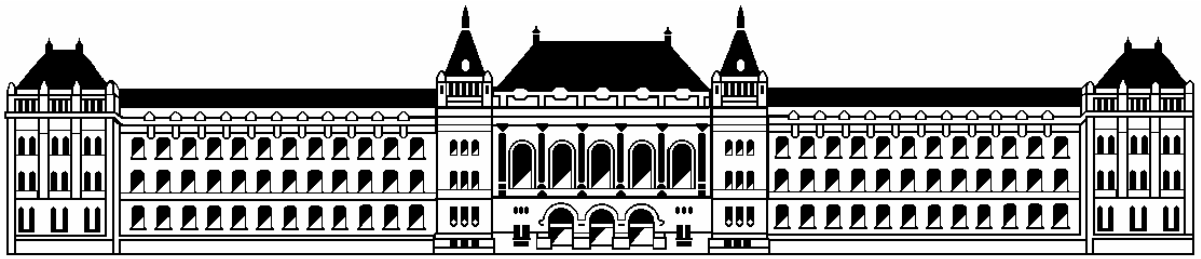

Department of Organic Chemical Technology
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General and industrially feasible synthesis of benyzlpiperidine and benzylpyrrolidine derivatives

Thesis

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2004

I. Introduction

N-Metyl-D-aspartate (NMDA) receptor antagonists are investigated as potential therapeutic agents for disease associated with neuronal acute and chronic excitotoxicity such as epilepsy and Parkinson's disease.

My PhD work is closely connected to the research of Gedeon Richter Ltd., which goal was to synthesise new NR2B selective NMDA receptor antagonists. To establish the relation between the chemical structure and the biological effect different substituted benzylpiperidines were necessary to be prepared. It was also necessary to examine the effect of the size of the pyridine ring on the biological effect of the final product. Furthermore, the effect of the elimination of the basic character of benzylpiperidine was also important to be determined.

In my PhD work I had to develop such methods for preparation benzylpiperidine and benzylpirrolidine derivatives that are scalable, general and industrially feasibly.

The first number in the general formulas mean the 4-, the middle number the 3- and the last one the 2 substituted pyridine or piperidine. The number of the formulas are the same as in the PhD dissertation itself.

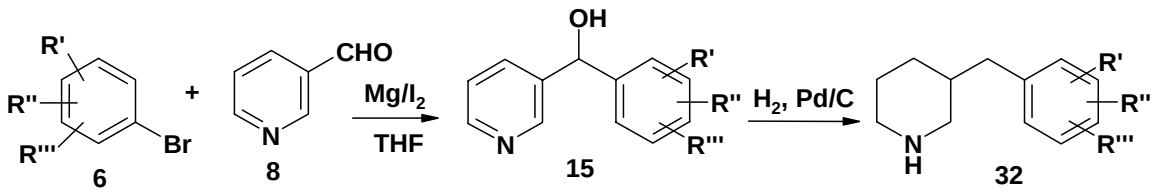
II. Methods of investigation

Preparative chemical methods were used during the research work. The products were analysed and identified by NMR, IR and GC-MS.

III. New scientific results

1. Synthesis of 3-benzylpiperidenes

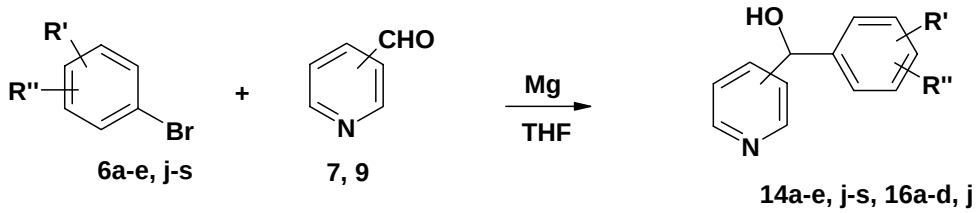
The Grignard-reactions of substituted bromobenzenes (6) and readily available pyridine-3-carboxaldehyde (5) provided aryl-3-pyridylmethanol (15) in moderate to good yields (60-86 %). The crude products were dissolved in glacial acetic acid and hydrogenated in the presence of 10% Pd/C (Montecatini) catalysts (pressure: 8-10 bar, temperature: 60-80 °C, yield: 62-91%, Scheme 1.).



Scheme 1.

2. Synthesis of 2- and 4-benzylpiperidines, I.

The Grignard-reactions of substituted bromobenzenes (6) and pyridine-4 and 2-carboxaldehyde gave the same good results (64-95 %), Scheme 2.)

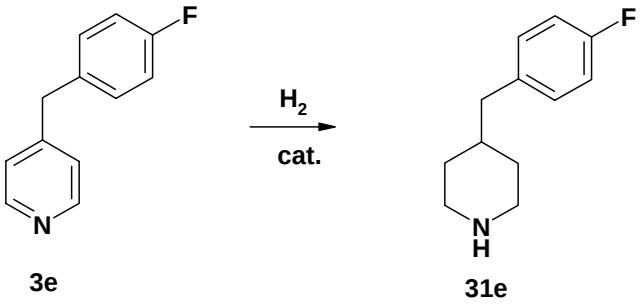


Scheme 2.

In the case of some derivatives the previous developed method – hydrogenation in glacial acetic acid at 60-80 °C – resulted in the formation of arylpiperidylmethanols besides or instead of the desired benyzlpiperidines. We concluded that the position of the benzylic group as well as the nature of the substituent on the aromatic group, have strong effect on the rate of dehydroxylation in the benzylic position. Consequently, we should have finished dehydroxylation before ring saturation is started.

3. Kinetical investigations

The effects of solvents, temperature, catalytic metals and amount of catalyst on the conversion and the rate of the hydrogenation of 4-(4-fluorobenzyl)pyridine were investigated (Scheme 3.).



Scheme 3.

Effect of solvents:

In non-acidic medium the saturation of the pyridine ring was very slow, presumably due to poisoning of the catalyst. Under acidic conditions the reductions were fast and complete after 0.8-1 h reaction time.

Influence of catalytic metals:

Using palladium, platinum or rhodium almost the same good activity was obtained, while ruthenium was practically ineffective in this hydrogenation.

Effect of amount of catalyst:

The linearity of the conversion "curves" seems to indicate, this hydrogenation reaction is zero-order with respect to the substrate. The initial rates were almost the same, which means that the rate-determining step of this hydrogenation is the hydrogenation reaction itself on the surface of the catalyst.

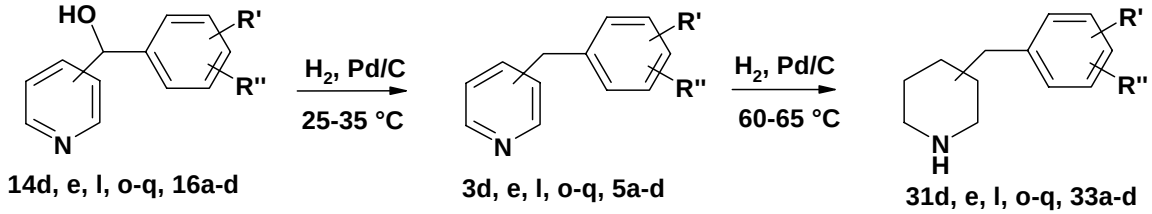
Effect of the temperature:

Decreasing the temperature from 70°C to 30°C the initial rate decreased by eight. On the basis of these results, the ending of the dehydroxylation can be expected before the pyridine ring saturation during the catalytic reduction of arylpyridylmethanols at lower temperature. After this the saturation of the pyridine ring should be carried out at 60 °C, at least, in order to obtain high reaction rate.

From the scope of Arrhenius plot, the apparent activation energy (ΔE_a) was calculated to be 45.3 $kJmol^{-1}$. This value of ΔE_a gives indication of that, the rate-controlling step in the hydrogenation is the surface chemical reaction itself.

4. Synthesis of 2- and 4-benzylpiperidines, II.

According to the results of the kinetical investigations we determined the optimum conditions for stepwise dehydroxylation and pyridine ring saturation. In the first step the dehydroxylation was carried out in protic solvent in the presence of mineral acid at ambient temperature. Then, in a separate reaction, benzylpyridines were transformed into the corresponding piperidine derivatives in glacial acidic acid (Scheme 4.).



14d, e, l, o-q, 16a-d **3d, e, l, o-q, 5a-d** **31d, e, l, o-q, 33a-d**

Scheme 4.

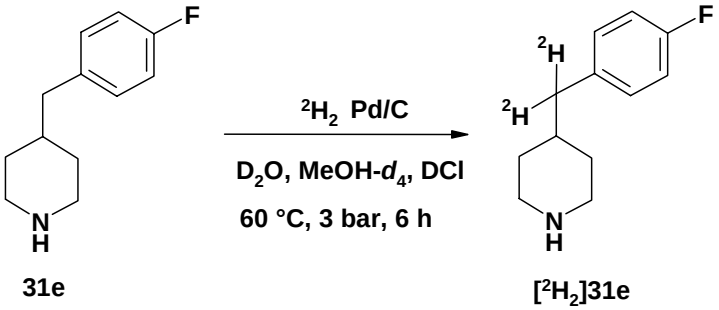
The separate and stepwise intermediate purification of the two reactions may cause waste of material, therefore we also developed a one-pot version of the process. Dehydroxylation of the substrates was accomplished with hydrogen in a vigorously stirred mixture of a protic solvent and mineral acid at 20-30 °C in the presence of Pd/C catalyst and, after consumption of 1 equiv. of hydrogen gas, the temperature of the reaction mixture was increased to 60-65 °C for pyridine ring saturation. Using this temperature-programmed catalytic hydrogenation process a series of Grignard adducts were transformed into the desired products (**31,33**) in good yield (62-83 %).

We established that our method is suitable for the reduction of arylpyridylmethanones, so not only the carbinols but also their oxidized analogues, the ketones can be the staring materials of our newly developed method for preparation benzylpiperidines. Of course, in that case the temperature must be increased after of 2 equiv. hydrogen gas.

A number of benzylpiperidines were prepared simply in two step procedure in a good yield. We should highlight the environmental advantages of the new method. We eliminated from the procedure such an environmentally dangerous materials like thionylchloride, triphenylphosphine, hydrazine, hydrogen iodide, hydrogen bromide etc. The aqueous phase contains only magnesium salts and the solvents of the Grignard-reaction and the hydrogenation and the catalyst can be recycled.

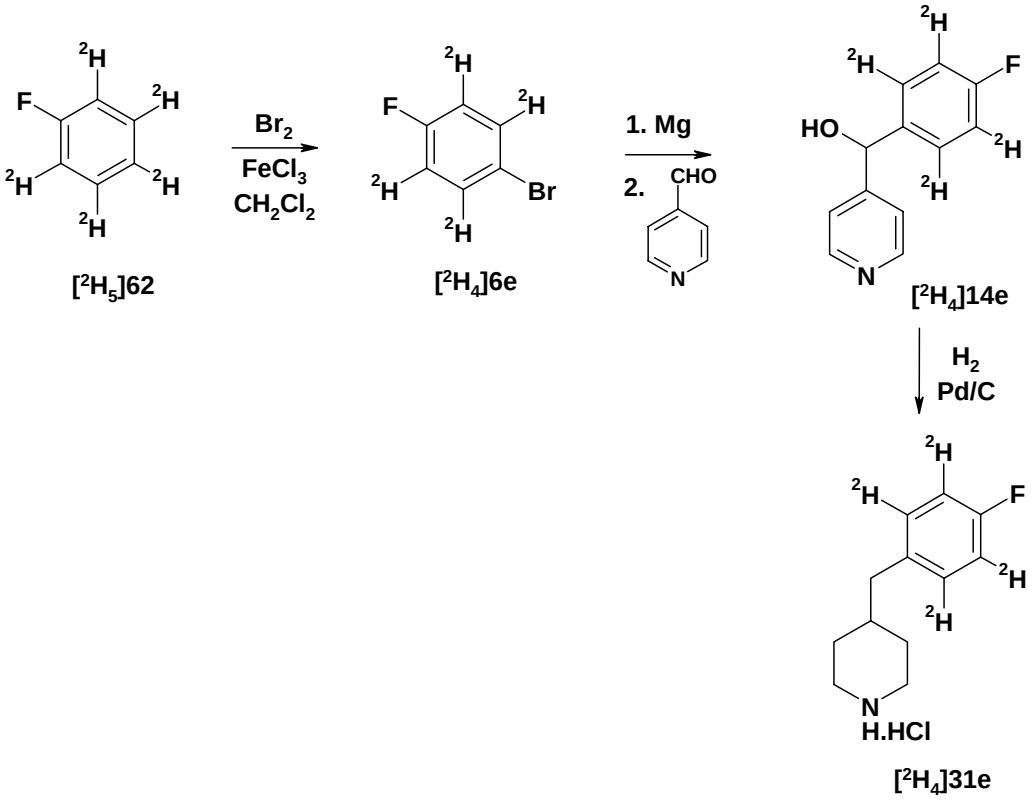
5. Synthesis of deuterium labelled benzylpiperidines

We concluded that because of the quick H/D exchange reaction in the presence of Pd/C catalyst the pyridine ring saturation with deuterium gas is not suitable for preparation isotopomerically pure products. We developed a method for H/D exchange in the benzylic position of benzylpiperidines and prepared d_2 and d_6 (d_4 isotopomer) isotopomers (Scheme 5.).



Scheme 5.

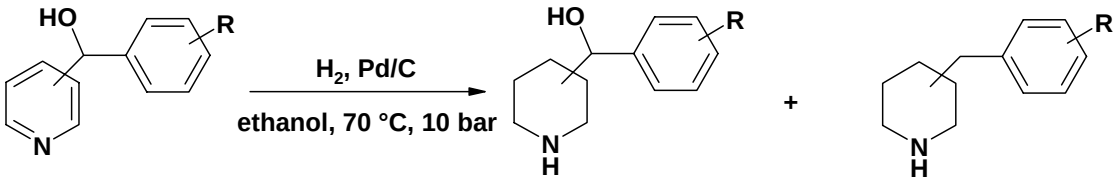
We established that our procedure for synthesis benzylpiperidines is suitable for preparation phenyl labelled d_4 derivative (Scheme 6.).



Scheme 6.

6. Synthesis of arylpiperidylmethanols

For preparation arylpiperidylmethanols we changed the condition of the reduction used in the synthesis of benzylpiperidines. To slow down the dehydroxylation of arylpyridinemethanols (**14, 15, 16**) we used ethanol as a solvent and the hydrogenation was carried out at 70 °C at 10 bar to speed the pyridine ring saturation (Scheme 7.).



14a, b, d, e, x
15a-e
16a-e

57a, b, d, e, x
58a-e
59a-e

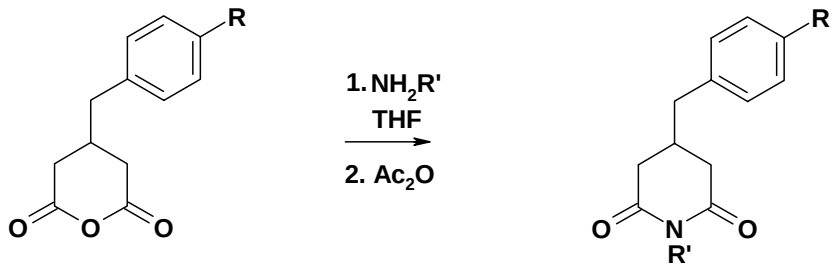
31a, b, d, e, x
32a-e
33a-e

Scheme 7.

The diastereomers of **59** were separated and via forming of bicyclic urethane the conformation of the main product was determined (the *erithro* conformer). The diastereomeric ratio was shifted by changing the reaction conditions.

7. Synthesis of benzylpiperidine-2,6-diones

To achieve the nonbasic nitrogen of the benyzlpiperidines benzylpiperidine-2,6-diones (**83, 84, 85, 86**) were produced. The method based on the cyclization of benzylglutaric anhydride (**82**) with different amines (Scheme 8.).



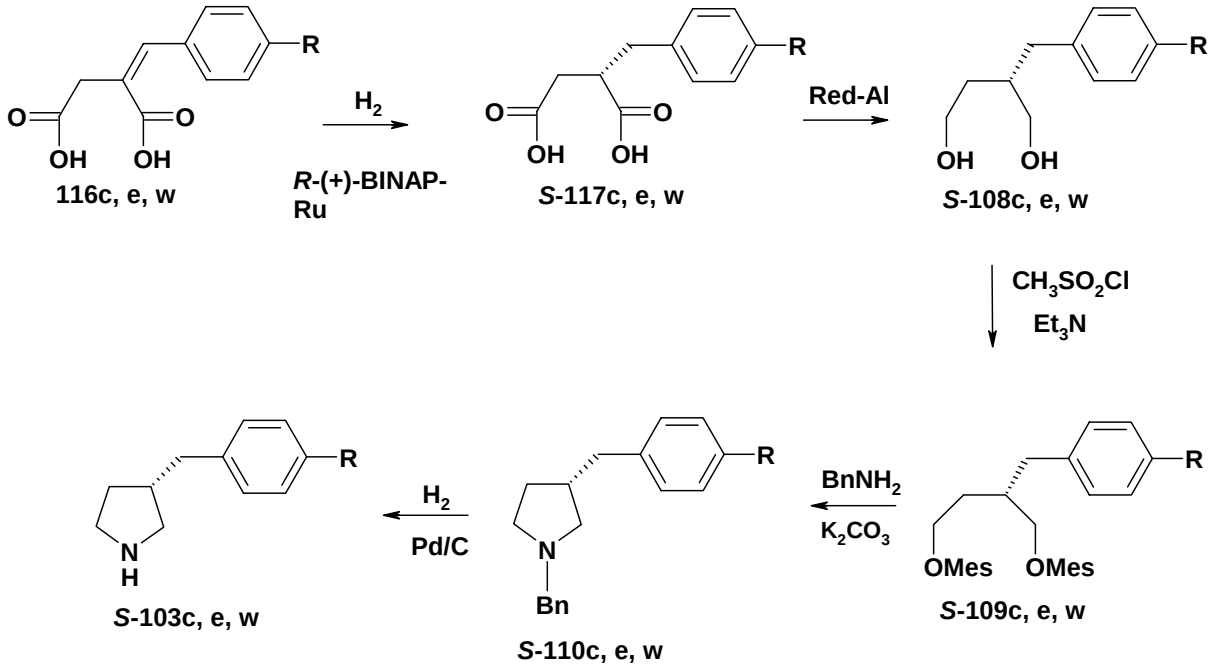
82a, c, e, w

83a, c, e, w
84a, c, e, w
85a, c, e, w
86a, c, e, w

Scheme 8.

8. Synthesis of benzylpyrrolidines

To establish the relation between the biological effect and the chemical structure we developed a method for synthesis of 3-benyzlpyrrolidines, based on the cyclization of 2-benzylbutane-1,4-diols, which provides more possibility for preparation enantiomerically pure benzylpyrrolidines. Than we worked out one of the opportunities, which was based on the asymmetric hydrogenation of arylidenesuccinic acid (Scheme 9.).



Scheme 9.

The general methods for preparation benzylpiperidines and benyzlpyrrolidines made the synthesis of a number of potential NR2B selective NMDA receptor antagonists possible. As a result of our work, the clinical investigation of one derivative is in progress.

Publications:

1. Ágai, B.; Nádor, A.; Proszenyák, Á.; Tárkányi, G.; Faigl, F. *Tetrahedron* **2003**, *59*, 7897-7900. A facile synthesis of 3-(substituted benzyl)piperidines

2. Ágai, B.; Proszenyák, Á.; Tárkányi, G.; Vida, L.; Faigl, F. *Eur. J. Org. Chem.* **2004**, 3623-3632. Convenient, Benign and Scalable Synthesis of 2- and 4-Substituted Benzylpiperidines

3. Proszenyák, Á.; Ágai, B.; Hegedűs, L.; Faigl, F. *Applied Cat. A: General* **2004**, *269*, 249-253. Hydrogenation of a 4-benzylpyridine derivative over supported precious metal catalysts

4. Barta-Szalai, G.; Borza, I.; Bozó, É.; Kiss, Cs.; Ágai, B.; Proszenyák, Á.; Keserű, M. Gy.; Gere, A.; Kolok, S.; Galgóczy, K.; Horváth, Cs.; Farkas, S.; Domány, Gy. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3953-3956. Oxamides as novel NR2B selective NMDA receptor antagonists

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Publication which is not connected with the PhD work:

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1. Proszenyák Ágnes, Nádor Adrienn, Tárkányi Gábor, Faigl Ferenc, Ágai Béla *Session of Heterocyclic Working Committee HAS* Balatonszemes, **2002**. Benzil-piperidinek racionális szintézise

2. Proszenyák Ágnes, Kállai Mariann, Tárkányi Gábor, Faigl Ferenc, Ágai Béla *25th Chemical Performing Days* Szeged, **2002.** Benzil-piperidinek racionális szintézise

3. Proszenyák Ágnes, Ágai Béla, Faigl Ferenc, Tárkányi Gábor, Kállai Mariann *7th International Chemical Symphosium TTS* Kolozsvár, 258-260. **2002.** Preventív környezetvédelem a gyógyszeripari intermedier gyártásban

4. Proszenyák Ágnes, Ágai Béla, Vida László, Tárkányi Gábor, Faigl, Ferenc *8th International Chemical Symphosium TTS* Kolozsvár, 262-264. **2003.** Fenil-piperidil-metanolok kemoszelektív redukciója

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1. Proszenyák Ágnes, Kállai Mariann, Ágai Béla, Tárkányi Gábor, Faigl Ferenc *Chemical Symphosium* Hajdúszoboszló, **2002**. Szubsztituáltbenzil-piperidinek új, racionális szintézise

2. Bartáné Szalai Gizella, Ágai Béla, Proszenyák Ágnes, Demeter Ádám, Kolok Sándor, Domány György *Chemical Symphosium* Hajdúszoboszló, **2002**. Új NR2B altípus szelektív NMDA receptor antagonisták

3. Proszenyák Ágnes, Ágai Béla, Tárkányi Gábor, Vida László, Faigl Ferenc *10th Belgian Organic Synthetic Symphosium*, Belgium, Louvain-La-Neuve, **2004.** Facile and convenient synthesis of benzylpiperidines and phenylpiperidylmethanols