



SYNTHESIS OF DIFFERENT HETEROCYCLIC COMPOUNDS IN THE PRESENCE OF A MICROPOROUS ZEOLITE

PhD theses

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1. Introduction

Nowadays an important target in the preparative organic chemistry is the development of new reagents and catalysts which are more active and selective than the traditional ones, they are easy to handle and reusable. The application of solid acids and bases (natural and modified clay minerals, montmorillonites, zeolites, mixed oxides, layered double hydroxides) is a significant aim from environmental point of view, too. They are environmentally-friendly materials. Finishing the reactions the catalyst can be recovered by simple filtration. There is no need for neutralization, so the salt- or base contamination of waste waters decreases and other corrosive factors do not appear. In addition, the filtered catalysts are usually reusable. They are cheap because of their natural origin and non-toxic, some of them could be used in medical treatments. Finally, because of their ordered cavernous structure in some reactions significant regio- or stereoselectivity could be obtained.

My research work was performed at the Budapest University of Technology and Economics, Department of Organic Chemical Technology. At department for many years there are examination of the applicability of different mineral-based reagents and catalysts in organic syntheses. During my PhD work I studied the application of a commercially available zeolite-type adsorbent family, Ersorb as catalysts in different condensation reactions. The aim of my work was not the characterization of the catalyst, but to find reactions in which the use of Ersorb adsorbents could be marketable in contrast with the traditional reagents.

Ersorb acid-resistant molecular sieve adsorbents (E) are produced by Erdökémia-ker Ltd, Hungary. The raw material of the procedure is a volcanic rock with 70 % clinoptylolite content. The different fractions of the adsorbents are made by milling and sieving from the natural raw material. The chemical and physical properties of the product are achieved by ionic exchanges and other water-phase technologies followed by a thermal treatment yielding adsorbents with variable pore sizes and variable catalytic properties. There are many variants of Ersorb adsorbents according to the different applications. Used products in the research work:

Ersorb-4 (E4):

Ca-K mixed cation-based acid-resistant clinoptylolite-type adsorbent with 4 Å pore size. It can adsorb only small molecules such as water, methanol, methane, hydrogen sulfide, ammonia or hydrochloric acid, so it is a widely used dryer in gas or liquid phase.

Ersorb-K (EK):

Potassium form of clinoptylolite. Its pore sizes are larger than in the case of E4. So it can adsorb organic molecules with two carbons such as ethanol.

Cation-free Ersorb (EA):

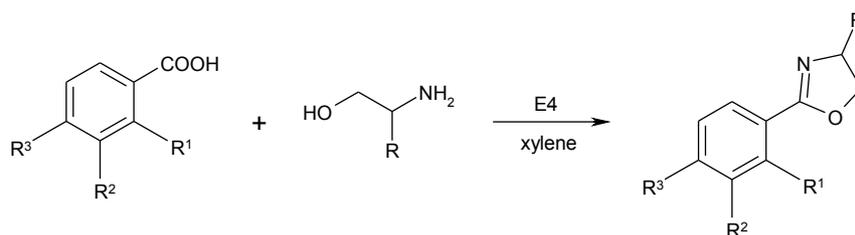
The original mineral is modified by ion exchange with ammonia followed by thermal treatment. After the ion exchange the amount of Fe and Al did not change significantly, but significant Ca, Mg and K exchange was observed. The treatment does not modify the surface acidity of the product but changes the structure of the pores and enhances the hydrogen chloride adsorbing ability.

Acidic modified Ersorb-4 (E4a):

The original E4 is modified by ionic exchange in order to increase the surface acidity. The pH of its aqueous suspension is about 3.

2. Results

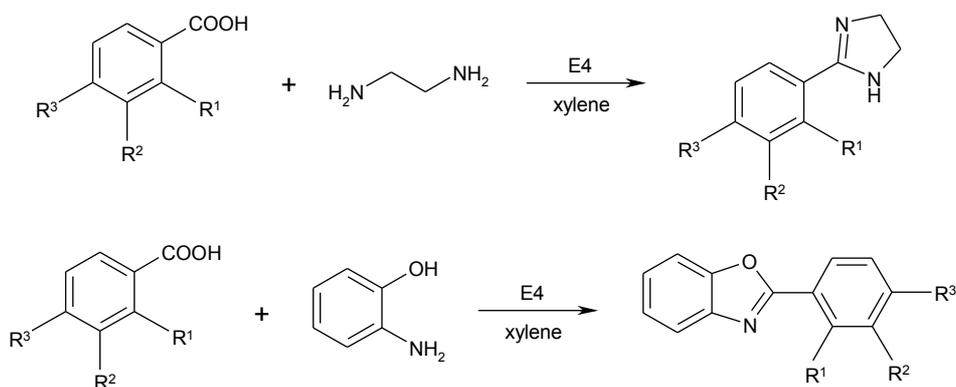
2.1. New, simple, one-pot synthesis of 2-substituted oxazolines was developed from β -aminoalcohols and aromatic carboxylic acids in the presence of weakly acidic E4 adsorbent.¹ The small aliphatic carboxylic acids – acetic acid and propionic acid – failed to give any product and completely destroyed the structure of E4. Aromatic carboxylic acids gave good results. According to the literature the cyclization of the *N*-acyl intermediate does not work spontaneously, Al_2O_3 catalyst is necessary at 350 °C for the synthesis of oxazoline derivatives.



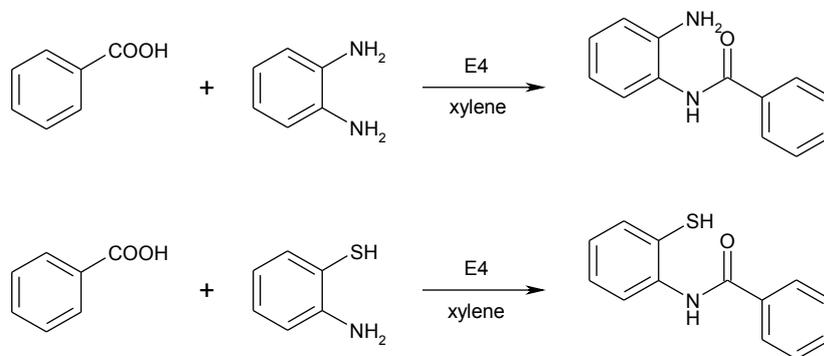
After a simple regeneration method (stirring in acetone at room temperature for 30 min following by drying at 120 °C for 4 h) E4 is reusable without significant loss of activity.

¹ Cwik, A.; Hell, Z.; Hegedüs, A.; Finta, Z.; Horváth, Z. *Tetrahedron Lett.* **2002**, 43, 3985.

2.2. According to the synthesis of oxazoline derivatives a new method was developed for the synthesis of 2-arylimidazolines and 2-arylbenzoxazoles with good yield.² No significant substituent effects were found and no considerable amounts of by-products were observed. After regeneration the filtered catalyst can be easily recycled without significant loss of activity.

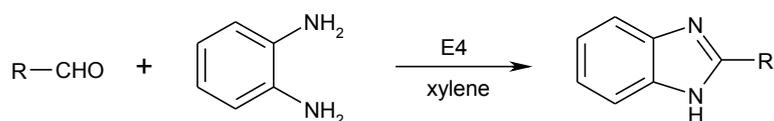


The reaction of *o*-phenylenediamine or *o*-aminothiophenol with benzoic acid gave only the monoamide intermediates. Compounds containing sulfur destroyed the structure of E4.



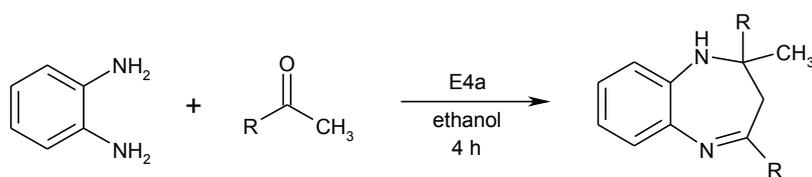
² Hegedüs, A.; Vigh, I.; Hell, Z. *Heteroatom Chem.* **2004**, *15*, 428.

- 2.3. The reaction of *o*-phenylenediamine and aldehydes in the presence of E4 resulted the appropriate benzimidazole derivatives with good yield.³



The catalyst could be easily recycled without significant loss of activity, but only after 2 h boiling in ethanol followed by drying at 120 °C for 4 h instead of stirring in acetone at room temperature to remove the tarry materials from the catalyst surface.

- 2.4. I have successfully performed the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and ketones in the presence of E4a.⁴ All reactions gave the appropriate 2,3-dihydro-1*H*-1,5-benzodiazepine derivatives in good yield.

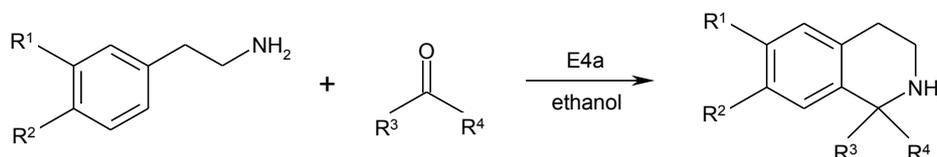


Both aliphatic and aromatic ketones reacted similarly. In case of non-symmetric aliphatic ketones the reaction was regioselective differently from using other catalysts described in the literature, the 3-substituted isomer was not detected in the reaction mixture. The filtered catalyst could be recycled without regeneration, too.

³ Hegedüs, A.; Hell, Z.; Potor, A. *Synth. Commun.* **2006**, *36*, 3625.

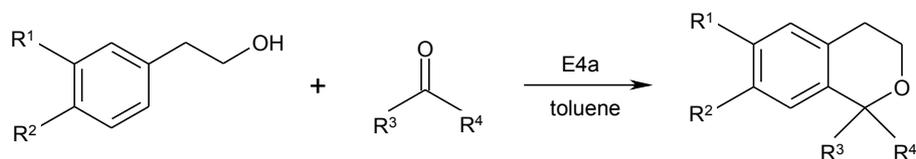
⁴ Hegedüs, A.; Hell, Z.; Potor, A. *Catal. Lett.* **2005**, *105*, 229.

2.5. I have developed a new method for the one-pot Pictet-Spengler reaction using E4a catalyst.⁵ The reaction time was significantly shorter than in the case of other catalysts described in the literature. The appropriate 1,2,3,4-tetrahydroisoquinolines were obtained quantitatively.



Using E4 adsorbent as catalyst instead of E4a the conversion significantly decreased. Using the more acidic KP10 montmorillonite catalyst in the reaction, no product was obtained. Aliphatic ketones and aldehydes also gave the tetrahydroisoquinoline derivatives, but with poorer yield. The filtered catalyst could be recycled and reused with good results.

2.6. I have worked out the synthesis of isochromans via the oxa-Pictet-Spengler reaction from 2-phenylethanols and aldehydes or ketones in the presence of E4a.⁶ Also in the case of not activated 2-phenylethanol the reaction gave isochromans with high yield.

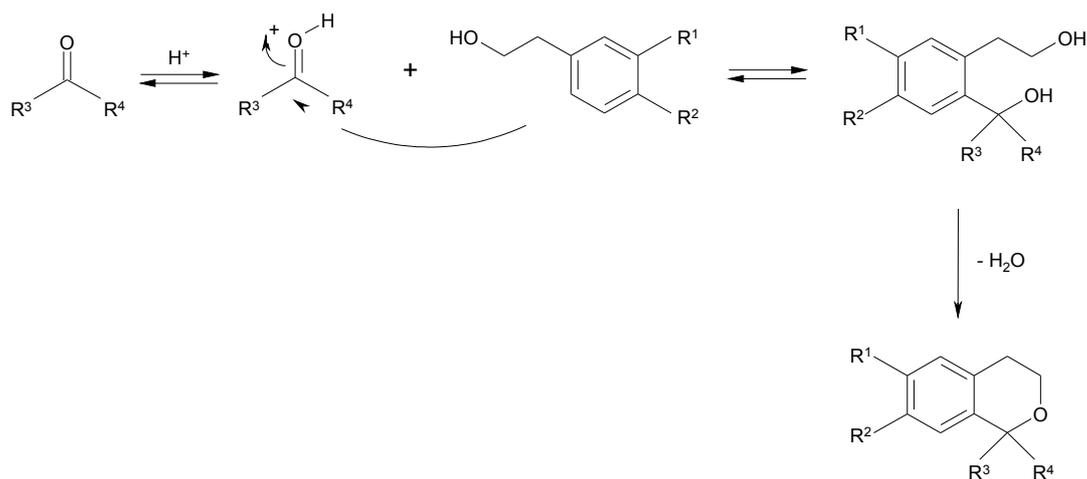


The catalyst could be easily removed by filtration from the reaction mixture, and after regeneration could be reused without loss of activity.

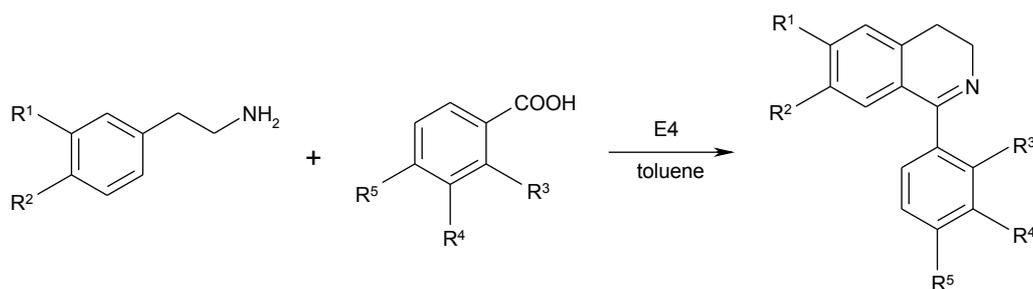
A new, two-step mechanism was proposed for the oxa-Pictet-Spengler reaction catalyzed by zeolite. The first step is an electrophilic aromatic substitution, and the intermediate thus formed loses water yielding the isochroman.

⁵ Hegedüs, A.; Hell, Z. *Tetrahedron Lett.* **2004**, *45*, 8553.

⁶ Hegedüs, A.; Hell, Z. *Org. Biomol. Chem.* **2006**, *4*, 1220.

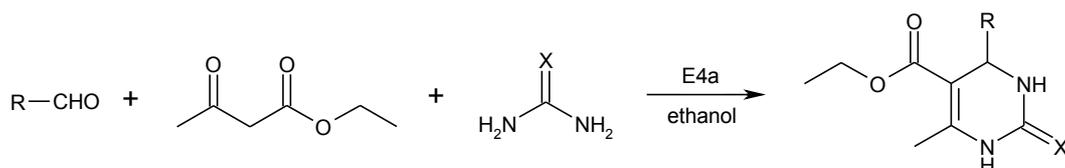


2.7. I have developed a new method for the Bischler-Napieralski reaction.⁷ Using E4 adsorbent instead of previously used harmful catalysts with strong acidic character 3,4-dihydroisoquinolines were obtained from carboxylic acids and β -phenylethylamines in excellent yield.



There was no significant substituent effect of the carboxylic acid observed in the reactions, but activating groups on the amine component significantly decreased the reaction time required for the good conversion. In all cases the appropriate isoquinolines were obtained in high yield. The catalyst could be easily regenerated and reused in this reaction, too.

2.8. A new, simple, environmentally-friendly synthesis of dihydropyrimidinones was developed using E4a adsorbent as catalyst via three-component one-pot Biginelli reaction.⁸



⁷ Hegedüs, A.; Hell, Z.; Potor, A. *Catal. Commun.* **2006**, 7, 1022.

⁸ Hegedüs, A.; Hell, Z.; Vigh, I. *Synth. Commun.* **2006**, 36, 129.

Aromatic and aliphatic aldehydes gave similar results. When a weakly acidic E4 was used instead of E4a in the reaction, the yield was significantly poorer. The catalyst filtered from the reaction mixture also gave good results after regeneration.

3. Publications

3.1. Published articles on the subject of the dissertation

1. Cwik, A.; Hell, Z.; Hegedüs, A.; Finta, Z.; Horváth, Z.
A simple synthesis of 2-substituted oxazolines and oxazines
Tetrahedron Lett. **2002**, *43*, 3985. (IF: 2,357)
2. Hegedüs, A.; Vigh, I.; Hell, Z.
Zeolite-catalyzed simple synthesis of different heterocyclic rings, Part 2
Heteroatom Chem. **2004**, *15*, 428. (IF: 0,830)
3. Hegedüs, A.; Hell, Z.; Potor, A.
Zeolite-catalyzed environmentally-friendly synthesis of benzimidazole derivatives
Synth. Commun. **2006**, *36*, 3625. (IF: 0,965)
4. Hegedüs, A.; Hell, Z.; Potor, A.
A simple environmentally-friendly method for the selective synthesis of 1,5-benzodiazepine derivatives using zeolite catalyst
Catalysis Lett. **2005**, *105*, 229. (IF: 1,904)
5. Hegedüs, A.; Hell, Z.
One-step preparation of 1-substituted tetrahydroisoquinolines via the Pictet-Spengler reaction using zeolite catalysts
Tetrahedron Lett. **2004**, *45*, 8553. (IF: 2,484)
6. Hegedüs, A.; Hell, Z.
Zeolite-catalyzed simple synthesis of isochromans via the oxa-Pictet-Spengler reaction
Org. Biomol. Chem. **2006**, *4*, 1220. (IF: 2,19)
7. Hegedüs, A.; Hell, Z.; Potor, A.
A new, environmentally-friendly method for the Bischler-Napieralski cyclization using zeolite catalyst
Catal. Commun. **2006**, *7*, 1022. (IF: 1,878)
8. Hegedüs, A.; Hell, Z.; Vigh, I.
Convenient one-pot heterogeneous catalytic method for the preparation of 3,4-dihydropyrimidin-2(*IH*)-ones
Synth. Commun. **2006**, *36*, 129. (IF: 0,965)

3.2. Further published articles

1. Hegedüs, A.
A new efficient zeolite catalyst in organic syntheses
Periodica Polytechnica **2001**, *45*, 63. (IF: -)
2. Hegedüs, A.; Cwik, A.; Hell, Z.; Horváth, Z.; Esek, Á.; Uzsoki, M.
Microwave assisted conversion of oximes into nitriles in the presence of a zeolite
Green Chem. **2002**, *4*, 618. (IF: 2,547)
3. Hegedüs, A.; Vígh, I.; Hell, Z.
Zeolite-catalyzed environmentally-friendly tetrahydropyranylation of alcohols and phenols
Synth. Commun. **2004**, *32*, 4145. (IF: 0,965)
4. Hegedüs, A.; Hell, Z.
Zeolite-catalyzed Pechmann synthesis of coumarins
Catalysis Lett. **2006**, *112*, 105. (IF: 1,904)
5. Hegedüs, A.; Hell, Z.; Vargadi, T.; Potor, A.; Gresits, I.
A new simple synthesis of 1,2-dihydroquinolines via cyclocondensation using zeolite catalyst
Catalysis Lett. **2007**, *117*, 99. (IF: 1,904)

3.3. Conference publications

1. EMT VIII. Nemzetközi Vegyészkonferencia Kolozsvár, 2002. november 15-17.
Hegedüs, A. Ásványi alapú katalizátorok aktivitásának vizsgálata szerves szintézisekben 121-125. old.
2. XXVII. Kémiai Előadói Napok Szeged, 2004. október 25-27.
Hegedüs, A.; Hell, Z. Mikropórusos zeolit felhasználása heterociklusos vegyületek szintézisében 54-58. old.
3. EMT X. Nemzetközi Vegyészkonferencia Kolozsvár, 2004. november 12-14.
Hegedüs, A.; Hell, Z. Kis pórusmértű zeolit alkalmazása szerves kémiai reakciókban 224-227. old.
4. EMT XI. Nemzetközi Vegyészkonferencia Kolozsvár, 2005. november 11-13.
Potor, A.; Hegedüs, A.; Hell, Z. Heterociklusos vegyületek előállítása zeolit alapú katalizátorok jelenlétében 285-288. old.