

Zeolite-Catalyzed Simple Synthesis of Different Heterocyclic Rings, Part 2

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ABSTRACT: A simple and environmentally friendly synthesis was developed for the preparation of 2-arylimidazoline derivatives and 2-arylbenzoxazole derivatives using a small pore size zeolite. The similar reaction was not applicable to the preparation of the sulfur-containing analogs cysteamine or 2-aminothiophenol, probably because of a disadvantageous reaction between the zeolite and the thio compound. © 2004 Wiley Periodicals, Inc. *Heteroatom Chem* 15:428–431, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20036

INTRODUCTION

The examination of the applicability of different mineral-based reagents and catalysts in organic syntheses seems to be an important branch of the research work in the preparative organic chemistry even from the practical point of view. The application of solid acids and bases (natural and modified clay minerals, montmorillonites, zeolites, mixed oxides, layered double hydroxides) is a significant aim from the environmental point of view, too, since this way the salt and acid–base contamination of industrial waste waters appearing in the workup of the reaction mixtures containing liquid acids and bases could be avoided. In most cases these substances can

be recovered from the reaction mixture and reused with good results.

During our work with a zeolite-type small pore size adsorbent, Ersorb-4 (E4), we investigated the cyclization of benzoic acid derivatives with β -aminoalcohols. We obtained the appropriate oxazoline derivatives **3** in a simple reaction with good yield [1] (Scheme 1).

RESULTS AND DISCUSSION

The 2-arylimidazoline derivatives are important compounds because of their pharmaceutical activity [2]. The methods described for their preparation in the literature are based on the condensation of ethylenediamine or its salt [3] with benzonitrile in the presence of ZnCl_2 and NH_4Cl [4], P_2S_5 [5], with ethyl benzoate [6], or with benzoic acid in the presence of Ph_3P and Et_3N [7]. Some of these methods require reagents that are dangerous for the environment, or during the workup the safe disposal of the reagents is tedious. Thus, the development of a simple new method seemed to be useful from the environmental point of view, too.

We investigated whether our method developed for the preparation of oxazolines could be adapted for the preparation of imidazolines. The reaction of benzoic acid with ethylenediamine (**4**) in the presence of E4 in boiling xylene resulted in the formation of 2-phenylimidazoline (**5a**) in 73% yield. For changes of the reaction parameters insignificant changes in the yield were observed. Thus, when the reaction was conducted in boiling toluene, instead of xylene, the yield decreased to 71%

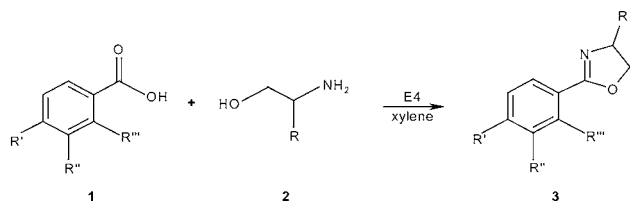
For Part one, see Ref. [1].

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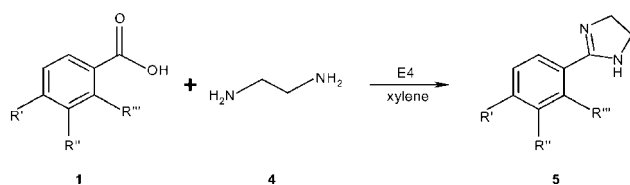
SCHEME 1

while when the reaction time was reduced to 3 h, 66% of **5a** were obtained. The catalyst can be easily recycled without significant loss of activity (73 and 69% in the first and second experiment, respectively). The reaction of substituted benzoic acids with ethylenediamine (Scheme 2) also yielded the appropriate substituted 2-phenylimidazolines with good yield (see Table 1). No significant substituent effects were found, and no considerable amount of by-products was observed.

Reaction of phenylacetic acid (**6**) with ethylenediamine gave the α -blocker tolazoline (**7**) with 69% yield (Scheme 3).

For the appropriate thiazoline compounds, cysteamine (**8**) was reacted in boiling xylene with benzoic acid, but the expected product was not obtained even after longer heating. In the reaction under normal atmospheric conditions, cystamine-bis-amide (**9**) was the product, while using Ar atmosphere we isolated cysteamine amide (**10**) from the reaction mixture (Scheme 4) In these reactions cysteamine destroyed the structure of E4.

We investigated the preparation of the appropriate condensed heterocycles, too. Replacing 2-aminoethanol with *o*-aminophenol (**11**) under the same conditions, the benzoxazole derivatives (**12**) were obtained (Scheme 5) with good yield (see Table 2), except in case of salicylic acid, where no product could be isolated. Surprisingly *o*-phenylenediamine (**13**) and *o*-aminothiophenol (**15**) gave only the monoamides **14** and **16**, respectively (Schemes 6 and 7). In the first case the lack of the dehydration might be explained with solubility problems; the amide precipitated from the reaction mixture. In the latter case the thiophenol, similarly to the cysteamine, destroyed the zeolite.



SCHEME 2

TABLE 1 Reaction of Ethylenediamine with Aromatic Carboxylic Acids 1

	<i>R'</i>	<i>R''</i>	<i>R'''</i>	Yield (%)
5a	H	H	H	73
5b	Cl	H	H	43
5c	H	H	CH ₃	71
5d	CH ₃	H	H	73
5e	(CH ₃) ₃ C	H	H	65
5f	CH ₃ O	NO ₂	H	73
5g	H	H	OCOCH ₃	59
5h	H	H	OH	62

EXPERIMENTAL

All compounds were characterized by ¹H NMR spectroscopy. Spectra were made on Bruker AW-250 (250 MHz) spectrometer in CDCl₃ using TMS as the internal standard. The spectral and physical data of the known compounds were identical with those reported in the literature.

The commercial chemicals were purchased from Merck-Hungary Ltd., except for E4, which is the product of Erdőkémia-ker Ltd., Hungary.

Pretreatment of the Catalyst

Before the experiments, a sample of E4 was powdered and heated at 120°C for 2 h.

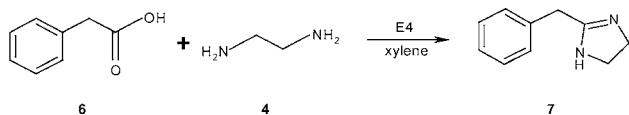
Typical Procedure for the Preparation of 2-Arylimidazolines (**5**)

A mixture of **1** (5 mmol), ethylenediamine (**4**) (5 mmol, 0.3 g, 0.31 mL), and 0.8 g E4 was heated at 130°C for 5 h. The solid was then filtered out and washed with acetone; the filtrate was evaporated and the residue was characterized.

2-Phenylimidazoline (5a). White solid, mp 149–151°C (lit. 147–149°C [8]). ¹H NMR (CDCl₃, ppm): δ 3.7 (t, 4H, CH₂), 4.8 (t, 1H, NH), 7.2–7.6 (m, 3H, Ar), 7.8 (m, 2H, Ar). Anal. Found: C, 73.79; H, 6.81;

TABLE 2 Reaction of *o*-Aminophenol with Aromatic Carboxylic Acids 1

	<i>R'</i>	<i>R''</i>	<i>R'''</i>	Yield (%)
12a	H	H	H	73
12b	Cl	H	H	64
12c	(CH ₃) ₃ C	H	H	89
12d	H	H	CH ₃	77
12e	CH ₃	H	H	75
12f	H	H	OH	—



SCHEME 3

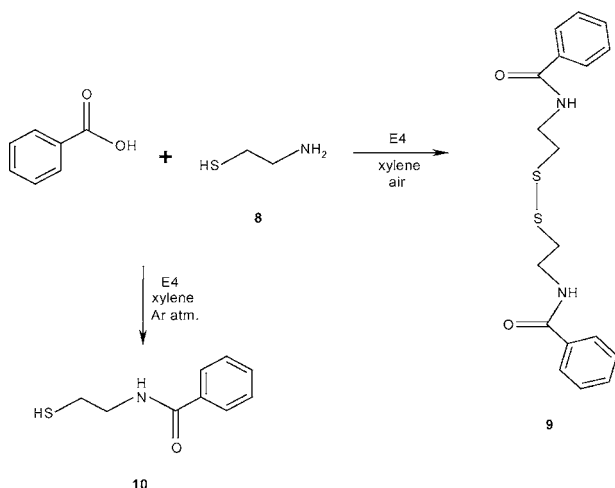
N, 19.28%. Calcd for (C₉H₁₀N₂): C, 73.94; H, 6.89; N, 19.16%.

2-(4-Chlorophenyl)-imidazoline (5b). Yellowish solid, mp 190–193°C (lit. 186–187°C [9]). ¹H NMR (CDCl₃, ppm): δ 3.6 (t, 4H, CH₂), 4.8 (t, 1H, NH), 7.2–7.7 (m, 4H, Ar). Anal. Found: C, 59.93; H, 5.21; N, 15.39%. Calcd for (C₉H₉N₂Cl): C, 59.84; H, 5.02; N, 15.51%.

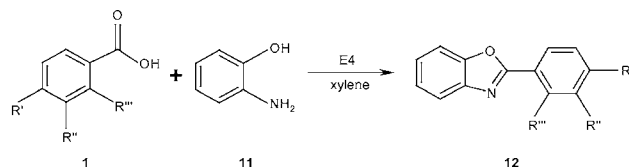
2-(2-Methylphenyl)-imidazoline (5c). Yellowish solid, mp 115°C (lit. 85–86°C [9]). ¹H NMR (CDCl₃, ppm): δ 2.3 (s, 3H, CH₃), 3.6 (t, 4H, CH₂), 4.7 (t, 1H, NH), 7.0–7.4 (m, 3H, Ar), 7.7 (d, 1H, Ar). Anal. Found: C, 75.11; H, 7.45; N, 17.51%. Calcd for (C₁₀H₁₂N₂): C, 74.97; H, 7.55; N, 17.48%.

2-(4-Methylphenyl)-imidazoline (5d). Yellowish solid, mp 179–181°C (lit. 178–179°C [9]). ¹H NMR (CDCl₃, ppm): δ 2.2 (s, 3H, CH₃), 3.7 (t, 4H, CH₂), 4.8 (t, 1H, NH), 7.0–7.3 (m, 2H, Ar), 7.8 (dd, 2H, Ar). Anal. Found: C, 74.82; H, 7.67; N, 17.39%. Calcd for (C₁₀H₁₂N₂): C, 74.97; H, 7.55; N, 17.48%.

2-(4-tert-Butylphenyl)-imidazoline (5e). White solid, mp 191–193°C. ¹H NMR (CDCl₃, ppm): δ 1.3 (s, 9H, CH₃), 3.6 (dt, 4H, CH₂), 4.8 (t, 1H, NH), 7.1–7.4 (m, 2H, Ar), 7.8 (dd, 2H, Ar). Anal. Found:



SCHEME 4



SCHEME 5

C, 77.01; H, 9.08; N, 13.92%. Calcd for (C₁₃H₁₈N₂): C, 77.18; H, 8.97; N, 13.85%.

2-(4-Methoxy-3-nitrophenyl)-imidazoline (5f). Yellow solid, mp 194–196°C. ¹H NMR (CDCl₃, ppm): δ 3.5 (t, 4H, CH₂), 3.9 (s, 3H, CH₃), 4.7 (t, 1H, NH), 7.2 (d, 1H, Ar), 7.9 (d, 1H, Ar), 8.3 (s, 1H, Ar). Anal. Found: C, 54.11; H, 5.19; N, 19.06%. Calcd for (C₁₀H₁₁N₃O₃): C, 54.30; H, 5.01; N, 18.99%.

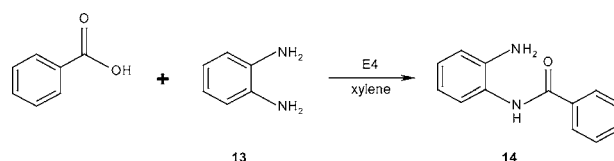
2-(2-Acetoxyphenyl)-imidazoline (5g). Oil. ¹H NMR (CDCl₃, ppm): δ 2.8 (s, 3H, CH₃), 3.6 (t, 4H, CH₂), 4.7 (t, 1H, NH), 7.3 (dd, 2H, Ar), 7.8 (d, 1H, Ar), 8.1 (d, 1H, Ar). Anal. Found: C, 64.81; H, 5.99; N, 13.58%. Calcd for (C₁₁H₁₂N₂O₂): C, 64.69; H, 5.92; N, 13.72%.

2-(2-Hydroxyphenyl)-imidazoline (5h). Yellowish solid, mp 211–212°C (lit. 214–216°C [10]). ¹H NMR (CDCl₃, ppm): δ 3.7 (dt, 4H, CH₂), 4.8 (t, 1H, NH), 5.4 (s, 1H, OH), 7.1–7.7 (m, 4H, Ar). Anal. Found: C, 66.81; H, 6.09; N, 17.19%. Calcd for (C₉H₁₀N₂O): C, 66.65; H, 6.21; N, 17.27%.

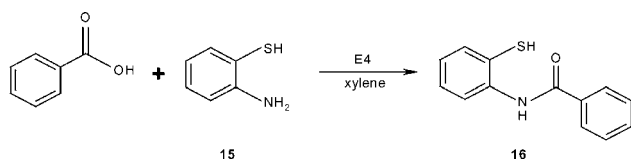
2-Benzylimidazoline (7). ¹H NMR (CDCl₃, ppm): δ 3.6 (m, 6H, CH₂), 4.4 (t, 1H, NH), 7.4 (m, 5H, Ar). Anal. Found: C, 72.81; H, 8.29; N, 18.99%. Calcd for (C₉H₁₂N₂): C, 72.94; H, 8.16; N, 18.90%.

Typical Procedure for the Preparation of 2-Arylbenzoxazole (12)

A mixture of **1** (5 mmol), *o*-aminophenol (**11**) (5 mmol, 0.55 g) and 0.8 g E4 in xylene was heated at 130°C for 5 h. The solid was then filtered out and washed with acetone; the filtrate was evaporated and the residue was characterized.



SCHEME 6



SCHEME 7

2-Phenylbenzoxazole (12a). Yellowish solid, mp 107°C (lit. 109–110°C [11]). ¹H NMR (CDCl₃, ppm): δ 7.3–7.6 (m, 5H, Ar), 7.8 (dd, 2H, Ar), 8.1 (m, 2H, Ar). Anal. Found: C, 79.83; H, 4.79; N, 7.25%. Calcd for (C₁₃H₉NO): C, 79.98; H, 4.65; N, 7.17%.

2-(4-Chlorophenyl)-benzoxazole (12b). Yellowish solid, mp 152°C (lit. 151–152°C [12]). ¹H NMR (CDCl₃, ppm): δ 7.4–7.6 (m, 4H, Ar), 7.8–8.0 (m, 4H, Ar). Anal. Found: C, 68.07; H, 3.59; N, 6.01%. Calcd for (C₁₃H₈NOCl): C, 67.99; H, 3.51; N, 6.10%.

2-(4-tert-Butylphenyl)-benzoxazole (12c). Yellowish solid, mp 105°C (lit. 105°C [13]). ¹H NMR (CDCl₃, ppm): δ 1.2 (s, 9H, CH₃), 7.2–7.7 (m, 4H, Ar), 7.9 (m, 4H, Ar). Anal. Found: C, 81.10; H, 6.89; N, 5.63%. Calcd for (C₁₇H₁₇NO): C, 81.24; H, 6.82; N, 5.57%.

2-(2-Methylphenyl)-benzoxazole (12d). Yellowish solid, mp 71°C (lit. 69°C [14]). ¹H NMR (CDCl₃, ppm): δ 2.4 (s, 3H, CH₃), 7.3–7.5 (m, 5H, Ar), 7.8–8.0 (m, 3H, Ar). Anal. Found: C, 80.19; H, 5.37; N, 6.87%. Calcd for (C₁₄H₁₁NO): C, 80.36; H, 5.30; N, 6.69%.

2-(4-Methylphenyl)-benzoxazole (12e). Yellowish solid, mp 117°C (lit. 116–117°C [15]). ¹H NMR (CDCl₃, ppm): δ 2.2 (s, 3H, CH₃), 7.2–7.7 (m, 4H, Ar), 8.0 (m, 4H, Ar). Anal. Found: C, 80.17; H, 5.42; N, 6.75%. Calcd for (C₁₄H₁₁NO): C, 80.36; H, 5.30; N, 6.69%.

N,N'-(3,4-Dithia-hexanedityl)-bis-benzamide (9). Yellow solid, mp 130°C (lit. 132–133°C [16]).

N-(2-Mercapto-ethyl)-benzamide (10). Yellow solid, mp 72°C (lit. 70–71°C [17]).

N-(2-Aminophenyl)-benzamide (14). Yellowish solid, mp 148–150°C (lit. 150–152°C [18]).

N-(2-Mercapto-phenyl)-benzamide (15). Yellow solid, mp 107–108°C (lit. 109–110°C [19]).

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