Heteroatom Chemistry
Volume 15, Number 6, 2004

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

Adrienn Hegedüs, Ilona Vígh, and Zoltán Hell

*Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary*

*Received 20 May 2004*

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.

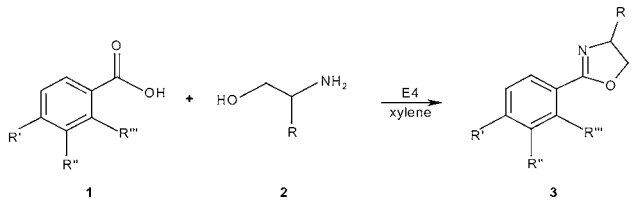
During our work with a zeolite-type small pore size adsorbent, Ersorb-4 (E4), we investigated the cyclization of benzoic acid derivatives with β-aminoalcohols. We obtained the appropriate oxazoline derivatives **3** in a simple reaction with good yield [1] (Scheme 1).

## *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].
*Correspondence to:* Zoltán Hell; e-mail: zhell@mail.bme.hu.
Contract grant sponsor: Hungarian Research Fund Programs.
Contract grant number: OTKA T 037757.



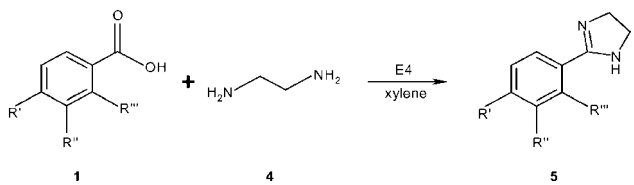

**SCHEME 1**

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**

| | *R′* | *R″* | *R‴* | *Yield (%)* |
|---|---|---|---|---|
| **5a** | H | H | H | 73 |
| **5b** | Cl | H | H | 43 |
| **5c** | H | H | $CH_3$ | 71 |
| **5d** | $CH_3$ | H | H | 73 |
| **5e** | $(CH_3)_3C$ | H | H | 65 |
| **5f** | $CH_3O$ | $NO_2$ | H | 73 |
| **5g** | H | H | $OCOCH_3$ | 59 |
| **5h** | H | H | OH | 62 |

## *EXPERIMENTAL*

All compounds were characterized by $^1$H NMR spectroscopy. Spectra were made on Bruker AW-250 (250 MHz) spectrometer in $CDCl_3$ using TMS as the internal standard. The spectral and physical data of the known compunds 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.

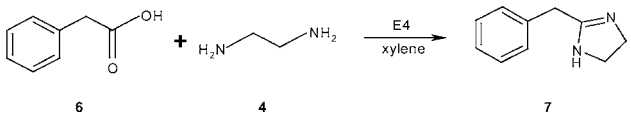
### *Typical Procedure for the Preparation of 2-Arylimidazolines (**5**)*

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]). $^1$H NMR ($CDCI_3$ ppm): $\delta$ 3.7 (t, 4H, $CH_2$ 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**

| | *R′* | *R″* | *R‴* | *Yield (%)* |
|---|---|---|---|---|
| **12a** | H | H | H | 73 |
| **12b** | Cl | H | H | 64 |
| **12c** | $(CH_3)_3C$ | H | H | 89 |
| **12d** | H | H | $CH_3$ | 77 |
| **12e** | $CH_3$ | H | H | 75 |
| **12f** | H | H | OH | — |




6 4 7

SCHEME 3

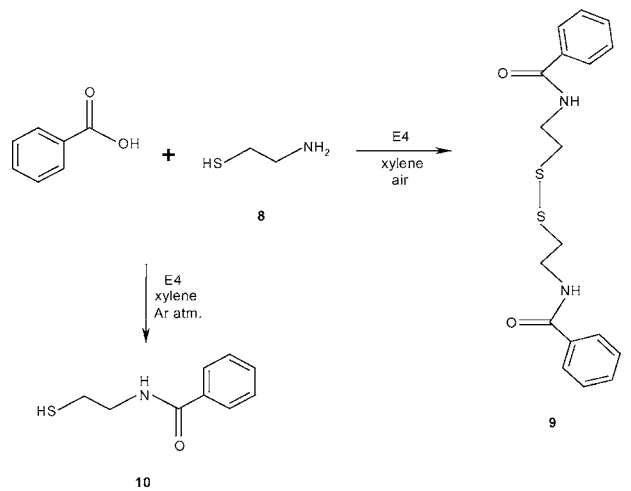
N, 19.28%. Calcd for ($C_9H_{10}N_2$): C, 73.94; H, 6.89; N, 19.16%.

*2-(4-Chlorophenyl)-imidazoline* (**5b**). Yellowish solid, mp 190–193°C (lit. 186–187°C [9]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 3.6 (t, 4H, $CH_2$), 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 ($C_9H_9N_2Cl$): C, 59.84; H, 5.02; N, 15.51%.

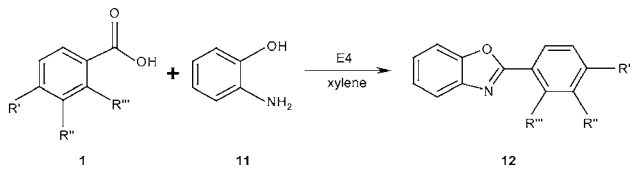
*2-(2-Methylphenyl)-imidazoline* (**5c**). Yellowish solid, mp 115°C (lit. 85–86°C [9]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 2.3 (s, 3H, $CH_3$), 3.6 (t, 4H, $CH_2$), 4.7 (t, 1H, NH), 7.0–7.4 (m, 3H, Ar), 7.7 (d, 1H, Ar). Anal. Found: C, 75.11; H, 7.45; N, 17.51%. Calcd for ($C_{10}H_{12}N_2$): C, 74.97; H, 7.55; N, 17.48%.

*2-(4-Methylphenyl)-imidazoline* (**5d**). Yellowish solid, mp 179–181°C (lit. 178–179°C [9]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 2.2 (s, 3H, $CH_3$), 3.7 (t, 4H, $CH_2$), 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 ($C_{10}H_{12}N_2$): C, 74.97; H, 7.55; N, 17.48%.

*2-(4-tert-Butylphenyl)-imidazoline* (**5e**). White solid, mp 191–193°C. $^1$H NMR ($CDCl_3$, ppm): $\delta$ 1.3 (s, 9H, $CH_3$), 3.6 (dt, 4H, $CH_2$), 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 ($C_{13}H_{18}N_2$): C, 77.18; H, 8.97; N, 13.85%.

*2-(4-Methoxy-3-nitrophenyl)-imidazoline* (**5f**). Yellow solid, mp 194–196°C. $^1$H NMR ($CDCl_3$, ppm): $\delta$ 3.5 (t, 4H, $CH_2$), 3.9 (s, 3H, $CH_3$), 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 ($C_{10}H_{11}N_3O_3$): C, 54.30; H, 5.01; N, 18.99%.

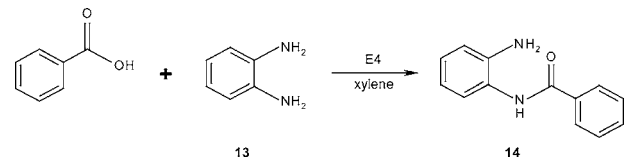
*2-(2-Acetoxyphenyl)-imidazoline* (**5g**). Oil. $^1$H NMR ($CDCl_3$, ppm): $\delta$ 2.8 (s, 3H, $CH_3$), 3.6 (t, 4H, $CH_2$), 4.7 (t, 1H, NH), 7.3 (dd, 2H, Ar), 7.8 (d, 1H, Ar), 8.1 (d, 1H, Ar). Anal. Found: C, 64.81; H, 5.99; N, 13.58%. Calcd for ($C_{11}H_{12}N_2O_2$): C, 64.69; H, 5.92; N, 13.72%.

*2-(2-Hydroxyphenyl)-imidazoline* (**5h**). Yellowish solid, mp 211–212°C (lit. 214–216°C [10]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 3.7 (dt, 4H, $CH_2$), 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 ($C_9H_{10}N_2O$): C, 66.65; H, 6.21; N, 17.27%.

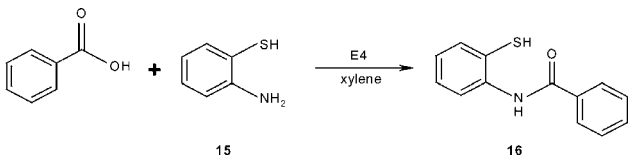
*2-Benzylimidazoline* (**7**). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 3.6 (m, 6H, $CH_2$), 4.4 (t, 1H, NH), 7.4 (m, 5H, Ar). Anal. Found: C, 72.81; H, 8.29; N, 18.99%. Calcd for ($C_9H_{12}N_2$): C, 72.94; H, 8.16; N, 18.90%.

### *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




15 16

SCHEME 7

*2-Phenylbenzoxazole (***12a***)*. Yellowish solid, mp 107°C (lit. 109–110°C [11]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 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 ($C_{13}H_9NO$): C, 79.98; H, 4.65; N, 7.17%.

*2-(4-Chlorophenyl)-benzoxazole (***12b***)*. Yellowish solid, mp 152°C (lit. 151–152°C [12]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 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 ($C_{13}H_8NOCl$): C, 67.99; H, 3.51; N, 6.10%.

*2-(4-tert-Butylphenyl)-benzoxazole (***12c***)*. Yellowish solid, mp 105°C (lit. 105°C [13]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 1.2 (s, 9H, $CH_3$), 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 ($C_{17}H_{17}NO$): C, 81.24; H, 6.82; N, 5.57%.

*2-(2-Methylphenyl)-benzoxazole (***12d***)*. Yellowish solid, mp 71°C (lit. 69°C [14]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 2.4 (s, 3H, $CH_3$), 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 ($C_{14}H_{11}NO$): C, 80.36; H, 5.30; N, 6.69%.

*2-(4-Methylphenyl)-benzoxazole (***12e***)*. Yellowish solid, mp 117°C (lit. 116–117°C [15]). $^1$H NMR ($CDCl_3$, ppm): $\delta$ 2.2 (s, 3H, $CH_3$), 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 ($C_{14}H_{11}NO$): 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]).

## *REFERENCES*

[1] Cwik, A.; Hell, Z.; Hegedüs, A.; Finta, Z.; Horváth, Z. Tetrahedron Lett 2002, 43, 3985–3987.
[2] Anastassiadou, M.; Danoun, S.; Crane, L.; Baziard-Mouysset, G.; Payard, M.; Caignard, D.-H.; Rettori, M.-C.; Renard, P. Bioorg Med Chem 2001, 9, 585–592.
[3] Oxley, S. J Chem Soc 1947, 497–500.
[4] Kubiczek, G.; Neugebauer, L. Monatsh Chem 1949, 80, 815–818.
[5] Anastassiadou, M.; Baziard-Mouysset, G.; Payard, M. Synthesis 2000, 13, 1814–1816.
[6] Hill, A. J.; Aspinall, S. R. J Am Chem Soc 1939, 61, 822–824.
[7] Vorbrueggen, H.; Krolikiewicz, K. Tetrahedron Lett 1981, 22, 4471–4474.
[8] Baker, B. R.; Erickson, E. H. J Med Chem 1969, 12, 408.
[9] Piskov, V. B. Chem Heterocycl Compd (Engl Transl) 1976, 12, 917–923.
[10] Wagner, G.; Briel, D.; Leistner, S. Z Chem 1981, 21, 261.
[11] Prot, T.; Parol, J. Rocz Chem 1971, 45, 1301–1313.
[12] Stephens, F. F.; Brower, J. D. J Chem Soc 1949, 2971.
[13] Kowalski, E.; Anliker, R.; Schmid, K. Mol Cryst Liq Cryst 1968, 4, 403.
[14] Passerini, R. J Chem Soc 1954, 2256.
[15] Skraup, S. Justus Liebigs Ann Chem 1919, 65, 419.
[16] Behringer, H.; Kuchinka, K. Justus Liebigs Ann Chem 1961, 650, 171–178.
[17] Goldberg, H.; Kelly, M. J Chem Soc 1958, 4524–4530.
[18] Kaiya, T.; Fijiwara, T.; Kohda, K. Chem Res Toxicol 2000, 13, 993–1001.
[19] Collings, K.; Morgan, J. Tetrahedron 1964, 20, 2167–2168.