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A simple environmentally-friendly method for the selective synthesis of 1,5-benzodiazepine derivatives using zeolite catalyst

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The modified small pore size zeolite E4a has been found to be an efficient catalyst for the regioselective synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines from *o*-phenylenediamine and ketones. This method is simple, cheap, environmentally-friendly and give the benzodiazepines in high yield.

KEY WORDS: 1,5-benzodiazepines; heterocycles; zeolites; green chemistry.

Benzodiazepines are very important compounds because of their pharmacological properties. Most of the members of this family have wide applications in medicinal chemistry such as anticonvulsant, analgesic, hypnotic, sedative and antidepressive agents [1,2]. In addition, 1,5-benzodiazepines are valuable synthons for the preparation of other fused ring compounds such as triazolo-, oxadiazolo-, oxazino- and furano-benzodiazepines [3–5]. Some benzodiazepine derivatives are also used in fine chemical industry, such as photographical dyes for acrylic fibers [6], and also as anti-inflammatory agents [7].

Despite their importance from pharmacological, industrial and synthetic point of view, comparatively few methods for the preparation of 1,5-benzodiazepines have been reported in the literature. These include a condensation reaction of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds [8], β-haloketones or ketones [9]. Many reagents have been reported for this condensation, e.g. BF_3-OEt_2 [10], polyphosphoric acid [11], $NaBH_4$ [12], SiO_2 [11], $MgO/POCl_3$ [13], $Yb(OTf)_3$ [14], $Sc(OTf)_3$ [15] and acetic acid under microwave irridation [16]. Recently, methods have been reported using ionic liquid medium [17,18].

However, many of these methods are associated with several disadvantages such as long reaction time, drastic reaction conditions, very expensive reagents, low yield, tedious work-up procedures and occurrence of several side products. The main disadvantage is that the catalysts are destroyed during the work-up procedure and cannot be recovered or reused. Therefore, it is important to find a simple, cheap, recoverable and/or reusable and selective catalyst for the synthesis of 1,5-benzodiazepines.

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Ersorb-4 (E4) is a clinoptylolite-type zeolite material with high silicium content (Si/Al ratio 5:1) [19]. The original mineral is modified with ionic exchanges and with other water-phase technologies followed by a thermal treatment yielding a Ca–K mixed cation-based adsorbent with 4 Å pore size. The composition of E4 can be described as follows: SiO_2 73.0%, Al_2O_3 11.2%, Fe_2O_3 1.17%, K_2O 5.12%, Na_2O 0.38%, CaO 2.20%, MgO 0.44%. It has a specific surface of 40 m^2/g (determined by the BET-method with nitrogen at the temperature of liquid nitrogen). It has high acid-proof property; its crystalline structure does not change even after a longtime treatment in hot 4 N hydrochloric acid. E4 has a slightly surfacial acidic character (the pH of its aqueous suspension is about 6) [20]. The high silicium content yields high chemical resistance. It is stable until 500–600 °C. It can adsorb small molecules such as water, hydrochloric acid, ammonia, methanol or hydrogen sulfide. It has several advantages, e.g. environmentally-friendly, non-toxic, inexpensive, recoverable and/or reusable. The small pore size does not allow the adsorption of molecules larger than the methanol in the pores. Based upon this adsorption ability, E4 has been used as large spectral drying agent (molecular sieve) in both gaseous and liquid phases, suitable for the dehydration of gaseous hydrochloric acid or even liquid chlorine and sulfur-dioxide.

E4a is the more acidic modification of E4 (the pH of its aqueous suspension is about 3.5). The original E4 was modified by ionic exchange to change the surface acidity of the material, but this treatment did not modified the original clinoptylolite-structure as it is shown on figure 1.

Recently we reported, that E4 showed good activity in different condensation reactions such as synthesis of oxazoline derivatives from β-aminoalcohols and carboxylic acids [21], preparation of 2-arylimidazolines

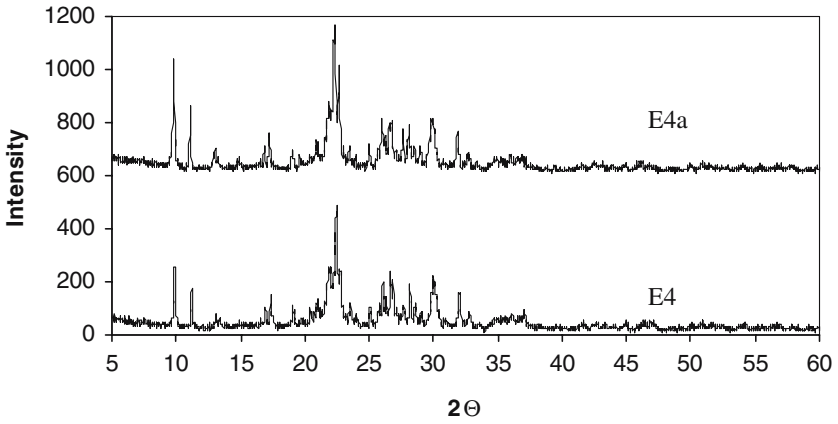


Figure 1. The XRD spectra of E4 adsorbents.

and 2-arylbenzoxazoles [22], and tetrahydropyranylation of alcohols and phenols [23]. E4a has been found to be a good catalyst in the preparation of 1-substituted tetrahydroisoquinolines *via* the Pictet-Spengler reaction [24], and in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones [25].

In continuation of our work to develop new synthetic methodologies in the presence of different type of E4, we examined the synthesis of 1,5-benzodiazepines from *o*-phenylenediamine and ketones. Thus, *o*-phenylenediamine and acetophenone in the presence of E4a in ethanol gave the appropriate 2-methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine in good yield (scheme 1).

The optimal reaction conditions were determined in this reaction. The results are shown in table 1. The best result was obtained using 0.5 g E4a/2 mmol *o*-phenylenediamine in ethanol as solvent at 80 °C for 4 h (table 1, entry 6). The weaker acidic E4 showed less activity (table 1, entry 2).

Based upon these experiments we examined the reaction of *o*-phenylenediamine with aromatic and aliphatic ketones (scheme 2). The results are summarized in table 2.

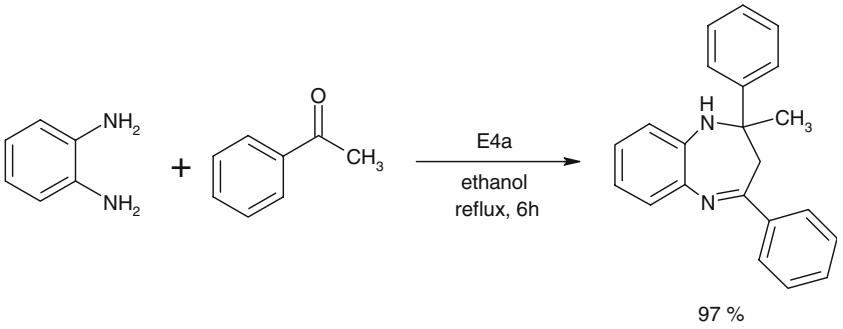
Both aromatic and aliphatic ketones reacted similarly. In case of non-symmetric aliphatic ketones such as ethyl methyl ketone or *i*-butyl methyl ketone (table 2, entries 13 and 14, resp.) we obtained only one regioisomer. The 3-substituted isomer (scheme 3) was not detected. The work-up of the reaction mixture was very simple; the catalyst was filtered out and the solvent was evaporated. The catalyst could be recycled easily without significant loss of activity after washing it with acetone following by heating at 120 °C for 4 h (table 2, entries 2–4).

Table 1
Reaction of *o*-phenylenediamine with acetophenone

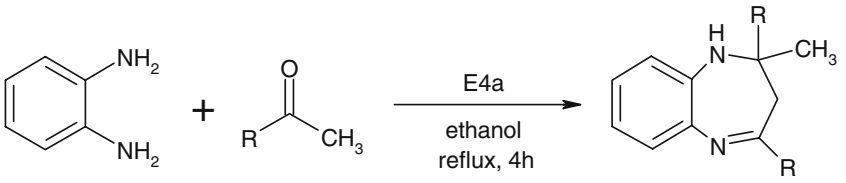
Entry	Catalyst	Amount of catalyst (g)	Solvent	Reaction temperature (°C)	Reaction time (h)	Yield[a,b] (%)
1	E4a	0.8	Ethanol	80	6	97
2	E4	0.8	Ethanol	80	6	52
3	–	–	Ethanol	80	6	–
4	E4a	0.8	Xylene	130	6	94
5	E4a	0.8	Ethanol	80	4	93
6	E4a	0.5	Ethanol	80	4	95
7	E4a	0.5	Ethanol	80	2	61

[a]2 mmol *o*-phenylenediamine/4.2 mmol acetophenone.
[b]Isolated yield.

In summary, the results show that the modified zeolite-type adsorbent E4a is a suitable catalyst for the synthesis of 1,5-benzodiazepines. The method is simple, convenient, cheap and environmentally-friendly, the catalyst can be recycled easily without any loss of activity.



Scheme 1.



Scheme 2.

1. Experimental

The commercial starting materials were purchased from Merck-Hungary Ltd. except of E4a which is the product of Erdökémia-ker Ltd., Hungary.

^{1}H NMR spectra were made on Bruker Avanche 300 spectrometer in $CDCl_3$ using TMS as internal standard.

Pretreatment of the catalyst. Before each experiment the sample of E4a was powdered and heated at 120 °C for 2 h.

General procedure for the preparation of 1,5-benzodiazepines. A mixture of 2 mmol (0.22 g) of *o*-phenylenediamine, 4.2 mmol of ketone and 0.5 g of E4a in ethanol (10 mL) was heated at 80 °C for 4 h. Then the solid was filtered out, the filtrate was evaporated and the residue purified by silica gel column chromatography using hexane/acetone 2:1 as eluent.

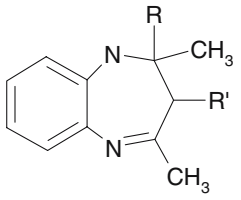
The known products were characterized by ^{1}H NMR and IR spectroscopy and by their melting points. The spectral and physical data of the known compounds were identical with those reported in the literature.

Spectral data of new compounds. 2,3-Dihydro-2-methyl-2,4-bis(3′-methoxyphenyl)-1*H*-1,5-benzodiazepine (table 2, entry 9): yellow solid; mp: 123–124 °C; IR (KBr): 3330 (s br), 1635 (s), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.74 (s, 3H, CH_3), 2.94 and 3.11 (d, 2H, $J=0.17$ Hz, CH_2), 3.13 (s, 1H, NH), 3.84 (s, 3H, OCH_3), 6.85–7.79 (m, Ar, 12H). $C_{24}H_{24}N_2O_2$ Anal. Calcd. C 77.42, H 6.45, N 7.53, Found C 77.18, H 6.41, N 7.48%.

Table 2
Reaction of *o*-phenylenediamine with ketones in the presence of E4a

Entry	R	Yield[a] (%)	M.p. (lit.) (°C)
1	C_6H_5	95	150–152 (151–152) [11]
2	C_6H_5	96[b]	150–152 (151–152) [11]
3	C_6H_5	95[c]	150–152 (151–152) [11]
4	C_6H_5	93[d]	150–152 (151–152) [11]
5	CH_3	98[e]	146–148 (147–148) [11]
6	4-Cl–C_6H_4	91	140–142 (143–144) [26]
7	4-CH_3–C_6H_4	87	99 (98) [26]
8	4-CH_3O–C_6H_4	89	116–118 (117) [26]
9	3-CH_3O–C_6H_4	84	123–124
10	2-CH_3–C_6H_4	79	106–109
11	2-Cl–C_6H_4	86	114–115
12	2-CH_3O–C_6H_4	77	–[f]
13	CH_3–CH_2	87	140–142 (137–139) [27]
14	$(CH_3)_2CH$–CH_2	82	117–118 (118–120) [27]

[a]Isolated yield.
[b]Recycled E4a.
[c]Third use of E4a.
[d]Fourth use of E4a.
[e]Excess acetone as solvent, 60 °C.
[f]Oil.



Scheme 3.

2,3-Dihydro-2-methyl-2,4-bis(2′-methylphenyl)-1*H*-1,5-benzodiazepine (table 2, entry 10): yellow solid; mp: 106–109 °C; IR (KBr): 3330 (s br), 1638 (s), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.75 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.93 and 3.10 (d, 2H, $J=0.17$ Hz, CH_2), 3.15 (s, 1H, NH), 6.80–7.93 (m, Ar, 12H). $C_{24}H_{24}N_2$ Anal. Calcd. C 84.71, H 7.06, N 8.23, Found C 84.52, H 7.04, N 8.31%.

2,3-Bis(2′-chlorophenyl)-2,3-dihydro-2-methyl-1*H*-1,5-benzodiazepine (table 2, entry 11): yellow solid; mp: 114–115 °C; IR (KBr): 3330 (s br), 1636 (s), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.75 (s, 3H, CH_3), 2.95 and 3.11 (d, 2H, $J=0.17$ Hz, CH_2), 3.15 (s, 1H, NH), 6.70–7.70 (m, Ar, 12H). $C_{22}H_{18}Cl_2N_2$ Anal. Calcd. C 69.29, H 4.72, N 7.35, Found C 69.01, H 4.78, N 7.06%.

2,3-Dihydro-2-methyl-2,4-bis(2′-methoxyphenyl)-1*H*-1,5-benzodiazepine (table 2, entry 12): yellow oil; IR (film): 3330 (s br), 1632 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.74 (s, 3H, CH_3), 2.95 and 3.11 (d, 2H, $J=0.17$ Hz, CH_2), 3.13 (s, 1H, NH), 3.82 (s, 3H, OCH_3), 6.75–7.80 (m, Ar, 12H). $C_{24}H_{24}N_2O_2$ Anal. Calcd. C 77.42, H 6.45, N 7.53, Found C 77.28, H 6.39, N 7.41%.

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