Zeolite-catalyzed simple synthesis of isochromans *via* the oxa-Pictet–Spengler reaction

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The modified small pore size zeolite E4a has been found to be an efficient catalyst for the synthesis of isochromans *via* the oxa-Pictet–Spengler reaction. This method is simple, cheap, environmentally-friendly and gives the isochromans in high yield.

The oxa-Pictet–Spengler reaction is the oxygen analogue of the Pictet–Spengler reaction. While in the Pictet–Spengler reaction a β-phenylethylamine derivative reacts with a carbonyl compound, generating an imine (Schiff's base), which undergoes cyclization *via* an intramolecular electrophilic aromatic substitution yielding an isoquinoline derivative,[1] in the oxa-Pictet–Spengler reaction a 2-phenylethanol derivative reacts with an aldehyde or a ketone to give an isochroman (3,4-dihydro-1*H*-benzo[*c*]pyrane) structure. This reaction was reported for the first time by Wunsch and Zott in 1992.[2] The authors used $ZnCl_2$ and HCl gas, 2–3 equivalents *p*-toluenesulfonic acid or Lewis acids ($TiCl_4$, $AlCl_3$, $SnCl_4$) as catalyst, dioxane, nitrobenzene or benzene as solvent, and high reaction temperatures. This method has some disadvantages: harmful, not recoverable catalysts and long reaction times (24–66 h).

There are some new methods in the literature for the oxa-Pictet–Spengler reaction, for example the use of catalytic amounts of *p*-toluenesulfonic acid in methanol at 4 °C,[3] oleic acid in methanol at 21 °C, or using dehydrating agents (molecular sieves or anhydrous Na_2SO_4) beside the catalyst.[4] But these methods also require long reaction times (48 h for ketones and 24 h for aldehydes; and one week in the case of oleic acid catalyst). Using HCl gas as catalyst in dioxane, the reaction time was only one hour.[5]

The application of solid acids and bases (natural and modified clay minerals, montmorillonites, zeolites, mixed oxides, layered double hydroxides) as efficient catalysts in organic synthesis has been widely studied.[6] They are important from the environmental point of view, because they produce less waste, but have excellent activity and selectivity even on industrial scales, and in most cases these substances can be recovered from the reaction mixtures and reused with good results.

Ersorb-4 (E4) is a clinoptylolite-type zeolite material with high silicon content (Si : Al ratio 5 : 1).[7] The original mineral is modified by ion 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%. The XRD spectrum

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of E4 was identical to the spectrum of clinoptylolite. It has a specific surface of 40 m^2 g^{-1} (determined by the BET method with nitrogen at the temperature of liquid nitrogen). E4 has a slightly surface acidic character. The pH of its aqueous suspension is about 5.5. The high silicon content yields high chemical resistance. It is stable until 500–600 °C. It can adsorb small molecules such as water, hydrochloric acid, ammonia, methanol, *etc.* It is environmentally-friendly, nontoxic, recoverable, reusable and inexpensive. E4a is the more acidic modification of E4 (the pH of its aqueous suspension is about 3). The original E4 was modified by ionic exchange to change the surface acidity of the material.

Recently we reported that E4 showed good activity in different condensation reactions such as synthesis of oxazoline derivatives from β-aminoalcohols and carboxylic acids,[8] preparation of 2-arylimidazolines, 2-arylbenzoxazoles,[9] and 2-arylbenzimidazoles.[10] E4a has been found to be a good catalyst in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones,[11] and 1,5-benzodiazepine derivatives,[12] and in the preparation of 1-substituted tetrahydroisoquinolines *via* the Pictet–Spengler reaction.[13]

Based on the results obtained for the Pictet–Spengler cyclization, we examined the oxa-Pictet–Spengler reaction under mild conditions. The reaction of 2-(3,4-dimethoxyphenyl)ethanol and 4-chlorobenzaldehyde in the presence of E4a in toluene resulted in the formation of 1-(4-chlorophenyl)-6,7-dimethoxyisochroman with good yield (Fig. 1). The optimal reaction conditions were determined in this reaction. The best result was obtained using 0.5 g E4a and 2 mmol 2-phenylethanol in toluene as solvent at 110 °C. The weaker acidic E4 showed no activity. No reaction was observed using the strongly acidic KSF/0 montmorillonite alone or in a mixture with 4 Å molecular sieves. This can be explained by the fact that in the Ersorb catalysts both acidic sites and pores for binding water are present, thus, deliberated water can be immediately fixed in the pores of the catalyst.

We examined the reaction of 2-phenylethanol derivatives with aromatic and aliphatic aldehydes and ketones. The results are summarized in Tables 1 and 2. The optimal reaction time was 15 h for aldehydes and 35 h for ketones in the reaction of 2-(3,4-dimethoxyphenyl)ethanol. These were significantly shorter than the reaction time required using *p*-toluenesulfonic acid or $ZnCl_2$/HCl as catalyst.[2–4] In the case of 2-phenylethanol the required reaction time was 40 h for aldehydes and 48 h for ketones, because of the lack of the activating methoxy groups. Aliphatic aldehydes and ketones also gave the appropriate isochroman derivatives. For aliphatic aldehydes the optimal reaction time was 20 h. In these cases the reaction temperature was lower (Table 1, entries 10 and 11), because of the lower boiling points of the aldehydes. The workup of the reaction mixture was very easy;
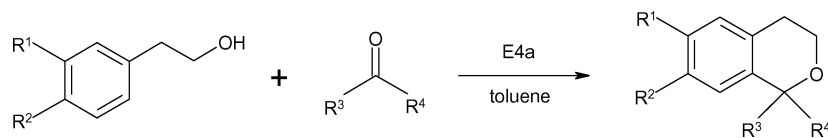
Fig. 1

Table 1 Reaction of 2-phenylethanol derivatives with aldehydes[a]

Entry	R^1	R^2	R^3	R^4	Reaction time/h	Yield[b] (%)
1	CH_3O	CH_3O	$4\text{-}Cl\text{-}C_6H_4$	H	15	97
2	CH_3O	CH_3O	$4\text{-}Cl\text{-}C_6H_4$	H	15	95[c]
3	CH_3O	CH_3O	$4\text{-}Cl\text{-}C_6H_4$	H	15	95[d]
4	CH_3O	CH_3O	$4\text{-}CH_3O\text{-}C_6H_4$	H	15	92
5	CH_3O	CH_3O	C_6H_5	H	15	83
6	CH_3O	CH_3O	C_6H_5	H	15	83[c]
7	CH_3O	CH_3O	$4\text{-}(CH_3)_2N\text{-}C_6H_4$	H	15	89
8	CH_3O	CH_3O	$3\text{-}NO_2\text{-}C_6H_4$	H	15	85
9	CH_3O	CH_3O	$2\text{-}Br\text{-}C_6H_4$	H	15	77
10	CH_3O	CH_3O	$CH_3\text{-}CH_2$	H	20	70[e]
11	CH_3O	CH_3O	$CH_3\text{-}CH_2\text{-}CH_2$	H	20	79[f]
12	$O\text{-}CH_2\text{-}O$		$4\text{-}CH_3O\text{-}C_6H_4$	H	15	91
13	$O\text{-}CH_2\text{-}O$		C_6H_5	H	15	86
14	H	H	C_6H_5	H	40	81
15	H	H	$4\text{-}Cl\text{-}C_6H_4$	H	40	88
16	H	H	$4\text{-}CH_3O\text{-}C_6H_4$	H	40	90
17	H	H	$3\text{-}NO_2\text{-}C_6H_4$	H	40	84

[a] 2 mmol alcohol, 2 mmol aldehyde, 0.5 g E4a, toluene, 110 °C. [b] Preparative yield. [c] Recycled E4a. [d] Third use of E4a. [e] Reaction temperature 50 °C. [f] Reaction temperature 70 °C.

Table 2 Reaction of 2-phenylethanol derivatives with ketones[a]

Entry	R^1	R^2	R^3	R^4	Reaction time/h	Yield[b] (%)
1	CH_3O	CH_3O	C_6H_5	CH_3	35	83
2	CH_3O	CH_3O	C_6H_5	CH_3	35	80[c]
3	CH_3O	CH_3O	$4\text{-}CH_3O\text{-}C_6H_4$	CH_3	35	87
4	CH_3O	CH_3O	$4\text{-}CH_3\text{-}C_6H_4$	CH_3	35	90
5	CH_3O	CH_3O	$4\text{-}Cl\text{-}C_6H_4$	CH_3	35	91
6	CH_3O	CH_3O	$3\text{-}CH_3O\text{-}C_6H_4$	CH_3	35	77
7	CH_3O	CH_3O	$2\text{-}CH_3\text{-}C_6H_4$	CH_3	35	75
8	CH_3O	CH_3O	$CH_3\text{-}CH_2$	CH_3	35	64[d]
9	H	H	C_6H_5	CH_3	48	77
10	H	H	$4\text{-}CH_3O\text{-}C_6H_4$	CH_3	48	82

[a] 2 mmol alcohol, 2 mmol ketone, 0.5 g E4a, toluene, 110 °C. [b] Preparative yield. [c] Recycled E4a. [d] Reaction temperature 80 °C.

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 1, entries 2, 3 and 6; Table 2, entry 2).

In the literature there is a three-step mechanism for the oxa-Pictet–Spengler reaction.[3] In the first step, the reaction of the carbonyl compound and the alcohol results in a hemiacetal in the presence of acid catalyst, then this hemiacetal loses water and gives a reactive intermediate, which finally undergoes an intramolecular electrophilic aromatic substitution yielding the isochroman derivative (Scheme 1). We examined the mechanism of the reaction of 2-(3,4-dimethoxyphenyl)ethanol and 4-chlorobenzaldehyde. The reaction was stopped after 8 h and the reaction mixture was investigated by TLC. Two compounds were detected; the expected product and another, which was separated by column chromatography. The ^{1}H NMR spectrum of this

compound showed a sharp singlet at 6.2 ppm which corresponds to the signal of the CH group in the appropriate diphenylmethanol derivative.[14] This compound subjected to further reaction under the same reaction conditions gave the appropriate isochroman. Based on these data we propose a new two-step mechanism 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 (Scheme 2).

In summary, the results show that the modified zeolite-type adsorbent E4a is a suitable catalyst for the oxa-Pictet–Spengler reaction. The method is simple, convenient, cheap and environmentally-friendly, the catalyst can be recycled without any loss of activity.†

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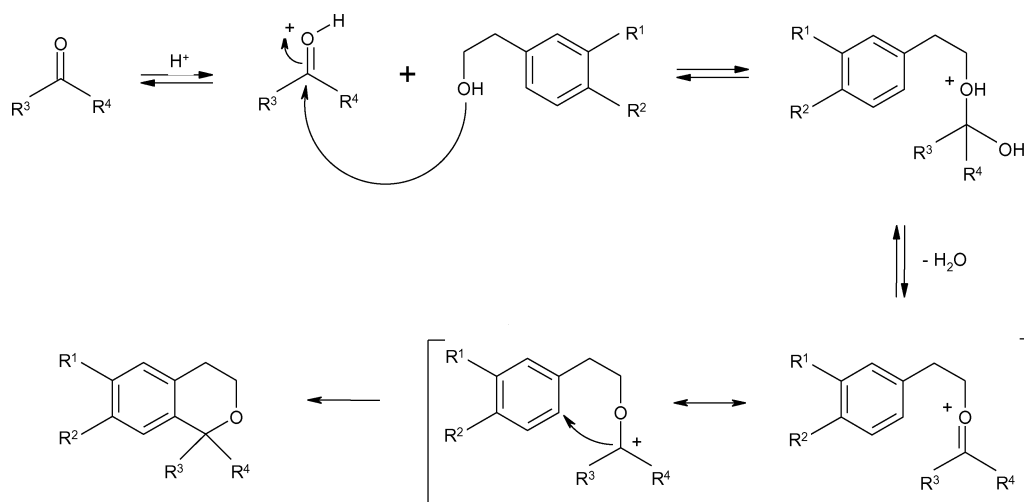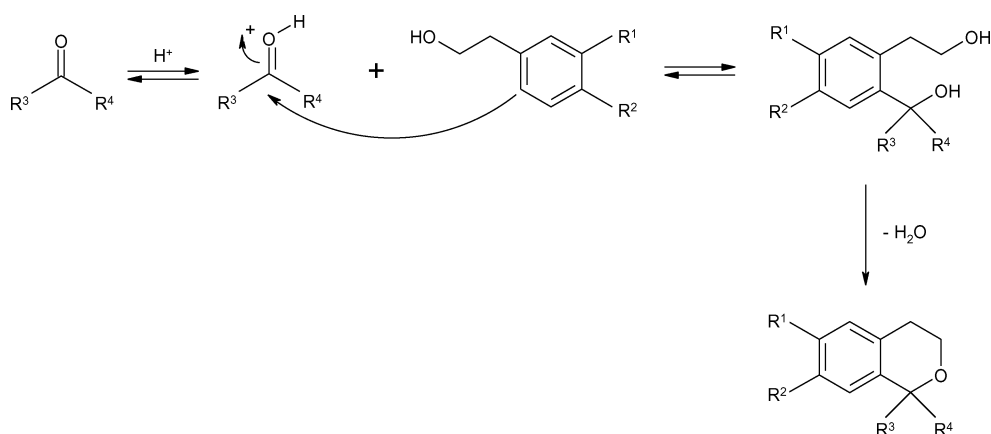
Scheme 1

Scheme 2

Notes and references

† Pretreatment of the catalyst: before each experiment, a sample of E4a was powdered and heated at 120 °C for 2 h. A typical protocol for the reaction: a mixture of 2 mmol of 2-phenylethanol derivative, 2 mmol of aldehyde/ketone and 0.5 g E4a in toluene (10 mL) was heated at 110 °C for a time indicated in Tables 1 and 2. The solid was filtered off, the filtrate was evaporated and the residue characterized. All products have satisfactory physical and spectral data (melting point, ^{1}H NMR). Selected data of 1-(4-methoxy-phenyl)-6,7-dimethoxyisochroman (Table 1, entry 4): mp 97–98 °C (ethanol); ^{1}H NMR (300 MHz, CDCl$_3$): 2.60 and 2.95 (m, 2H, CH$_2$), 3.90 and 4.18 (m, 2H, CH$_2$), 3.72 (s, 9H, CH$_3$O), 5.62 (s, 1H, CH), 6.30–7.20 (m, 6H, Ar).

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