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One-step preparation of 1-substituted tetrahydroisoquinolines via the Pictet–Spengler reaction using zeolite catalysts

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Abstract—A new, environmentally friendly variation of the Pictet–Spengler reaction has been elaborated using a small pore size zeolite. The easily separable and recyclable catalyst provided high conversions and a shorter reaction time than the classical acetic acid or trifluoroacetic acid.

1. Introduction

Numerous naturally occurring alkaloids, that is, tetrahydro-β-carbolines (indole alkaloids) or tetrahydroisoquinoline derivatives mediate pharmacologically useful physiological effects. Therefore, the synthesis of these natural products as well as their analogues is interesting for both organic synthesis and medicinal chemistry. One of the most powerful methods for the construction of these heterocyclic compounds is the Pictet–Spengler cyclisation.[1] The reaction consists of the condensation of a β-phenylethylamine derivative with a carbonyl compound, generating an imine (Schiff's base), which undergoes cyclisation via an intramolecular electrophilic aromatic substitution yielding the isoquinoline derivative.

The Pictet–Spengler reaction was traditionally carried out in a protic solvent with acid catalysts,[2–4] usually using acetic acid or trifluoroacetic acid. The reaction have been widely investigated;[5–8] thus papers has been published about the effect of an aprotic media,[5] the stereochemistry[6,7] and the use of solid supported reagents,[8] but the main principles of the reaction remain the same. It is a two-step method; first the Schiff's base is prepared and the water is distilled out from the reaction mixture, then the catalyst is added and the cyclisation is effected. The method has some disadvantages: long reaction times (48 h for ketones and 24 h for aldehydes) and the catalysts are harmful to the environment.

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.[9] 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 reaction mixtures and reused with good results.

Ersorb-4 (E4) is a weakly acidic zeolite-type adsorbent with a 4 Å pore size. It can adsorb small molecules such as water, hydrochloric acid, ammonia, methanol, etc. It has several advantages—it is environmentally friendly, nontoxic, recoverable, reusable and inexpensive. Recently we reported that E4 showed good activity in different condensation reactions such as acylation of amino acids with aromatic acid chlorides,[10] cyclisation of β-aminoalcohols with carboxylic acids to oxazoline derivatives,[11] synthesis of 2-arylimidazoline derivatives and 2-arylbenzoxazole derivatives[12] and tetrahydropyranylation of alcohols and phenols.[13]

2. Results and discussion

Based on the results obtained for these condensation reactions, we examined the Pictet–Spengler cyclisation under mild conditions. E4 having only a slightly acidic character,[14] we used its more acidic modification (E4a) in our reactions. The original E4 was modified by ionic exchange to change the surface acidity of the material. The reaction of β-phenylethylamine and acetophenone in the presence of E4a in ethanol resulted in the

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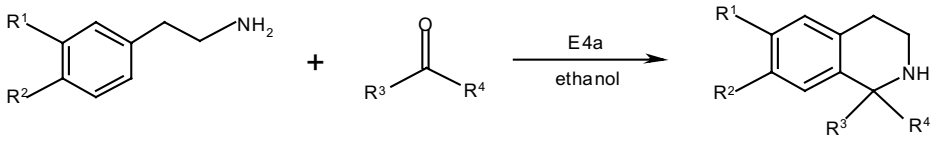

Figure 1.

formation of 1-phenyl-1-methyl-1,2,3,4-tetrahydroisoquinoline in one step and good yield (Fig. 1). We examined the reaction of β-phenylethylamine derivatives with aromatic and aliphatic ketones and aldehydes. The results are summarised in Tables 1 and 2. In all cases, the starting carbonyl compound and the amine disappeared from the reaction mixtures and only the intermediate Schiff's base and the product were observed.

On increasing the reaction time, the yield increased (Table 1, entries 1, 2 and 3; Table 2, entries 1 and 2), but the longest reaction time was significantly shorter than the reaction time required using acetic acid or trifluoroacetic acid as catalyst.[1,2] Aliphatic ketones and aldehydes also gave the appropriate tetrahydroisoquinoline derivatives, but with poorer yields (Table 1, entry 13; Table 2, entry 10). Using the more acidic KP10 montmorillonite catalyst instead of E4a in the reaction, no product was obtained. Although KP10 is more acidic than E4a, it is unable to bind the water formed during the Schiff's base formation. The workup of the reaction was very easy; the catalyst was filtered out and the solvent was evaporated. The catalyst could be easily recycled without significant loss of activity (Table 1, entries 4 and 5; Table 2, entry 3).

Thus a new, one-step variation of the Pictet–Spengler reaction has been developed.

Table 1. Reaction of β-phenylethylamine derivatives with ketones

Entry	R^1	R^2	R^3	R^4	Reaction time (h)	Yield[a] (%)
1	H	H	C_6H_5	CH_3	10	50
2	H	H	C_6H_5	CH_3	20	75
3	H	H	C_6H_5	CH_3	40	87
4	H	H	C_6H_5	CH_3	40	83[b]
5	H	H	C_6H_5	CH_3	40	86[c]
6	H	H	C_6H_5	CH_3	40	—[d]
7	H	H	4-Cl-C_6H_4	CH_3	40	85
8	OCH_3	OCH_3	4-Br-C_6H_4	CH_3	40	84
9	H	H	4-CH_3O-C_6H_4	CH_3	40	89
10	OCH_3	OCH_3	4-CH_3-C_6H_4	CH_3	40	91
11	OCH_3	OCH_3	3-CH_3O-C_6H_4	CH_3	40	87
12	H	H	2-Cl-C_6H_4	CH_3	40	81
13	OCH_3	OCH_3	2-CH_3-C_6H_4	CH_3	40	77
14	OCH_3	OCH_3	CH_3-CH_2	CH_3	40	65

[a] ^{1}H NMR yield.
[b] Recycled E4a.
[c] Third use of E4a.
[d] KP10 montmorillonite catalyst instead of E4a.

Table 2. Reaction of β-phenylethylamine derivatives with aldehydes

Entry	R^1	R^2	R^3	R^4	Reaction time (h)	Yield[a] (%)
1	H	H	C_6H_5	H	12	82
2	H	H	C_6H_5	H	20	100
3	H	H	C_6H_5	H	20	97[b]
4	H	H	4-CH_3O-C_6H_4	H	20	94
5	H	H	4-$N(CH_3)_3$-C_6H_4	H	20	98
6	OCH_3	OCH_3	4-Cl-C_6H_4	H	20	95
7	H	H	3-NO_2-C_6H_4	H	20	93
8	OCH_3	OCH_3	2-Br-C_6H_4	H	20	89
9	OCH_3	OCH_3	2-OH-C_6H_4	H	20	81
10	OCH_3	OCH_3	CH_3-CH_2	H	20	70

[a] ^{1}H NMR yield.
[b] Recycled E4a.

3. Experimental

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

A typical protocol for the reaction: a mixture of 5 mmol of the β-phenylethylamine derivative, 5 mmol of the aldehyde/ketone and 0.8 g E4a in ethanol was heated at 80 °C for 20/40 h. The solid was filtered off, the filtrate was evaporated and the residue characterised.

Characterisation of the new compounds:

6,7-Dimethoxy-1-methyl-1-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinoline (Table 1, entry 8): ^{1}H NMR ($CDCl_3$, ppm) δ 2.0 (s, 1H, NH), 2.8–3.1 (m, 4H, CH_2), 6.9–7.9 (m, 6H, Ar), IR (KBr): NH: 3445 cm^{-1}. Anal. Found: C, 59.51; H, 5.60; N, 3.81%. Calcd for ($C_{18}H_{20}O_2NBr$): C, 59.68; H, 5.56; N, 3.87%.

1-Methyl-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-isoquinoline (Table 1, entry 9): ^{1}H NMR ($CDCl_3$, ppm) δ 2.0 (s, 1H, NH), 2.8–3.3 (m, 4H, CH_2), 6.9–7.6 (m, 8H, Ar), IR (KBr): NH: 3440 cm^{-1}. Anal. Found: C, 80.71; H, 7.50; N, 5.58%. Calcd for ($C_{17}H_{19}ON$): C, 80.60; H, 7.56; N, 5.53%.

6,7-Dimethoxy-1-methyl-1-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (Table 1, entry 10): ^{1}H NMR ($CDCl_3$, ppm) δ 2.2 (s, 1H, NH), 2.6 (s, 3H, CH_3), 2.9–3.3 (m, 4H, CH_2), 7.0–8.1 (m, 6H, Ar), IR (KBr): NH: 3450 cm^{-1}. Anal. Found: C, 76.79; H, 7.70; N, 4.81%. Calcd for ($C_{19}H_{23}O_2N$): C, 76.74; H, 7.79; N, 4.71%.

6,7-Dimethoxy-1-methyl-1-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (Table 1, entry 11): ^{1}H NMR ($CDCl_3$, ppm) δ 2.1 (s, 1H, NH), 2.9–3.3 (m, 4H, CH_2), 7.0–7.8 (m, 6H, Ar), IR (KBr): NH: 3440 cm^{-1}. Anal. Found: C, 72.89; H, 7.42; N, 4.40%. Calcd for ($C_{19}H_{23}O_3N$): C, 72.82; H, 7.39; N, 4.47%.

6,7-Dimethoxy-1-methyl-1-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (Table 1, entry 13): ^{1}H NMR ($CDCl_3$, ppm) δ 2.3 (s, 1H, NH), 2.6 (s, 3H, CH_3), 3.0–3.4 (m, 4H, CH_2), 6.8–7.9 (m, 6H, Ar), IR (KBr): NH: 3445 cm^{-1}. Anal. Found: C, 76.52; H, 7.71; N, 4.79%. Calcd for ($C_{19}H_{23}O_2N$): C, 76.74; H, 7.79; N, 4.79%.

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