Clay/Water Mixtures − A Heterogeneous and Ecologically Efficient Catalyst for the Three-Component Stereoselective Synthesis of Tetrahydroquinolines

Giovanni Sartori,*[a] Franca Bigi,[a] Raimondo Maggi,[a] Alessandro Mazzacani,[a] and Giovanni Oppici[a]

Keywords: Cycloadditions / Environmental chemistry / Heterogeneous catalysis / Multicomponent reactions / Nitrogen heterocycles

The three-component synthesis of tetrahydroquinolines **5** from aromatic amines **1**, aromatic aldehydes **2** and cyclopentadiene (**4**) can be efficiently performed in water in the presence of the commercially available bentonite Bieliaca. The overall process involves the rapid initial production of the imines **3**, which subsequently undergo aza-cycloaddition processes with cyclopentadiene, affording products in good yields and with excellent selectivities. The cycloaddition step is regiospecific and stereospecific, exclusively giving the *endo* product. It was possible to reuse the catalyst several times without lowering its efficiency. The process represents a clean, safe and environmentally friendly route for the production of a class of natural products displaying a wide range of biological activities.

Introduction

Multicomponent reactions (MCRs), as defined by Ugi, are "reactions involving more than two starting reagents that form a product which contains the essential parts of all of the starting materials".[1] These processes have the great advantage that the desired compounds can be prepared without having to carry out the reactions in sequence and without having to isolate and purify any intermediates. The consequent advantages from the environmental and economic points of view are clearly understandable, since these procedures allow money to be saved and the production of waste at source to be minimised. Indeed, the need for alternative production technologies that are cleaner, safer and environmentally more friendly represents one of the most important targets facing chemistry both in the plant and in the laboratory.[2]

In previous studies of the preparation of fine chemicals with the aid of heterogeneous catalysis,[3] we described the use of clays as efficient solid catalysts for performing multistep[4] and multicomponent[5] reactions in aqueous media. These results encouraged us to reinvestigate the three-component tetrahydroquinoline synthesis from aromatic amines, aromatic aldehydes and electron-rich alkenes[6] in the presence of solid acid catalysts operating in water, thus avoiding the use of homogeneous protic or Lewis acids, which require quenching and extraction procedures that are responsible for the production of various amounts of organic and inorganic waste. Tetrahydroquinoline derivatives constitute an important class of natural products displaying a wide range of biological activities[7] and many research groups have consequently focused their attention on the synthesis of these compounds.

Tetrahydroquinolines have previously been synthesised by cycloaddition of *N*-alkylideneanilines and electron-rich olefins in the presence of different Lewis acids, frequently utilised in stoichiometric amounts. These have included montmorillonite K10 combined with $FeCl_3$ in Et_2O/*t*BuOH,[8] $BF_3 \cdot Et_2O$,[9] $AlCl_3/Et_3N$[10] and $Co_2(CO)_8$.[11] The one-pot approach based on the three-component condensation between aromatic amines, aldehydes and electron-rich olefins has been further developed by use of stoichiometric amounts (with respect to the amine) of HCl[12] or CF_3COOH in acetonitrile.[13] In addition, lanthanum, scandium and ytterbium triflates in acetonitrile or dichloromethane have been utilised as efficient catalysts of the process.[14] Scandium catalysts supported on nafion and on polyacrylonitrile have also been utilised for the preparation of libraries of tetrahydroquinolines.[15]

We now show that the three-component tetrahydroquinoline synthesis described above can be efficiently performed in the presence of natural clays in water, under safer and cleaner conditions.

Results and Discussion

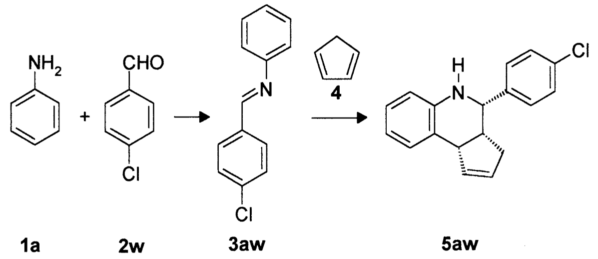
We initially examined the use of different commercially available clays as solid acid catalysts for the model reaction between aniline (**1a**), *para*-chlorobenzaldehyde (**2w**) and cyclopentadiene (**4**), aiming at finding the best catalyst and at evaluating whether or not it played positive roles both in the production of the imine intermediate **3aw** and in the further aza-Diels−Alder cycloaddition to give the final product **5aw** (Scheme 1).

---

[a] Dipartimento di Chimica Organica e Industriale dell'Università,
Parco Area delle Scienze, 17A, 43100 Parma, Italy
Fax: (internat.) + 39-0521/905472
E-mail: sartori@unipr.it

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjoc or from the author.

1434−193X/01/0713−2513 $ 17.50+.50/0



Scheme 1. The three-component reaction for tetrahydroquinoline synthesis

Experiments were performed according to the following procedure:[5] a mixture of **1a** (5 mmol, 0.5 g, 0.5 mL), **2w** (5 mmol, 0.6 g), **4** (7.5 mmol, 0.5 g, 0.6 mL), catalyst (0.5 g) and acetonitrile (5 mL) in a small autoclave was vigorously shaken at 40 °C for 5 h. For comparison, the reaction was also carried out in the absence of any catalyst (Table 1).

The catalysts studied were smectite-type laminar silicates. The structure of an elementary sheet of these materials consists of an octahedral layer of $Al[O_4(OH)_2]$ [for acid montmorillonite KSF (H-Mont),[16] sodium montmorillonite (Na-Mont)[17] and acid bentonite Bieliaca (H-Bent)[18] (Table 1, Entries 1, 2 and 4)] or $Mg[O_4(OH)_2]$ [for hectorite[19] (Table 1, Entry 5)] sandwiched between two tetrahedral layers of SiO_4 tetrahedra. Isomorphous substitution of aluminium, magnesium or silicon by cations with lower valencies induces negative charges in the layers, which are compensated by exchangeable cations (including protons) in the interlamellar space, producing materials with different acid-base properties.[20] The total concentration of acid sites on the catalyst surface was determined by NH_3 adsorption[21] and the surface area by the BET method.[22]

The most salient feature of the results shown in Table 1 is that production of the imine intermediate **3aw** in almost quantitative yield does not require any catalyst, and hence clays are only involved in the aza-Diels−Alder process (Table 1, Entry 6). Moreover, the key factor for the reaction is the acidity of the clay, while the surface area seems to play a less important role. Indeed, all clays display activity in the production of tetrahydroquinoline **5aw**, but of all the catalysts examined, the bentonite Bieliaca, which shows the greatest overall acidity, is the most efficient catalyst (Table 1, Entry 2). As expected, Na clays such as Na-Mont were found to be much less active (Table 1, Entry 4).[23]

This catalytic system takes advantage of the joint presence in the clay of pools of polarised water molecules and of Lewis acid sites inside the interlayer spacing or in the outside surface of the clay. According to previous reports from the literature,[24] however, the activity of clay catalysts is mainly due to the Brønsted acidity, which stems from the hydration sphere of the exchangeable cations polarising the coordinated water molecules. This conclusion was reinforced by the fact that the most efficient Bieliaca catalyst (H-Bent) lost some activity after being heated at 350 °C for 5 h (Table 1, Entry 3), because all clays dehydrate at high temperatures, their Brønsted acidity consequently decreasing and their Lewis acidity increasing.[25] The three-component model reaction in MeCN on Bieliaca (H-Bent) catalyst was then analysed, comparing the concentrations of reagent **1a** and products **3aw** and **5aw** over time (Figure 1).

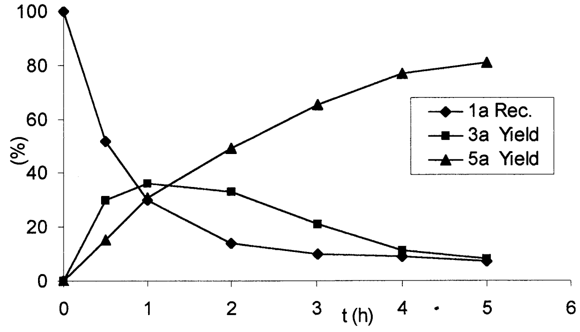


Figure 1. Reactivity of aniline (**1a**) in the model reaction (Scheme 1) on Bieliaca (H-Bent) as a function of time

The results confirmed that the entire process followed the trend of a typical irreversible sequential reaction. The fast initial production of the imine intermediate **3aw** was concomitant with the formation of tetrahydroquinoline **5aw**, the yield of which was very low at first, but gradually increased with time and reached 81% after 5 h.

The solvent effect in the aza-cycloaddition step was then examined, since the results shown above (Table 1, Entry 6) confirmed that production of imine intermediate **3aw** occurred very rapidly and in high yield in the absence of any catalyst and without any need to remove the water produced. The model cycloaddition reaction between imine **3aw** and cyclopentadiene (**4**) with the best Bieliaca catalyst (H-Bent) was performed in different solvents, the choice of which was dictated by results previously reported in the lit-

Table 1. Three-component tetrahydroquinoline **5aw** synthesis; effect of catalysis by different clays

Entry	Clay	Surface acidity [mequiv. H^+/g]	Surface area [m^2/g]	**1a** conversion (%)	**3aw** yield (%)	**5aw** yield (selectivity) (%)
1	KSF (H-Mont)	0.70 ± 10	15 ± 10	99	22	76 (77)
2	Bieliaca (H-Bent)	0.77 ± 10	205 ± 5	99	17	81 (82)
3	Bieliaca (350)[a]	0.50 ± 10	104 ± 5	98	55	40 (41)
4	Na-Mont	0.10 ± 2	32 ± 1	99	40	58 (59)
5	Hectorite	0.21 ± 3	63 ± 1	98	38	60 (61)
6	−	−	−	98	97	1 (−)

[a] Heated at 350 °C for 5 h before use.

erature[13] or obtained in our laboratory.[5] We used four solvents with different polarities, which promoted complete miscibility of all reagents and products (and can consequently produce high concentrations of interlayer reagents) (Table 2, Entries 1−4). We also utilised water, a much poorer solvent in this regard but capable of enhancing the reactivity of the system through hydrophobic interactions, which have been reported to increase the rates of Diels−Alder cycloaddition reactions profoundly (Table 2, Entry 5).[26]

Table 2. Solvent effects in the aza-cycloaddition over Bieliaca (H-Bent) catalyst

Entry	Solvent	E_T^N[a]	**5aw** yield (%) 2 h	**5aw** yield (%) 5 h
1	CCl_4	0.052	40	53
2	PhMe	0.099	45	60
3	MeCN	0.460	49	70
4	MeOH	0.762	60	93
5	H_2O	1.000	65	96

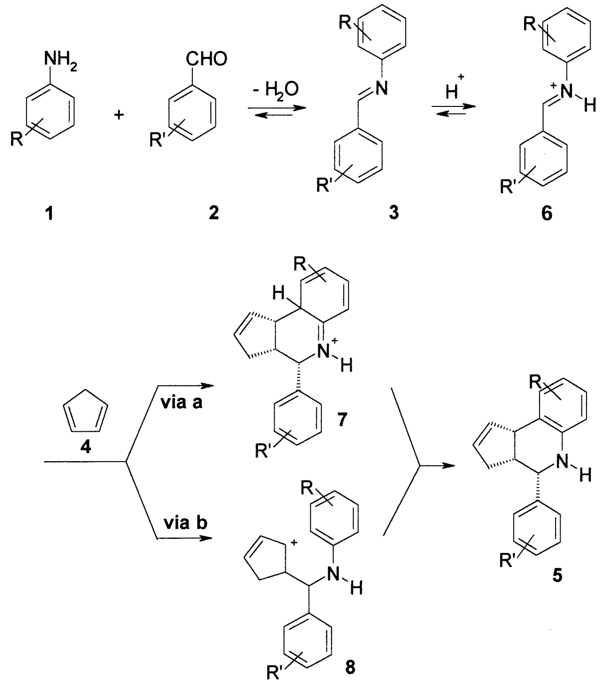
[a] Normalised E_T(**30**) parameter (Reichardt).[27]

The solvent polarity was expressed in normalised E_T(**30**) Reichardt parameters (E_T^N), used because there are good linear correlations between these values and some other empirical solvent polarity parameters.[27] In all cases, the sole detectable compounds were the unchanged imine **3aw** and the tetrahydroquinoline **5aw**. The results reported in Table 2 confirmed that the observed yields of tetrahydroquinoline **5aw** and the polarity parameters of selected pure solvents showed some correlation. In other words, the aza-Diels−Alder cycloaddition is favoured by polar solvents. We suggest that the solvent polarity can exert a positive effect on the efficiency of the process by stabilising the strongly polar, or even ionic, transition state. Moreover, polar solvents can also facilitate access to the interlayer active sites of the catalyst through the swelling process. In fact, negatively charged layered silicates such as the bentonite Bieliaca, containing exchangeable balancing cations, undergo topotactic solid-state reversible reaction upon interaction with polar solvents, which induces the swelling of the lamellar structure. This process occurs because of solvation of both the surface siloxane groups and the positive counter ions in the interlayer area. The specific effect of water and protic polar solvents in favouring this process is well documented.[28]

As far as the high yield achieved when the reaction is carried out in water is concerned (Table 2, Entry 5), hydrophobic packing, if present, of azadiene and cyclopentadiene is not the sole effect responsible for the activation, since a fairly similar high reactivity was observed in methanol, in which both reagents are soluble (Table 2, Entry 4). We might instead suggest an activation of the azadiene by proton transfer from the acid catalyst active sites, which become more and more accessible with the increasing swelling effect.

Since the catalyst Bieliaca is a natural bentonite treated with hydrochloric acid, we suspected that the activation of reagents in water and methanol might be due to the protic acidity developed from the clay. Thus, we examined two comparative three-component model reactions between compounds **1a** (5 mmol), **2w** (5 mmol) and **4** (7.5 mmol) at 40 °C for 5 h, using the acidic water (5 mL) obtained after filtration of a stirred suspension of Bieliaca clay (0.5 g) (pH = 5.46) and the same washed clay in neutral water (5 mL). The production of the imine **3aw** in 98% yield in the first case and of tetrahydroquinoline **5aw** in 94% yield, accompanied by traces (2%) of **3aw**, in the second confirmed the essential role played by the solid acid catalyst in the process. It is noteworthy that montmorillonite KSF, which afforded more acidic water (pH = 1.55) under the treatment described above, proved to be less efficient than Bieliaca (which afforded acidic water with pH = 5.46) in promoting the three-component process, further confirming that the catalytic activity strongly depends on the "supported protic acidity".

Although little is known about the detailed mechanism of such aza-cycloaddition processes, available results point to a mechanism involving a strongly polar, or even ionic, transition state. The reaction may proceed either through concerted polar [$4\pi^+ + 2\pi$] cycloaddition with subsequent tautomerisation (through a) or by an intermolecular 1,2 C=N$^+$ addition-intramolecular cationic cyclisation sequence (through b).[29] The active species are produced by H-bond activation or by protonation (Scheme 2, intermediate **6**) of the nitrogen atom of **3** by the strongly acidic clay, which makes the azadiene even more electron-deficient and thus active in the present reaction.



Scheme 2. The tetrahydroquinoline synthesis reaction mechanism

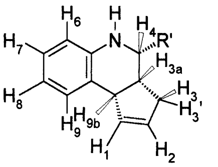
The problem of catalyst recycling in the same three-component model reaction was then addressed. The catalyst was recovered by filtration, washed with water and acetone, heated at 100 °C for 8 h and immediately reused for a further five times without significant loss of efficiency [yield (selectivity) determined for each cycle: 1st: 95 (97); 2nd: 97 (98); 3rd: 95 (96); 4th: 96 (97); 5th: 95 (96); 6th: 96 (97)]. These results make this methodology particularly attractive from both the economical and the environmental points of view.

The scope of this procedure was finally extended to the synthesis of various tetrahydroquinolines **5**. The results reported in Table 3 confirm that the methodology is compatible with different functional groups being present on the aromatic rings both of aldehyde and of amine. In general, tetrahydroquinolines **5** were obtained in high yields and with good selectivities, independently of the electronic effect of substituents.

Table 3. Synthesis of variously substituted tetrahydroquinolines

Entry	R	R′	**5** Yield [Sel.] (%)
1	H	4-Cl	**5aw** 96 [98]
2	H	4-NO_2	**5ax** 95 [97]
3	H	4-OH	**5ay** 93 [96]
4	H	H	**5az** 86 [97]
5	4-Cl	H	**5bz** 98 [99]
6	4-COOEt	H	**5cz** 96 [98]
7	4-NO_2	H	**5dz** 96 [99]
8	4-Me	H	**5ez** 97 [98]
9	3-Me	H	**5fz** 97 [98]
10	3,4-$(OMe)_2$	H	**5gz** 85 [97]

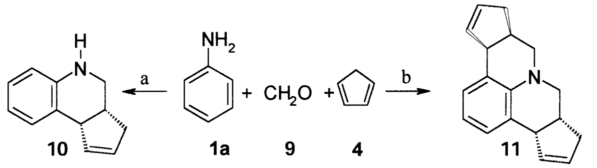
The reaction is regiospecific and stereospecific, exclusively producing the *endo* product **5**; this was also the predominantly obtained isomer under homogeneous catalysis conditions with different Lewis acids.[10,14a,14b,30] The structures of the compounds **5aw** and **5bz** were determined by ^{1}H NMR NOESYTP experiments (Scheme 3), attesting that the additions are regiospecific (only 3*H* isomers are formed) and stereospecific (the aryl group is oriented *cis* with respect to the cyclopentene ring).



Scheme 3. Numbering of 3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline protons

In particular, the cross-peak correlations in the 2D spectra of compound **5bz** showed strong though-space interactions between the proton H-3a (δ = 3.00) and both protons H-9b (δ = 4.07) and H-4 (δ = 4.61). The *cis* stereochemistry is thus unequivocally established. Regarding the double-bond position, the cross-peak correlation between the signals due to H-9b and H-1 (δ = 5.82), as well as that between the signals due to H-3a and the methylene proton H-3 (δ = 1.82) confirm the structure of the depicted regioisomer. The 2D spectra of compound **5aw** show the same cross-peak correlations, confirming the *endo* structure.

Attempts to use aliphatic aldehydes instead of aromatic ones resulted in decreases in both yield and selectivity, due mainly to the formation of autocondensation products from the enolizable aldehydes. In contrast, the use of paraformaldehyde (**9**) resulted in the formation of the tetrahydroquinoline **10**[12] (75% yield, 92% selectivity) or of the pentacyclic product **11**[6] (91% yield, 95% selectivity) when using 1:1:1.5 or 1:3:3 aniline/paraformaldehyde/cyclopentadiene molar ratios, respectively (Scheme 4).



a: **1a/9/4** = 1/1/1.5; b: **1a/9/4** = 1/3/3

Scheme 4. The reaction pathways in the paraformaldehyde/aniline/cyclopentadiene reaction

Conclusion

In conclusion, we have shown that the three-component tetrahydroquinoline synthesis from aromatic amines, aromatic aldehydes and cyclopentadiene can be efficiently performed in aqueous solvent and in the presence of acid clays, with the natural and commercially available bentonite Bieliaca being the most efficient catalyst. Although water is the best medium from the economic and environmental points of view, the reaction can be efficiently performed in different polar and protic solvents (such as CH_3CN and MeOH). The overall process involves the rapid initial production of the imine, which subsequently undergoes an aza-cycloaddition process with cyclopentadiene. The cycloaddition step is regiospecific and stereospecific, affording the *endo* product (all-*cis* product) exclusively. The catalyst could be reused five times without reducing its efficiency.

Experimental Section

General Remarks: Melting points are uncorrected. − ^{1}H NMR spectra were recorded at 300 and 400 MHz. ^{1}H assignments were confirmed with the aid of the 2D experiments. − Mass spectra were obtained in EI mode at 70 eV. − Microanalyses were carried out by the Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università di Parma, Italy. − All reagents were of commercial quality, from freshly opened containers. The clays were purchased from Fluka (KSF Montmorillonite), Hlinka (Bieliaca) and Source Clay Repository (Na-Montmorillonite and Hectorite). All clays were heated at 100 °C before use.

Synthesis of Tetrahydroquinolines 5. − General Procedure: A mixture of the selected aldehyde (5 mmol), the selected aniline (5 mmol), freshly prepared cyclopentadiene[31] (7.5 mmol, 0.5 g, 0.6 mL) and Bieliaca (0.5 g) in water (5 mL) was vigorously shaken at 40 °C for 5 h in a small autoclave; after filtration and washing with

with hot acetone, the solvents were removed under reduced pressure and the crude product was chromatographed on silica gel, using a mixture of hexane/ethyl acetate (90:10) as eluent (alternatively, the product was sometimes crystallised from cold methanol). Products **5aw**, **5az**, **5bz**, **5dz**,**10** and **11** gave melting points and spectroscopic data consistent with those reported.

(3aα,4β,9bβ)-4-(4-Nitrophenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5ax): Yield 2.78 g (95%), yellow solid, m.p. 200−201 °C. − ^{1}H NMR ($CDCl_3$) δ = 1.6−1.9 (m, 1 H,), 2.5−2.7 (m, 1 H,), 3.02 (qd, 1 H, *J* = 8.9 and 3.3 Hz), 3.7 (br. s, 1 H,), 4.15 (d, *J* = 8.6 Hz, 1 H), 4.76 (d, *J* = 3.1 Hz, 1 H), 5.6−5.8 (m, 1 H,), 5.8−6.0 (m, 1 H,), 6.67 (dd, 1 H, *J* = 7.8 and 1.2 Hz), 6.80 (td, 1 H, *J* = 7.8 and 1.2 Hz), 7.02 (td, 1 H, *J* = 7.8 and 1.2 Hz), 7.08 (dd, 1 H, *J* = 7.8 and 1.2 Hz), 7.63 (d, *J* = 8.7 Hz, 2 H), 8.24 (d, *J* = 8.7 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ = 3364 cm^{-1}. − MS; *m/z*: [M^+] 292 (100), 156 (28). − $C_{18}H_{16}N_2O_2$: calcd. C 74.0, H 5.5, N 9.6; found C 74.2, H 5.8, N 9.4.

(3aα,4β,9bβ)-4-(4-Hydroxyphenyl)-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5ay): Yield 2.45 g (93%), yellow solid, m.p. 69.5−70.5 °C. − ^{1}H NMR ($CDCl_3$): δ = 1.86 (1 H, br dd, *J* = 16.1 and 8.8 Hz), 2.5−2.8 (m, 1 H,), 2.9−3.1 (qd, 1 H, *J* = 8.8 and 3.2 Hz), 4.11 (d, *J* = 8.8 Hz, 1 H), 4.2 (br. s, 1 H,), 4.59 (d, *J* = 3.2 Hz, 1 H), 5.6−5.7 (m, 1 H,), 5.8−5.9 (m, 1 H,), 6.63 (d, *J* = 7.7 Hz, 1 H), 6.77 (t, *J* = 7.7 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 7.00 (t, *J* = 7.7 Hz, 1 H), 7.08 (d, *J* = 7.7 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ = 3359 cm^{-1}. − MS; *m/z*: [M^+] 263 (100), 262 (70), 168 (33). − $C_{18}H_{17}NO$: calcd. C 82.1, H 6.5, N 5.3; found C 82.3, H 6.6, N 5.1.

Ethyl (3aα,4β,9bβ)-4-Phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline-8-carboxylate (5cz): Yield 3.07 g (96%), brown solid, m.p. 154−155 °C. − ^{1}H NMR ($CDCl_3$): δ = 1.37 (t, *J* = 7.1 Hz, 3 H), 1.7−1.9 (m, 1 H,), 2.5−2.7 (m, 1 H,), 3.02 (qd, 1 H, *J* = 9.2 and 3.3 Hz), 4.13 (d, *J* = 9.2 Hz, 1 H), 4.2 (br. s, 1 H,), 4.33 (q, *J* = 7.1 Hz, 2 H), 4.70 (d, *J* = 3.3 Hz, 1 H), 5.6−5.7 (m, 1 H,), 5.8−6.0 (m, 1 H,), 6.60 (d, *J* = 8.4 Hz, 1 H), 7.3−7.5 (m, 5 H,), 7.69 (dd, 1 H, *J* = 8.4 and 1.8 Hz), 7.77 (d, *J* = 1.8 Hz, 1 H). − IR (KBr): $\tilde{\nu}$ = 3336 cm^{-1}. − MS; *m/z*: [M^+] 319 (100), 228 (40). − $C_{21}H_{21}NO_2$: calcd. C 79.0, H 6.6, N 4.4; found C 79.2, H 6.7, N 4.2.

(3aα,4β,9bβ)-8-Methyl-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5ez): Yield 2.54 g (97%), white solid, m.p. 108−110 °C. − ^{1}H NMR ($CDCl_3$): δ = 1.96 (1 H, br dd, *J* = 16.2 and 8.6 Hz), 2.12 (s, 3 H,), 2.4−2.6 (m, 1 H,), 2.84 (qd, 1 H, *J* = 8.8 and 3.2 Hz), 3.4 (br. s, 1 H,), 3.93 (d, *J* = 8.8 Hz, 1 H), 4.43 (d, *J* = 3.2 Hz, 1 H), 5.4−5.6 (m, 1 H,), 5.6−5.8 (m, 1 H,), 6.37 (d, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 6.75 (s, 1 H,), 7.13 (1 H, tt, *J* = 6.9 and 1.4 Hz), 7.22 (2 H, td, *J* = 6.9 and 1.1 Hz), 7.29 (dd, 2 H, *J* = 6.9 and 1.4 Hz). − IR (KBr): $\tilde{\nu}$ = 3356 cm^{-1}. − MS; *m/z*: [M^+] 261 (100), 184 (42), 170 (60). − $C_{19}H_{19}N$: calcd. C 87.3, H 7.3, N 5.4; found C 87.2, H 7.5, N 5.3.

(3aα,4β,9bβ)-7-Methyl-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5fz): Yield 2.54 g (97%), white solid, m.p. 109−111 °C. − ^{1}H NMR ($CDCl_3$): δ = 1.7−1.9 (m, 1 H,), 2.22 (s, 3 H,), 2.5−2.7 (m, 1 H,), 2.97 (qd, 1 H, *J* = 8.7 and 3.5 Hz), 3.7 (br. s, 1 H,), 4.06 (d, *J* = 8.7 Hz, 1 H), 4.69 (d, *J* = 3.5 Hz, 1 H), 5.5−5.7 (m, 1 H,), 5.8−5.9 (m, 1 H,), 6.42 (s, 1 H,), 6.58 (d, *J* = 7.6 Hz, 1 H), 6.94 (d, *J* = 7.6 Hz, 1 H), 7.2−7.5 (m, 5 H,). − IR (KBr): $\tilde{\nu}$ = 3359 cm^{-1}. − MS; *m/z*: [M^+] 261 (100), 184 (44), 170 (58). − $C_{19}H_{19}N$: calcd. C 87.3, H 7.3, N 5.4; found C 87.1, H 7.4, N 5.5.

(3aα,4β,9bβ)-7,8-Dimethoxy-4-phenyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*c*]quinoline (5gz): Yield 2.61 g (85%), pale brown solid, m.p. 113−114 °C. − ^{1}H NMR ([D_6]DMSO): δ = 1.60 (1 H, br dd, *J* = 15.9 and 9.1 Hz), 2.3−2.6 (m, 1 H,), 2.90 (1 H, br q, *J* = 9.0 Hz), 3.65 (s, 6 H,), 3.94 (d, *J* = 8.7 Hz, 1 H), 4.45 (d, *J* = 2.7 Hz, 1 H), 5.5−5.6 (m, 1 H,), 5.8−6.0 (m, 1 H,), 6.44 (s, 1 H,), 6.61 (s, 1 H,), 7.26 (t, *J* = 7.2 Hz, 1 H), 7.36 (t, *J* = 7.2 Hz, 2 H), 7.45 (d, *J* = 7.2 Hz, 2 H). − IR (KBr): $\tilde{\nu}$ = 3345 cm^{-1}. − MS; *m/z*: [M^+] 307 (100), 292 (78), 91 (55). − $C_{20}H_{21}NO_2$: calcd. C 78.1, H 6.9, N 4.6; found C 78.3, H 7.0, N 4.5.

Acknowledgments

The authors acknowledge the support of the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Italy, the Consiglio Nazionale delle Ricerche (CNR), Italy and the University of Parma (National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni"). The authors are grateful to the Centro Interdipartimentale Misure (CIM) for the use of NMR and MS instruments and to Mr. Pier Antonio Bonaldi for technical collaboration.

---

[1] [1a] A. Dömling, E. Herdtweck, I. Ugi, *Acta Chem. Scand.* **1998**, *52*, 107. − [1b] L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366.

[2] R. A. Sheldon, *J. Mol. Catal. A* **1996**, *107*, 75.

[3] [3a] F. Bigi, R. Maggi, G. Sartori, E. Zambonin, *Chem. Commun.* **1998**, 513. − [3b] F. Bigi, B. Frullanti, R. Maggi, G. Sartori, E. Zambonin, *J. Org. Chem.* **1999**, *64*, 1004. − [3c] M. Ballabeni, R. Ballini, F. Bigi, R. Maggi, M. Parrini, G. Predieri, G. Sartori, *J. Org. Chem.* **1999**, *64*, 1029.

[4] F. Bigi, L. Chesini, R. Maggi, G. Sartori, *J. Org. Chem.* **1999**, *64*, 1033.

[5] F. Bigi, S. Carloni, B. Frullanti, R. Maggi, G. Sartori, *Tetrahedron Lett.* **1999**, *40*, 3465.

[6] P. A. Grieco, A. Bahsas, *Tetrahedron Lett.* **1988**, *29*, 5855.

[7] [7a] J. V. Johnson, S. Rauckman, P. D. Baccanari, B. Roth, *J. Med. Chem.* **1989**, *32*, 1942. − [7b] R. W. Carling, P. D. Leeson, A. M. Moseley, R. Baker, A. C. Foster, S. Grimwood, J. A. Kemp, G. R. Marshall, *J. Med. Chem.* **1992**, *35*, 1942. − [7c] P. D. Leeson, R. W. Carling, K. W. Moore, A. M. Moseley, J. D. Smith, G. Stevenson, T. Chan, R. Baker, A. C. Foster, S. Grimwood, J. A: Kemp, G. R. Marshall, K. Hoogsteen, *J. Med. Chem.* **1992**, *35*, 1954. − [7d] R. W. Carling, P. D. Leeson, A. M. Moseley, J. D. Smith, K. Saywell, M. D. Trickelbank, J. A. Kemp, G. R. Marshall, A. C. Foster, S. Grimwood, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 65.

[8] J. Cabral, P. Laszlo, *Tetrahedron Lett.* **1989**, *30*, 7237.

[9] [9a] Y. S. Cheng, E. Ho, P. S. Mariano, H. L. Ammon, *J. Org. Chem.* **1985**, *50*, 5678. − [9b] V. Lucchini, M. Prato, G. Scorrano, P. Tecilla, *J. Org. Chem.* **1988**, *53*, 2251.

[10] T.-P. Loh, K. S.-V. Koh, K.-Y. Sim, W.-K. Leong, *Tetrahedron Lett.* **1999**, *40*, 8447.

[11] T. Joh, N. Hagihara, *Tetrahedron Lett.* **1967**, 4199.

[12] H. Posson, J.-P. Hurvois, C. Moinet, *Synlett* **2000**, 209.

[13] [13a] P. J. Campos, I. Lamaza, M. A. Rodriguez, G. Canal, *Tetrahedron Lett.* **1997**, *38*, 6741. − [13b] J. M. Mellor, G. D. Merriman, *Tetrahedron* **1995**, *51*, 6115.

[14] [14a] S. Kobayashi, M. Araki, H. Ishitani, S. Nagayama, I. Hachiya, *Synlett* **1995**, 233. − [14b] S. Kobayashi, H. Ishitani, S. Nagayama, *Synthesis* **1995**, 1195. − [14c] R. Annunziata, M. Cinquini, F. Cozzi, V. Molteni, O. Schupp, *Tetrahedron* **1997**, *53*, 9715.

[15] [15a] S. Kobayashi, S. Nagayama, *J. Org. Chem.* **1996**, *61*, 2256. − [15b] S. Kobayashi, S. Nagayama, *J. Am. Chem. Soc.* **1996**, *118*, 8977. − [15c] A. S. Kiselyov, L. Smith II, R. W. Armstrong, *Tetrahedron* **1998**, *54*, 5089. − [15d] A. S. Kiselyov, L. Smith II, A. Virgilio, R. W. Armstrong, *Tetrahedron* **1998**, *54*, 7987.

[16] KSF (Fluka) is a natural montmorillonite treated with sulfuric acid, with the following chemical composition (average values): SiO_2 (54.0%), Al_2O_3 (17.0%), Fe_2O_3 (5.2%), CaO (1.5%), MgO (2.5%), Na_2O (0.4%), K_2O (1.5%).

[17] Na-Montmorillonite is a natural sodium montmorillonite with the following chemical composition (average values): SiO_2 (58.7%), Al_2O_3 (18.9%), TiO_2 (0.2%), Fe_2O_3 (4.0%), CaO (0.8%), MgO (2.7%), Na_2O (1.2%), K_2O (0.3%).

[18] Bieliaca is a natural bentonite, mainly constituted from montmorillonite, treated with hydrochloric acid, with the following chemical composition (average values): SiO_2 (65.1%), Al_2O_3 (14.4%), TiO_2 (0.2%), Fe_2O_3 (1.4%), CaO (0.3%), MgO (2.5%), Na_2O (0.3%), K_2O (0.4%).

[19] Hectorite is a natural clay with the following chemical composition (average values): SiO_2 (42.5%), Al_2O_3 (0.8%), TiO_2 (0.1%), Fe_2O_3 (0.4%), CaO (13.7%), MgO (18.9%), Na_2O (1.2%), K_2O (0.2%), Li_2O (1.9%).

[20] J. R. Butruille, T. J. Pinnavaia, "Alumina Pillared Clays" in *Comprehensive Supramolecular Chemistry* (Eds.: G. Alberti, T. Bein), Pergamon, **1996**, vol. 7, pp. 219−250.

[21] Determined in our laboratory by temperature-programmed desorption of ammonia gas (NH_3-TPD): P. Berteau, B. Delmon, *Catal. Today* **1989**, *5*, 121.

[22] Determined in our laboratory by the BET method: S. Brunauer, P. H. Emmett, E. Teller, *J. Am. Chem. Soc.* **1938**, *60*, 309.

[23] For a similar low activity of Na-exchanged clays, see for example: D. Chatterjee, H. M. Mody, K. N. Bhatt, *J. Mol. Catal. A* **1995**, *104*, L115.

[24] M. Balogh, P. Laszlo, *Organic Chemistry Using Clays*, Springer Verlag, N. Y., **1993**.

[25] J. M. Adams, S. E. Davies, S. H. Graham, J. M. Thomas, *J. Catal.* **1982**, *78*, 197.

[26] [26a] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7817. − [26b] H.-J. Schneider, N. K. Sangwan, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 896. − [26c] N. K. Sangwan, H.-J. Schneider, *J. Chem. Soc., Perkin Trans. 2* **1989**, 1223. − [26d] W. Blokzijl, M. J. Blandamer, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1991**, *113*, 4241.

[27] C. Reichardt, "*Solvents and Solvent Effects in Organic Chemistry*", VCH, Weinheim, **1988**.

[28] M. Onikata, M. Kondo, S. Yamanaka, *Clays Clay Min.* **1999**, *47*, 678.

[29] [29a] R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 212. − [29b] T. Shono, Y. Matsumura, K. Inoue, H. Ohmizu, S. Kashimura, *J. Am. Chem. Soc.* **1982**, *104*, 5753.

[30] [30a] H. Ishitani, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 7357. − [30b] G. Babu, P. T. Perumal, *Tetrahedron* **1998**, *54*, 1627.

[31] R. B. Moffett, *Org. Synth., Coll. Vol.* **1963**, *IV*, 238.

Received November 29, 2000
[O00607]