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Multicomponent reactions under clay catalysis

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Abstract

Three-component reactions for the synthesis of substituted dihydropyrimidines (**4**), chromenes (**8**) and tetrahydroquinolines (**11**) have been performed in water and in the presence of a montmorillonite KSF clay. The products, easily isolated from the reaction mixture by crystallisation, are obtained in high yield and selectivity and the catalyst can be recycled for many runs without losing its activity. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Due to the increasing sensitivity for environmental protection in both the political and economical world during recent years, the main challenge for a modern synthetic research group is optimising economic factors (i.e. maximum overall yield, minimum cost and execution time) while considering the environmental ones. In our opinion this challenge must be taken into account not only by industrial groups but also by academic laboratories.

One of the tools of the organic chemist to strive for the ideal synthesis (in which, as reported by Wender et al. [1], *the target molecule is made from readily available starting materials in one simple, safe, environmentally acceptable and resource-effective operation that proceeds quickly and in quantitative yield*) is represented by the multicomponent reaction (MCR); *this process consists of a number* (≥ 2) *of synthetic steps which are carried out in the same flask without isolation of any intermediate, thus reducing time, saving money, energy and raw materials with both economic and environmental benefit* [2,3] and leads to a product containing the main parts of all starting materials. The MCRs, firstly described by Strecker [4] in 1850, after having been considered as exotic variants of organic reactions have become very popular in recent years [5–9] for the preparation of chemicals following environmentally friendly and cheaper strategies.

As part of our program aimed at developing new selective and preparatively useful methodologies based on the use of clays as promoters of fine chemicals preparation [10–13], we decided to combine the above-mentioned advantages of the MCRs with those of heterogeneous catalysis (high selectivity, easy removal of catalyst, waste minimisation, recycling of the catalyst) by carrying out MCRs under montmorillonite KSF catalysis for the synthesis of dihydropyrimidines, chromenes and tetrahydroquinolines.

2. Experimental

2.1. Reagents

All the reagents were from freshly opened containers. Montmorillonite KSF was purchased from Fluka.

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*2.2. Synthesis of substituted dihydropyrimidines (**4**)*

A mixture of the selected aldehyde (0.010 mol), selected β-dicarbonyl compound (0.010 mol), urea (0.015 mol, 0.9 g) and montmorillonite KSF (0.5 g) in water (5 ml) was refluxed for 48 h under vigorous stirring; after filtration and washing of the catalyst with hot methanol, the solvents were removed under reduced pressure and the products crystallised from methanol.

*2.3. Synthesis of substituted 2-amino-2-chromenes (**8**)*

A mixture of the selected aldehyde (0.010 mol), α-naphthol (0.010 mol, 1.4 g), malononitrile (0.010 mol, 0.7 g) and hot water (50 ml) washed montmorillonite KSF (1.0 g) in water (10 ml) was refluxed for 3 h under vigorous stirring; after filtration and washing of the catalyst with hot acetone (4×25 ml), the solvents were removed under reduced pressure and the products crystallised from methanol.

*2.4. Synthesis of substituted tetrahydroquinolines (**11**)*

A mixture of the selected aldehyde (0.010 mol), aniline (0.010 mol, 0.9 g, 0.9 ml), freshly prepared cyclopentadiene (0.015 mol, 1.0 g, 1.2 ml) [14] and montmorillonite KSF (0.3 g) in water (5 ml) was vigorously shaken at 40°C for 4 h in a small autoclave; after filtration and washing of the catalyst with hot acetone, the solvents were removed under reduced pressure and the products crystallised from cold methanol.

3. Results and discussion

Montmorillonite KSF is an acid treated cationic clay with surface acidity 0.70 meq H^+/g,[1] surface area 15±10 m^2/g, basal distance of the montmorillonite sheets ∼10 Å, showing the following chemical composition (average value): 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%).[2]

In a recent paper [15], we described the revision of the Biginelli reaction under heterogeneous catalysis; the production of variously substituted dihydropyrimidines (**4a–i**) [products showing important pharmacological properties, i.e. calcium channels blockers, alpha$_1$-a-antagonists, antihypertensive agents], usually carried out in the presence of strong protic acids or polyphosphoric esters [16–18] was achieved by reacting an aldehyde (**1**), a β-dicarbonyl compound (**2**) and urea (**3**) at 100°C for 48 h in the presence of montmorillonite KSF. It is worthy to note that the process affords good yields (70–85%) and selectivities (>95%) when carried out in water as solvent even if two molecules of water are produced in the global reaction. The catalyst, recovered by filtration, washed with methanol and heated at 120°C for 5 h, can be reused at least three times without losing its activity.

The possibility of building up complex molecules from cheap reagents in a “mud batch” (clay and water) prompted us to try to perform multicomponent reactions under these conditions for the production of chromenes (**8**) and tetrahydroquinolines (**11**). At first we studied the three-component condensation between benzaldehydes (**1**), malononitrile (**5**) and α-naphthol (**7**) (Scheme 1).

The reaction, usually performed in the presence of an excess of piperidine in ethanol [19], was first carried out in water and KSF at 100°C for 2 h using *para*-nitrobenzaldehyde as model substrate, yielding the corresponding chromene (**8a**) in modest yield and selectivity (51 and 87%, respectively). On the contrary, the recycled catalyst (filtered and washed with methanol and acetone) afforded the product **8a** in 87% yield and 96% selectivity. These different behaviours are probably due to the fact that the commercial montmorillonite KSF (Fluka) is pretreated with sulphuric acid and this additional acidity can work against the second step; of course, during the recycle of the catalyst the residual acidity is remarkably decreased.

Concerning the reaction mechanism, surprisingly, we discovered that the condensation between aldehyde and malononitrile can be achieved without any promoter if carried out in polar solvent like water or alcohols [24] even though many authors reported the

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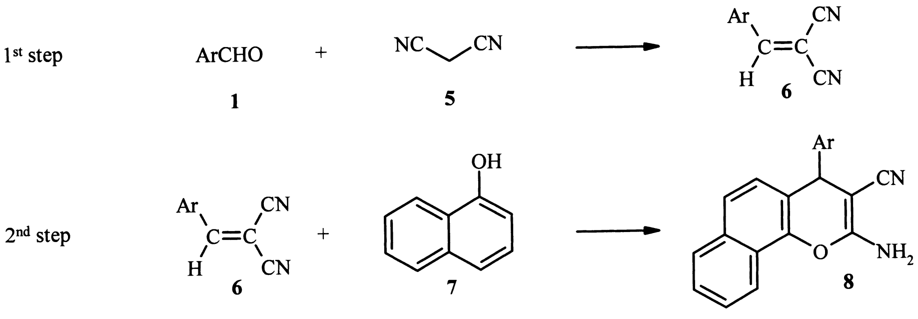
[1] Determined in our laboratory by temperature programmed desorption of ammonia gas (NH_3-TPD).

[2] Data from Süd-Chemie.



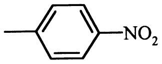
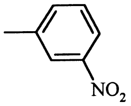
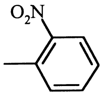
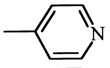
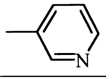
Scheme 1. The synthesis of substituted chromenes (**8**).

use of various homogeneous and heterogeneous catalysts, including exotic ones [20–23]. Only the second step, the cyclocondensation reaction between benzylidenemalononitrile (**6**) and α-naphthol (**7**), requires the presence of the catalyst; it is important to underline that if the reaction is simply carried out by mixing the three model reagents in water without catalyst it affords the corresponding chromene in 79% yield and 91% selectivity.

By using different aromatic aldehydes we were able to synthesise in good yields and excellent selectivities a large class of 2-amino-2-chromenes (**8a–e**) products that represent potential biodegradable agrochemicals [25–27] (Table 1).

In addition, the heterogeneous catalyst, simply filtered and washed with methanol, has been reused five times to promote the model reaction affording the corresponding chromene in 85, 87, 86, 88 and 86% yield, respectively, and with the same excellent selectivity.

Table 1
Synthesis of substituted 2-amino-2-chromenes (**8**)

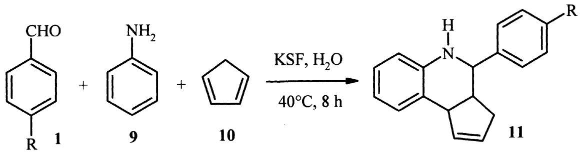
Entry	Ar	Yield (%)	Selectivity (%)
a		87	97
b		88	96
c		83	95
d		93	94
e		91	96

Concerning the substituted tetrahydroquinolines (**11**), the usual syntheses utilise strong protic acids in acetonitrile [28–31]; there is only one example utilising an heterogeneous catalyst, the iron(III) exchanged montmorillonite K10 [32]. In this paper, the authors did not report any comment concerning either the recycling of the catalyst or the possible leaching of the metal into the solution [33].

We decided to try the production of such compounds via a three-component domino reaction under heterogeneous catalysis using the montmorillonite KSF without any modification. The model reaction between *para*-chlorobenzaldehyde, aniline (**9**) and cyclopentadiene (**10**) was carried out at 40°C in a small autoclave for 4 h. We tested acetonitrile, diethyl ether, methanol and water as solvent and we found that water was the best diluent affording the corresponding tetrahydroquinoline (**11a**) in 93% yield and 96% selectivity. By changing the substituent on the aromatic ring of aldehyde, we were able to produce substituted tetrahydroquinolines (**11a–c**) in very high yields and selectivities (Table 2). These products can be employed for pharmacological purposes (anticancer, antibiotic, antidepressant and antiallergenic) or as antioxidant or agrochemical [34–37].

Concerning the reaction mechanism, the first step, that does not require catalyst, involves the condensation between the aldehyde and the aniline for the formation of the imine intermediate; the second one is a Diels-Alder process in which the imine, acting as azadiene, is the electron-poor system and the dienophile, the cyclopentadiene, is the electron-rich one. As we

Table 2
Synthesis of substituted tetrahydroquinolines (**11**) in water under clay catalysis



Entry	R	Yield (%)	Selectivity (%)
a	Cl	94	95
b	OH	93	94
c	H	86	87[a]

[a] The only by-product detected is represented by the imine intermediate.

have never isolated possible intermediates, it can be presumed that the reaction proceeds via a concerted mechanism.

Last, we faced the problem of the catalyst recycle; montmorillonite KSF, after being filtered, washed with water and heated at 120°C was reused as catalyst in the model reaction. After six runs, yield and selectivity remained unchanged.

Due to the planarity of all the three classes of compounds (dihydropyrimidines, chromenes and tetrahydroquinolines) and due to the swelling of clays in water (as it can be deduced from data reported in the literature [38], the basal distance between the montmorillonite sheets can increase from ~3 to 6 Å) and we can presume that the reactions can occur in the interlamellar region.

4. Conclusions

The synthesis of substituted dihydropyrimidines (**4**), chromenes (**8**) and tetrahydroquinolines (**11**) was efficiently performed with high yields and excellent selectivities over clay catalysts in water. The simplicity of work-up and isolation of the products (the reaction crude is filtered, the clay washed with a solvent and the products crystallised from the same solvent) together with the low cost of the catalyst and the reagents, make the present reactions convenient routes to these kinds of fine chemicals. In addition, the possibility to synthesise complex molecules from simple starting reagents in a mud batch (a mixture of montmorillonite clay and water) is in agreement with the theory that clays could have acted as templates for elaboration of the first biomolecules in prebiotic times [39].

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