

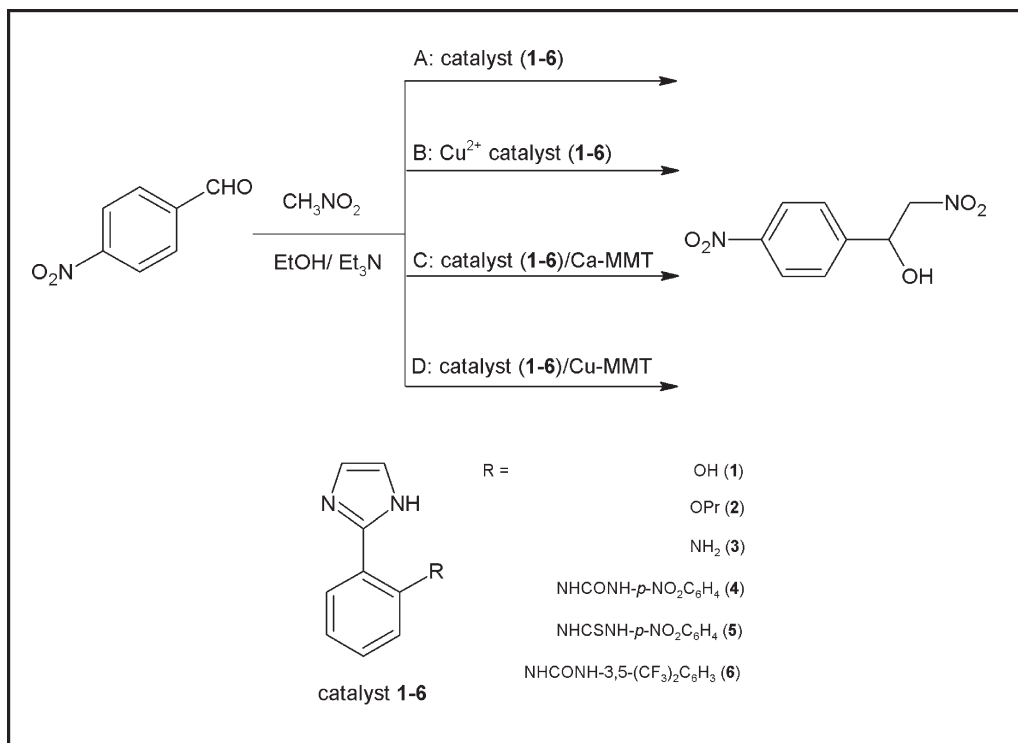
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Six derivatives (**1–6**) of 2-phenyl-1*H*-imidazole were tested as catalysts of Henry reaction. Three new (**4–6**) 2-phenyl-1*H*-imidazole derivatives, differently substituted (thio)ureas, were synthesized and determined by ¹H NMR and IR spectroscopy and elemental analysis. Two types of catalysis, homogeneous and heterogeneous, were examined and compared. Clay minerals Ca-MMT and Cu-MMT were used as solid supports for heterogeneous catalysis. The best results were obtained using compound **2** under conditions of heterogeneous method **D** from the point of view of yield and reaction time.

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INTRODUCTION

Heterocyclic compounds including the imidazole ring, which is part of biologically significant compounds histidine (essential amino acid) and his derivative histamine, have many important properties. They act as nucleophile or proton-transfer agent in biological systems [1], they play significant role in the binding of metallic ions to proteins during enzyme reactions [2], they have antibacterial and/or antifungal effects [3,4], and last but not least they are applied as catalysts in quite a few organic reactions.

The nitroaldol (Henry) reaction is one of the classical reactions forming C–C bonds in organic synthesis [5].

C-nucleophile generated from nitroalkane reacts with an electrophilic carbonyl carbon which gives versatile synthetic intermediate β-nitroalcohol. Several efficient catalytic methods for performing mainly enantioselective version of this reaction have been described in recent years. First pioneers Shibasaki and coworkers reported a series of bimetallic catalysts [6]. Trost and Yeh showed new generation of dinuclear zinc complexes yielding high enantioselectivity [7]. One of the classes of compounds that could be used as ligands for Cu catalysts are five-membered heterocycles, for example bis(oxazolines) [8], bis(thiazolines) [9], and/or imidazole derivatives [10,11]. Henry reaction was catalyzed without

presence of metals with the aid of derivatives of following compounds, guanidine [12], (thio)ureas [13], or guanidine-thiourea bifunctional catalysts [14], too.

The development of new heterogeneous catalysts to promote organic reactions is field of growing interest [15–18], because of their advantages over homogeneous catalysts, such as simplification of the work-up, easy separation, and recyclability of catalyst. Recently, mesoporous silica and/or similar materials were used as solid support for catalysis of the Henry reaction under heterogeneous conditions. Abdi and coworkers anchored chiral BINOL ligand on silica and mesoporous MCM-41 [19]. Several Cu(II) diamine complexes have been anchored on amine functionalized silica, Cu-exchanged zeolite and on nanoporous carbon and used for Henry reaction [20].

Clay minerals have continuously attracted attention also for the possibility of modifying their layered structure by intercalation, thus creating new materials such catalysts [21]. The clay mineral montmorillonite, a member of dioctahedral smectite group, is the most important smectite used in catalytic applications. Smectites have a layered structure formed by two tetrahedral sheets linked with an octahedral sheet. The octahedral sites of montmorillonite are occupied mainly by Al^{3+} cations which are to some extent replaced by Fe^{3+} and/or Mg^{2+} ions. The tetrahedron contains as the central atoms mostly Si^{4+} , partially substituted by Al^{3+} . Nonequivalent substitution of the central atoms in the octahedron and/or tetrahedron generates a negative charge on the layers, which is balanced by hydrated exchangeable cations in the interlayers, most frequently Ca^{2+} , Mg^{2+} , and Na^{+} in natural samples.

We focused on comparison of homogeneous *versus* heterogeneous catalysis using our catalytic systems in Henry reaction between 4-nitrobenzaldehyde and nitromethane as model reaction. Two types of clay minerals, natural Ca(II)-montmorillonite (Ca-MMT) and modified Cu(II)-montmorillonite (Cu-MMT), were used as solid supports for heterogeneous catalysis. Cu-MMT was chosen on the basis of studies deal with catalysis of Henry reaction by Cu(II) complexes of five-membered heterocycles, which are good catalysts, and Ca-MMT was chosen as starting material for comparison. Three previously prepared 2-(2-hydroxyphenyl)-1*H*-imidazole (**1**), 2-(2-propoxyphenyl)-1*H*-imidazole (**2**) [22], and 2-(2-aminophenyl)-1*H*-imidazole (**3**) [23], and three novel prepared derivatives of 1-subst.-3-[2-(1*H*-imidazol-2-yl)phenyl] (thio)ureas (**4–6**) were chosen as catalysts. Syntheses of mentioned (thio)ureas started from 2-(2-aminophenyl)-1*H*-imidazole with appropriate iso(thio)cyanate.

RESULTS AND DISCUSSION

The synthetic part of our work includes syntheses of three derivatives of 2-phenyl-1*H*-imidazole (**1–3**) previ-

ously described in literature [22,23] and three novel derivatives of 2-phenyl-1*H*-imidazole (**4–6**). All derivatives have substituted *ortho* position on the benzene ring.

2-(2-hydroxyphenyl)-1*H*-imidazole (**1**) and 2-(2-propoxyphenyl)-1*H*-imidazole (**2**) were synthesized following the method of Pařík *et al.* [22].

The syntheses of novel 1-subst.-3-[2-(1*H*-imidazol-2-yl)phenyl](thio)ureas (**4–6**) started from 2-(2-aminophenyl)-1*H*-imidazole (**3**), which was prepared according following two-step synthesis. 2-Nitrobenzaldehyde reacted with glyoxal trimer dihydrate and ammonium acetate in acetic acid to form 2-(2-nitrophenyl)-1*H*-imidazole as intermediate in quite low yield 19%, but opposite literature [23], it was more than double yield. This compound was then hydrogenated using Pd/C as catalyst in high yield 91%.

1-(subst.phenyl)-3-[2-(1*H*-imidazol-2-yl)phenyl]ureas (**4, 6**) were synthesized from 2-(2-aminophenyl)-1*H*-imidazole (**3**) by reactions with appropriate isocyanates. It was important to find an appropriate solvent for the successful accomplishment of reaction; acetonitrile appeared to be the best option. First urea derivative 1-(4-nitrophenyl)-3-[2-(1*H*-imidazol-2-yl)phenyl]urea (**4**) was obtained in average yield 49%; on the other hand, second urea derivative 1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(1*H*-imidazol-2-yl)phenyl]urea (**6**) was obtained in very high yield 95%.

1-(4-nitrophenyl)-3-[2-(1*H*-imidazol-2-yl)phenyl]thiourea (**5**) was synthesized from 2-(2-aminophenyl)-1*H*-imidazole (**3**) by reaction with appropriate isothiocyanate, but in contrast with structurally similar urea derivative, it had to use milder reaction conditions and dichloromethane was used as solvent. We obtained product (**5**) in quite low yield 33%.

The purity and structure of prepared novel compounds (**4–6**) were determined by the ^1H NMR spectroscopy, IR spectroscopy, and elemental analysis. Figures 1–3 show ^1H NMR spectra of novel prepared compounds (**4–6**). For detailed data see Experimental section.

The prepared compounds (**1–6**) and their modifications were examined as catalysts for Henry nitroaldol condensation. We focused on comparison of two types of catalysis, homogeneous *versus* heterogeneous. In the first case two subtypes, method **A** and **B**, were used. Reaction was catalyzed either by derivatives **1–6** (method **A**) or these derivatives acted as ligands in reaction with metal precursor copper(II)acetate (method **B**) in ratio ligand/Cu(II) (1:1). In the case of heterogeneous catalysis, two subtypes were examined, because we used two clay minerals as solid supports, Ca-MMT (method **C**) and Cu-MMT (method **D**).

Clay-supported catalysts were characterized by XRD analysis and IR spectroscopy. The Figure 4(a) shows

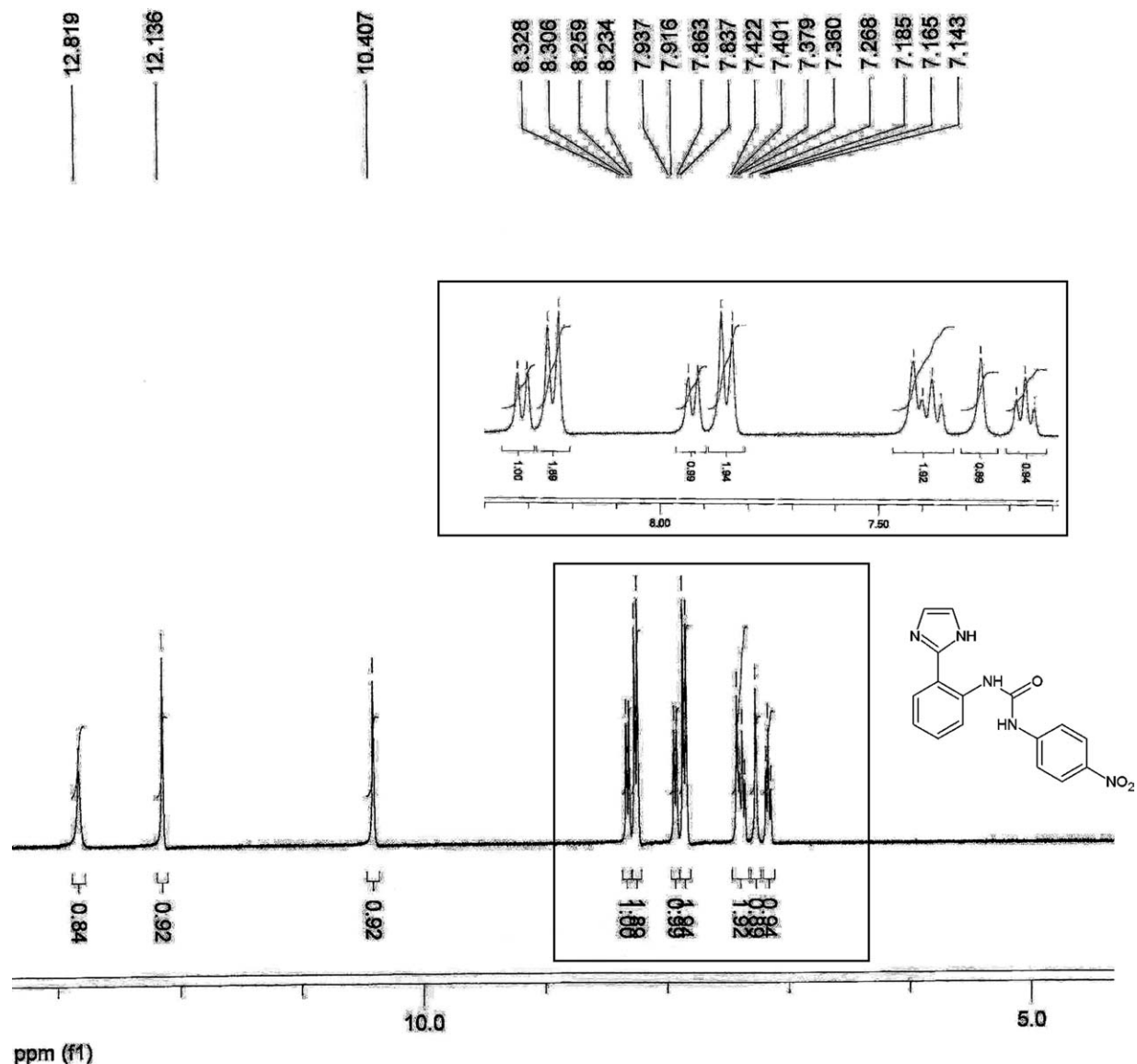


Figure 1. ^1H NMR spectrum of 1-(4-nitrophenyl)-3-[2-(1*H*-imidazol-2-yl)phenyl]urea (4).

XRD patterns of original Ca-MMT ($d_{001} = 1.56$ nm) and its modified forms by compounds **1–6**. The changes of basal spacing reflect the intercalation stages of compounds **1** ($d_{001} = 1.84$ nm), **2** ($d_{001} = 1.76$ nm) and **3** ($d_{001} = 1.64$ nm) into interlayer spaces of Ca-MMT. Other compounds **4–6** were probably anchored on clay surface. Figure 4(b) shows XRD patterns of Cu-MMT ($d_{001} = 1.36$ nm) and its modified forms by compounds **1–6**. In comparison with starting material Ca-MMT, the XRD patterns of Cu-MMT shows decrease of basal spacing caused by difference in ionic radius of Cu^{2+} ion, which is smaller than Ca^{2+} ion.

The mid-IR spectra of Ca-MMT and its modified forms by compounds **1–6** are shown on Figure 5(a).

Broad band in the Ca-MMT spectrum is attributed to stretching vibrations of structural O—H groups (3631 cm^{-1}) and water molecules (3423 cm^{-1}). The most intense band due to the Si—O—Si stretching mode is observed at 1040 cm^{-1} . The presence of IR bands about 2930 cm^{-1} and 2860 cm^{-1} (Fig. 5) were attributed to asymmetric and symmetric C—H stretching bands of aromatic skeleton of compounds **1–6** supported by clay matrix. Compared to the Ca-MMT, the Cu-MMT [Fig. 5(b)] has additional band appearing at 3365 cm^{-1} which can be attributed to the O—H stretching vibration in dimerized Cu^{2+} ions bridging two hydroxyls [24].

Catalysis of Henry reaction was assessed from point of view of yield and reaction time (see Table 1).

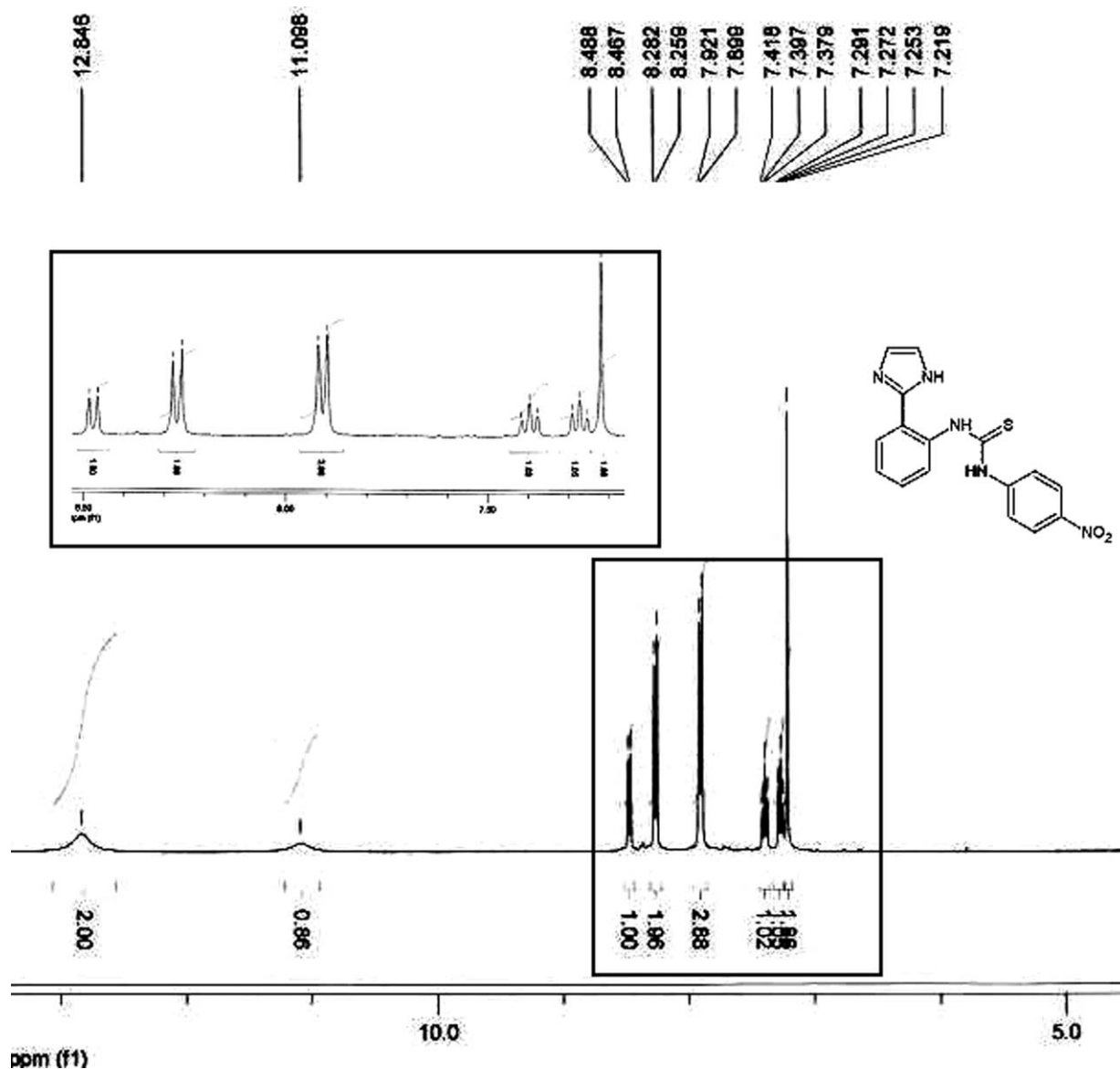


Figure 2. ^1H NMR spectrum of 1-(4-nitrophenyl)-3-[2-(1H-imidazol-2-yl)phenyl]thiourea (5).

Primarily, reaction was accomplished without application of catalyst for further comparison; in this case, the reaction time was 24 h and yield 58%. Second, reaction was accomplished in presence of solid supports Ca-MMT and Cu-MMT. In both cases, reaction times are comparable with reaction time of reaction without catalyst, but yields are evidently higher (see Table 1). So, from the point of view of yield, chosen solid supports are catalytically active.

The best results were obtained using compound 2 under conditions of heterogeneous method D. On the other hand, heterogeneous method C did not provide such a good results. This difference could be caused by type of clay counterion. There is a possibility that com-

pounds create stable complexes with Cu^{2+} counterion. Generally, the lowest yields and longest reaction times were achieved by homogeneous method B, which is conventionally used [10,11]. Very good yields were obtained by homogeneous method A, but reaction times were comparable with reaction without application of catalyst, except catalysis by compound 3.

EXPERIMENTAL

Instrumentation, analysis and starting materials. The purity of novel prepared (thio)urea derivatives 4–6 was checked by elemental analysis using an automatic analyser EA 1108 (Fisons). ^1H NMR spectra were measured at 25°C using 5%

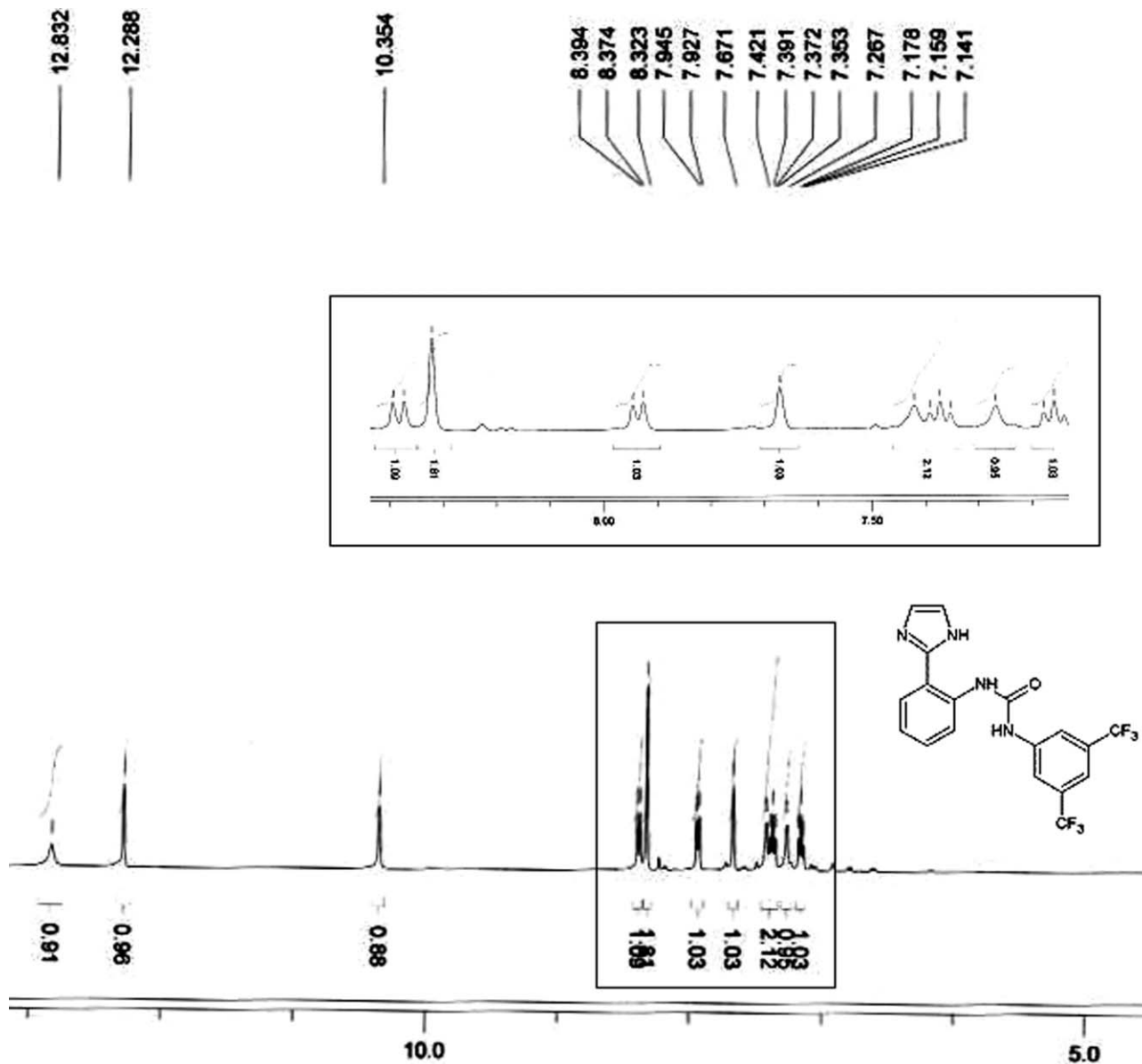


Figure 3. ^1H NMR spectrum of 1-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(1*H*-imidazol-2-yl)phenyl]urea (6).

solutions of compounds in DMSO-d_6 on a NMR AVANCE 400 at 400 MHz; the chemical shifts were referenced to the solvent signal. Proton numbering for assignment of ^1H NMR shifts shows Figure 6. The mid-infrared spectra were obtained on a Perkin Elmer 2000 Fourier transform infrared spectrometer. For each sample, 32 scans were recorded in the $4000\text{--}400\text{ cm}^{-1}$ spectral range with a resolution of 4 cm^{-1} at room temperature using the KBr pressed disc technique (0.8 mg of sample and 290 mg of KBr). XRD analysis was used for characterization of clay-supported catalysts obtained by the X-ray diffractometer INEL equipped with a curved position-sensitive detector CPSD 120 (reflection mode, Ge-monochromatized $\text{CuK}\alpha_1$ radiation) and next infrared spectroscopy with experimental arrangement above mentioned was used for characterization. Progress of Henry reactions was monitored by thin-

layer chromatography (TLC) using Precoated TLC-sheets ALUGRAM[®] SIL G/UV₂₅₄ and ethyl acetate/hexane (1:4) as mobile phase. Other chemical materials were purchased from Aldrich, Fluka and Merck Companies.

2-(2-Hydroxyphenyl)-1*H*-imidazole (1) and 2-(2-propoxyphenyl)-1*H*-imidazole (2). Compounds **1** and **2** were synthesized following the procedure reported in literature [22].

2-(2-Aminophenyl)-1*H*-imidazole (3). Compound **3** was synthesized according the procedure reported in literature [23].

1-(4-Nitrophenyl)-3-[2-(1*H*-imidazol-2-yl)phenyl]urea (4). To a mixture of 0.25 g (1.57 mmol) of 2-(2-aminophenyl)-1*H*-imidazole in acetonitrile was added 0.26 g (1.57 mmol) of 4-nitrophenyl isocyanate. Reaction mixture was refluxed under stirring for 5 h, following with stirring overnight under laboratory temperature. Pale yellow crystals were collected by

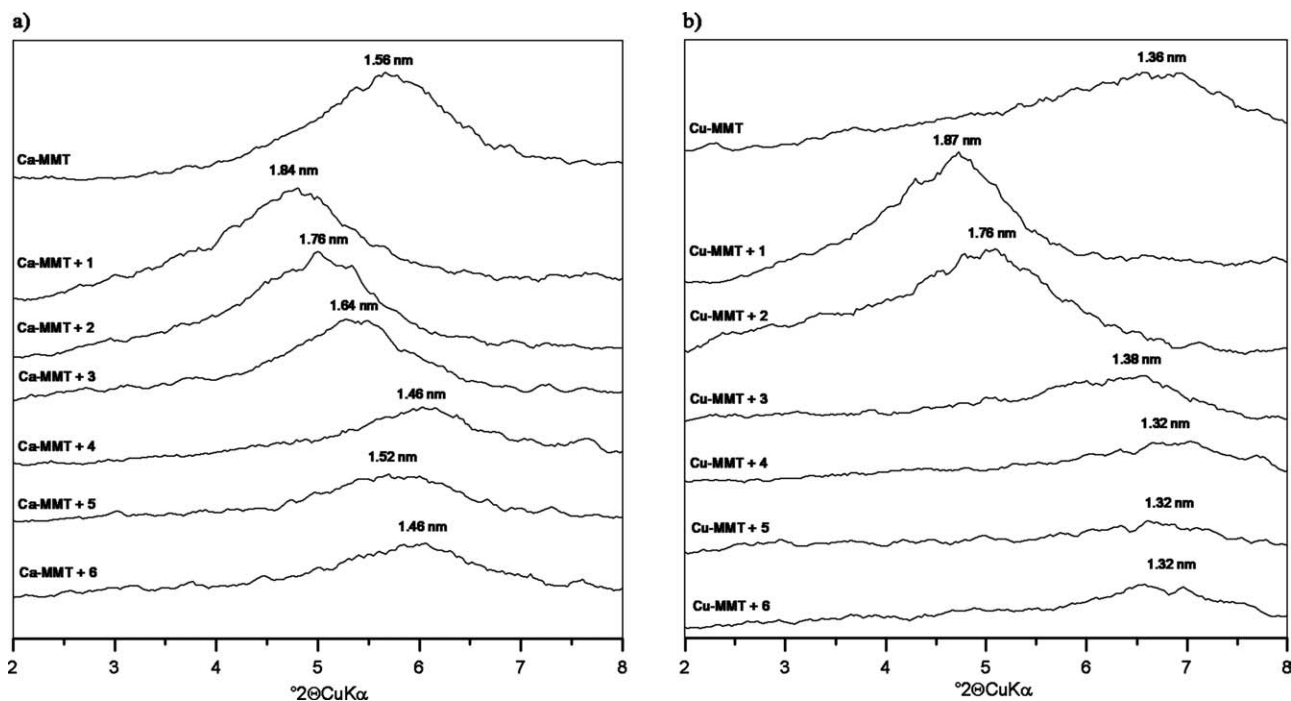


Figure 4. XRD patterns of (a) Ca-MMT and its modified forms by compounds 1–6 and (b) Cu-MMT and its modified forms by compounds 1–6.

filtration to yield 0.25 g (49%) of **4**; mp 198–202°C; ^1H NMR (DMSO- d_6 , 400 MHz): δ 12.82 (s, 1H, H-8), 12.14 (s, 1H, H-5), 10.41 (s, 1H, H-9), 8.32 (d, 1H, H-1), 8.25 (d, 2H, H-10), 7.93 (d, 1H, H-4), 7.85 (d, 2H, H-11), 7.36–7.42 (m, 2H, H-3, H-6[7]), 7.27 (s, 1H, H-6[7]), 7.17 (t, 1H, H-2); IR (KBr): 3215 (NH), 1687 (C=O), 1504 (NO $_2$); Anal. Calcd for

$\text{C}_{16}\text{H}_{13}\text{N}_5\text{O}_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.26; H, 4.24; N, 21.42.

1-(4-Nitrophenyl)-3-[2-(1H-imidazol-2-yl)phenyl]thiourea (5). A mixture of 0.1 g (0.628 mmol) of 2-(2-aminophenyl)-1H-imidazole in dichloromethane was stirred under argon atmosphere and cooled in ice. To this mixture was added 0.11 g (0.628

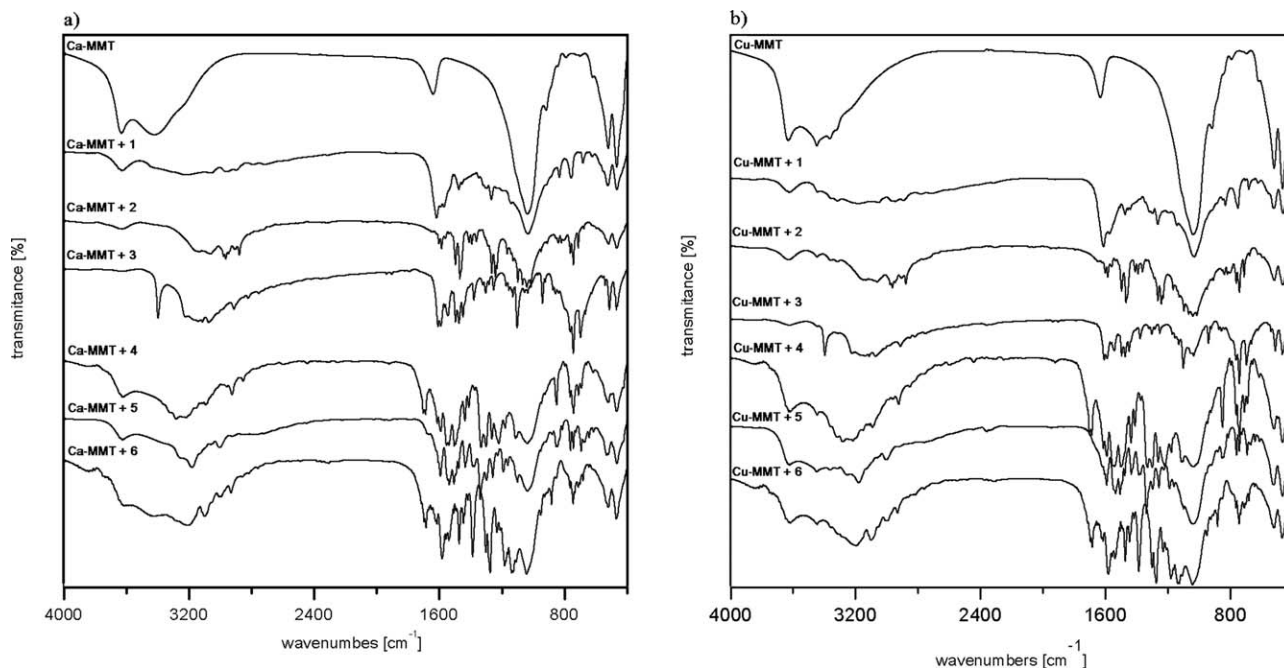


Figure 5. IR spectra of (a) Ca-MMT and its modified forms by compounds 1–6 and (b) Cu-MMT and its modified forms by compounds 1–6.

Table 1

Yields and reaction times of realized Henry reactions.

Compound	Method of catalysis	Yield (%)	Reaction time ^a (h)
–	Without catalyst	58	24
–	Ca-MMT	75	25
–	Cu-MMT	84	20
1	A	63	26
	B	47	48
	C	45	16
	D	60	6
2	A	51	25
	B	47	25
	C	42	22
	D	82	5
3	A	76	5
	B	46	48
	C	34	5
	D	60	5
4	A	72	25
	B	53	75
	C	59	4
	D	56	7
5	A	44	15
	B	27	72
	C	39	8
	D	48	10
6	A	76	24
	B	32	72
	C	44	21
	D	40	24

^aReaction time corresponds to the disappearance of starting aldehyde monitored by TLC.

mmol) of 4-nitrophenyl isothiocyanate and 3 drops of dry triethylamine, reaction mixture was stirred for 30 min. Cooling bath was then removed and mixture was stirred overnight under laboratory temperature and argon atmosphere. Yellow crystals were collected by filtration to yield 0.07 g (33%) of **5**; mp: 140–145°C; ¹H NMR (DMSO-d₆, 400 MHz): δ 12.85 (s, 2H, H-5, 8), 11.10 (s, 1H, H-9), 8.48 (d, 1H, H-1), 8.27 (d, 2H, H-10), 7.91 (d, 3H, H-4, 11), 7.40 (t, 1H, H-3), 7.27 (t, 1H, H-2), 7.22 (s, 2H, H-6, 7); IR (KBr): 3180 (NH), 1507 (NO₂), 1259 (C=S); Anal. Calcd for C₁₆H₁₃N₅O₂S: C, 56.36; H, 3.86; N, 20.64; S, 9.45. Found: C, 55.90; H, 4.24; N, 20.41; S, 9.75.

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[2-(1*H*-imidazol-2-yl)phenyl]urea (6). To a mixture of 0.25 g (1.57 mmol) of 2-(2-aminophenyl)-1*H*-imidazole in acetonitrile was added 0.271 mL (1.57 mmol) of 3,5-bis(trifluoromethyl)phenyl isocyanate. Reaction mixture was refluxed under stirring for 5 h, following with stirring overnight under laboratory temperature. White crystals were collected by filtration to yield 0.62 g (95%) of **6**; mp 222–230°C; ¹H NMR (DMSO-d₆, 400 MHz): δ 12.83 (s, 1H, H-8), 12.29 (s, 1H, H-5), 10.35 (s, 1H, H-9), 8.38 (d, 1H, H-1), 8.32 (s, 2H, H-10), 7.94 (d, 1H, H-4), 7.67 (s, 1H, H-11), 7.35–7.42 (m, 2H, H-3, H-6[7]), 7.27 (s, 1H, H-6[7]), 7.16 (t, 1H, H-2); IR (KBr): 3193 (NH), 1686 (C=O), 1388 (CF); Anal. Calcd for C₁₈H₁₂F₆N₃O: C, 52.18; H, 2.92; N, 13.52. Found: C, 52.40; H, 3.22; N, 13.73.

General procedure for clay-supported catalyst. The natural Ca-MMT from a deposit Ivancice in the Czech Republic, selected as a starting material, was fractionated to less than <45 μm particles. The structural formula of this montmorillonite as calculated from the chemical analysis is (Al_{2.52}Fe_{0.54}Mg_{0.90}Ti_{0.04})(Si_{7.96}Al_{0.04})O₂₀(OH)₄(Ca_{0.24}K_{0.06}Na_{0.09}Mg_{0.10}). The Cu-MMT was prepared from 10 g Ca-MMT by cation exchange method

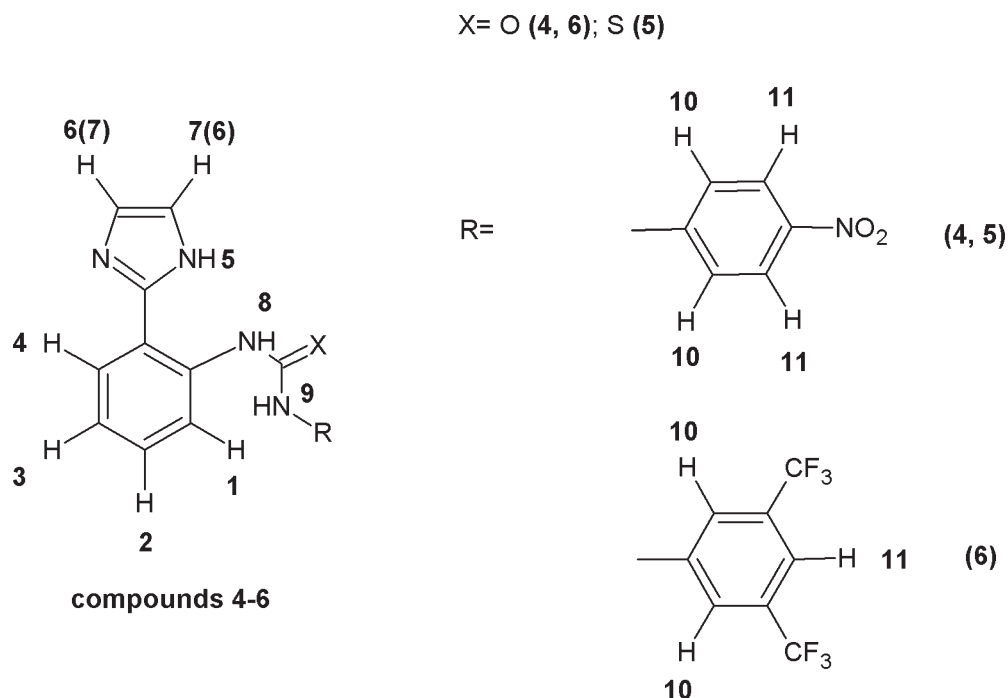


Figure 6. Proton numbering for assignment of ¹H NMR shifts.

via addition of 100 mL of 1M CuCl₂·2H₂O water solution, and the mixture was stirred and heated at 70°C for 2 h. After centrifugation, procedure was repeated next two times. The solid product was then washed by distilled water to remove the Cl⁻ anions and finally dried at 50°C. To prepare clay-supported catalysts mixture of 0.5 g of Ca-MMT or 0.5 g of Cu-MMT together with 0.5 g of **1–6** was heated at 70°C for 5 h.

General procedure for the Henry reaction. A solution of catalyst (0.1 mmol) (Method A: compounds **1–6**; Method B: compounds **1–6** together with 0.1 mmol of copper(II)acetate; Method C: compounds **1–6** supported by Ca-MMT; Method D: compounds **1–6** supported by Cu-MMT) in ethanol (5 mL) was stirred for 30 min at room temperature in a Teflon coated flask. It was used 10 wt % of Ca-MMT and/or Cu-MMT for reactions in presence of only solid support. 4-Nitrobenzaldehyde (0.151 g, 1 mmol), triethylamine (14 µL, 0.1 mmol), and nitromethane (0.55 mL, 10 mmol) were then added under stirring. Conversion of reaction was monitored by TLC (ethyl acetate/hexane 1:4). Only when starting aldehyde was not observed, ethanol was then evaporated under reduced pressure and replaced by ether. The precipitate was filtered off through a plug of silica and washed with ether. The ether extract was washed with aqueous sodium bisulfite, water and dried with sodium sulphate. Solvent was again evaporated under reduced pressure to give product.

2-Nitro-1-(4-nitrophenyl)ethanol. ¹H NMR (DMSO-d₆, 400 MHz), δ 4.66–4.71 (m, 1H, CH(OH)CH₂NO₂), 4.98–5.02 (dd, 1H, CH(OH)CH₂NO₂), 5.47–5.50 (dd, 1H, CH(OH)CH₂NO₂), 6.48 (bs, 1H, CH(OH)CH₂NO₂), 7.79 (d, 2H, ArH), 8.28 (d, 2H, ArH).

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