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The utilization of copper/zeolite as catalyst in the microwave-assisted synthesis of some novel sulfonamide derivatives

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Abstract. Zeolite Y clay modified copper nitrate catalyst was prepared. The obtained catalyst was analyzed by SEM, EDS, and powder XRD techniques. The zeolite Y clay modified copper nitrate catalyst was used for the synthesis of various substituted mesalazine by sulfonylation. The synthesized sulfonamides have been characterized by GC-MS, IR, ^{1}H, ^{13}C and HSQC NMR techniques. The yield percentages of sulfonamides are more than 85%.

Keywords: sulfonamides, copper-zeolites, FT-IR, NMR spectra, GC-mass, SEM, EDS, powder XRD.

1. Introduction

In recent years the microwave techniques play an important role with more attention to the organic chemists. Because the solvent free microwave method has more selectivity, easiest separation, higher yield, eases of isolation of product, less energy consumption than the conventional solvent methods, this method is used in industries to avoid large volume consumption of solvents [1]. In order to protect mesalazine (5-aminosalicylic acid) compound, sulfonyl chloride based nitrogen protecting method is easy to carryout. In general sulfonamides possess -SO_2-NH- moiety in their structures. Sulfonamides have been obtained by condensation between primary or secondary amine with sulfonyl chloride. Zeolites are generally known to be an alumina silicate composition. Due to its high porous structure, shape selectivity, good thermal stability, ease of handling, non-corrosiveness, reusability and low cost, zeolites show more interest between researchers, being widely used as absorbents and also catalysts. They have considerable advantages, such as ordered and use of nonpolluting natural minerals [2]. Therefore these catalysts avoid the long reaction time, unsatisfactory yield, expensive and hazardous nature. In the past years many solid supported reusable catalysts are employed for the preparation of sulfonamides, such as CuO ([2]), montmorillonite – KSF, montmorillonite – K10, CsF – Celite [3-6], metal carbonates (Na_2CO_3, K_2CO_3) [7], metal oxides (CdO [8], and acid acceptor's such as pyridine [9], triethylamine [10], NaOH has also been used in the earlier reported reaction. In order to avoid the side reaction in formation of bis-tosylated by-products, industrial researchers are searching a new toolkit for a selectivity based reactions. Within the above view there is no report available in literature for the use of the Cu^{2+}/zeolite catalyst in the microwave-assisted synthesis of sulfonamides. Therefore, the authors have taken efforts to prepare the Cu^{2+}/zeolite catalyst and used it for synthesis of sulfonamides.

2. Experimental

2.1. Materials and methods

All the chemicals used in this investigation were purchased from the Sigma-Aldrich, Alfa Aesar and E. Merck chemical companies. Melting points of all sulfonamides have been determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected. Infrared spectra (KBr, 4000–400 cm^{-1}) were recorded on OMNIC Fourier-transform spectrophotometer. Bruker AV400 & 500 NMR spectrometer operating at 400 MHz & 500 MHz was used to record ^{1}H, ^{13}C and HSQC (Heteronuclear Single Quantum Coherence Spectroscopy) NMR spectra in DMSO solvent, using TMS as internal standard. Mass spectra were recorded on a Simadzu GC-MS2010 spectrometer using Chemical Impact (CI) techniques. The SEM images of the catalysts were recorded on the Ametex SEM instrument. The Bruker AXS D8 Advance X-ray diffractometer was used to record powder XRD pattern of catalyst. The CHN elemental analysis of all sulfonamides was performed in Thermo Finnigan analyzer.

2.2. Preparation and characterization of Cu^{2+}/zeolite clay catalyst

About 50 mL of 0.05M $Cu(NO_3)_2$ in isopropanol solution was added to zeolite clay suspension drop

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wise using separating funnel, with constant stirring, using a magnetic stirrer. Zeolite suspension was prepared by about 1 gm of zeolite clay was dispersed in 50 mL of isopropanol in a 250 mL beaker. After complete the transformation of $Cu(NO_3)_2$ solution to the zeolite suspension, the mixture was sonicated to get a fine power. The resulting solution was stirred for 4 h at room temperature. The solution was slowly evaporated at room temperature. The obtained solid was dried at 110°C for 5 h and grind with a pestle and mortar affords the Cu^{2+}/zeolite clay catalyst as fine powder. This catalyst was calcined at 250°C. The obtained Cu^{2+}/zeolite catalyst was characterized by the powder XRD (X-Ray Diffraction), SEM (Scanning Electron Microscopy), and EDS (Energy Dispersive X-ray Spectroscopy) analysis.

2.3. Experimental procedure for the sulfonylation of mesalazine

An equimolar concentration of substituted sulfonyl chlorides (1 mmol), mesalazine (1 mmol) and Cu^{2+}/zeolite (80 mg) clay catalyst were taken in 100 mL beaker and mixed thoroughly. This mixture was subjected to microwave irradiation for 5-8 minutes in a microwave oven (Scheme 1) at 450W (Samsung Grill, GW73BD Microwave oven, 230V A/c, 50 Hz, 2450 Hz, 100–750 W (IEC–705)). During the reaction 0.1 mL of triethylamine was added to neutralize the formation of hydrochloride. The completion of the reaction was monitored by thin layer chromatography. The resulting product was washed with *n*-hexane and separated the catalyst using methanol by filtration, and dried. The catalyst was reused for further reaction runs.

3. Results and Discussion

3.1. SEM analysis of Cu^{2+}/zeolite catalyst

The SEM analysis reveals the surface morphology and range of size of loaded ions present in the catalyst. Zeolite and Cu^{2+}/zeolite catalyst surface morphology were shown in Fig. 1 (a, b). In Fig. 1.a, the SEM image shows the cubical shape with the clear surface, which is typical structure for zeolite. Fig. 1.b reveals the modification of zeolite surface by copper, the Cu^{2+} ions being spread over on the zeolite surface, as it was confirmed by EDS spectrum (Fig. 1.d) coupled with SEM.

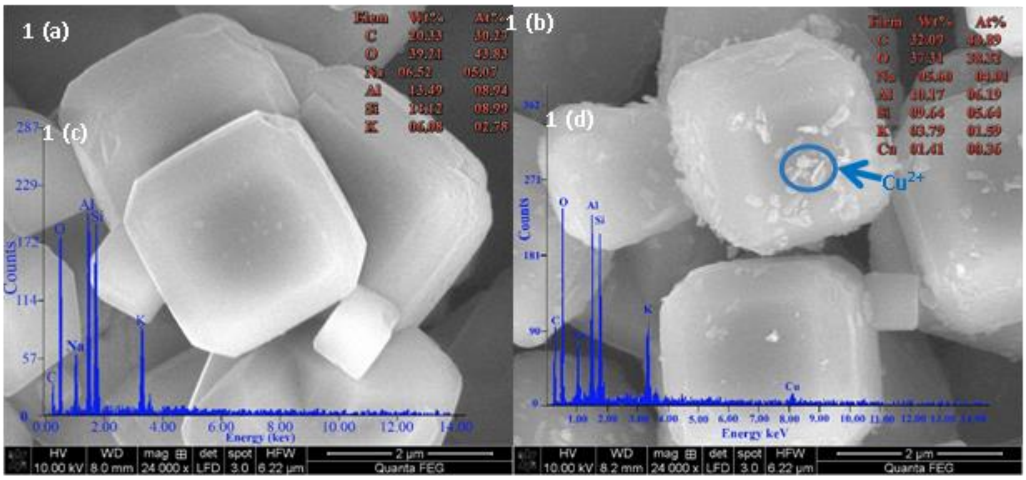


Figure 1. SEM image of (a) zeolite (b) copper on zeolite catalyst; EDS spectra of (c) zeolite (d) copper on zeolite catalyst

The surface morphology on the cubical shape indicates Cu^{2+} particles perfectly located on zeolite matrix. The modifications of surface by copper ions are indicated by circle. The chemical composition of zeolite and copper loaded zeolite catalyst were examined by EDS analysis and it is shown in Fig. 1(c-d). In Fig. 1.c, the EDS spectrum reveals that the major components such as SiO_2, Al_2O_3 were present, in addition with Na, K elements, also observed in zeolite. In the Fig. 1.d, the EDS spectrum shown that the Cu^{2+}/zeolite catalyst have the chemical composition of Cu, SiO_2, and Al_2O_3. The results show that the Cu^{2+} ions are successfully loaded on the zeolite matrix.

3.2. Powder X-ray diffraction analysis of Cu^{2+}/zeolite catalyst

The crystalline phase of zeolite and copper loaded zeolite were examined by powder X-ray diffraction (XRD) patterns and are shown in Fig. 2.a and b. The zeolite is a mixture of silica and alumina oxides. Fig. 2.b shows the powder XRD pattern of copper loaded zeolite. The diffraction of Cu^{2+} loaded zeolite patterns are appeared at 10.35°, 21.54°, 26.31°, 34.19°, 53.35°, and 69.66°. The corresponding diffraction planes are (100), (012), (112), (122), (112), (112), (142) and (602). These diffraction peaks were in good agreement with the corresponding crystallography open database (COD No-96-403-0745) [11].

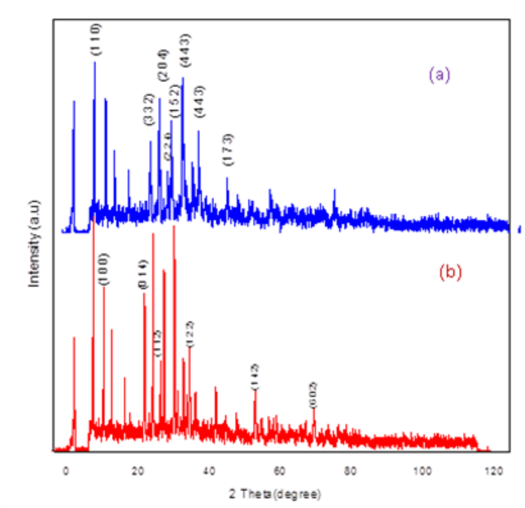
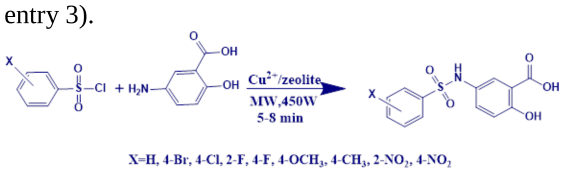


Figure 2. XRD patterns of (a) zeolite Y (b) copper loaded zeolite catalyst.

3.3. Effect of catalyst loading

In the present investigation, the authors have synthesized various substituted mesalazine sulfonamides by microwave method. In this synthesis work the authors have studied the effect of catalyst loading by obtained product percentage by the reaction between equimolar quantity of 4-chlorosulfonylchloride and mesalazine (Scheme 1, entry 3).



Scheme 1. Synthesis of substituted mesalazines.

The yields about 80% of product were obtained up to the 20-40 mg of catalyst loading (Fig. 3). The yield was increased from 80 to 90% by increasing the amount of the catalyst.

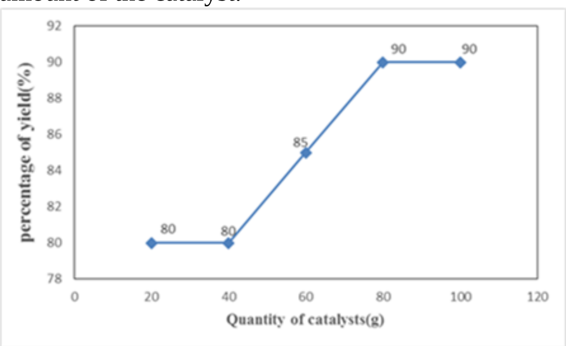


Figure 3. Effect of catalyst loading.

From these observations, the optimum quantity of the catalyst found to be 80 mg for the synthesis of sulfonamides. Beyond 80 mg of catalyst loading, there is no increasing the yield of product.

3.4. Optimization of catalyst

Further the authors have investigated the efficiency of this Cu^{2+}/zeolite catalyst by combines with various metal oxide catalysts such as ZnO, NiO, TiO_2, CuO, Al_2O_3 and copper on Al_2O_3, SiO_2 and copper on SiO_2 by microwave irradiation method. The amount of the catalyst and the yield of the reaction were tabulated in Table 1.

Table. 1. Optimization of the reaction conditions.

Entry	Catalyst	Weight (mg)	Base	Time (min)	Yield (%)
1	ZnO	100	NEt_3	10	50
2	NiO	100	NEt_3	9	30
3	TiO_2	100	NEt_3	15	30
4	CuO	100	NEt_3	5	70
5	Al_2O_3	150	NEt_3	20	70
6	Cu on Al_2O_3	100	NEt_3	10	80
7	SiO_2	150	NEt_3	20	70
8	Cu on SiO_2	100	NEt_3	8	80
9	Zeolite	150	NEt_3	15	60
10	Cu on zeolite	80	NEt_3	5	90

In the optimization study 100 mg of ZnO catalyst gave 50% yield with 10 minutes (50% entry 1). The same amount of NiO and TiO_2 catalysts gave poor yield (30%, entry 2 and 3). About 150 mg of CuO, Al_2O_3, and SiO_2 catalysts gave 70% yields (entry 4, 5 and 7). The catalysts Cu-Al_2O_3 and Cu-SiO_2 gave 80% product (entries 6 and 8). Only 60% of the product was observed in the reaction catalyzed by zeolite catalyst (entry 9). The prepared 80 mg of Cu on zeolite catalyst gave highest yield 90% of mesalazine within 5 minutes. Within the observations, the Cu-zeolite catalyst (Table 1, entry 10) have good efficiency for catalyzing the reaction between sulfonyl chloride and mesalazine. The percentage of obtained product with catalysts in the optimized condition was illustrated in Fig. 4.

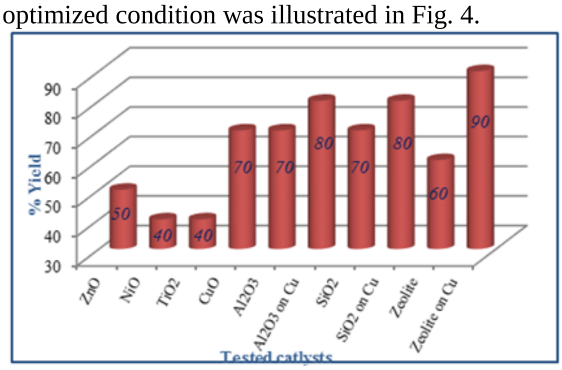


Figure 4. Effect of various catalyst loading on synthesis of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid.

In this reaction, the proposed mechanism was illustrated in Fig. 5. The lone pair electrons of nitrogen atom of amine donates the sulfur atom of sulfonyl chloride, the nitrogen gets the charge and leads to quaternary ammonium chloride analogs. Leaves one proton from quaternary ammonium chloride moiety as HCl by the addition of triethylamine leads to form the sulfonamides.

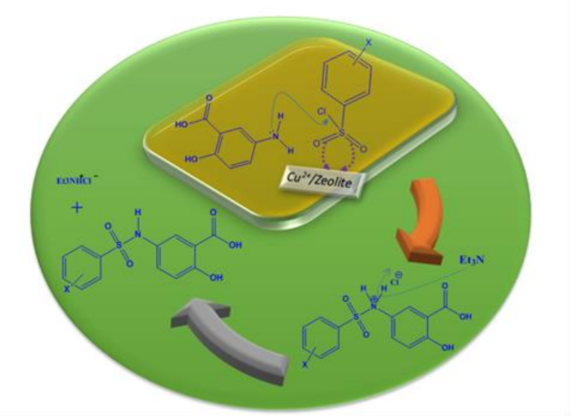


Figure 5. Plausible mechanism of formation of substituted mesalazine sulfonamide derivatives.

3.5. Stability and reusability of catalyst

In order to activate the reaction with the recovered catalyst for next run, it was washed with methanol and regenerated by calcined at 110^{0}C for subsequent reactions. From Table 2 is shown that the catalytic activity was decreased significantly with the freshly prepared catalysts.

Table 2. Reusability of Cu^{2+}/zeolite catalyst on synthesis of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid under microwave irradiation (entry 3).

No of runs	1	2	3	4	5
% of the product	90	88	87	86	86

The correlated diagram of % of product *vs* number of runs is shown in Fig. 6.

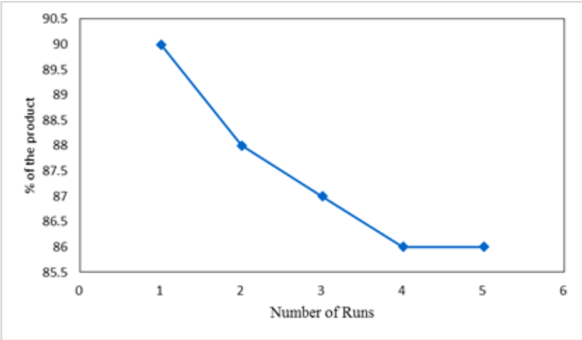


Figure 6. Reusability of catalyst on synthesis of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid.

3.6. HSQC spectrum

These data of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid compound (entry 3, Table 3 and Table 4) was confirmed by HSQC (Fig. 7).

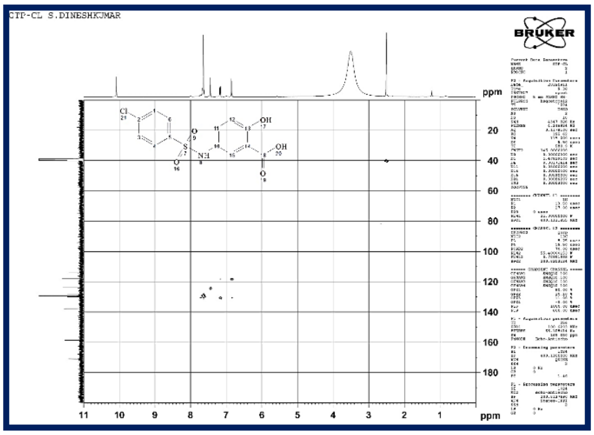


Figure 7. HSQC spectrum of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid.

Table 3. The physical constants, analytical and mass spectral data of mesalazine sulfonamide compounds.

Entry	X	M.F	M.W	Yield (%)	Time (min)	M.p (ºC)	C (%) Obd (calcd)	H (%) Obd (calcd)	N (%) Obd (calcd)	Mass (m/z)
1	H	$C_{13}H_{11}NO_5S$	293.30	88	5.30	276	53.26 (53.24)	3.76 (3.78)	4.72 (4.78)	293 $[M^+]$
2	4-Br	$C_{13}H_{10}BrNO_5S$	372.19	90	5	305	41.99 (41.95)	2.69 (2.71)	3.71 (3.76)	370$[M^+]$, 372 $[M^{2+}]$
3	4-Cl	$C_{13}H_{10}ClNO_5S$	327.74	90	5	310	47.68 (47.64)	2.99 (3.08)	4.18 (4.27)	327$[M^+]$, 329 $[M^{2+}]$
4	2-F	$C_{13}H_{10}FNO_5S$	311.29	86	7	277-281	50.20 (50.16)	3.18 (3.24)	4.46 (4.50)	311$[M^+]$, 313$[M^{2+}]$
5	4-F	$C_{13}H_{10}FNO_5S$	311.29	88	5	291-293	50.14 (50.16)	3.20 (3.24)	4.45 (4.50)	311$[M^+]$, 313 $[M^{2+}]$
6	4-OCH_3	$C_{14}H_{13}NO_6S$	323.32	85	8	301	52.08 (52.01)	4.01 (4.05)	4.29 (4.33)	323 $[M^+]$
7	4-CH_3	$C_{14}H_{13}NO_5S$	307.32	85	8	282	54.68 (54.71)	4.22 (4.26)	4.49 (4.56)	307.05 $[M^+]$
8	2-NO_2	$C_{13}H_{10}N_2O_7S$	338.29	86	7	314	46.18 (46.16)	2.92 (2.98)	8.26 (8.28)	338.02 $[M^+]$

Table 4. The spectroscopic data of substituted mesalazine sulfonamides.

Entry	X	Infrared bands (ν, cm^{-1})				Chemical Shifts (δ, ppm)		
		N-H	S=O$_{as}$	S=O$_s$	C=O	^{1}H NH	^{13}C COOH	^{13}C C-OH
1	H	3262.4	1311.9	1158.0	1695.9	10.832	172.4	159.64
2	4-Br	3263.2	1332.8	1156.0	1670.8	10.853	172.36	159.83
3	4-Cl	3262.5	1333.8	1157.3	1670.8	10.077	171.06	158.71
4	2-F	3264.4	1321.2	1168.7	1694.1	10.364	171.58	158.10
5	4-F	3264.5	1325.7	1161.5	1670.8	10.290	171.53	159.15
6	4-OCH$_3$	3250.1	1333.9	1158.0	1677.3	9.893	171.67	158.69
7	4-CH$_3$	3262.8	1333.3	1157.3	1669.9	10.330	171.65	158.74
8	2-NO$_2$	3293.2	1322.8	1175.9	1665.6	10.446	171.53	159.35
9	4-NO$_2$	3263.6	1311.9	1159.5	1670.8	10.399	171.5	159.21

The NH proton chemical shift obtained at 10.077 was not correlated with any of the ^{13}C chemical shifts. The ring proton chemical shifts are centered with the ring carbon chemical shifts. The solvent peak was correlated.

3.7. Mass spectral study

The mass spectrum and the splitting pattern of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid (entry 3, Table 3) are shown in Fig. 8.

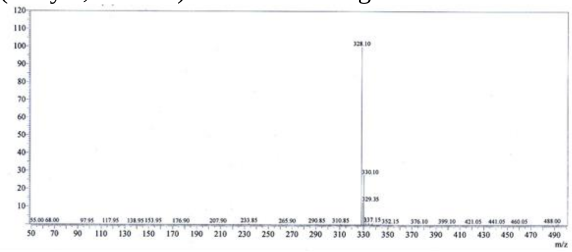


Figure 8. Mass spectrum of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid compound.

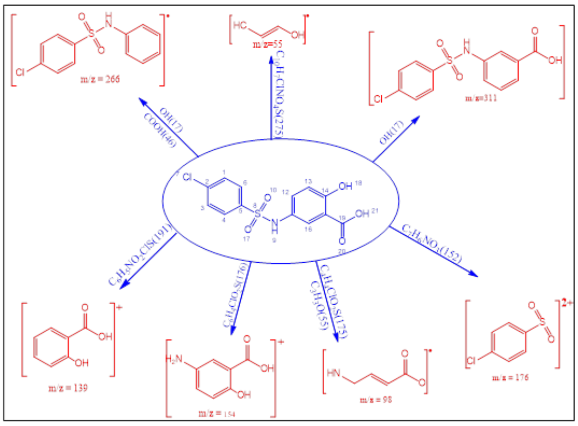


Figure 9. Mass splitting pattern of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid compound.

The mass of mesalazine sulfonamide derivative of 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid are M^{+2} because of the halogen substitution it shows 329.35. From the chemical impact spectrum, the splitting pattern of the 5-(4-chlorophenylsulfonamido)-2-hydroxybenzoic acid is shown in Fig. 9.

Consequently, the experimental data confirmed the synthesis of substituted mesalazine sulfonamides. On the basis of their potential antibacterial activity, the obtained sulfonamide derivative may be used as drugs. Therefore, the study of substituted mesalazine sulfonamides properties looks promising in terms of a future work.

4. Conclusions

The copper/zeolite, obtained by a liquid phase deposit method in the reaction between a Y zeolite clay and copper nitrate, was successfully used as catalyst in the microwave-assisted synthesis of some novel sulfonamide derivatives.

This microwave assisted highly reusable Cu^{2+}/zeolite catalyzed sulfonamide synthesis protocol offers a simple, easier work-up procedure, no side reactions and high yield.

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