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Introduction of Brönsted acidic ionic liquid supported on nanoporous Na^+-montmorillonite as an efficient catalyst for the synthesis of 2-amino-tetrahydro-4*H*-pyrans

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ABSTRACT

Nanoporous sodium montmorillonite clay (Na^+-MMT) was used as a support for the immobilization of 1-methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate (Na^+-MMT-[pmim]HSO_4). This catalyst showed excellent catalytic activity for the preparation of 2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4*H*-benzopyrans *via* three-component reactions between aldehydes, dimedone and malononitrile. The procedure gave the products in high yields within short reaction times. Also, this catalyst can be reused at least for five times without loss of its catalytic activity. All the products were characterized using melting point, IR, ^{1}H NMR and ^{13}C NMR and were identified by comparison of their spectra with those of authentic samples.

Keywords: *Na^+-montmorillonite, Clay, Immobilization of ionic liquid, Multi-component reactions, Pyran, 2-Amino-4H-pyrans.*

1. Introduction

The development of environmentally benign, efficient and economical methods for the synthesis of biologically interesting compounds remains a significant challenge in the synthesis of organic compounds. Multi-component reactions, via which the products are formed from readily available starting materials in a single step, comply with the principles of green chemistry in terms of economy of steps as well as their simple experimentation, atom economy and high yields of the products [1].

Heterocyclic compounds are widely distributed in nature and are essential to life. 4*H*-Pyran derivatives are important classes of heterocyclic compounds that have been of considerable interest to chemists [2]. This importance can be attributed to their broad scope of pharmaceutical and biological properties such as antimycobacterial [3], antitumor [4], anti-HIV [5], anticancer [6], antimicrobial and cytotoxicity [7] activities. Functionally substituted 4*H*-pyran including 2-amino-4*H*-pyran motif has attracted interest because it exhibits a wide range of biological activities [8,9] as well as the photochemical reactivity [10]. The conventional synthetic method for the preparation of this type of compounds is based on the condensation of dimedone with aromatic aldehydes and malononitrile. For this purpose, a variety of catalysts such as NaBr [11], I_2 [12], tetrabutylammonium fluoride (TBAF) [13], hexadecyldimethylbenzyl ammonium bromide (HDMBAB) [14], PEG-1000-based dicationic acidic ionic liquid (PEG1000-DAIL) [15], SiO_2-Pr-SO_3H [16], polyphosphoric acid (PPA–SiO_2) [17], Caro's acid–silica gel (CA-SiO_2) [18], metformin-modified silica-coated MNPs (Fe_3O_4/SiO_2-Met) [19], $RuBr_2(PPh_3)_4$ [20], 2,2,2-trifluoroethanol (TFE) [21], SO_4^{2-}/MCM-41 [22], urea:choline chloride [23], Fe_3O_4@SiO_2/DABCO [24], silica-bonded N-propylpiperazine sodium n-propionate (SBPPSP) [25], silica-bonded S-sulfonic acid (SBSSA) [26], [MPIm][HSO_4]@SBA-15 [27] have been used to facilitate this reaction. Although these procedures provide some improvements in the synthesis of these compounds, many of them suffer from disadvantages such as long reaction times, harsh reaction conditions, need for an excessive amounts of the reagent, low yields of the products and non-recoverability of the

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catalyst. Therefore, introducing simple, efficient and mild procedures with easily separable and reusable solid catalysts to overcome these problems is still in demand.

Recently, we have reported the preparation and characterization of a new Brönsted acidic ionic liquid supported on nanoporous sodium montmorillonite (Na^+-MMT-[pmim]HSO_4) (Fig. 1), and its applicability in the synthesis of the 4,4'- (arylmethylene)- bis- (3-methyl-1-phenyl-1H-pyrazol-5-ols) [28] and formylation of amines and alcohols [29]. In continuation of this study and in order to overcome the above-mentioned restrictions, we were interested in investigating the applicability of this reagent in the promotion of the synthesis of 2-amino-tetrahydro-4*H*-pyrans derivatives, which need the acidic catalyst to speed-up.

2. Experimental

2.1. General procedure

All chemicals were purchased from Merck, Aldrich and Fluka Chemical Companies and used without further purification. Products were characterized by their physical constant and comparison with authentic samples. The purity determination of the substrates and reaction monitoring were accompanied by TLC using silica gel SIL G/UV 254 plates.

2.2. General procedure for the preparation of Preparation of 1-methyl-3-(trimethoxysilylpropyl)-imidazolium hydrogen sulfate supported on sodium montmorillonite (Na^+-MMT-[pmim]HSO_4)

A mixture of 10 mmol 1-methylimidazole and 10 mmol (3-chloropropyl)trimethoxysilane was refluxed at 90°C for 30 h. Then, the reaction mixture was cooled down. The crude product was washed with Et_2O (2 x 5 mL) and dried under vacuum to obtain [pmim]Cl as a slightly yellow viscous oil. Then, 1.2 g (4 mmol) of [pmim]Cl was dissolved in 25 mL of CH_2Cl_2 and treated with 2 g of sodium montmorillonite. The reaction mixture was refluxed with stirring for 3 days. Then, the reaction mixture was cooled to room temperature, the solid was isolated by filtration and washed with 20 mL of boiling dichloromethane to remove the unreacted ionic liquid. In the next step, the material was dried to obtain MMT-[pmim]Cl. Following that, 3 g of Na^+-MMT-[pmim]Cl was suspended in 20 mL of dry CH_2Cl_2. Under vigorous stirring and in an ice bath (0ºC) 3 mmol of concentrated H_2SO_4 (97%) was added dropwise to this mixture. The mixture was then warmed to room temperature and heated under reflux for 30 h. When the formed HCl was completely distilled off the solution was cooled and CH_2Cl_2 was removed under vacuum to afford Na^+-MMT-[pmim]HSO_4 as the product (Fig. 1).

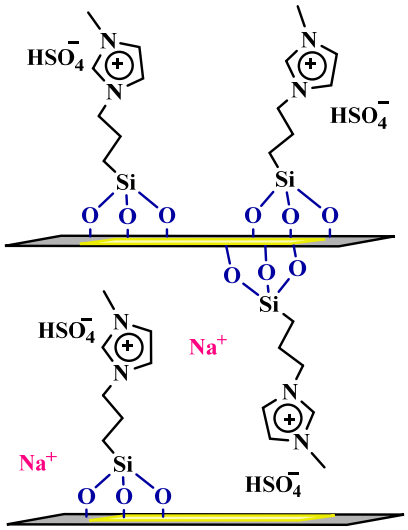


Fig. 1. The acidic ionic liquid immobilized on Na^+–MMT (Na^+-MMT-[pmim]HSO_4).

2.3. General procedure for the preparation of 2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4H-benzopyrans

A mixture of aldehyde (1 mmol), dimedone or 1,3-cyclohexadione (1 mmol), malononitrile (1.1 mmol), Na^+-MMT-[pmim]HSO_4 (10 mg) and EtOH:H_2O (1:1) (4 mL) was taken in a round bottomed flask and heated at 80°C. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the solvent was evaporated, EtOH was added and the catalyst was separated by filtration. The products were purified by recrystallization from aqueous ethanol.

Selected Spectral data

*2- amino- 3- cyano- 4- (4- thiomethyl- phenyl)- 7,7-dimethyl- 5- oxo- 5, 6, 7, 8- tetrahydro- 4H-benzopyran (**Table 2, entry 18**):*

m.p.= 223-225°C. ^{1}HNMR (DMSO-d_6, 400 MHz): δ= 1.87-1.99 (2H, m), 2.22-2.32 (2H, m), 2.45 (3H, s, SCH3), 2.60-2.62 (2H, m), 4.16 (1H, s, CH), 7.03 (1H, s, NH), 7.11 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H) ppm. ^{13}CNMR (DMSO-d_6, 100 MHz): δ= 15.29, 20.31, 26.98, 35.50, 36.83, 58.57, 114.19, 120.29, 126.49, 128.35, 136.60, 142.09, 158.94, 164.87, 196.37 ppm.

*4,4'- phenylbis (2- amino-3- cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran) (**Table 2, entry 19**):*

m.p.= 266-268°C. IR (neat): $\bar{\nu}$ = 3448, 3327, 3189, 2960, 2194, 1655, 1602, 1363, 1210, 1148, 1029 cm^{-1}. ^{1}HNMR (DMSO-d_6, 400 MHz): δ= 0.985 (s, 3H, CH_3), 1.035 (s, 3H, CH_3), 2.16 (d, J_{AB}= 16.4 Hz, 1H), 2.23 (d, J_{AB}= 16.4 Hz, 1H), 2.50 (s, 2H), 4.14 (s, 1H), 6.98 (s, 2H), 7.04 (s, 2H) ppm. ^{13}CNMR (DMSO-d_6, 100 MHz): δ= 27.4, 27.6, 28.6, 32.3, 35.4, 50.4, 58.8, 113.1, 120.2, 127.4, 143.3, 159.0, 163.1, 196.1 ppm.

3. Results and Discussion

First, for the optimization of the reaction conditions, the reaction of 4-chlorobenzaldehyde, dimedone (5,5-dimethyl-1,3-cyclohexanedione) and malononitrile leading to 2-amino-3-cyano-4-(4-**c**hlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzopyran was selected as a model reaction in various conditions (Table 1). For choosing the reaction media, different solvents such as EtOH, H_2O, and EtOH: H_2O were used and the best results were obtained in EtOH:H_2O (1:1). Having accomplished the optimization of the reaction media, more experiments were performed to delineate the best reaction. It was observed that 10 mg of Na^+-MMT-[pmim]$HSO_4$was the optimal catalyst loading for this reaction, and higher catalyst loading did not improve the yield of the product to a greater extent. In addition, the results indicated that the reaction at 80°C proceeded in the highest yield and shortest time. Finally, the best result was obtained using 10 mg of Na^+-MMT-[pmim]HSO_4in EtOH:H_2O (1:1) at 80°C.

After optimization of the reaction conditions and in order to establish the efficiency and the acceptability of the method, we explored the protocol with a variety of simple readily available substrates under the optimal conditions (Table 2). It was observed that under similar conditions, a wide range of aromatic aldehydes containing electron-withdrawing as well as electron-donating groups such as Cl, Br, CH_3, OCH_3, NO_2 and OH in the ortho, meta, and para positions on the benzene ring easily converted to the corresponding 2-amino-4*H*-pyrans in short reaction times with good to excellent isolated yields (Table 2, entries 1-9). As it can be seen, the nature of the substituents on the aromatic ring had clearly obvious effects on the reaction. The aromatic aldehydes with electron-withdrawing groups reacted faster than their electron-donating counterparts. The α,β-Unsaturated, polycyclic aromatic, and heterocyclic aldehydes also provided the desired products in good yields (Table 2, entries 10-12). Furthermore, 1,3-cyclohexadione was employed in place of dimedone to produce the corresponding products in high yields (Table 2, entries 13-18).

This method was also found to be useful for the usage of dialdehydes (Table 2, entry 19). In this reaction, 2 equivalents of dimedone and malononitrile successfully condensed with 1 equivalent of terephthaldialdehyde with high yield at short time that shows the practical synthetic efficiency of this reaction.

The proposed mechanism for the synthesis of 2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4*H*-benzopyrans in the presence of Na^+-MMT-[pmim]HSO_4 as a promoter is shown in Scheme 1. The α-cyanocinnamonitrile (III) was formed initially by theKnoevenagel condensation between aldehyde and malononitrile in the presence of Na^+-MMT-[pmim]HSO_4. Then, the Michael addition of the enolizable dimedone (IV) on the intermediate (III), followed by intramolecular cyclization and final tautomerization of intermediates afforded the desired product.

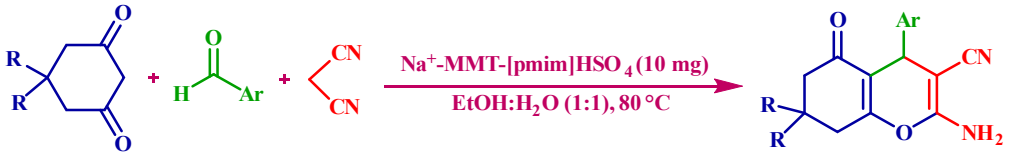
To check the reusability of the catalyst, the reaction of 4-nitrobenzaldehyde, dimedone and malononitrile under the optimized reaction conditions was studied again. When the reaction completed, the solid was filtered off, ethanol was added and the catalyst was separated by filtration. The recovered catalyst was washed with ethyl acetate, dried and reused for the same reaction. This process was carried out over five runs and all reactions led to the desired products without significant changes in terms of the reaction time and yield, which clearly demonstrates practical recyclability of this catalyst (Fig. 2).

Table 1. Optimization of the reaction conditions for the reaction of 4-chlorobenzaldehyde, dimedone and malononitrile catalyzed by Na^+-MMT-[pmim]HSO_4.

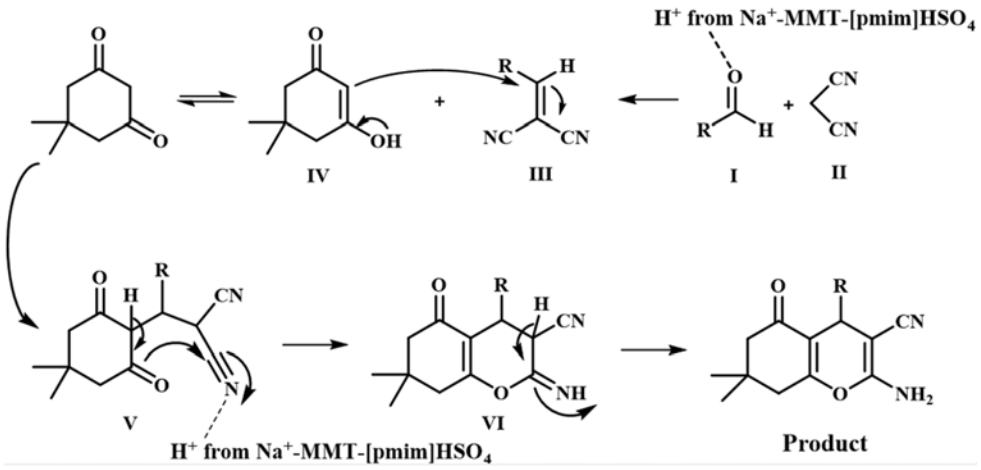
Entry	Catalyst (mg)	Solvent	Temp. (°C)	Time (min)	Yield (%)
1	0	EtOH	80	120	Trace
2	10	EtOH	80	40	89
3	10	H_2O	80	20	90
4	10	CH_3CN	80	120	Trace
5	10	EtOH: H_2O[a]	80	12	93
6	5	EtOH: H_2O[a]	80	30	80
7	20	EtOH: H_2O[a]	80	15	93
8	10	EtOH: H_2O[a]	60	30	90
9	10	EtOH: H_2O[a]	100	8	93

[a]EtOH:H_2O (1:1).

Table 2. Preparation of 2-amino-4*H*-pyran derivatives catalyzed by Na^+-MMT-[pmim]HSO_4.



Entry	Ar	R	Time (min)	Yield (%)	m.p (°C)		Ref.
					Found	Reported	
1	C_6H_5–	Me	10	91	228-230	231-233	[11]
2	2-Cl-C_6H_4–	Me	25	92	208-210	213-215	[22]
3	4-Cl-C_6H_4–	Me	12	93	217-219	215-217	[11]
4	4-Br-C_6H_4–	Me	10	93	201-203	200-203	[18]
5	4-CH_3O-C_6H_5–	Me	30	92	199-201	195-197	[15]
6	2-NO_2-C_6H_4–	Me	15	93	232-234	233-234	[13]
7	3-NO_2-C_6H_4–	Me	12	94	210-212	212-214	[14]
8	4-NO_2-C_6H_4–	Me	5	95	180-182	177-178	[11]
9	4-OH-C_6H_4–	Me	22	94	206-208	204-205	[15]
10	2-naphthaldehyde	Me	10	95	258-260	258-260	[30]
11	Cinnamaldehyde	Me	15	92	193-195	183-185	[25]
12	Isatin	Me	5	96	298-300	295-297	[31]
13	4-Cl-C_6H_4–	H	8	91	241-243	244-248	[27]
14	4-CH_3O-C_6H_5–	H	40	90	202-205	192-194	[14]
15	3-NO_2-C_6H_4–	H	10	94	238-240	202-204	[14]
16	4-NO_2-C_6H_4–	H	8	95	232-234	234-236	[14]
17	2-Naphthaldehyde	H	7	94	251-253	254-255	[30]
18	4-SCH_3-C_6H_5–	H	12	93	223-225	-	-
19	4-CHO–C_6H_4–	Me	20	13	266-268	-	-



Scheme 1. Proposed mechanism for the reaction of aldehyde, dimedone and malononitrile using Na^+-MMT-[pmim]HSO_4.

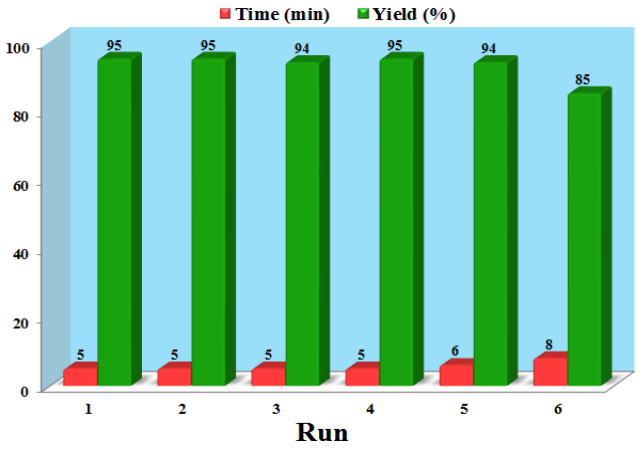


Fig. 2. Reusability of the catalyst.

However, after the 6th run, the yield of reaction was decreased. Furthermore, the fresh and recovered Na^+–MMT-[pmim]HSO_4 was characterized by FT-IR spectra (Fig. 3), which prove the fine reusability of catalyst.

To highlight the merits of our newly developed procedure, we have compared our results for the synthesis of 2-amino-3-cyano-4- (4-nitrophenyl)- 7,7-dimethyl- 5- oxo-5,6,7,8- tetrahydro-4*H*-benzopyran using the Na^+-MMT-[pmim]HSO_4 catalyst with other results reported in the literature for the same transformation. As shown in Table 3, the newly developed method avoids some of the disadvantages associated with other procedures such as long reaction times, harsh reaction conditions, large excesses of the reagents, and low yields. This comparison also clarifies an important point about this catalyst. As it can be seen, Na^+-MMT and Na^+-MMT-[pmim]Cl are also able to catalyze this type of reactions, but in longer reaction times rather than Na^+-MMT-[pmim]HSO_4. These results give clear evidence to confirm the important role of the covalently bounded ionic liquid and also HSO_4^- group in the catalyst to obtain the best performance.

4. Conclusions

In conclusion, in this study we have introduced the Na^+-MMT-[pmim]HSO_4 as a highly powerful supported acidic ionic liquid for the simple and efficient synthesis of 2-amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4*H*-benzopyrans. The obtained results showed that the catalytic activity of Na^+-MMT-[pmim]HSO_4 was convincingly superior to other reported procedures in terms of reaction times and yields. Lower loading of the catalyst, simple experimental procedure, use of an inexpensive and reusable catalyst are other advantages of the procedure. Further work to explore this catalyst in other organic transformations is in progress in our laboratory.

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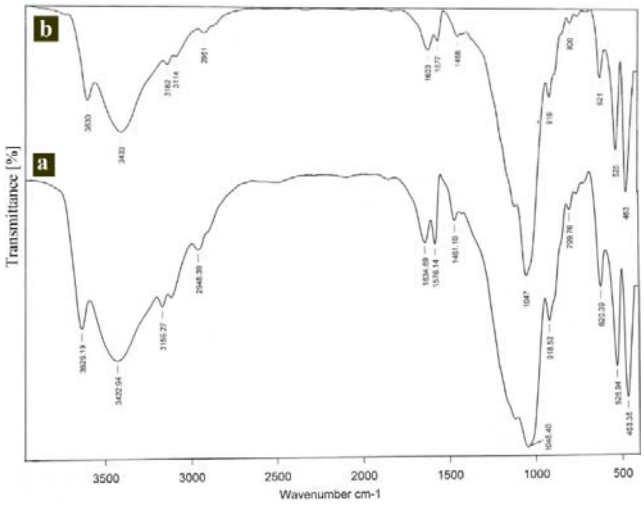

Fig. 3. FT-IR spectra of fresh (a) and recovered (b) Na^+–MMT-[pmim]HSO_4.

Table 3. Comparison of the results obtained from the synthesis of 2-amino-3-cyano-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzopyranin the presence of Na^+-MMT-[pmim]HSO_4 with those obtained using other procedure.

Entry	Catalyst (loading)	Reaction conditions	Time (min)	Yield (%)	Ref.
1	TBAF (10 mol%)	Reflux/ H_2O	30	75	[13][a,b]
2	HDMBAB (12 mol%)	90ºC / H_2O	7 h	93	[14][b,c]
3	PEG1000-DAIL (2 mL)	80ºC/ toluene	60	93	[15][b,c]
4	SiO_2-Pr-SO_3H(30 mg)	Reflux/ EtOH:H_2O	15	93	[16][d]
5	PPA-SiO_2 (100 mg)	Reflux/ H_2O	8	85	[17][b,c,d]
6	CA-SiO_2 (16 mol%)	Reflux/ EtOH:H_2O	15	93	[18][c,d]
7	$RuBr_2(PPh_3)_4$ (5 mol%)	Reflux/ CH_3OH	12	75	[20][a,d]
8	$SO4^{2-}$/MCM-41 (25 mg)	Reflux/ EtOH	30	85	[22][a,b,d]
9	Fe_3O_4@SiO_2/DABCO (50 mg)	80ºC/ H_2O	25	92	[24][b,c]
10	[MPIm][HSO_4]@SBA-15 (30 mg)	45ºC/ H_2O	2 h	95	[27][b]
11	Na^+-MMT-[pmim]HSO_4 (10 mg)	80ºC/ EtOH:H_2O	3	96	This work

[a]Low yield of product.
[b]Long reaction time.
[c]High catalyst loading.
[d]Reflux conditions.

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