Selective acetylation of 5-numbered aromatic heterocycle compounds using metal-exchanged clay catalysts

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Acetylation of 5-numbered aromatic heterocycle compounds under very mild conditions to 2-acetyl derivatives selectively in good yields using metal-exchanged clays as catalysts is described for the first time.

KEY WORDS: acetylation; metal-exchanged clays; selectivity

1. Introduction

2-acetyl 5-numbered aromatic heterocycle compounds such as pyrrole, furan and thiophene are very important intermediates for fine chemicals such as drugs and pharmaceuticals, flavors and flavoring agents for food stuffs [1,2]. The fine chemical industry demands highly pure 2-acetyl 5-numbered heterocycles of pyrrole, furan and thiophene, as the contamination of 3-acetyl heterocycle compounds is detrimental to the quality of the end products. Therefore, the removal of the 3-acetyl heterocycle compound, a usual by-product in chemical reaction from the heterocycle compound, is an essential operation that requires special and tedious efforts in the additional step, *i.e.*, 3-acetylthiophene contaminating 2-acetylthiophene is removed by a selective electrophilic substitution process, bromination followed by fractional distillation [3].

In the conventional acetylation process, heterocyclic compounds such as pyrrole, furan and thiophene are acetylated by Lewis acid metal chlorides and other protic acids [4–9]. The 3-acetyl heteroaromatic compound is the usual contaminant present to the extent of 20% in the acetylation process using soluble acids [7–9]. Apart from this, the inherent drawback in the use of conventional Lewis acid metal chlorides and other protic acids for Friedel–Crafts acylation are that they are highly corrosive and non-recoverable and require more than stoichiometric amounts because of strong complexation with the carbonyl product formed. Work-up to decompose the resultant intermediate complex by hydrolysis forms a large amount of waste product that warrants special attention for the solid disposal and the process of separation is lengthy and expensive. These disadvantages have driven to develop an eco-friendly catalytic process for the acetylation of 5-numbered heterocycle compounds employing a non-toxic and/or non-corrosive medium that generates no effluent and concomitantly to attain total selectivity of the 2-isomer to meet the customer's specification. Moreover, the catalyst should be easily separable and reusable to make the methodology very simple.

In this direction, Hölderich [10] described a procedure for the vapor phase acetylation of heterocycle aromatic compounds with acylating agents in the presence of zeolite catalysts. The reaction of thiophene with acetic anhydride at 250 °C on a boron zeolite leads to 2-acetylthiophene with 99% selectivity at 24% conversion. On the use of Ce-doped boron zeolite at 200 °C, 2-acetylfuran is obtained with 99% selectivity and 23% conversion. On the other hand, in the case of pyrrole, which tends to polymerize, the acidity of catalyst and the temperature of the reaction are reduced in order to achieve a high selectivity while keeping the conversion at 41%. There is no description of the by-product, which is formed in these reactions. Although the high selectivity towards the desired product 2-acetyl heteroaromatic compound is achieved, serious limitations are the low conversions and high-energy requirement for the vapor phase reactions.

We report in this letter the selective acetylation of heterocyclic compounds, pyrrole, thiophene and furan employing metal-ion-exchanged mesoporous clay in catalytic amounts in liquid phase in quantitative yields under mild conditions for the first time.

2. Experimental

2.1. Preparation of catalysts

K10 montmorillonite purchased from Fluka Chemicals was used as such. To a 1 M solution of metal chloride (1.0 M), 80 g of K10 montmorillonite was added. Stirring was maintained for 24 h in order to saturate the exchange capacity of montmorillonite K10. The clay suspension was centrifuged and the supernatant solution was discarded. The clay catalyst was washed each time with fresh distilled water

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Table 1
Acetylation of 5-numbered heterocycle aromatic compounds with acetic anhydride in the presence of metal-exchanged clay catalysts.

Entry No.	Heteroaromatic	Catalyst	Acidity (μmol/g)	Temp. (°C)	Time (h)	Conv. (%)[a]	Selectivity 2-acetylheteroaromatic (%)
1	Pyrrole	Fe^{3+}-mont.	337	25	12	86	99
2	Pyrrole	Fe^{3+}-mont.	337	80	6	98	95
3	Pyrrole	K10 mont.	310	80	8	60	96
4	Pyrrole	Zn^{2+}-mont.	344	80	6	87	95
5	Pyrrole	Al^{3+}-mont.	257	80	10	58	98
6	Pyrrole	H^{+}-mont.	313	80	8	76	99
7	Thiophene	Fe^{3+}-mont.		25	8	56	99
8	Thiophene	Fe^{3+}-mont.		80	5	97	99
9	Thiophene	Zn^{2+}-mont.		80	5	92	99
10	Furan	Fe^{3+}-mont.		40	8	98	92
11	Furan	Fe^{3+}-mont.		25	12	82	100
12	Furan	Zn^{2+}-mont.		25	12	77	99

[a] Based on acetic anhydride; based on the GC.

and centrifuged till the disappearance of Cl^- ions from the discarded water. The clay was dried overnight in an oven at 120 °C and finely ground in a mortar. H^+-montmorillonite was prepared according to the procedure [11].

2.2. Methods of characterization

The formation of acylated products were monitored by analysing samples of the reaction mixture collected in regular intervals by gas chromatography (GC) using an OV-17 column. Proton nuclear magnetic resonance (^{1}H NMR) spectra were taken on a Gemini Varian 200 MHz.

3. Catalytic reactions

3.1. Typical procedure

A mixture of thiophene (40 mmol, 3.36 g), acetic anhydride (10 mmol, 1.02 g) and catalyst (0.5 g) was taken in a 50 ml round bottomed flask. The reaction was carried out under nitrogen atmosphere at 25 °C. After completion of the reaction (monitored by GC), the reaction mixture was filtered, distilled to remove unreacted reactants and acetic acid and purified by column chromatography using ethyl acetate 5% in hexane as eluant mixture to obtain a pure product. The product analysis was confirmed by ^{1}H NMR.

^{1}H NMR data: (δ ppm, $CDCl_3$):

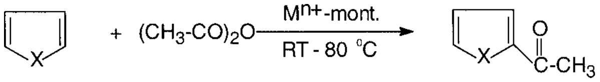
2-acetylpyrrole: $\delta = 2.5$ (3H, S), $\delta = 6.25$ (1H, dd), $\delta = 6.85$ (1H, m), $\delta = 7.0$ (1H, d), $\delta = 10$ (1H, brs).

2-acetyl furan: $\delta = 2.45$ (3H, S), $\delta = 6.5$ (1H, dd), $\delta = 7.25$ (1H, d), $\delta = 7.7$ (1H, d).

2-acetyl thiophene: $\delta = 2.5$ (3H, S), $\delta = 7.1$ (1H, dd), $\delta = 7.5$ (1H, d), $\delta = 7.7$ (1H, d).

3.2. Results and discussion

Metal-exchanged clays are obtained by ion exchange process of acid-treated montmorillonite, commercially known as montmorillonite K10, a mesoporous clay for the acetylation of the heterocycle compounds (scheme 1). The results on catalytic activity, selectivity and acidity of various metal-exchanged mesoporous clays in the acetylation of heteroaromatic compounds, pyrrole, furan and thiophene with acetic anhydride conducted are presented in table 1.



X = NH, S, O; $M^{n+} = Fe^{3+}, Zn^{2+}, H^{+}, AL^{3+}$

Scheme 1.

The acetylation of pyrrole was carried out using various cation-exchanged clays, H^+, Al^{3+}, Fe^{3+} and Zn^{2+}. Fe^{3+}- and Zn^{2+}- montmorillonite have displayed higher activity. Using these efficient catalysts, furan and thiophene are also acetylated. The conversions and selectivity of 2-acetylpyrrole and 2-acetylfuran varies with the reaction temperatures used. In the acetylation of pyrrole and furan, at high temperature the conversion increases with the decrease of selectivity. The 3-acetyl product is the predominant minor by-product. The reactions conducted at ambient temperature afford 2-acetyl products in almost pure form and even traces of 3-acetyl products are not detected. The low selectivity is ascribed to the kinetic effect. Selective acetylation of thiophene to 2-acetylthiophene is independent of temperatures used in acetylation conducted in the presence of metal-ion-exchanged clays. The formation of 3-acetyl product is not detected in this case either. Thus, the highly pure and desired isomers are realized using modified clay catalysts.

4. Catalytic activity and selectivity

The activity in relation to the acidity and nature of the acidic sites of solid acid catalysts was investigated in the acylation of the 5-numbered aromatic heterocycle compounds (table 1).

In the course of development of the catalyst, we have explored various metal-exchanged clays with varied acidities for Friedel–Crafts acetylation. Clays exhibit both Brønsted and Lewis acid sites. The former has external –OH groups, while the Lewis sites are the exposed three-fold coordinated Al^{3+} ions substituting the Si^{4+} ions in the tetrahedral sheets or transition metal ions incorporated by ion exchange process. As the classical acylation of heteroaromatic compounds is mediated when both the soluble protic and Lewis acids are used independently [4–9], the influence of Lewis and Brønsted acidic sites composed in modified clays are visualized for effective acylation of heteroaromatic compounds.

The hydrated cationic aqua complexes in montmorillonite are more acidic than their corresponding homogeneous analogues. The origin and display of Brønsted acidity in metal-exchanged montmorillonite is ascribed to the polarizing influence of the cation on the water molecule in spatially restricted interlayers [12,13]. The interlayer acidity increases with increasing ratio of charge to ionic radius of the cation. Besides this, the exchanged metal on montmorillonite also introduces Lewis acidity of the clay. The content and type of the metal thus play a vital part in displaying Lewis acidity. The rate of acetylation reaction is increased as the total acidity is increased which is in the order: $Fe^{3+} \approx Zn^{2+} > H^{+} > K10 > Al^{3+}$ (table 1). The activity is thus correlated to the acidity of the clay catalysts.

The acetylation on clays proceeds selectively at the 2-position of heteroaromatic compounds to yield the bulkier product. The high selectivity cannot be attributed to the shape selectivity imparted by the two-dimensional mesoporous material, but to the electronics and kinetic effects which determine the course of reaction. To summarize, it may be stated that in the acylation of heteroaromatic compounds on clays, it is the high acidity of the catalyst that brings about the reaction and the electronic and kinetic factors which largely determine the direction of substitution. The catalyst showed consistent activity for a number of cycles in the acylation of pyrrole conducted to understand the recycle profile.

5. Conclusion

The two-dimensional mesoporous clay catalysts offer the highly pure and desired isomer to be used as an intermediate for the manufacture of specialized drugs and pharmaceuticals. Unlike soluble Lewis acids, the solid acid catalysts employed here do not produce any effluents. As the clay catalyst is cheap and reusable for several cycles under mild reaction conditions, the process described here is not only eco-friendly but also economically viable.

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