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Mild liquid-phase Friedel-Crafts acylation of heteroaromatic compounds over zeolite Beta

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ABSTRACT

Heteroaromatic compounds, such as thiophenes, pyrroles and furans, were acylated using zeolite Beta, with and without modifications, and acetic anhydride. Amenable conditions were found to carry out these acylations in high yield, sometimes in a very short time (10 min). Indium modified catalyst have provided a way of attaining good yields in the acylation of pyrrole.

1. Introduction

Simple heteroaromatic compounds are readily available substances with a great potential to be used in the synthesis of highly functionalized molecules. However, despite of over a century of research, the selective functionalization of pyrroles, thiophenes and furans remains challenging and interesting, mainly because they are substructures in a wide variety of high value organic compounds [1,2], prompting for multiple approaches for their modification, being the Friedel-Crafts acylation one of the most prominent reactions for this purpose. With increasing pressure on environmental and economic issues, synthetic methods must be optimized and, for tackling both the problems of selectivity and undesired waste of dangerous chemicals associated with the traditional methods available for the modification of aromatic compounds, zeolites are increasingly being used [3].

There have been several approaches to the optimization of the Friedel-Crafts acylation through the use of zeolites [4], although the focus of this research remains more on the acylation of simple activated aromatic compounds than on the more useful heteroaromatic ones [5]. Most of the current research attempts to provide greener and efficient alternatives to the use of "non-catalytical" amounts of harmful and difficult to recover Lewis acids such as $AlCl_3$ and, consequently, alternative catalysts, such as $FeCl_3$ [6], $ZnCl_2$ [7], $BiCl_3$ [8] and other metallic chlorides [7], heteropolyacids [9,10], the application of triflates in ionic liquids [11] and electrochemical methods [12] have been used to achieve this goal. Since the late nineties, the convenient use of zeolites in the Friedel-Crafts acylation of aromatic compounds has been reported by Derouane et al. [13] and several other groups [14–22]. Our contribution to this vast field is the acylation of heteroaromatic compounds under mild liquid-phase conditions promoted by zeolite Beta, with and without modification, using preferably acetic anhydride as acylating agent.

2. Experimental

2.1. Materials and catalyst preparation

All chemicals were purchased from Aldrich and used as such. The catalyst NH_4-BEA (ammonium form of zeolite Beta) with Si/Al = 12 was obtained from Zeolyst International. Non-modified HBEA samples were obtained by calcination of the parent ammonium form, under a flux of dry air at 550 °C for 12 h.

Samples of zeolite Beta were impregnated with an aqueous solution of $InCl_3$ by the incipient wetness technique (5–20 wt% metal load). The water was evaporated under vacuum at 120 °C for 8 h.

Before the catalytic tests, all samples were checked for structural integrity by X-ray powder diffraction on a Panalytical X'Pert Pro diffractometer using CuKα radiation filtered by Ni.

2.2. Reaction procedures

The acylation reaction was performed by addition of a mixture of thiophene (0.88 g, 10.5 mmol) and acetic anhydride (5.40 g, 52.9 mmol), to a sample of HBEA (200 mg), at 60 °C. Periodically,

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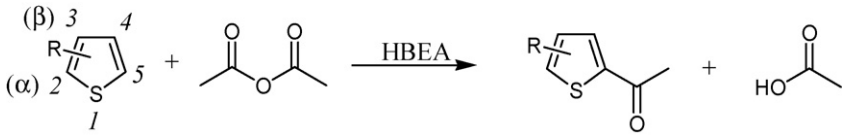

Fig. 1. Acylation of thiophene and substituted thiophenes catalyzed by zeolite Beta (HBEA).

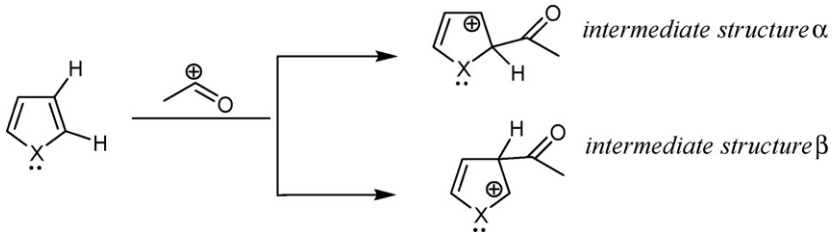

Fig. 2. α and β intermediate structures.

Table 1
Acylation of thiophene derivatives with acetic anhydride catalyzed by zeolite Beta after 10 min reaction time.

Entry	R	Acetylated positions(s): yield (%)
1	H	2 (78)
2	2-methyl	5 (84)
3	3-methyl	5 (34); 2 (27)
4	3-phenyl	5 (3); 2 (1)
5	3-chloro	5 (4); 2 (1)
6	3-butyl	5 (36); 2 (13)

small aliquots of the reaction mixture were analyzed by gas chromatography on a CHROMPACK CP 9001 chromatograph equipped with a Macherey-Nagel Optima-5 column. The identification of the products was achieved by injecting standard products and by GC–MS analysis of selected samples on a Agilent Technologies 5973 chromatograph equipped with a HP-5-MS column and a mass detector.

The acylation of thiophene derivatives and other aromatic compounds followed the same procedure, adapting the amounts of each reactant to preserve the substrate to acylating agent ratio (1:5 molar ratio).

3. Results

In order to minimize errors, reactions were carried as much as possible under the same conditions. Experiments were occasionally repeated to verify consistency and the XRD patterns of all zeolite samples obtained after each treatment indicated that all the samples retain the structural integrity when compared with the parent material.

3.1. Acylation of thiophenes

Both acetic anhydride and acetyl chloride were initially tested in the acylation of thiophene. It was found that, at 60 °C and using a ratio of 1:5 (thiophene to acylating agent), the conversion of thiophene to 2-acetylthiophene was over 90% after 15 min (92% in 20 min) using acetic anhydride whereas with acetyl chloride reached only 44% with the same reaction time and was incomplete after one 1 h. With a 1:4 thiophene to acetic anhydride ratio the reaction was slightly faster (90% in 10 min) but, for experimental convenience in the acylation of a wider range of substrates, the ratio 1:5 was generally used. At lower ratios, acylation was, as expected, slower due to the deactivation of the catalyst probably resulting from the competitive adsorption of the reactants [13].

Using the above conditions, several substituted thiophenes were tested (Table 1; Fig. 1). The only products observed were α-monoacylated (positions 2 or 5). As expected, the thiophene derivative reacting faster was 2-methylthiophene producing exclusively 2,5-dimethylthiophene in 84% yield in 10 min (92% in 20 min; entry 2). Methyl group is a small activating group and there is only a reactive position available. The 3-methylthiophene has the methyl group in a position that is not effectively activating and, therefore reaction is slower. Also, there are two available positions for acylation and, in fact, a mixture of 2,3- and 3,5-dimethylthiophene is obtained, with predominance of the less hindered product (entry 3). The α-product is preferred because of the greater stability of the α-intermediate structure (Fig. 2). A simple evaluation at a B3LYP/6-31G level of theory indicates that intermediate structure α is 35.3 kJ/mol more stable than the corresponding β. With bulkier groups, *n*-butyl, chloro and phenyl (entries 4–6) reactions are slower and less selective than with 2-methyl substituted thiophene.

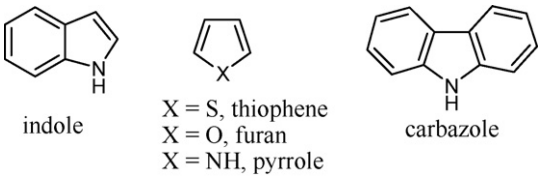

Fig. 3. Heteroaromatic structures tested.

Table 2
Acylation of thiophene, furan, pyrrole and indole with acetic anhydride over zeolite Beta.

Entry		Time (min)	Yield (%); products	Time (min)	Yield (%); products
1	Thiophene	10	78; 2-acetylthiophene	60	97; 2-acetylthiophene
2	Furan	10	70; 2-acetylfurane	120	91; 2-acetylfurane
3	Pyrrole	10	7; 3-acetylpyrrole 28; 2-acetylpyrrole	420	17; 3-acetylpyrrole 72; 2-acetylpyrrole
4	Indole	50	11; 3-acetylindole	420	35; 3-acetylindole

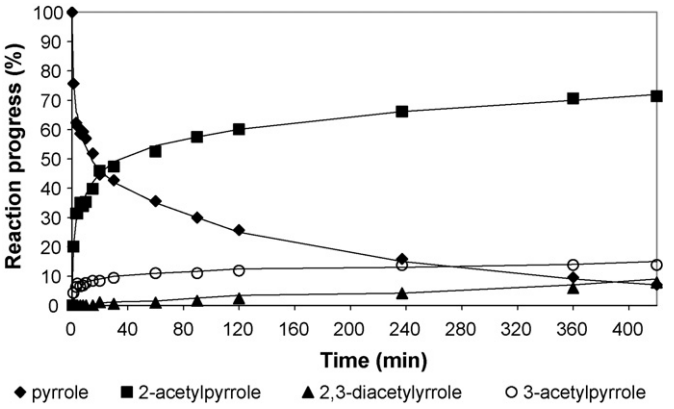

Fig. 4. Reaction progress for the acylation of pyrroles catalyzed by zeolite Beta (HBEA).

3.2. Acylation of other heteroaromatic compounds

Having found good experimental conditions for the acylation of thiophene we have tried to expand the scope of the reaction by testing compounds, such as indole, carbazole, furan and pyrrole (Fig. 3) under those acylation conditions. It was found that only furan, pyrrole an indole reacted to an acceptable extent, even though with meaningful differences (Table 2). Also, mainly due to solubility problems, conditions under which carbazole could be acylated were not found. Furan is slightly less reactive than thiophene (entry 2) maintaining the exclusive preference for position α, but the acylation of pyrrole is significantly slower than the acylation of thiophene and of furan and is also less selective, with acylation occurring both at positions α and β (entry 3).

As shown in Table 2, using mild and straightforward experimental conditions excellent results were obtained for acylation of thiophene and furan. However, contrasting with these, the results for the acylation of pyrrole were a bit disappointing and, therefore, we have looked further into this reaction.

3.3. Acylation of pyrrole and related compounds

The difference in reactivity between thiophene and pyrrole must result from structural differences as well as from their different

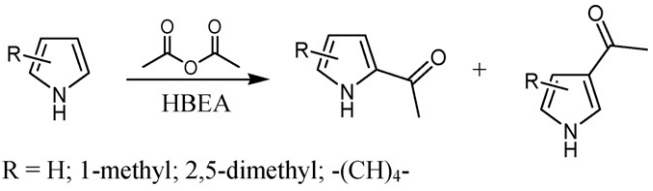

Fig. 5. Acylation of pyrroles and indole catalyzed by zeolite Beta (HBEA).

behaviors in the presence of the catalyst. To gain some insight into this, the competitive adsorption of thiophene and pyrrole was evaluated by stirring solutions of both substrates with the zeolite at room temperature for short periods of time. Not surprisingly, pyrrole gets more adsorbed than thiophene which may also mean that pyrrole partially poisons the catalyst. In agreement with this, carrying out the acylation with an excess of pyrrole also retards the reaction.

Structural rationalization for predicting reactivity in heteroaromatic rings is not always possible even for reactions in the liquid phase [23]. Pyrrole is more π-*excessive* than thiophene and, consequently, reacts more easily with electrophiles under classical conditions, but contrasting with the results we have obtained with zeolite Beta. On the other hand, the selectivity of pyrrole towards electrophiles correlates well in all conditions. Apart from the greater (19.6 kJ/mol) stability of intermediate structure α (Fig. 2, X = NH), selectivity also results from the higher electrophilic susceptibility of carbon β relatively to the carbon α in pyrrole than the one found in thiophene. From another perspective, the difference in activation hardness [24] for atoms α and β is bigger in thiophene than in pyrrole so thiophene reacts essentially through the more favorable carbon α and pyrrole reacts through both α and β carbons (Fig. 4).

Acylation was also attempted on substituted pyrroles (Figs. 5 and 6) and it was found that the reactivity varied in the order 2,5-dimethylpyrrole < indole < 1-methylpyrrole < pyrrole.

Finally, some catalyst modifications were performed in order to enhance its reactivity in conditions similar to those used for thiophene. So, further to some very unsuccessful experiments with zeolite Beta treated with steam and hydrochloric acid [13,25], we have tried impregnation with indium chloride and a metal load of 20% proved to be effective in the acylation of pyrrole, even though without solving the problem of selectivity (Fig. 7); in 2 h pyrrole

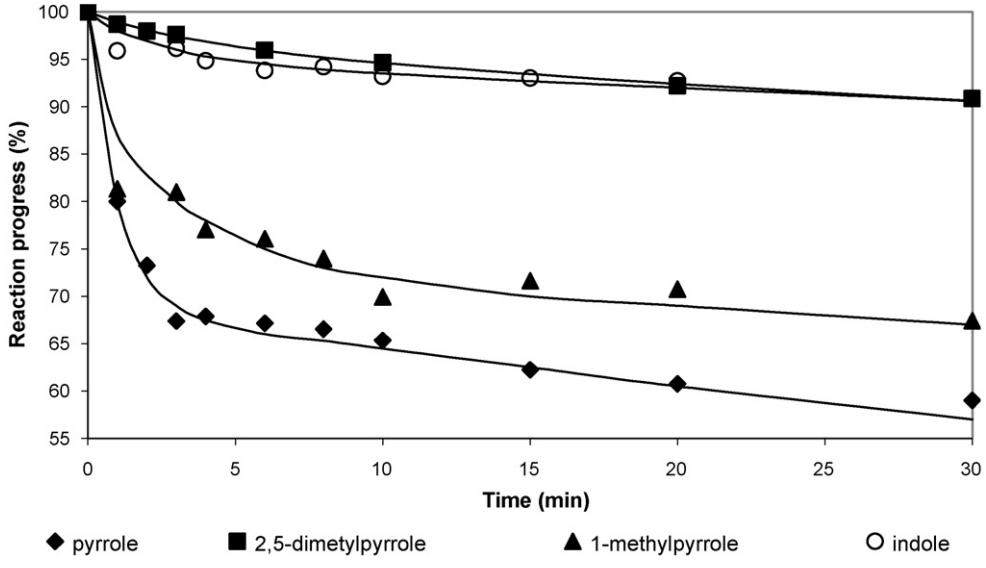

Fig. 6. Reaction progress for the acylation of pyrrole derivatives catalyzed by zeolite Beta (HBEA).

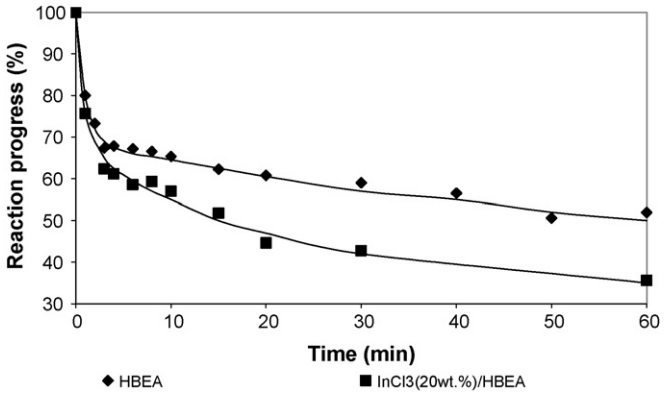

Fig. 7. Reaction progress for the acylation of pyrrole catalyzed by zeolite Beta (HBEA) and by indium modified zeolite Beta [$InCl_3$(20%)/HBEA].

was acylated to 2-acetylpyrrole in 74% yield with side products 3-acetylpyrrole (12%) and 2,5-diacethylpyrrole (2%). Metal loads lower than 20% did not show any beneficial effect on the activity or selectivity. Possibly, indium promotes the reaction by increasing the number of Lewis acid sites. Further studies are in progress in order to clarify the promoting effect of Indium in this reaction and improve the selectivity. These studies involve the complete characterization of materials and optimization of experimental procedures both in preparation of catalysts and reaction.

4. Conclusions

Under the mild conditions used in the present work, and in reasonably short reaction times, several non-activated thiophene related compounds were acylated in a Friedel-Crafts process catalyzed by zeolite Beta and using acetic anhydride as acylating agent. The same conditions can be applied to the acylation of pyrrole, though in this last case, acylation is slower and less regioselective. However, if modified with indium chloride zeolite Beta can also be an efficient catalyst for the acylation of pyrrole.

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