



SELECTIVE ACETYLATION OF AROMATIC HETEROCYCLIC COMPOUNDS

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(Received : 27.10.2011; Revised : 06.11.2011; Accepted : 10.11.2011)

ABSTRACT

A series of acetylated heterocycles were efficiently, selectively prepared from the corresponding heterocyclic molecules with the silica gel-GF-254-5% phosphoric acid, ferric oxide as catalysts at 30-80°C temperatures. This present protocol illustrates a simple acylation process and has wide range of applicability and was applied to the thiophene, furan, pyrrole and pyridine furnishing as an alternate method for the preparation of these drug intermediates.

Key words: Acetylated aromatic heterocycles, Catalysts, Selectivity.

INTRODUCTION

2-acetylated thiophene, furan, pyrrole, pyridine¹ are very important intermediates for the fine chemicals such as drugs and pharmaceuticals, flavouring agents for food stuffs². 2-acetyl thiophene has been used by Zeneca as a raw material for potential fungicides and by Eli Lilly as a raw material for the antidepressant duloxetine. It is also used as a raw material in patents for experimental anti-inflammatory and potential antiviral drugs³⁻⁶. It also has applications as a raw material for drugs with the so many pharmaceutical industries and research labs demands highly pure 2-acetylated 5-membered aromatic heterocycles of thiophene, furan, pyrrole. The substitution of 3-acetyl heterocyclic compounds is disadvantage to the quality of the end products therefore the removable of the usual byproduct 3-acetyl heterocycle is an essential operation which requires special and tedious efforts in the additional step that is, 3-acetylthiophene contaminating 2-acetyl thiophene is removed by a selective electrophilic substitution process, bromination followed by fractional distillation. For the conventional acetylation process, heterocyclic compounds such as thiophene, furan, and pyrrole are acetylated by Lewis acid-metal chlorides and some other solid catalysts⁷⁻⁹. The 3-acetyl heteroaromatic compound is the usual contaminate present to the extent of 20-25 % in the acetylation process by directly using soluble acids. The main and major drawback in the use of conventional Lewis acid-metal chlorides and directly using of other protic acids for Friedelcrafts 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 acquired 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 ecofriendly catalytic process for the acetylation of 5-membered aromatic heterocycles employing a nontoxic, that generates no effluent and concomitantly to obtain high range of selectivity of the 2-isomer to meet the customer's desire. In this way Holderich¹⁰ found a procedure for the vapour phase acetylation with acylating agents in presence of zeolites. 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-acetyl furan is attained with 99% selectivity and 23% conversion. On the other hand in the case of pyrrole which tends to polymerize, the acidity of the 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 compounds achieved, serious limitations are low conversions and high energy requirement for the vapour phase reactions. We report in this work the selective acetylation of hetero aromatic compound, furan, thiophene, pyrrole, pyridine employing a very diluted or low percentage of orthophosphoric acid (5%) absorbed on a simple, cheapest and alumina free silica gel -GF-254 as catalyst A, and absorbed on iron oxide (ferric oxide) -silicagel-GF-254 as catalyst B in catalytic amounts in solid phase in quantitative yields under mild conditions for the first time.

EXPERIMENTAL

Preparations of catalysts

Catalyst-A: SiO₂ (silica gel-GF-254), phosphoric acid, purchased from Fluka chemicals were used as such. To a 100 g of SiO₂ add 5% ortho phosphoric acid (H₃PO₄) (dilute 5 mL of orthophosphoric acid in 100 mL of water). Take 5 g of SiO₂ and 7 mL of 5% H₃PO₄ on watch glass, make it pasty material, dried at 40°C in the hot oven for 4 hours.

Catalyst-B: SiO₂ (silica gel-GF-254), Fe₂O₃ (ferric oxide) and orthophosphoric acid, purchased from Fluka chemicals were used as such. To a 5 g of SiO₂ add 5 g of ferric oxide and grind the material till it becomes the homogeneous amorphous powder in the mortar. To this amorphous powder add 14 mL of 5% orthophosphoric acid (dilute 5 mL of orthophosphoric acid, in 100 mL of water) and mixed in a mortar, dried at 40°C in hot oven for 4 hours.

Acetylation of 5-membered heterocyclic aromatic compounds with acetic anhydride in the presence of very low concentrated phosphoric acid absorbed on silicagel and silicagel ferric oxide catalysts.

Methods of characterizations for the molecules

The formation of acetylated products were monitored by analysis of reaction mass samples, collected in regular intervals by GC (Gas chromatography) using ov-column. Proton ¹H NMR spectra were taken on a Gemini Varian 200 MHz .

Catalytic reactions

Typical procedures

A mixture of thiophene (42 mmol, 3.30 g), acetic anhydride (11 mmol, 1.02 g) and catalyst (0.5 g) was taken in a 50 mL round bottom flask .The reaction was carried out under nitrogen atmosphere. After the completion of the reaction (Monitored by GC), the reaction mixture was filtered, distilled to remove acetic acid and unreacted reactants and purified by ¹H NMR DATA: (δ ppm, CDCl₃):

2-acetyl thiophene: δ = 2.5 (3H, s), δ = 7.1 (1H, dd), δ = 7.6 (1H, d), δ = 7.66 (1H, d)

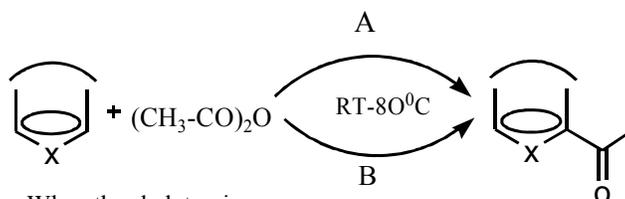
2-acetyl furan: δ = 2.48 (3H, s), δ = 6.8 (1H, dd), δ = 7.2 (1H, d) δ = 7.65 (1H, d).

2-acetyl pyrrole: $\delta = 2.5$ (3H, s), $\delta = 6.3$ (1H, dd), $\delta = 6.9$ (1H, m), $\delta = 7.1$ (1H, d), $\delta = 10$ (1H, brs).

2-acetyl-pyridine: $\delta = 2.5$ (3H, s), $\delta = 8.0$ (1H, d), $\delta = 8.31$ (1H, t), $\delta = 7.6$ (1H, t), $\delta = 9.1$ (1H, d)

RESULTS AND DISCUSSION

Both the catalysts for the acetylation of aromatic heterocyclic molecules are shown in the Scheme 1 as catalytic path A and catalytic path B. The results on catalytic activity, selectivity of various catalysts in the acetylating of heteroaromatic compounds, thiophene, furan, pyrrole and pyridine with acetic anhydride conducted are represented in Table 1.



When the skeleton is
pyrrole, furan, thiophene $x = \text{NH}, \text{O}, \text{S}$ (respectively)

When the skeleton is
pyridine, $x = \text{N}$

Catalysts:

A = SiO_2 -5% H_3PO_4 , B = SiO_2 - Fe_2O_3 -5% H_3PO_4

Scheme 1 : Acetylation of 5-membered heterocyclic aromatic compounds with acetic anhydride in the presence of very low concentrated phosphoric acid absorbed on silica gel and silica gel ferricoxide catalysts

Table 1.

| S. No. | Heteroaromatic | Catalyst | Temp. (°C) | Time (h) | conversion (%) ^a | Selectivity 2-acetyl heteroaromatic |
|--------|----------------|----------|------------|----------|-----------------------------|-------------------------------------|
| 1 | Thiophene | A | 50 | 6 | 59 | 98 |
| 2 | Thiophene | A | 80 | 4 | 78 | 96 |
| 3 | Furan | A | 30 | 10 | 80 | 95 |
| 4 | Furan | A | 50 | 6 | 97 | 91 |
| 5 | Pyrrole | A | 30 | 11 | 85 | 99 |
| 6 | Pyrrole | A | 80 | 6 | 98 | 94 |
| 7 | Pyridine | A | 30 | 10 | 52 | 92 |
| 8 | Pyridine | A | 80 | 5 | 63 | 95 |
| 9 | Thiophene | B | 30 | 9 | 60 | 99 |
| 10 | Thiophene | B | 80 | 5 | 98 | 99 |
| 11 | Furan | B | 30 | 10 | 78 | 98 |
| 12 | Furan | B | 50 | 6 | 97 | 95 |
| 13 | Pyrrole | B | 30 | 10 | 77 | 99 |
| 14 | Pyrrole | B | 80 | 7 | 97 | 96 |
| 15 | Pyridine | B | 28 | 10 | 50 | 95 |
| 16 | Pyridine | B | 80 | 7 | 65 | 97 |

^aBased on acetic anhydride, based on GC monitoring

The acetylation of thiophene was carried out using SiO_2 -5% H_3PO_4 , and SiO_2 - Fe_2O_3 -5% H_3PO_4 have displayed higher activity. Using these efficient catalysts, furan, pyrrole, pyridine are also acetylated. The conversions and selectivity of 2-acetyl pyridine, 2-acetyl pyrrole varies with the reaction temperatures used. In the acetylation of pyrrole, furan, pyridine¹¹ at high temperatures the conversion increases with the decrease of selectivity. The 3-acetyl product is the predominant minor by product. The reactions moved at ambient temperature afford 2- acetyl products in almost pure form and even traces of 3-acetyl products are not at all detected. The low selectivity is ascribed to the kinetic effect. Selective acetylation of thiophene to 2-acetyl thiophene is independent of temperatures used in acetylation conducted in presence of dried SiO_2 - Fe_2O_3 -5% H_3PO_4 , SiO_2 - 5% H_3PO_4 catalysts, the formation of 3-acetyl product is not detected in this case either. Thus, the highly pure and desired isomers are realised using low percentage or that is very diluted ortho phosphoric acid (5%) absorbed on alumina free silica gel and amorphous mixture of alumina free silica gel - Fe_2O_3 used as catalysts.

Catalytic activity and selectivity

In the case of development of the catalyst, we have explored various silica gel-supported acid catalysts with varied acidities for Friedel-crafts acetylation. Catalysts exhibit both Bronsted, Lewis acid sites for the acetylation of our starting materials. The former has external $-\text{OH}$, NH_2 ^{12,13} groups. Where the Lewis sites are the exposed three fold coordinated Al^{3+} ions substituting the Si^{4+} ions in the tetrahedral shapes or transition metals incorporated by ion exchange methods. The acetylation of hetero aromatic compounds is mediated when both types of soluble acids and lewis acids are used independently⁷⁻⁹. The influence of the Lewis acidic sites composed in silica gel-ferric oxide orthophosphoric acid, and protic acid takes a silica gel as solid support. The acidification by the dilution about 5% phosphoric acid on the silica gel as well as on silica gel-ferric oxide amorphous powder made complexes acts as good homogeneous acetylating catalysts. The inter layer acidity¹⁴ increases with the 5% phosphoric acid play a vital role in displaying the acetylation. The acetylation reaction selectivity increases up to little extent in presence of catalyst B due to additional ferric oxide support. The acetylation of the heteroaromatic compounds are highly selective at 2 -position of the ring with these catalysts and to yield the bulkier product. To summarize, that it may be stated as in the acetylation of aromatic heterocycles on SiO_2 - 5% H_3PO_4 , and SiO_2 - Fe_2O_3 -5% H_3PO_4 , it is the acidity of the catalyst that brings about the reaction and the electronic and the kinetic factors which largely determine the direction of the substitution. High selectivity for a number of cycles in the acetylation of the pyridine, pyrrole, thiophene, furan shows maximum selectivity at higher temperature 50°C not at 80°C and all were conducted to understand the recycle profile.

CONCLUSION

These 5% phosphoric acid absorbed silica gel and silica gel-ferric oxide supported catalysts offer the highly efficient and selective acylation procedure for pure and desired isomer, to be used as an intermediate, using acetic anhydride for the manufacture of important drugs and pharma industries. These catalysts are first reported and do not produce any effluents unlike Lewis acid and their corresponding acids. These are very cheap and easily prepared in our research laboratory. Our methodology described here is not only eco-friendly but also an economically reduced.

ACKNOWLEDGEMENT

Authors are thankful to Aditya group of Companies, Hyderabad for providing all required chemicals, Dr. Ch. V. N. Murthy PDF (P, U.S.A), Dr S. Azeza. MBY, and special thanks to M. V. R. R and D. Samsonu for encouragement and financial assistance.

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