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Ferric Triflate $\text{Fe}(\text{OTf})_3$ as a Highly Efficient Catalyst for the Acetylation of Alcohols, Phenols, Thiols and Amines: Reaction Mechanism Understanding through Density Functional Theory

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Abstract: Ferric triflate used as an efficient catalyst for the quick acylation of alcohols, phenols, thiols and amines in catalytic amounts. And, will be a favorable procedure for industrial application due to usage of less toxic ferric metal as a part of catalyst, with devoid of any racemization of chiral alcohols in reaction products. We have also carried out the density functional calculations to clarify the factors that affect the catalytic function of Ferric triflate, examined the activity and proposed the possible reaction mechanism for acetylation of alcohols.

Keywords: acetylation, Ferric triflate, density function theory.

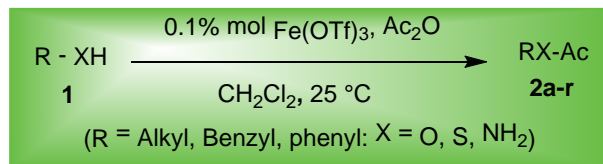
Introduction

Acylation is one of the most frequently used transformations in multi stage organic synthesis. Among the various protecting groups, acetyl is the most common group due to its easy introduction, being stable to the acidic reaction conditions, and also due to ease of deprotection.^[1,2] Although, numerous methodologies described in literature for acylation,^[3] newer methods continue to attract the attention of researchers for their experimental simplicity,

mild reaction conditions and productivity.

Very recently, we have demonstrated the catalytic nature of ferric triflate $[\text{Fe}(\text{OTf})_3]$ for the synthesis of bis-indoles.^[4] In continuation to our systematic evaluation of the efficacy of metal catalyst, we wish to report herein, the acylation of alcohols, phenols, amines and thiols with $\text{Fe}(\text{OTf})_3$ as a highly efficient catalyst for the swift acetylation (**Scheme 1**). In our attempt, we examined the catalytic amount of $\text{Fe}(\text{OTf})_3$ for acetylation of primary,

secondary, benzylic and cyclic alcohols, phenols, thiophenols and amines using acetic anhydride in dichloromethane as solvent and found, very short reaction time with excellent yields, at room temperature.



Scheme 1. catalytic acetylation

Acetylated products by using catalytic amount of $\text{Fe}(\text{OTf})_3$ have been represented in the **Figure 1** along with yields and for all the conversions, reaction time was very less i.e., less than 1 min. Further, chiral molecules were treated for acylation to obtain the products (**2i**, **2j** & **2l**) and no racemization has been observed under the reaction conditions. Further, this acetylation methodology is working well for the complex chemical molecules (**2l** & **2j**). During the acetylation, $\text{Fe}(\text{OTf})_3$ is acting as Lewis acid and the proposed mechanism for reaction has been represented in **Figure 2**. When, evaluated the acetylation results by using $\text{Fe}(\text{OTf})_3$ against experimental data obtained without using the reagent, it is found that, longer reaction times observed for acetylation. Hence, it was concluded that, acetylation mediated with $\text{Fe}(\text{OTf})_3$ more effective and efficient. As on date, to the best of our knowledge, this is the first to report on catalytic nature of using $\text{Fe}(\text{OTf})_3$ for acylation of alcohols, phenols, amines and thiols, which have many advantages over the conventional methods like mild reaction conditions, cleaner reactions, faster reactions, good yields of products and low consumption of catalyst.

Further, the density function calculations were performed with the modeling program (DMol3, module of Accelrys Material Studio) using a local density approximation, the exchange-correlation local functional PWC (Perdew and Wang 1992). DMol3 uses numerical orbitals for the basis functions, each function corresponding

to an atomic orbital (AO). Double numerical plus d-functions (DND), it is like DN with a polarization d-function on all non-hydrogen atoms. This is the default basis set, providing reasonable accuracy for modest computational cost. The final energies were extrapolated to zero smearing.

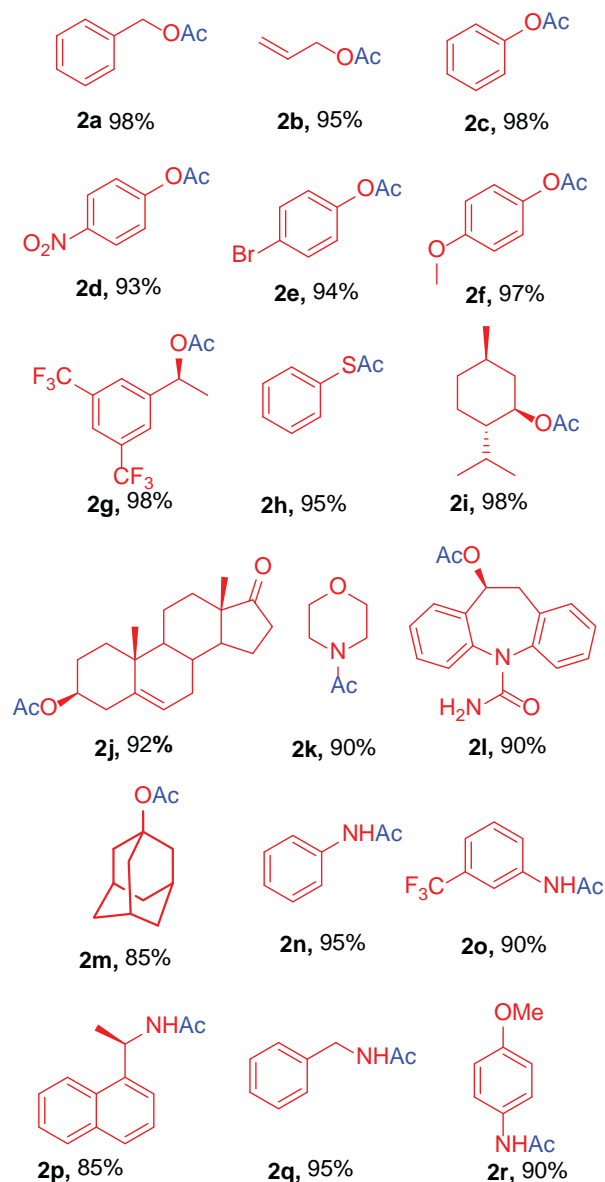


Figure 1. Acylation of diverse substrates by using $\text{Fe}(\text{OTf})_3$ and acetic anhydride. And, time reported in Seconds.

Transition states (TS) of acetylation reaction were located with the nudged elastic band

method.^[5] We calculated the reaction and activation energies in gas phase. Each of the transition state structures presented was probed by a normal-mode analysis, indeed exhibited only one vibrational mode with an imaginary frequency. However, there might be an energy difference of $\sim 20 - 30$ kJ/mol, if we change the methods used in calculations for transition state.

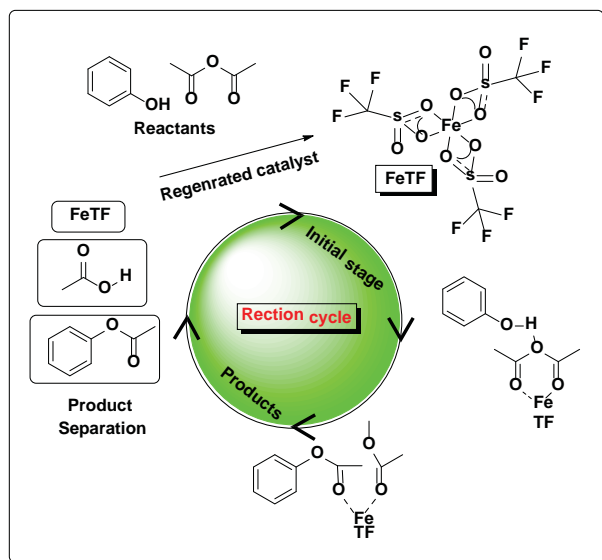


Figure 2. Reaction mechanism and catalyst regeneration by taking substrate as phenol ($\text{FeTF} = \text{Fe}(\text{OTf})_3$).

In the computations, we considered the reaction mechanism scheme as shown in **Figure 2**. Before trying to understand the reaction mechanism, we wanted to understand better about the catalyst and its structural existence. All the three ligands are bound to Fe^{3+} in three planes of intersection keeping Fe in the origin as shown in **Figure 3(a)**. All the three ligands bind to the Fe atom through a strong ionic bond via oxygen carrying a negative charge and through a weak bond with oxygen of sulfonate group on the ligand. It is to be noted, all the three ligands encapsulate the catalytic active metal centre using their respective van der Waals volume as shown in **Figure 3(b)**. Pearson et al.,^[6] has given a very good perspective of chemical hardness and its direct correlation with highest occupied orbital and lowest unoccupied molecular orbital

(HOMO-LUMO) energy gap. According to Pearson et al, the larger the HOMO–LUMO gap the harder the molecule will be and vice versa. Chemical hardness is crucial while discussing the reactivity potential of catalyst with its reactants. In other words, we can also discuss about the energy required to open up the catalytic metal centre to reaction medium. If this energy is exothermic, reaction tends to be faster and if this energy is endothermic then the first rate limiting step will be to lessen the chemical hardness and improves the metal centre exposure to the reaction medium. As shown in the **Figure 3(b)**, van der Waals volume encapsulates the Fe metal centre and shields it from the reaction medium. However, in our present reactants, HOMO-LUMO energy gap of acetic anhydride overlays with that of $\text{Fe}(\text{OTf})_3$. This overlaying enables reduction in chemical hardness in turn leading to an exothermic reaction, where Fe metal centre exposes to reaction medium as shown in **Figure 3(c)**.

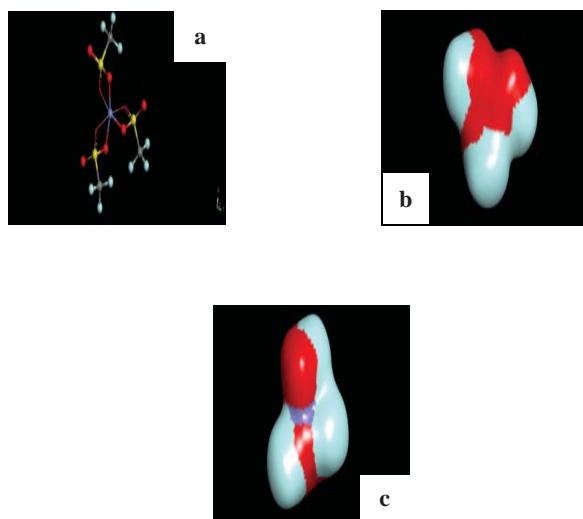


Figure 3. (a) Molecular structure of $\text{Fe}(\text{OTf})_3$ - red color for oxygen; yellow for sulfur; light blue for Fluorine & blue for Iron (b) van der Waals surface of the $\text{Fe}(\text{OTf})_3$ - red color is the oxygen surface and light blue is the fluorine surface (c) Metal center exposure - colored in blue.

Structurally, there is a realignment of ligands on the metal center, where the weak oxygen bonds

of sulfonates gets debonded while retaining the strong ionic bond through other oxygen atoms. The de-bonding of these weak bonds enable a space on the metal centre to accommodate the acetic anhydride on the Fe surface as shown in the **Figure 5(a)**. As depicted in **Figure 5**, initial state for the reaction occurs through a weak binding of acetic anhydride on the metal centre and a very weak hydrogen bond between phenol and acetic anhydride. We would like to mention here that theoretically there are other possibilities of aligning both the reactants bound to the metal centre and to start locating the transition state.

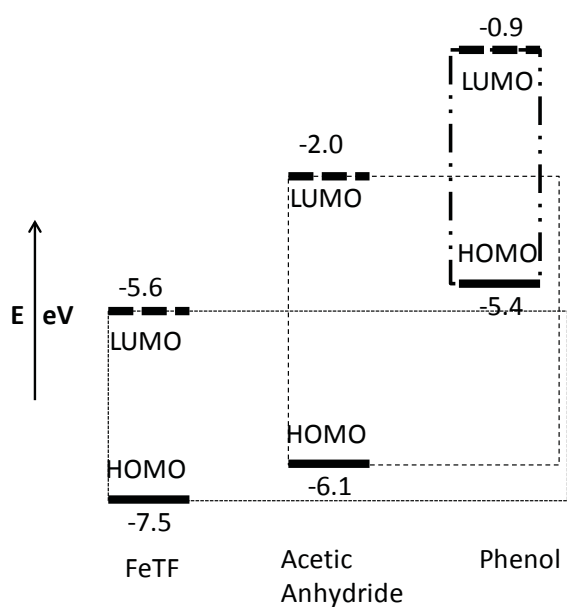


Figure 4. HOMO-LUMO energy gaps of $\text{Fe}(\text{OTf})_3$; Acetic anhydride and phenol. Boxes represents the over laying of energy gaps.

However, we have finalized the initial state as shown in **Figure 5(a)** as our initial state due to the possibility of easy attack on hydrogen of phenol to the oxygen located in the middle of acetic anhydride; whereas, in other possibilities, the reaction has to pass through multiple transitions to get to the final product. Also, due to non overlay of HOMO-LUMO energy gap of $\text{Fe}(\text{OTf})_3$ catalyst and phenol the initial state as shown in **Figure 5(a)** could be more realistic initial state than that of other possibilities.

And, energetically most of the possibilities are similar.

Bond	Initial state	Transition state	Final state
r(O2-H)	2.74	1.18	0.98
r(O1-H)	0.98	1.28	4.32
r(O1-H)	2.71	1.55	1.33
r(O2-H)	1.37	1.86	3.02

Table 1. Bond formation and breaking during acetylation reaction, all units are in angstrom. IS – initial state; TS – transition state; FS – final state.

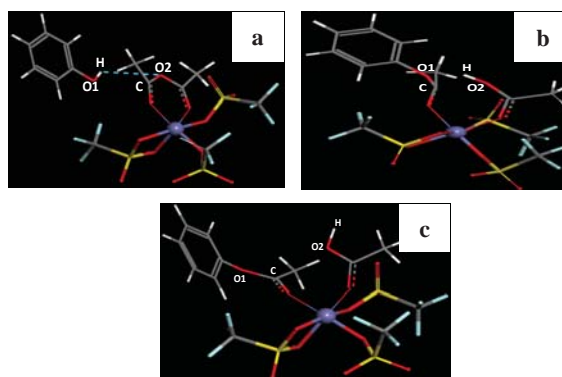


Figure 5. (a) Initial state (IS) wherein both reactants, phenol and acetic anhydride are in close vicinity of Fe center of the catalyst; (b) Transition State (TS); (c) Final State (FS).

During the initial state phenol bounds to oxygen through hydrogen bond of 2.74 Å. As shown in reaction energy diagram (Figure 6), the formation of this initial state is about 300 kJ/mol exothermic. This also shows that kinetically $\text{Fe}(\text{OTf})_3$ is a preferred catalyst because it is quick to shift its chemical hardness to softness in the presence of acetic anhydride. The two unpaired electrons on oxygen of phenol tend to get shared with the carbon of acetic anhydride. The existing double bond of oxygen with carbon of acetic anhydride becomes weak and forms a bond with oxygen of phenol by imparting a positive charge on oxygen of phenol, which in turn donates its hydrogen and gets bind to the other half of acetic anhydride leading to acetylation of phenol. The said phenomenon of

bond elongations and charge transfer happens with activation energy of about 150 kJ/mol as depicted in reaction energy diagram shown in **Figure 6**. Structurally all the bonds are elongated in the transition state as shown in the 'transition state' column of the Table 1. During the density functional theory (DFT) calculations of locating transition state, we have defined the reaction path as shown in **Figure 5** through labeling of atoms. Hydrogen (H) of phenol has to be bound to oxygen (O2) of acetic anhydride where as carbon (C) of acetic anhydride has to form a bond with oxygen (O1) of phenol. Also, final state formation as shown in **Figure 5(c)**, is exothermic. Because of this exothermicity, separation of products, acetic acid and acylated phenol is a little difficult as we need to use energy for separation. According to the reaction energy diagram, about 300 kJ/mol is required to separate products and regenerate catalyst. However, the total reaction is exothermic.

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References and Notes

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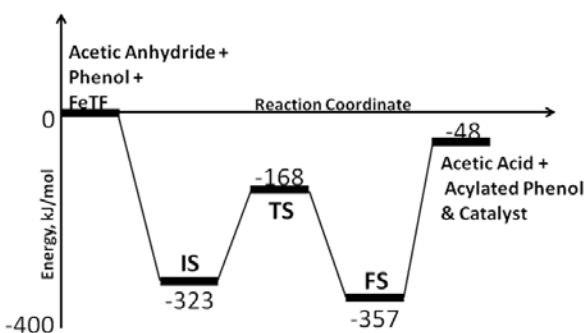


Figure 6. Reaction energy diagram for acetylation of phenol using Fe(OTf)₃ catalyst. (Fe(OTf)₃ = FeTF).

In conclusion, we have demonstrated an efficient and simple methodology for the acylation of Alcohols, Phenols, Thiols and amines by using catalytic amount of Ferric triflate. Further, experimental simplicity, substantial yields and spontaneity make this methodology more attractive alternative over the conventional method for acylation. Also, we have carried out the density functional calculations to clarify the factors that affect the catalytic function of Ferric Triflate and examined the activity and proposed the possible reaction mechanism.