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作 品 名 稱：以離子溶液催化醇與酸酐的之酯化反應

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學校／作者：臺北市立中山女子高級中學　楊欣瑜

作者小傳　　　　（楊欣瑜)

小時後的我，總是喜歡拉著爸爸媽媽的手，張著大大的雙眼向他們問東問西，因為我總是對這個世界充滿好奇，想探索它的奧妙；從小到大，我一直抱持著這種對萬物感興趣的童心，觀察人生路上的一草一木。

高中離鄉來到台北就讀中山女高，是我人生的一大轉捩點，我不但在這進步的城市裡拓展視野，更在其中成長許多，也開啟了走向科學研究的大門。雖然課業的壓力纏繞於心，我仍然在課餘及假日的時間往實驗室跑去，在那裡享受自己的一片天。站在學業和科展、社團的翹翹板上著實不易，有時把我累壞了，但是得到的東西讓我覺得一切都是值得的，那就是------經驗。

這次有機會參加國際科展，我很高興，也非常感恩；若沒有人在旁支持與協助，也不會有今天的我；希望能在這次科展更上一層樓，再一次自我突破。

以離子液體催化醇與酸酐的酯化反應

An Efficient Protocol for Acyl-Forming Reaction Catalyzed by Ionic Liquid

作　　者：楊欣瑜
學　　校：台北市立 中山女子高級中學
指導老師：中山女高 吳淑芳 老師
指導教授：師大化學系 陳建添 教授

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目錄

摘要

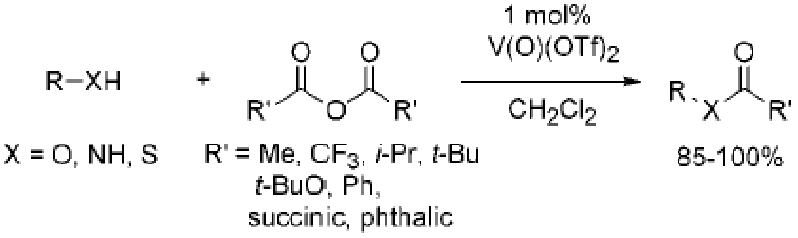
在酯化反應中，經由實驗結果，我們發現離子液體對於此反應有催化的效果。離子液體是在室溫下呈現液態的離子化合物，將醇類與酸酐放入離子液體中有助於酯化反應的進行，基於這個新的發現，我們開始尋找使用不同種類的離子液體做實驗，選出適當的離子液體，並且測試離子液體在不同環境下的催化效果，以及適合的使用計量；更進一步，我們找出離子液體在催化反應之後，將離子液體回收的方法：利用有機溶劑將離子液體和產物分層並萃取出產物，把離子液體回收再利用，符合現代推動綠色化學的趨勢。接下來我們探討離子液體對催化反應的擴展性與應用，先由不同結構的一級醇反應到醯胺鍵的生成，最後推展到合成阿斯匹靈，實驗結果說明，用離子液體做催化劑，也可以成功的合成阿斯匹靈。

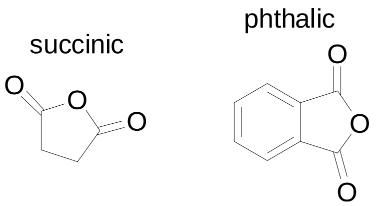
Abstract

We have established for the first time that ionic liquids, which possess the property of Lewis acid, can facilitate acylation of alcohols with anhydrides to form esters with photo-excitation. With the initial finding, we then screen through different types of ionic liquids with varying counter anions, loading, and external light or heat sources to sort out the best reaction conditions. To gain insights into the working mechanism, the dynamic profile of the catalytic reaction was monitored by analyzing the reaction mixture by using ‘H NMR spectroscopy. The ionic liquids can be recovered by extractive separation from the acylation product, which meets the major theme of green chemistry. To extend the substrate scope and applications of the new catalytic process, different functional primary alcohols and amines were further examined. More importantly, we have utilized the new catalytic protocol for the acetylating of salicylic acid, leading to aspirin with high efficiency.

壹、 研究動機與背景

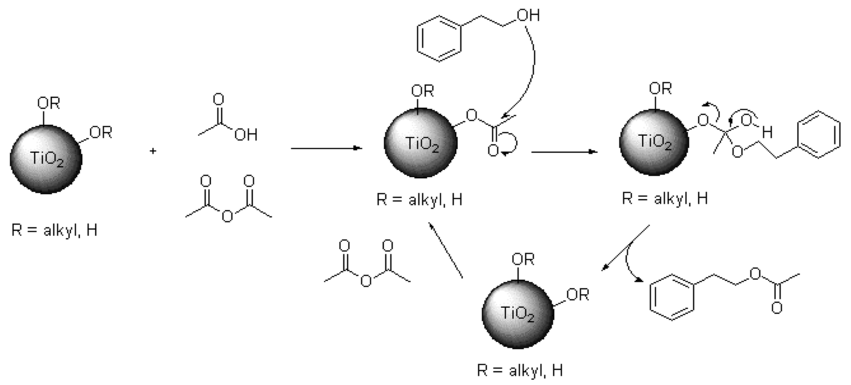
在高中化學實驗中，我們在有機實驗裡合成阿斯匹靈時，是以濃硫酸當作催化劑，將柳酸(水楊酸)與乙酸酐反應合成市面上常見的阿斯匹靈。在實驗時，老師叫我們要格外小心，因為濃硫酸在催化時溫度上升極快，危險性極高；而且最後做出來的阿斯匹靈轉換率不佳。查資料後了解，原來濃硫酸會同時催化正、逆反應的進行，導致轉換率無法升高，從此引發了對此實驗的好奇心，想對酯化反應有更深入的探討與研究，希望能以安全、轉換率又高的方式來催化；而在陳建添教授的實驗室中，有改以一系列氧釩金屬錯合物應用在親核性醯基取代反應上有良好的成果，其成果發表在 Org.Lett.2001,3,869 上(參考文獻-八)；



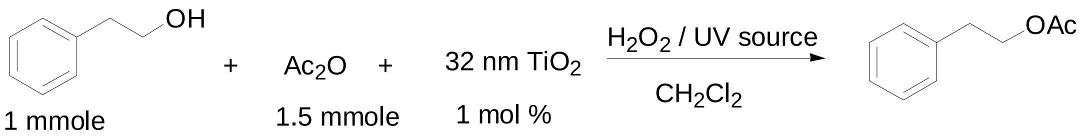


其中，釩氧鍵(V=O)同時具有路易士酸、鹼兩性性質($^{+}$V－O^{-})，可能是一逐步推、拉電子的反應機構，促使反應進行。

藉由此研究給予的方向，並加以搜尋資料後(參考資料-八、九)，推測並且成功以奈米 TiO_2 來光激催化此反應，



但是以目前的實驗結果，在使用不同的金屬氧化物(Y_2O_3、WO_3、ZrO_2)，不同的奈米粒徑(9nm、32 nm、4400nm)，各種共氧化劑(TBHP(第三丁基過氧酸)、H_2O_2、O_2)與溶劑(二氯甲烷、甲苯、THF、乙醚、氫甲烷、正己烷、乙酸乙酯、丙酮)中，在最好的使用環境下(如下圖)，此酯化反應的最高速率是 24 hrs (轉換率 97 %) ，TiO_2 的催化效果稍嫌緩慢，



因此我們一直尋找讓反應速率加快的方法，在不斷的文獻搜尋及研究過程中，發現了 TiO_2 在離子液體中反應速度會突然加快，開始了對離子液體的深入探討。

經過實驗後，發現離子液體在親核性醯基取代反應上，有獨立催化的效果，引發了對離子液體催化酯化反應的一系列研究。離子液體是少數在常溫下為液態的離子化合物，物理與化學性質都很特別。它在催化酯化反應中有不錯的表現，反應速率在可以接受的範圍，轉換率更高達 100 %；另外值得一提的是在本研究中，我們嘗試將離子液體經過萃取方法回收再利用，實驗証明確實可行；總體來說，此新的催化劑能夠讓反應有良好轉換率並且使反應快速又安全的完成，並且成功地把環保的觀念帶入有機化學中。本實驗以乙醯化反應為例，做離子液體在其中催化作用的相關探討。

貳、 實驗目的

進行以新的方法酯化反應(反應式如下)

一、測試不同種類的離子液體對酯化反應的效果。

二、照光是否會對催化速率造成影響，以及在 40˚C 下反應的效果。

三、找出以離子液體催化此反應的最佳當量。

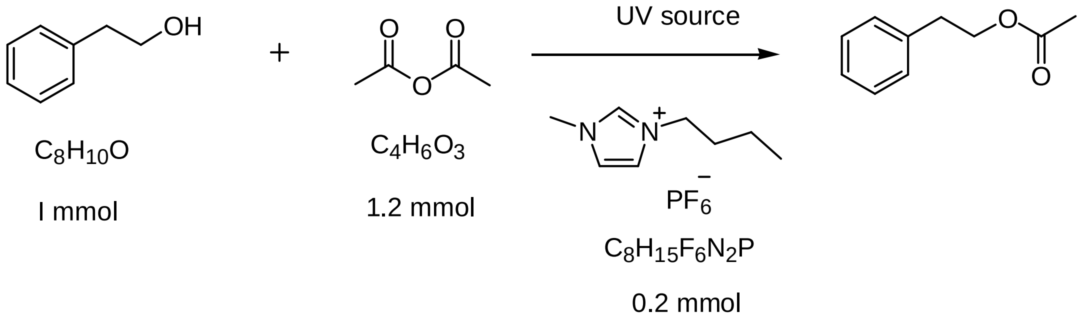
四、測試有機溶劑對離子液體的溶解效果與回收離子液體對反應的影響。

五、以不同醇類當反應物的結果。

六、探討以不同的酸酐反應的效果。

七、阿斯匹靈的製作

◎ 新型酯化反應的反應式



參、 使用器材

一、試管、毛細管、針筒(抽取反應物用)、刮勺、TLC 片、展開槽、NMR tube

二、洗瓶、圓底瓶、萃取瓶

三、實驗藥品、抽濾裝置、真空幫浦

四、UV table (波長 356 or 254 nanometer)、迴旋濃縮儀、管柱層析、超音波震盪器、核磁共振光譜儀(400 or 200 MHz NMR)

肆、 實驗步驟

一、 取乾淨的石英管數隻，貼上編號，各加入 1 mmol 的苯乙醇和 1.2 mmol 的醋酸酐，再加入離子液體當催化劑。

二、 在超音波震盪器中震盪數秒。

三、 放入 UV table 中照光。

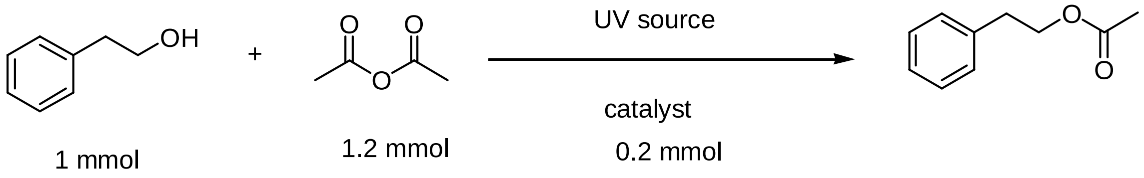
四、 持續以 TLC 片 (薄層色層分析法) 追蹤反應進行。

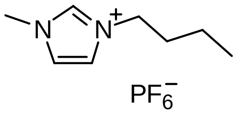
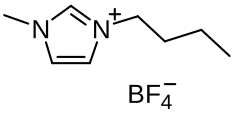
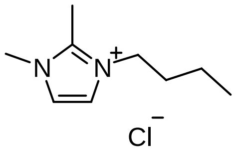
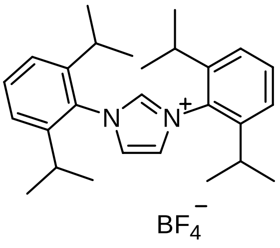
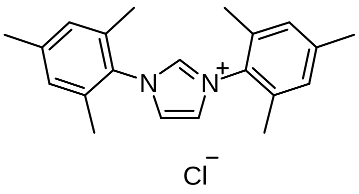
五、 以核磁共振光譜儀(200 或 400 MHz NMR)確認轉換率。

六、 以適合的溶劑回收離子液體。

伍、 過程與討論

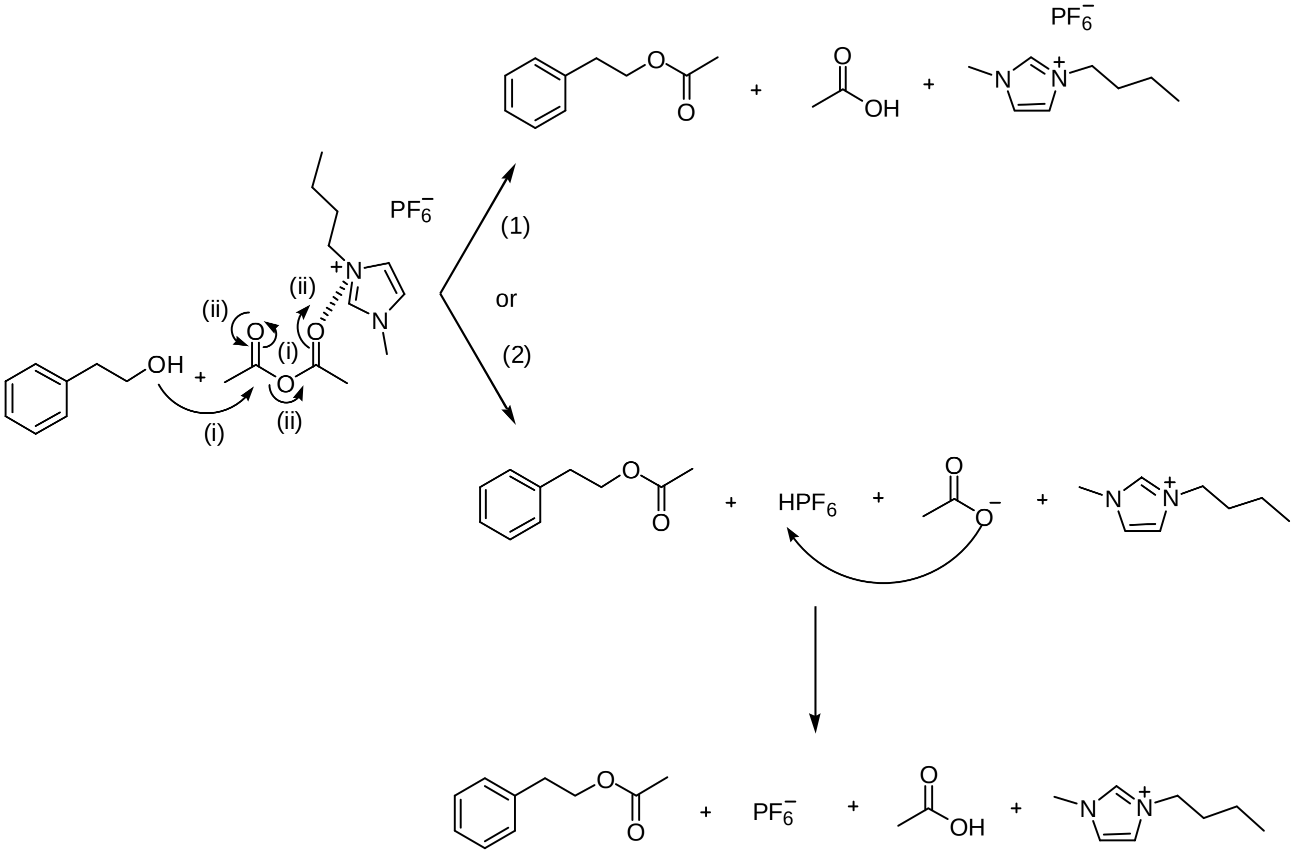
一、 測試不同種類的離子液體對酯化反應的效果，本實驗分別以 PF_6^-、BF_4^-、Cl^-為陰離子、以及不同結構的陽離子的離子液體作試驗。



catalyst	Time	Yield (%)
	2 hrs	100.0 %
	24 hrs	80.1 %
	48 hrs	57.6 %
	24 hrs	82.6 %
	48 hrs	79.6%

討論：結果在我們使用的離子液體中，由實驗結果我們發現，陰離子與陽離子種類皆為影響反應的主要因素，其中陰離子以 PF_6^-的離子液體催化效果最好，推測是由於 PF_6^-的整體極化度﹝polarizability﹞比 BF_4^-及 Cl^-大，故比較容易穩定以 imidazolium 陽離子活化酸酐後的結構中心，使反應順利進行。因此，以下實驗主要是以 PF_6^-陰離子的離子液體來進行催化反應。

◎ 推測可能的反應機制如下:

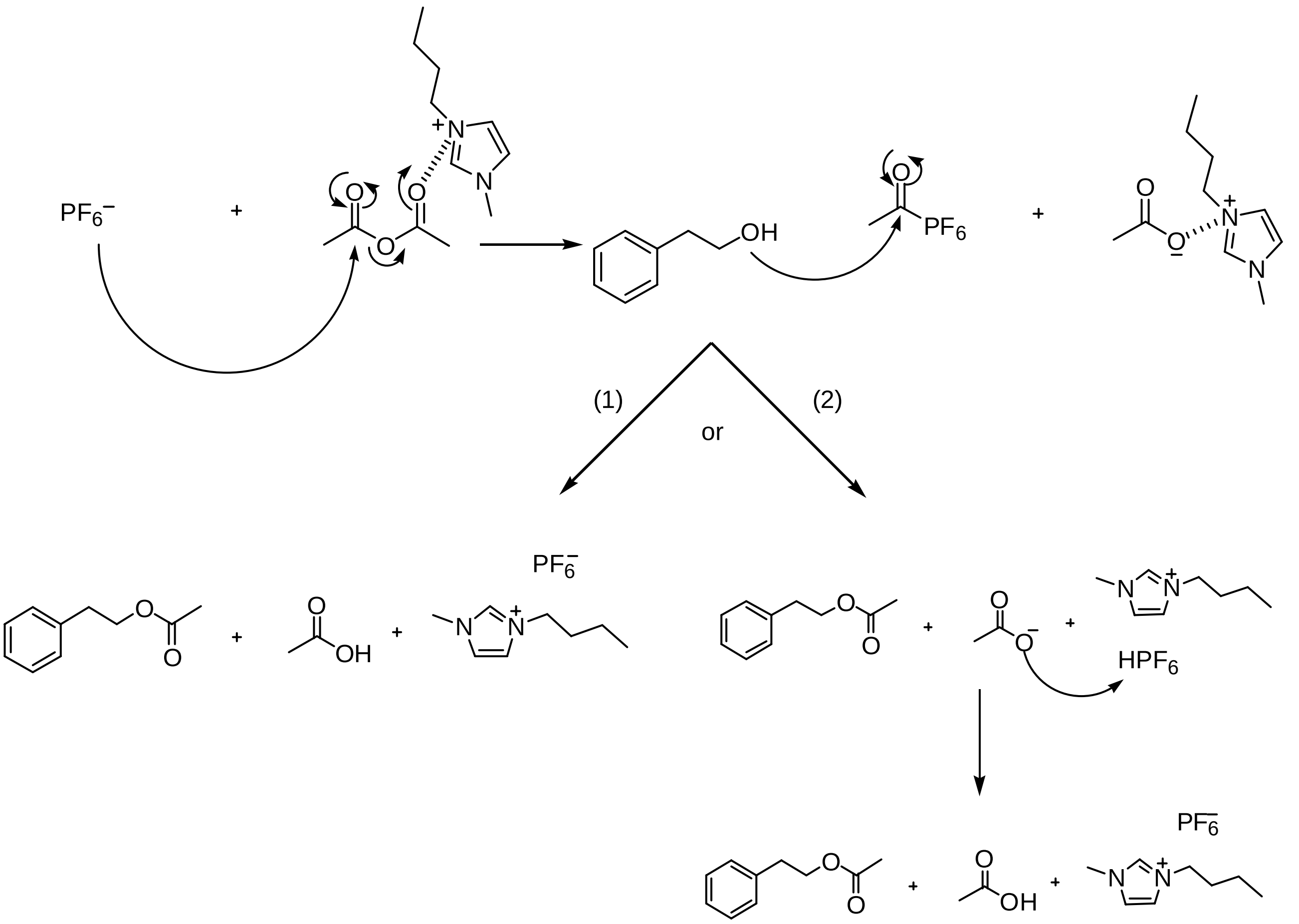


1. →由陽離子先活化酸酐

→苯乙醇氧上的孤對電子攻擊以 imidazolium 陽離子活化酸酐後酸酐的結構中心，使酸酐的電子轉移，結構發生改變

→(1)直接形成產物乙酸苯乙酯、醋酸以及離子液體

或(2)先形成 HPF_6，醋酸根再與氫結合→然後才形成產物乙酸苯乙酯、醋酸以及離子液體



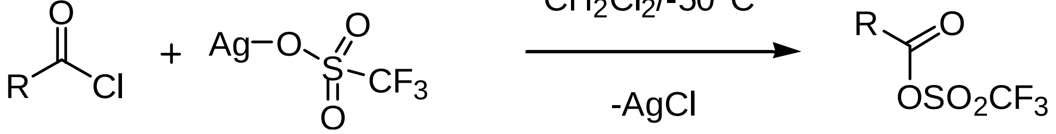
2. →由陽離子先活化酸酐

→PF_6^-攻擊酸酐的結構中心，使酸酐的電子轉移，結構發生改變，形成 $CH_3C(O)PF_6$ 之高活性態中間體，雖然我們沒有直接證據，證實反應是經由此高活性中間體，但參考文獻—(六)、(七) 中有非常類似的概念，因此我們提出這個假說

→(1)直接形成產物乙酸苯乙酯、醋酸以及離子液體

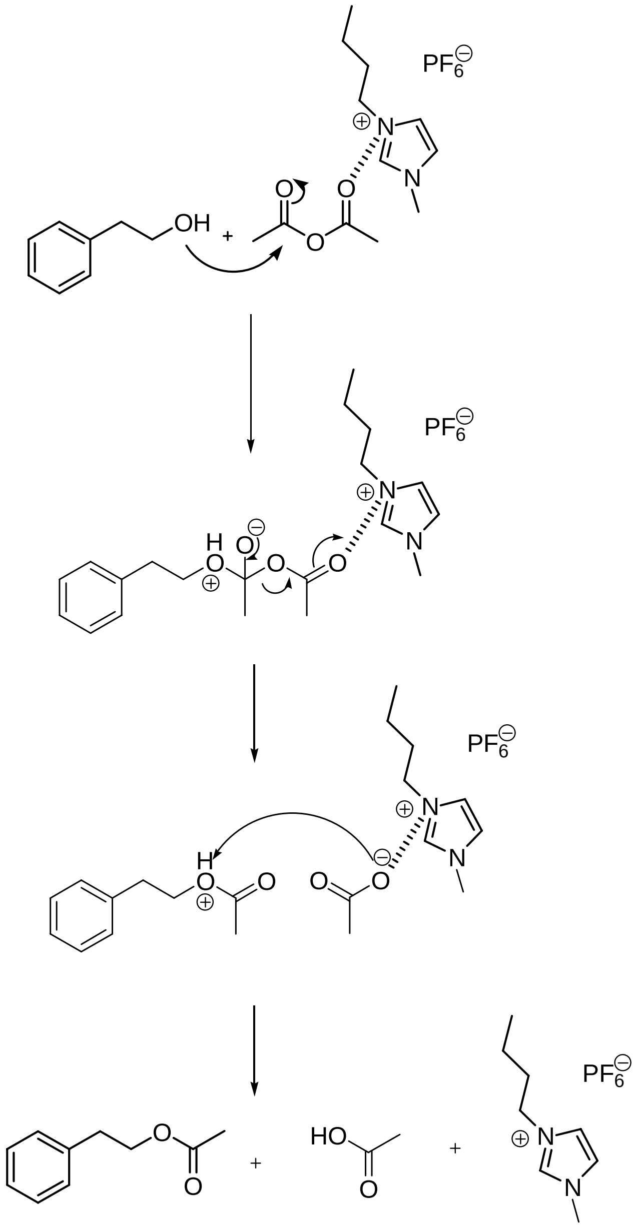
或(2)先形成 HPF_6，醋酸根再與氫結合→然後才形成產物乙酸苯乙酯、醋酸以及離子液體

註:參考文獻--六、七

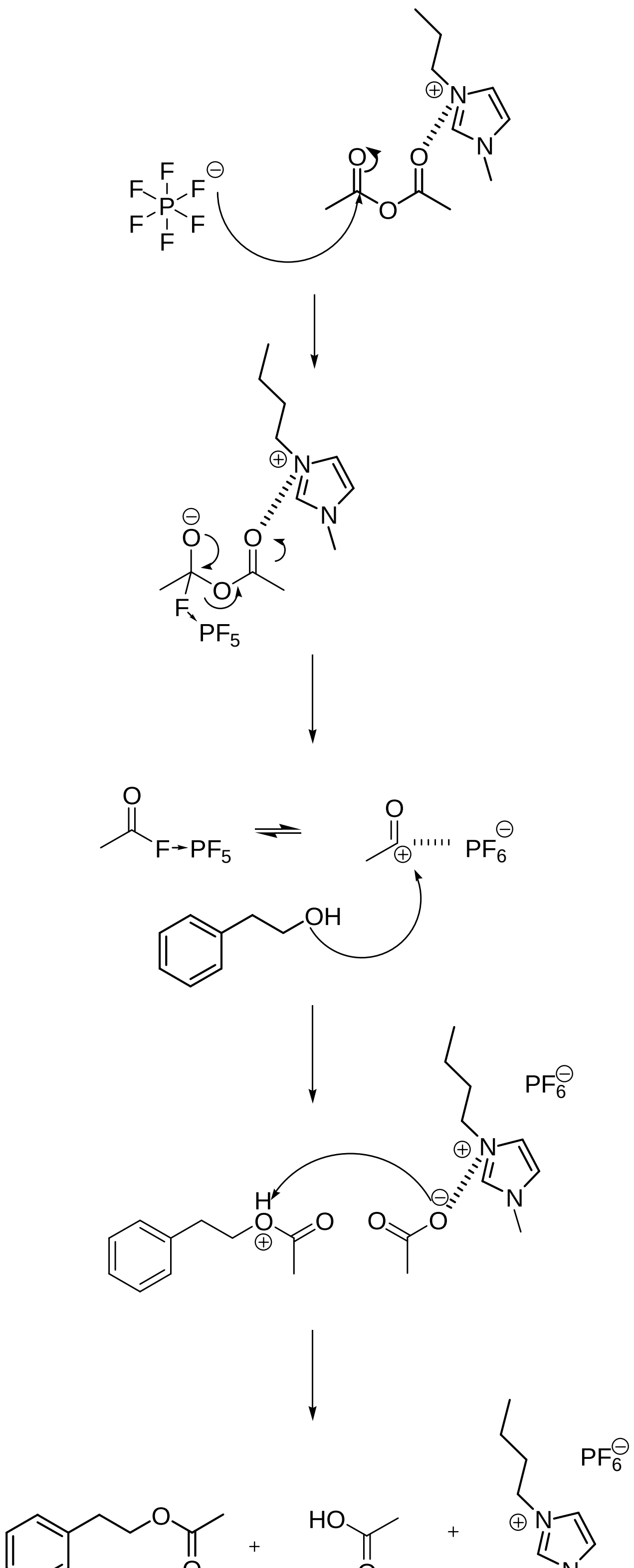


◎以下為兩種推測反應機制的詳細步驟解析圖

1.



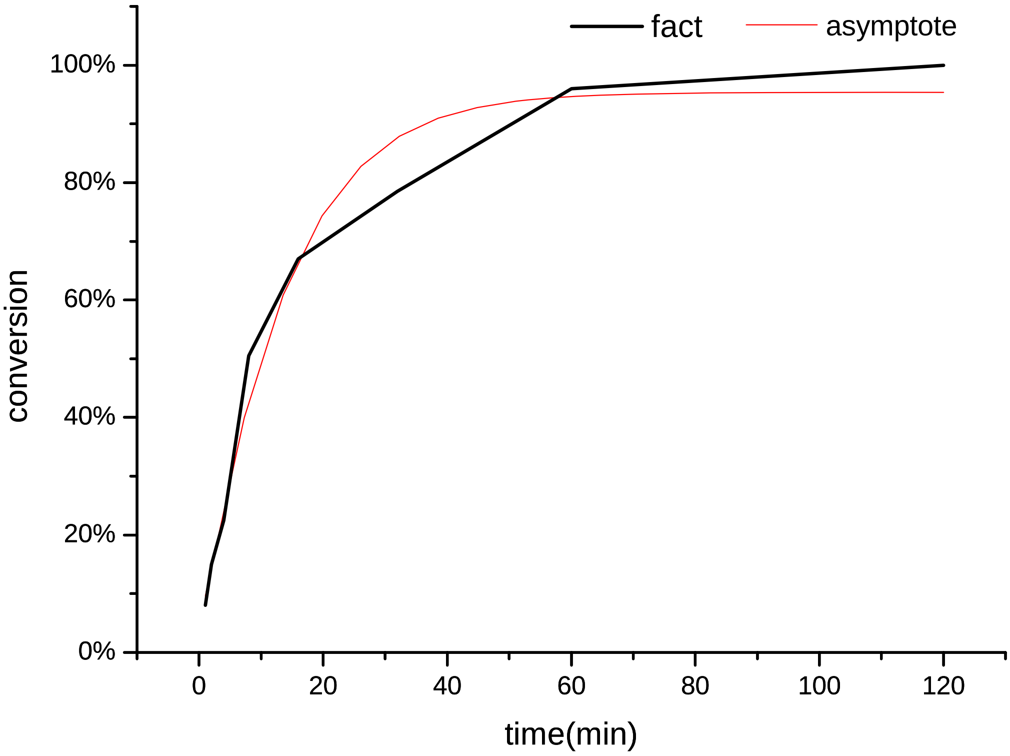
2.



◎ 附表:轉換率與時間之關係

以 PF6$^-$為陰離子的離子液體中反應。

反應時間 (minutes)	轉換率 (%)
1 min	8.0 %
2 min	15.0 %
4 min	22.5 %
8 min	50.5 %
16 min	67.0 %
32 min	78.5 %
60 min	96.0 %
120 min	100.0 %



二、 照光是否會對催化速率造成影響，以及在 40˚C 下反應的效果。

反應條件	反應時間	轉換率（%）
照 UV 光	2 hrs	100.0 %
在 40˚C 下反應	10 min	100.0 % (5 min 89.5 %)
否	2 hrs	74.2 %

討論：由轉換率的差別可以看出，加熱可以提供反應所需的能量，而照光可能可以更進一步活化 imidazolium 陽離子，兩者都有助於反應的進行。其中在 40˚C 的條件下反應最快，但是因為我們想進一步探討其他影響反應的變因，所以我們選用 2 小時在照光下反應完的反應時間作為實驗基準，時間比較容易掌握，故接下來的反應都以照光的條件下實驗。

三、 找出以離子液體催化此反應的最佳當量。

離子液體當量	反應時間	轉換率（%）
1.0	2 hrs	100.0 %
0.5	2 hrs	100.0 %
0.3	2 hrs	100.0 %
0.2	2 hrs	100.0 %
0.1	2 hrs	92.6 %

討論：由以上結果得知，離子液體在 1~0.1 的當量之間都有高達 90 %以上的轉換率。而在實驗中，我們希望能以最少的離子液體來催化，故依實驗需求逐量減少使用量。接下來的實驗，我們皆以 0.2 當量的離子液體進行反應。

四、 測試有機溶劑對離子液體的溶解效果與回收離子液體對反應的影響。

有機溶劑	對離子液體溶解情況
二氯甲烷（ CH_2Cl_2)	互溶
四氫呋喃（ THF)	互溶
乙醚（Ether)	分層
甲苯（Toluene)	分層
正己烷（ Hexane)	分層
乙酸乙酯（EA)	互溶
丙酮（Acetone)	互溶

測試與離子液體分層的有機溶劑對產物的溶解效果

有機溶劑	對產物溶解情況
乙醚（Ether)	互溶
正己烷（ Hexane)	互溶
甲苯（Toluene)	互溶

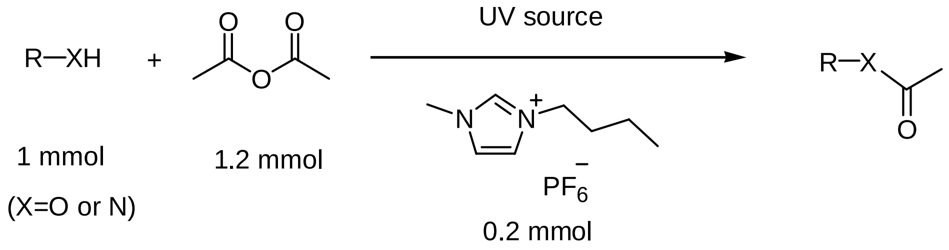
討論：我們找了幾個具有不同代表性的溶劑：CH_2Cl_2 代表非配位型的溶劑，THF 與乙醚雖然都是醚類，但分別代表了水相及有機相溶劑，甲苯為芳香族，正己烷和乙酸乙酯為脂肪族和酯類溶劑，丙酮為酮類溶劑。因為乙醚、正己烷、甲苯可與我們使用的離子液體分層，故回收離子液體時，我們選用乙醚來將產物與離子液體分開，回收以後再使用。(也可以用正己烷、甲苯)

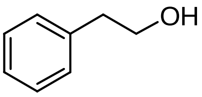
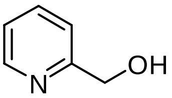
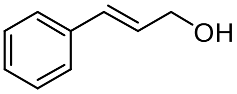
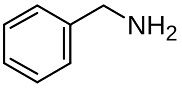
用回收的離子液體來催化反應(用 Ether 分離產物和離子液體)

使用的離子液體	反應時間	轉換率（%）
離子液體	2 hrs	100.0 %
回收的離子液體	2 hrs	100.0 %

討論：回收的離子液體反應的效果較原來的離子液體一樣好，所以離子液體在催化反應後，可以用乙醚、正己烷、甲苯將其與產物分離，回收再進行催化。

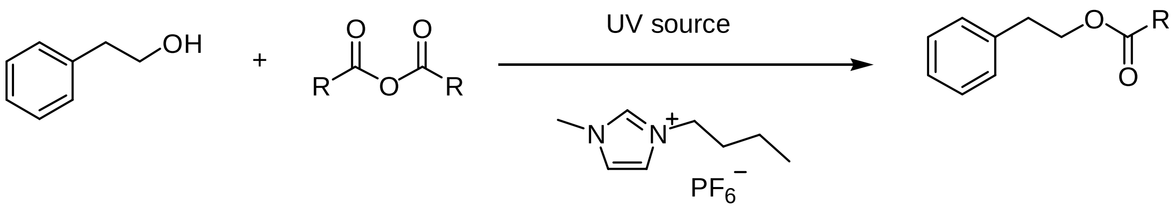
五、 探討以不同的醇類當反應物反應的效果與醯胺鍵的生成

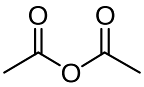
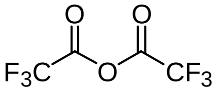
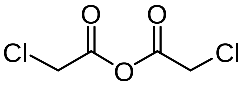
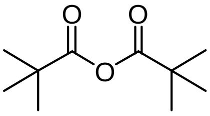
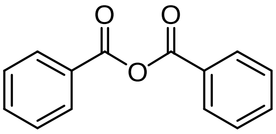


reactant	Time	Yield (%)
	2 hrs	100.0 %
	2 hrs	100.0 %
	2 hrs	100.0 %
	0.5 hrs	100.0 %

討論：由反應的結果可知，離子液體對於不同結構的一級醇做乙醯化反應與醯胺鍵的生成，都有不錯的催化效果。

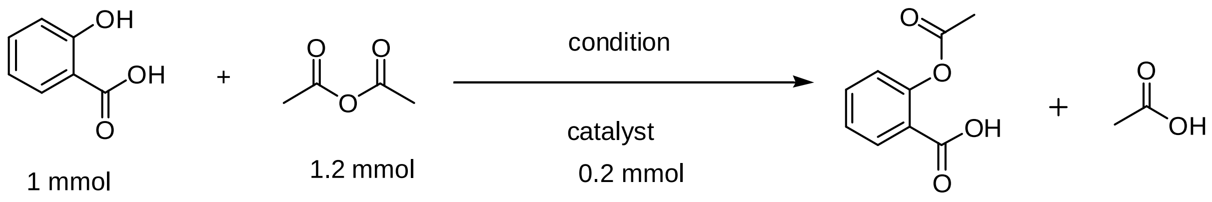
六、 探討以不同的酸酐反應的效果。

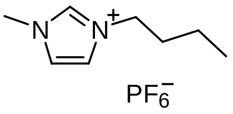
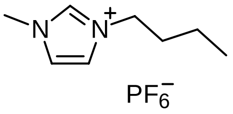


Anhydrides	Time	Yield (%)
	2 hrs	100.0 %
	2 hrs	100.0 %
	2 hrs	66.41 %
	24 hrs	55.8 %
	24 hrs	0.0 %

討論：反應進行有兩項主要的影響因素:第一個是推拉電子效應，由原子的電負度決定，例如氯的電負度大，拉電子的效應強，故反應進行得較快。第二個是立體障礙的大小，反應中心旁所包覆的結構愈擁擠，反應愈難進行。以上兩個影響因子的交互作用下，會產生不同反應效果。

七、 阿斯匹靈的製作



catalyst	condition	Time	Yield (%)	recycle	exothermic
	UV source	4 hrs	50.0 %	Yes	not very obvious
		5 hrs	67.0 %		
		10 hrs	100.0 %		
	40^oC	10 min	26.3 %	Yes	not very obvious
		1 hr	83.3 %		
		3 hrs	100.0 %		
H_2SO_4	r.t.	10 min	84.2 %	No	pretty hot
		3 hrs	86.2 %		

討論：用 PF_6^- 為陰離子的離子液體催化阿斯匹靈的形成，在 40˚C 的條件下，三小時內轉換率 100%；而硫酸催化的轉換率幾乎都停在 85%左右；離子液體使用完後可經萃取回收後再利用，並且反應不會像硫酸一樣放出大量的熱，造成危險。用離子液體催化，符合現在以綠色為主的現代化學，希望以後能在有機實驗上，呈現較好的一面。

陸、 結論

一、 由於離子溶劑具有很高的熱穩定性及可回收性，然而它是由一個陽離子片段和一個陰離子片段所構成，因此我們綜合了以上的特性，應用在親核性醯基取代反應上，同時具有高效率的催化效果。

二、 用以 PF_6^-為陰離子的離子液體 0.2 當量在 40˚C 環境下催化此反應最好。

三、 回收的離子液體可以用乙醚、正己烷、甲苯將其與產物分開重複再利用，符合現代的綠色化學。

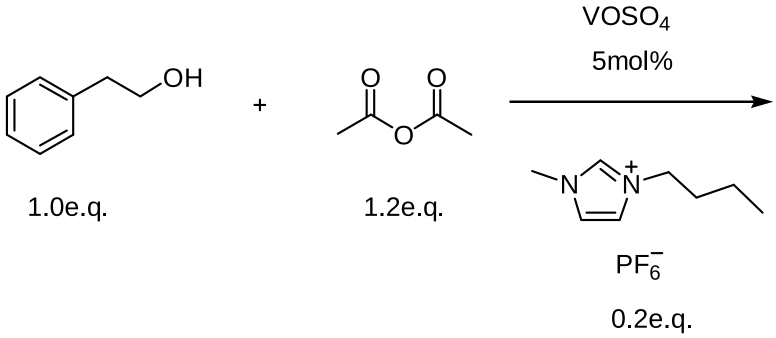
四、 此催化劑可應用在其他的親核性醯基取代反應，可對不同種的醯基做探討，也可以改變親核試劑為胺或硫醇來探討。

五、 用離子液體當催化劑，可以成功的合成轉換率 100 %的阿斯匹靈。

柒、 未來展望

一、將離子液體催化的反應推廣應用在香料(例如：香蕉油等)或其他有機合成。

二、



討論：目前正在努力使反應的時間再縮短，經教授的建議，在反應中加入 $VOSO_4$，因為釩金屬在液體中具有路易士酸的活性，能夠活化酸酐，使反應更容易進行。到目前為止實驗的結果是在十分鐘之內轉換率 100 %。期望能更進一步研究，將此種反應同時在速度與回收效益上，有更傑出的表現。

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七、 Effenberger, F.; Sohn, E.; Epple, G. *Chem. Ber.* **1983**, *116*, 1195-1208

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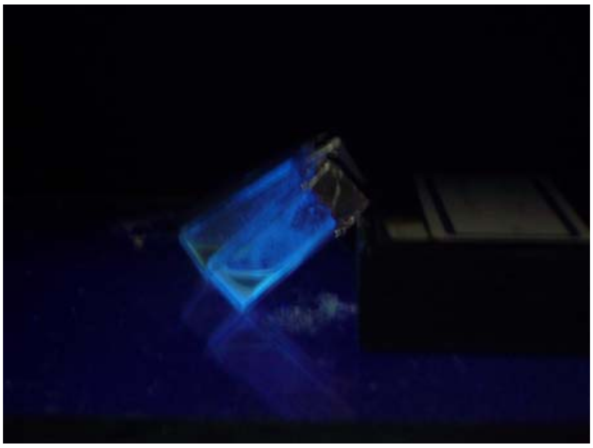
十二、 Ott, L. S.; Cline, M. L.; Deetlefs, M.; Seddon, K. R.; Finke R. G. “Nanoclusters in Ionic Liquids: Evidence for *N*-Heterocyclic Carbene Formation from Imidazolium-Based Ionic Liquids Detected by ^{2}H NMR” *J. Am. Chem. Soc.* **2005**, *127*,5758-5759.

玖、 實驗圖片

***UV table**

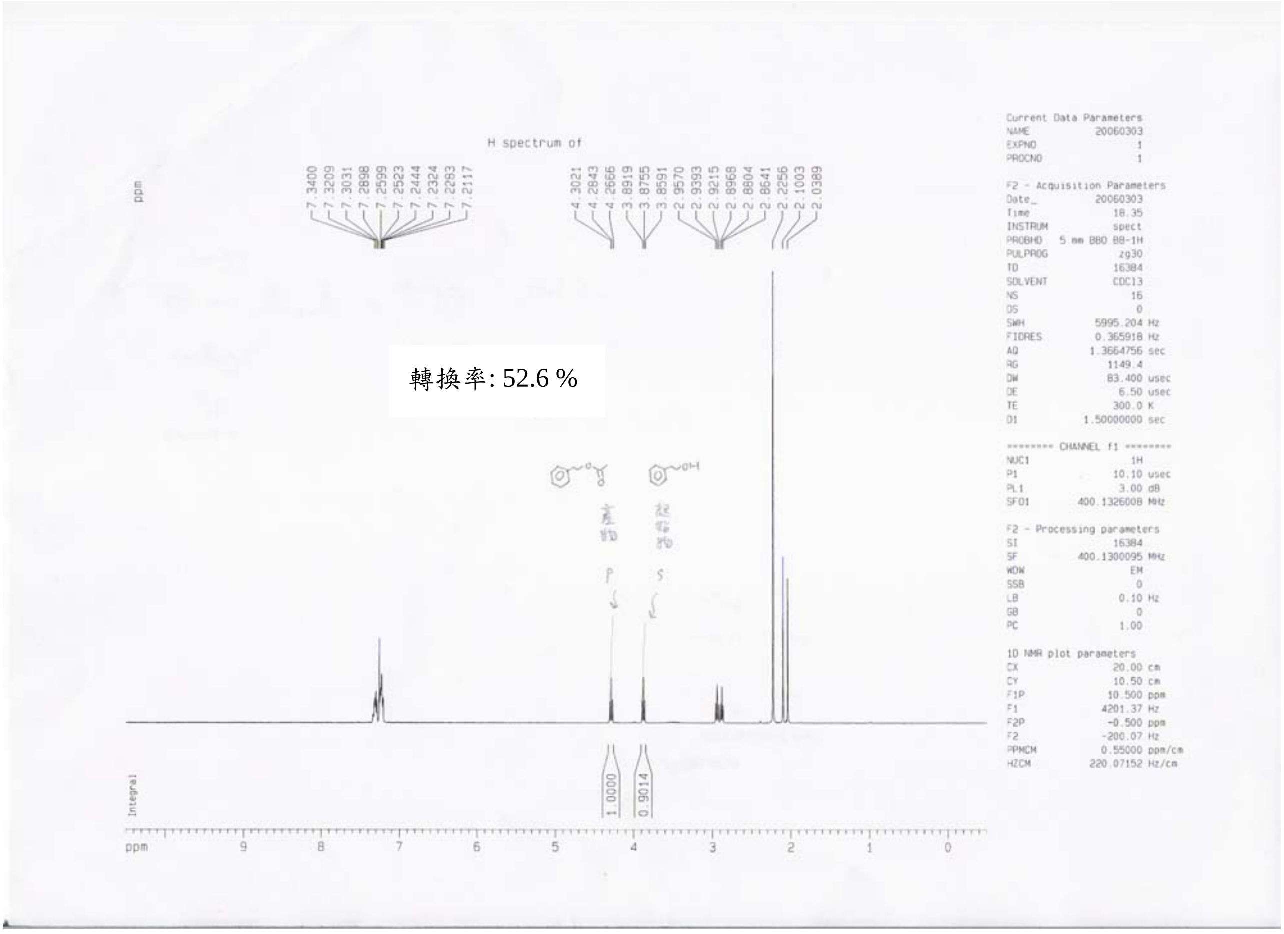
***超音波震盪器**

***在 UV 光下反應**



***用 Ether 使產物與離子液體分層**

*NMR 核磁共振儀光譜圖



轉換率: 52.6 %

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PROCNO                 1

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PULPROG             zg30
TD                 16384
SOLVENT            CDC13
NS                    16
DS                     0
SWH             5995.204 Hz
FIDRES          0.365918 Hz
AQ             1.3664756 sec
RG                1149.4
DW                83.400 usec
DE                  6.50 usec
TE                 300.0 K
D1            1.50000000 sec

======== CHANNEL f1 ========
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P1                 10.10 usec
PL1                 3.00 dB
SFO1         400.1326008 MHz

F2 - Processing parameters
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WDW                   EM
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GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
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F1P               10.500 ppm
F1               4201.37 Hz
F2P               -0.500 ppm
F2               -200.07 Hz
PPMCM            0.55000 ppm/cm
HZCM           220.07152 Hz/cm
```

$$轉換率=\frac{生成物積分值}{生成物+起始物積分值}\times 100\%$$

An Efficient Green Protocol for Acylation of Alcohols Catalyzed by Ionic Liquids

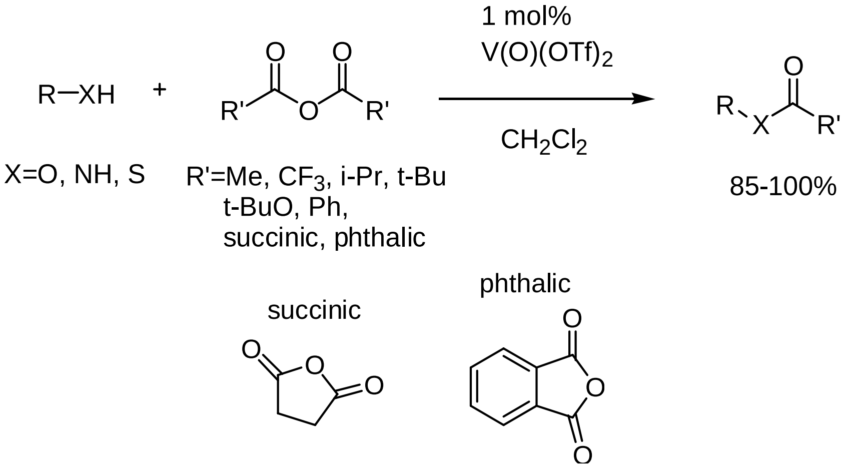
Contents

I. Abstract

We have established for the first time that ionic liquids, which possess the property of Lewis acids, can facilitate acylation of alcohols with anhydrides to form esters upon photo-excitation. With the initial finding, we then screen through different types of ionic liquids with varying counter anions, loading, and external light or heat sources in order to sort out the best reaction conditions. To gain insights into the working mechanism, the dynamic profile of the catalytic reaction was monitored by analyzing the reaction mixture by using ^{1}H NMR spectroscopy. The ionic liquids can be recovered by extractive separation from the acylation product, which meets the major theme of green chemistry. To extend the substrate scope and applications of the new catalytic process, different functional primary alcohols and amines were further examined. More importantly, we have utilized the new catalytic protocol for the acetylating of salicylic acid, leading to aspirin with high efficiency.

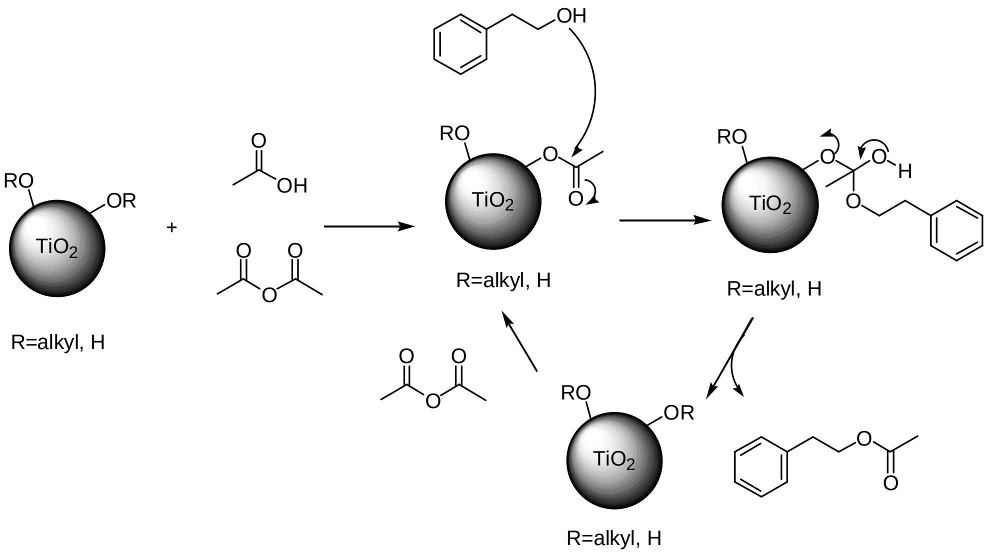
II. Research Incentive and Background

In chemistry experiments in high school, concentrated sulfuric acid is used as a catalyst to synthesize Aspirin. While performing this kind of experiment, teachers always alert us to handle the corrosive carefully since the reaction temperature rises extremely fast during the catalytic process. Besides, the catalytic conversion to Aspirin is often not satisfactory. After reading some related contexts, I realize that the catalytic reaction remains reversible by using concentrated sulfuric acid as the catalyst. Therefore, the chemical conversion ratio can not be raised once the reaction reaches equilibrium. Since then, I become curious about such kind of experiments and spend more time studying along with intensive discussions with my chemistry teachers studying in order to gain more insights into the catalytic esterification. Ultimately, I hope to improve the catalytic reaction with high efficiency and safety. In Professor Chien-Tien Chen's laboratory, there have been a series of oxovanadium (vanadyl) species used in catalytic acylation of alcohols. The preliminary achievement in that context has been published in *Organic Letters* in 2001, on page 3,869[8].

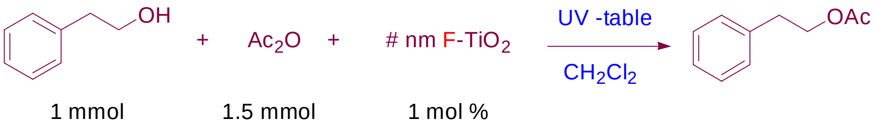


Notably, the vanadyl (V=O) center displays amphoteric property with polarized electron density which is better signified as $^{+}$V-O^{-}. Hence, the Vanadium center holds the property of a Lewis acid and the oxyanion serves as a Lewis base at the same time. This amphoteric behavior reflects the operating mechanism of the catalytic acylation reaction.

By taking advantage of the aerobic photoactivation on TiO_2 surface and the amphoteric concept for the activation of anhydride [8,9], Profesor Chen's group has recently succeeded in catalyzing acylation reaction by TiO_2 nanoparticle with photo-excitation in the presence of aliphatic anhydrides.



Besides, Chen and co-workers have used nanoparticles of different metal oxides (Y_2O_3 , WO_3, and ZrO_2) with varying particle sizes (9, 32, and 4400 nm) in the presence of a given cooxidant (TBHP, H_2O_2, or O_2) under 6 different solvents (dichloromethane, toluene, THF, ether, hexane, and ethyl acetate). The optimal reaction conditions (the following equation) requires a reaction time of of 10 hrs (at 97% conversion), which is about 4-5 times faster than that catalyzed by normal size TiO_2.



9 nm	81% (72h)
32 nm	**100% (10h)**
300 nm	74% (24h)
4,400 nm	71% (24h)
> 50,000 nm	94% (48h)
control w/o TiO_2	91% (96h)

Since then, we have been looking for a new catalytic protocol to further increase the reaction rate. After extensive search of new reaction conditions, we found that TiO_2 in ionic liquids meets the purpose. Therefore, our interests in using ionic liquids as reaction media in the catalytic acylation become a rational major focus.

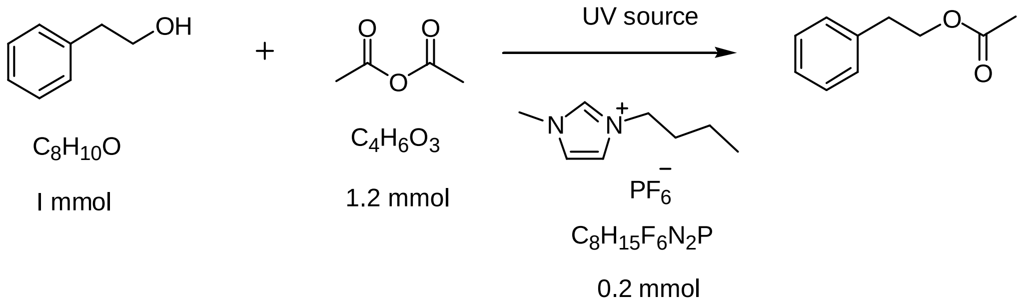
After screening through several control experiments, we found that ionic liquid alone can be an efficient catalyst in the nucleophilic acyl substitution of alcohols. The preliminary finding prompts us to further carry out a series of catalytic studies with ionic liquids. Ionic liquids are special salt-like chemicals which exist as liquid states at ambient temperature with unique physical and chemical properties. Our preliminary results indicate that they exhibit good reactivity in catalytic acylation of alcohols with satisfactory reaction rates and nearly quantitative conversion. It is worth mentioning that the ionic liquid employed can be readily recovered and re-used after the reaction with secured safety and environmental protection issues. We describe herein the new green, catalytic acylation protocol along with discussion on the working mechanism of the catalytic acylation by ionic liquids.

III. Experiment Goals

The strategies to find out a new catalytic methodology for the acylation of alcohols are listed as follows:

1. Examine the effects of acylation when treated with different ionic liquids.
2. Examine the influence of different energy sources, including light and heat (at 40 ^{o}C), on acylation.
3. Find out the optimization of catalyst loadings on the catalytic acylation of 2-phenylethanol by imidazolium hexafluorophosphate.
4. Screen the effects of different organic solvents on separating acylation products from ionic liquids.
5. Explore substrate classes including alcohols and amines for the optimized acylation protocol.
6. Determine the reactivity profiles of different anhydrides in the acylation.
7. Demonstrate the application of the new catalytic protocol towards synthesizing Aspirin.

◎ The proposed new catalytic acylation protocol by ionic liquids



IV. Apparatus and instruments required

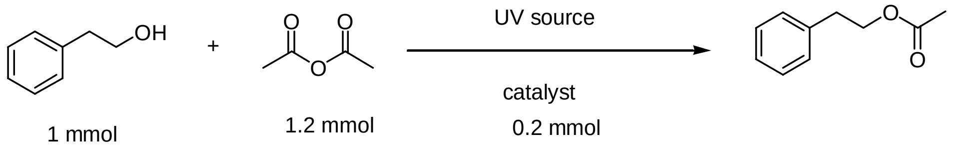
1. Test tubes, capillary tubes, quartz cells, syringes, spatulas, TLC plates, developing chamber, NMR tubes
2. Washing bottles , round-bottom flasks, separatory funnels
3. Experimental chemicals, suction funnels, vacuum pump
4. UV table (254 or 365 nm wavelength), rotary evaporator, column chromatographic analysis, ultrasonic sonicator, ^{1}H NMR spectroscopy (400 or 200 MHz NMR)

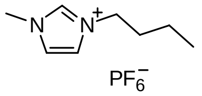
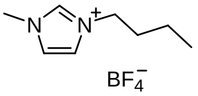
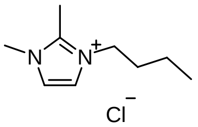
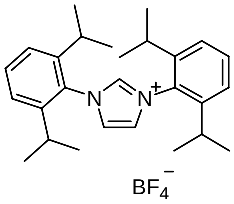
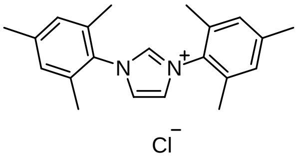
V. Experiment Procedures

1. To a quartz cell was placed 1.0 mmol of 2-phenylethanol, 1.2 mmol of acetic anhydride, and a catalytic amount (0.2 mmol) ionic liquid as the promoter.
2. The mixture was made homogenous by ultrasonic sonicator.
3. The quartz cell was exposed under UV light in a dark chamber on top of a UV table.
4. The reaction progress was monitored by TLC (thin layer chromatography) analysis.
5. The chemical conversion ratio was determined by ^{1}H NMR spectroscopy (200 or 400 MHz NMR).
6. The ionic liquid was recovered by extracting the acylation product with an appropriate solvent.

VI. Research Results and Discussions

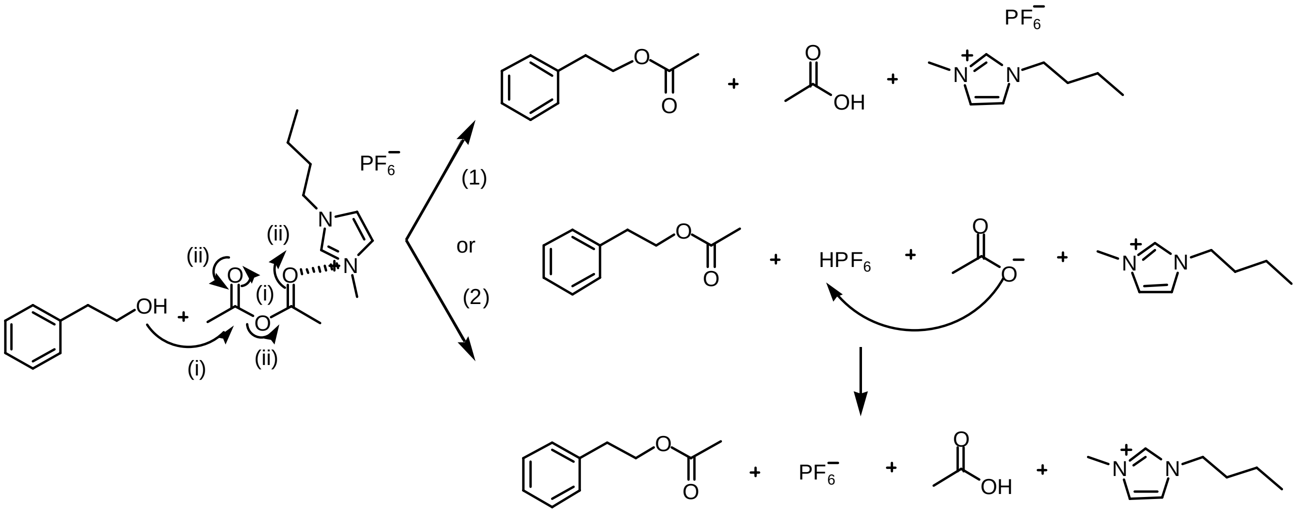
1. To examine the reactivity of acylation catalyzed by different ionic liquids with varying counter ions (e.g., PF_6^-, BF_4^-, and Cl^-), a series of experiments were carried out for a test acylation of 2-phenylethanol with acetic anhydride.



catalyst	Time	Yield (%)
	2 hrs	100 %
	24 hrs	80 %
	48 hrs	58 %
	24 hrs	83 %
	48 hrs	80 %

◎ Discussions: It was found that both counter anions and imidazolium cations play main factors on influencing the rates of the model acylation reaction. Among three counter anions examined, PF_6^- leads to the best acylation reactivity. Since the polarizability of PF_6^- is higher than that of $BF_4^-$and Cl^-, the incipient imidazolium cation is less associated to PF_6^- and is thus more reactive towards activation of anhydride, thus facilitating the subsequent nucleophilic acyl substation by an alcohol. Therefore, the following experiments are mainly carried out with an ionic liquid containing PF_6^- as the counter anion.

◎ A working mechanism is proposed as follows :



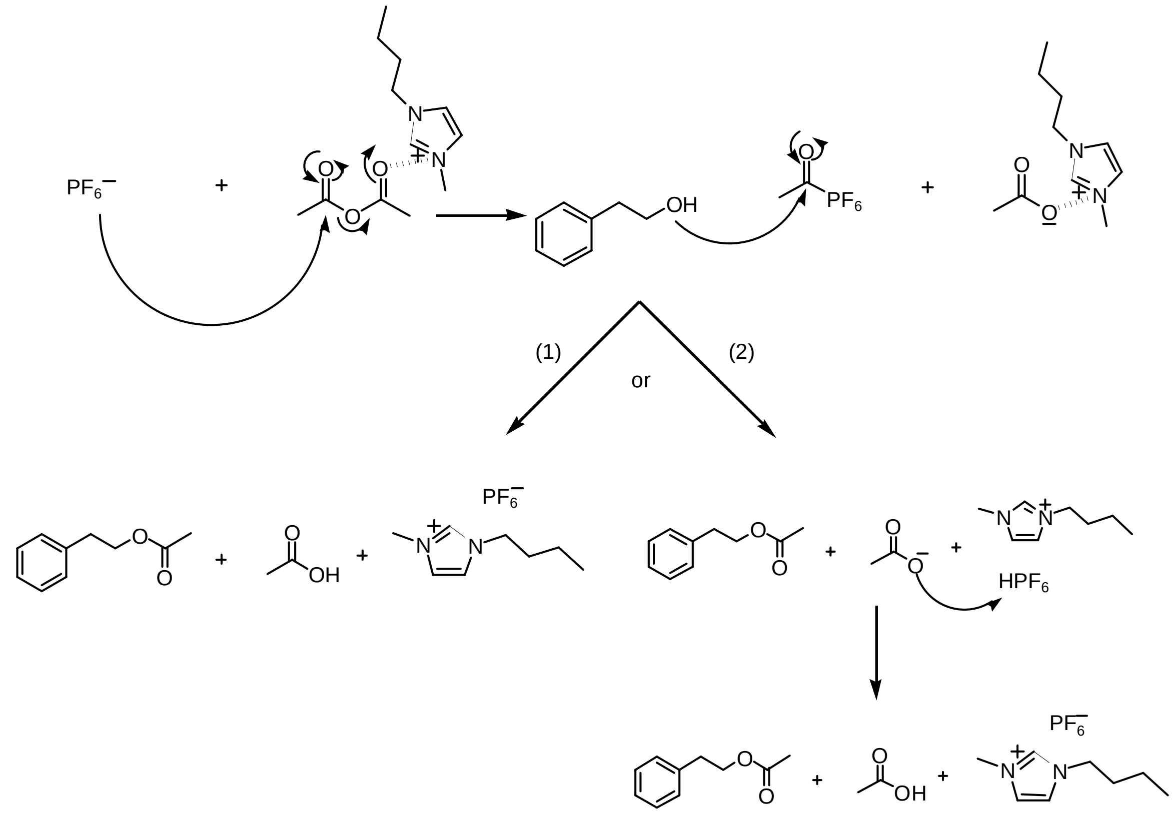
Pathway A.---[Activatation of the anhydride by the imidazolium cation]

→ Activatation of the anhydride by the imidazolium cation.

→ The oxygen lone pair on the 2-phenylethyl alcohol attacks the carbonyl center of the anhydride that is activated by imidazolium cation. A tetrahedral carbonyl addition intermediate (TCAI) is formed resulting from π-electron shift of the carbonyl.

→ The TCAI follows pathway-(1) to form ester product, acetic acid, and ionic liquid directly.

or follows pathway-(2) to form ester product and HPF_6. HPF_6 further reacts with imidazolium acetate to regenerate imidazolium hexafluorophosphate and acetic acid.



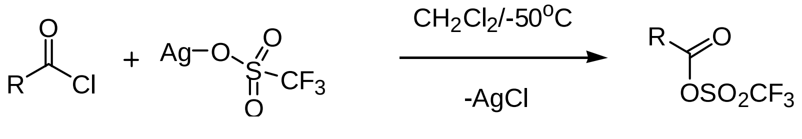
Pathway B. ---[Activation of the anhydride by the counter anion]

→Activatation of the anhydride by the imidazolium cation

→PF_6^- attacks the carbonyl carbon of the anhydride that is activated by imidazolium cation in a nucleophilic acyl substitution (NAS) fashion. A tetrahedral carbonyl addition intermediate (TCAI) is formed resulting from π-electron shift of the carbonyl. A highly active acylation intermediate, $CH_3C(O)PF_6$ is formed. Although we did not have a direct evidence to verify that the incipient formation of this highly active intermediate. The references (6) and (7) have indicated in-situ-generated acyl triflate responsible for acylation turn-over. So the proposed hypothetical acetyl hexafluorophosphate would follow pathway-(1) to form ester product, acetic acid and ionic liquid directly in a subsequent NAS.

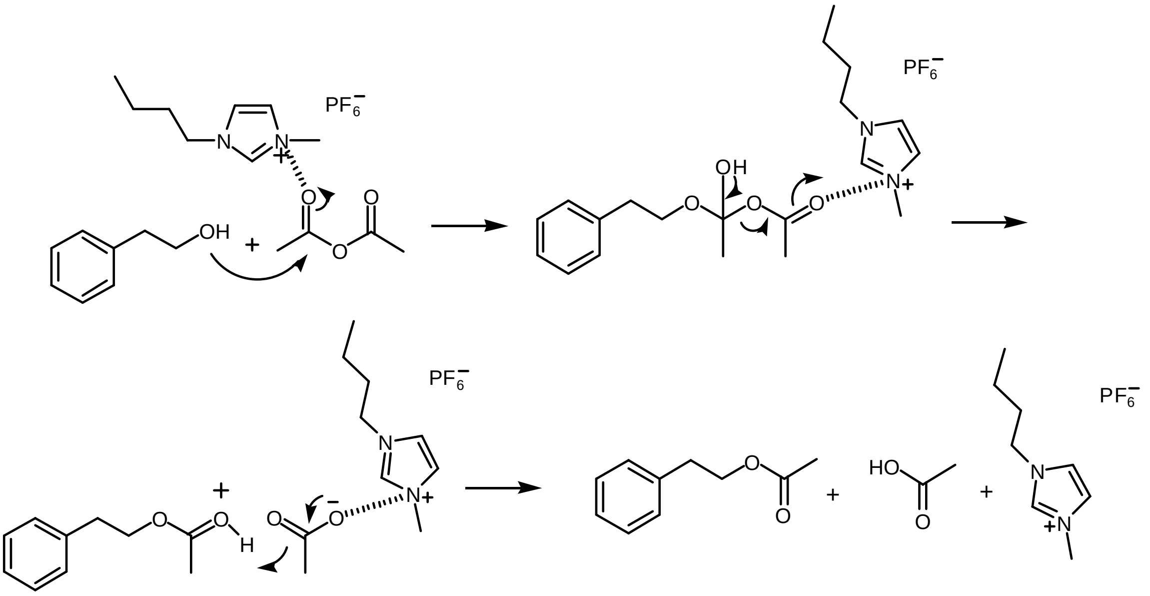
or follow pathway-(2) to form the ester product and HPF_6. HPF_6 further reacts with acetate to regenerate imidazolium hexafluorophosphate and acetic acid.

Note: List of references -- (6), (7)

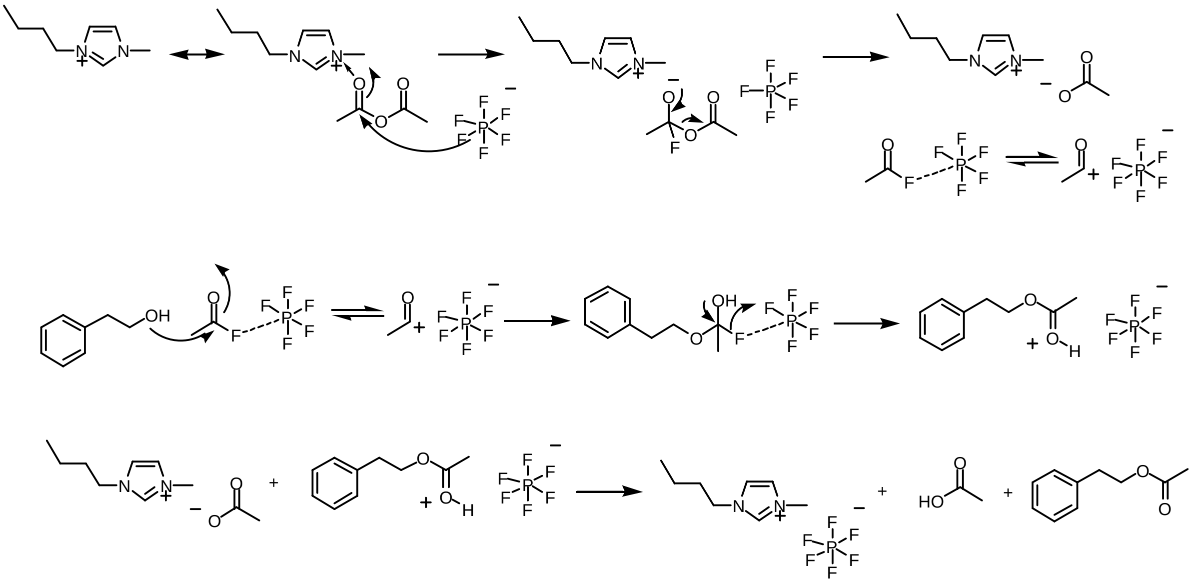


◎ The fully analyzed and stepwise details of two working mechanisms are shown as follows.

1.

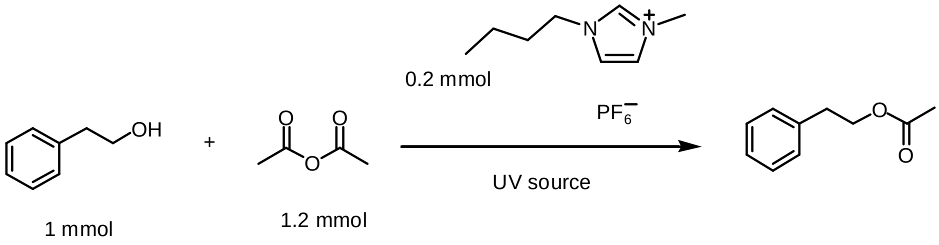


2.



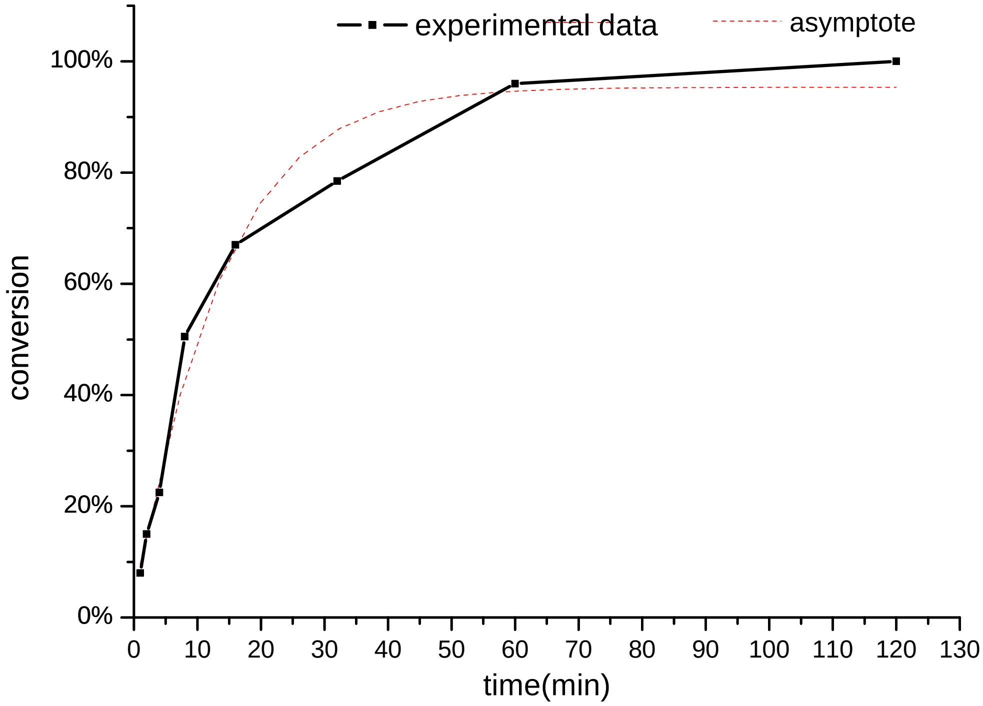
◎ Table 1: The dynamic profile between acylation conversion ratio and reaction time

(Use PF_6^- as a counter anion in ionic liquid to catalyze the acylation reaction of 2-phenylethanol)



Reaction time	Conversion ratio (%)
1 min	8 %
2 min	15 %
4 min	23 %
8 min	51 %
16 min	67 %
32 min	79 %
60 min	96 %
120 min	100 %

Figure 1: The dynamic profile plot between acylation conversion ratio and reaction time



2.The effect of energy sources on the acylation reactivity catalyzed by imidazolium hexafluorophosphate

Reaction condition	Reaction time	Conversion ratio (%)
UV light	2 hrs	100 %
at 40℃	10 min	100 % (5 min, 90 %)
without UV light and 40℃	2 hrs	74 %

◎ Discussion: According to the results of acylation conversion ratio with varying energy sources, we found that the heating condition can speed up the reaction by a factor 12 while UV light mediation condition can increase the Lewis acidity of the ionic liquid by activating the imidazolium cation to its corresponding excited state. Among the two energy sources examined, the heating condition at 40 ℃ is a lot better. But in order to further probe into other controlling factors on such reaction, we select the photoly activation condition as the standard experimental condition for subsequent optimization due to ease of following the reaction progress with time.

3.Optimization of catalyst loadings on the catalytic acylation of 2-phenylethanol by imidazolium hexafluorophosphate

Loading of ionic liquid (equiv)	Reaction time	Conversion (%)
1.0	2 hrs	100 %
0.5	2 hrs	100 %
0.3	2 hrs	100 %
0.2	2 hrs	100 %
0.1	2 hrs	93 %

◎ Discussion: Based on the results above, the chemical conversion is great than 93 % by the use of 0.1 to 1.0 equivalent of the ionic liquid. In practical applications, we intend to minimize the loading of the ionic liquid without considerably change of the reaction rate in catalyzing the acylation. Therefore, the amount of the ionic liquid is reduced to 0.2 equivalent for economic and green aspects.

4.Screening of solvents for efficient extraction of product from the ionic liquid.

Organic solvent	Observation result upon mixing with the ionic liquid
dichloromethane (CH_2Cl_2)	miscible
THF	miscible
Ether	Two separate layers
Toluene	Two separate layers
Hexane	Two separate layers
Ethyl acetate (EA)	miscible
Acetone	miscible

Test: the solubility test of 2-phenylethyl acetate in organic solvents which are separable from the ionic liquid

Organic solvent	Situation
Ether	Highly soluble
Hexane	soluble
Toluene	soluble

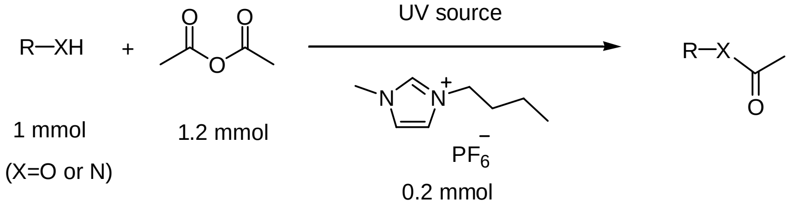
◎ Discussion: A series of solvents including six different classes such as haloalkanes, ethers, arenes, and alkanes, esters, and ketones with different polarity attributes are examined for the extractive separation. The individual representatives are CH_2Cl_2, THF, ether, toluene, hexane, ethyl acetate, and acetone. Because ether, hexane, and toluene are found separable from the ionic liquid, they were tested for their relative solubility on the ester product. Ether was chosen as the best solvent to separate the product from the ionic liquid along with its full recovery. (Hexane and toluene are also acceptable.)

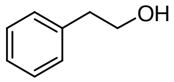
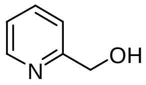
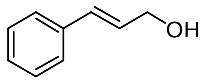
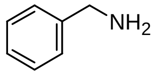
Recovery and reuse test for the ionic liquid after catalyzing the acylation by using ether as the extractraction solvent

	reaction time	Conversion ratio (%)
Ionic liquid	2 hrs	100 %
Recovered Ionic liquid	2 hrs	100 %

◎ Discussion: The ionic liquid can be recovered and reused after extracting the product by ether, hexane, or toluene. The repetitive runs of the recovered catalyst on the acylation indicate that the acylation reactions catalyzed by the recovered ionic liquid works as equally efficient as the original one.

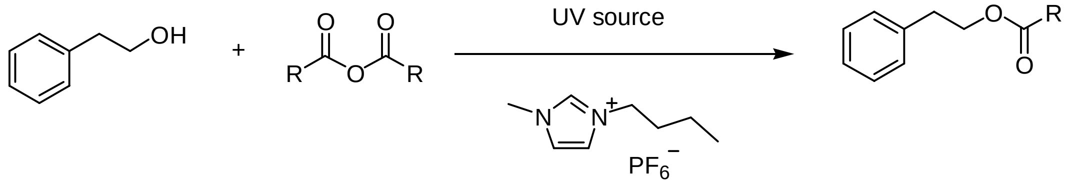
5. The effects of different alcohols and amines on the catalytic acylation reactions.

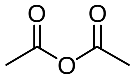
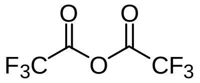
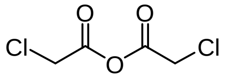
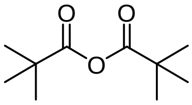
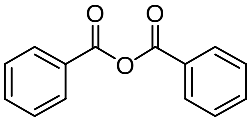


reactant	Time	Yield (%)
	2 hrs	100 %
	2 hrs	100 %
	2 hrs	100 %
	0.5 hrs	100 %

◎ Discussion: The ionic liquid can catalyze the acylation of several primary alcohols including an allylic alcohol (entry 3) and a benzylic alcohol (entry 2). Both the acylations were complete in 2 hours and the corresponding products are isolated in quantitative yields. A representative benzylamine was also examined and the amide bond formation is complete in 0.5 hours.

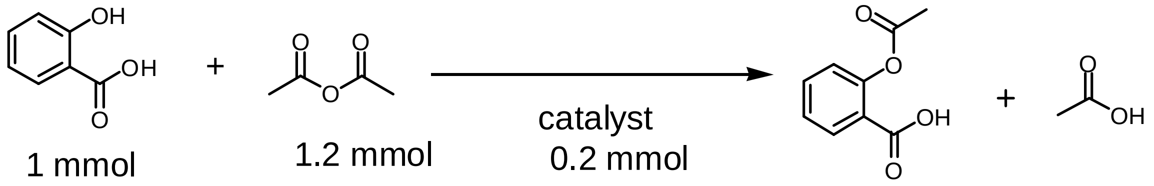
6.The effects of different acid anhydrides on the catalytic acylation

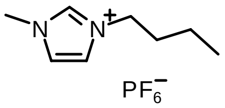
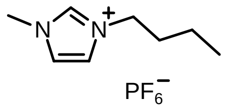


Anhydrides	Time	Yield (%)
	2 hrs	100 %
	2 hrs	100 %
	2 hrs	66 %
	24 hrs	56 %
	24 hrs	0 %

◎ Discussion: The rate of acylation reactions highly depend on the electronic and steric attributes of the anhydrides. The anhydride containing electron-withdrawing CF$_3$ group is more reactive than acetic anhydride.. The chloroacetyl anhydride is less reactive than acetic anhydride presumably due to the steric bulk of the Cl substituents even though Cl is an electron-withdrawing group. Therefore, the acylation is more sensitive to the steric hindrance of the anhydrides. The more crowded the reacting carbonyl center is, the more difficult the acylation proceed. Therefore, pivalic anhydride is the least reactive alkanoic anhydrides. In addition, the current catalytic acylation protocol is not amenable to aromatic anhydrides.

7.Synthetic application towards Aspirin



catalyst	condition	Time	Yield (%)	recycle	exothermic
	UV source	4 hrs 5 hrs 10 hrs	50 % 67 % 100 %	Yes	$31^{o}C$
	$40^{o}C$	10 min 1 hr 3 hrs	26 % 83 % 100 %	Yes	$31^{o}C$
H_2SO_4	$31^{o}C$	10 min 3 hrs	84 % 86 %	No	$80^{o}C$

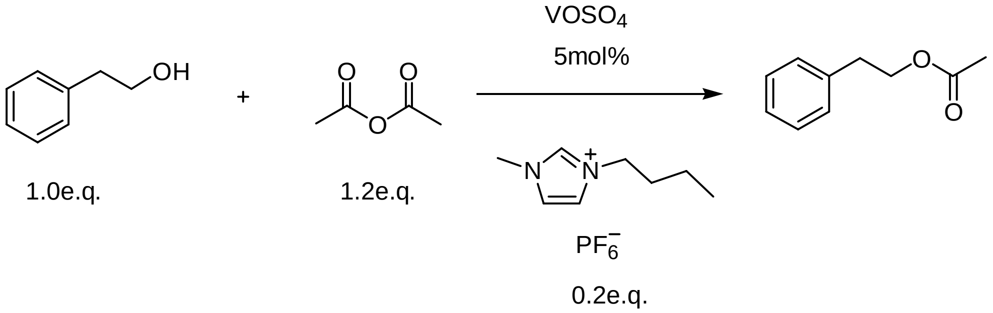
◎ Discussion: When imidazolium PF_6^- was used as the ionic liquid to catalyze the acylation of Aspirin at 40 ^{o}C, the chemical conversion is 100 % in 3 hours. In marked contrast, the acylation conversions catalyzed by sulfuric acid stop all at about 85 % for several trials. The catalytic reaction catalyzed by the ionic liquid does not generate heat. On the other hand, the same reaction catalyzed by sulfuric acid does raise the reaction temperature significantly and may potentially cause great danger during large scale preparation. The use of the ionic liquid as a new acylation and recoverable catalyst meets the high standard of modern green, organic chemistry and augurs well for its practical applications in pharmaceutical chemistry.

VII. Conclusion

1. We have documented a new green, catalytic acylation protocol based on ionic liquids. The ionic liquids show high thermostability and ease of recovery under photo-activation and thermal conditions during the acylation. The efficieny of acylations highly depends on their counter anions, where the most polarizable PF_6^- is the best in increasing the Lewis acidic character of the imidazolium ions.
2. Catalytic loading of imidazolium PF_6^- can be reduced to 0.1-0.2 equivalent with intact catalytic reactivity at 40℃.
3. The ionic liquid can be readily recovered and re-utilized again after extraction of the ester products with ether, hexane, or toluene, which accords with the requests of modern green chemistry.
4. The new catalytic acylation protocol can be applied to acylations of primary allylic and benzylic alcohols and amines.
5. Aspirin can be prepared at ambient temperature under neutral conditions with 100% conversion by useing ionic liquids as the catalysts.

VIII. Future prospectives

1. Apply ionic liquids as catalysts to synthesize other flavoring (eg., banana oil and fragrants) chemicals and other alcohol substrates containing acid-sensitive groups like tetrahydropyranyl and t-butyldimethylsilyl ethers organic synthesis.
2. Chemoselective acylation of carbohydrate-based diols.
3.



◎ Discussion: We have been making great efforts to further shorten the reaction time of acylation. According to professor Chen’s suggestions, we add catalytic amount of $VOSO_4$ into the reaction in view of the amphoteric and Lewis acidic character of the V=O unit in the ionic liquid. Therefore, the acid anhydride can be further activated with increased rate of acylation. The preliminary result indicates that the acylation can be completed with 100 % conversion within ten minutes. Further studies will be carried out on optimizing this new catalytic protocol.

IX. References

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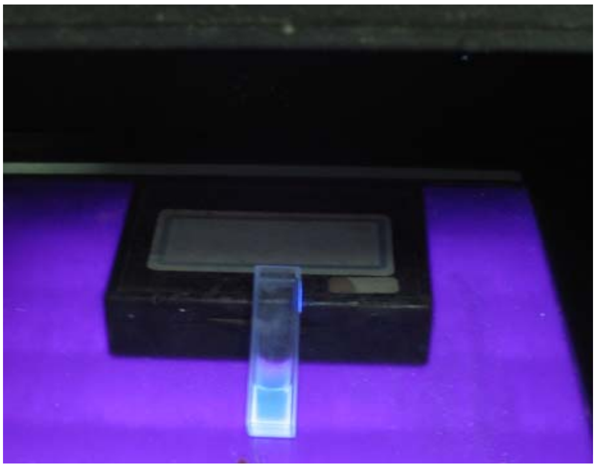
X. Experimental pictures

***UV table**

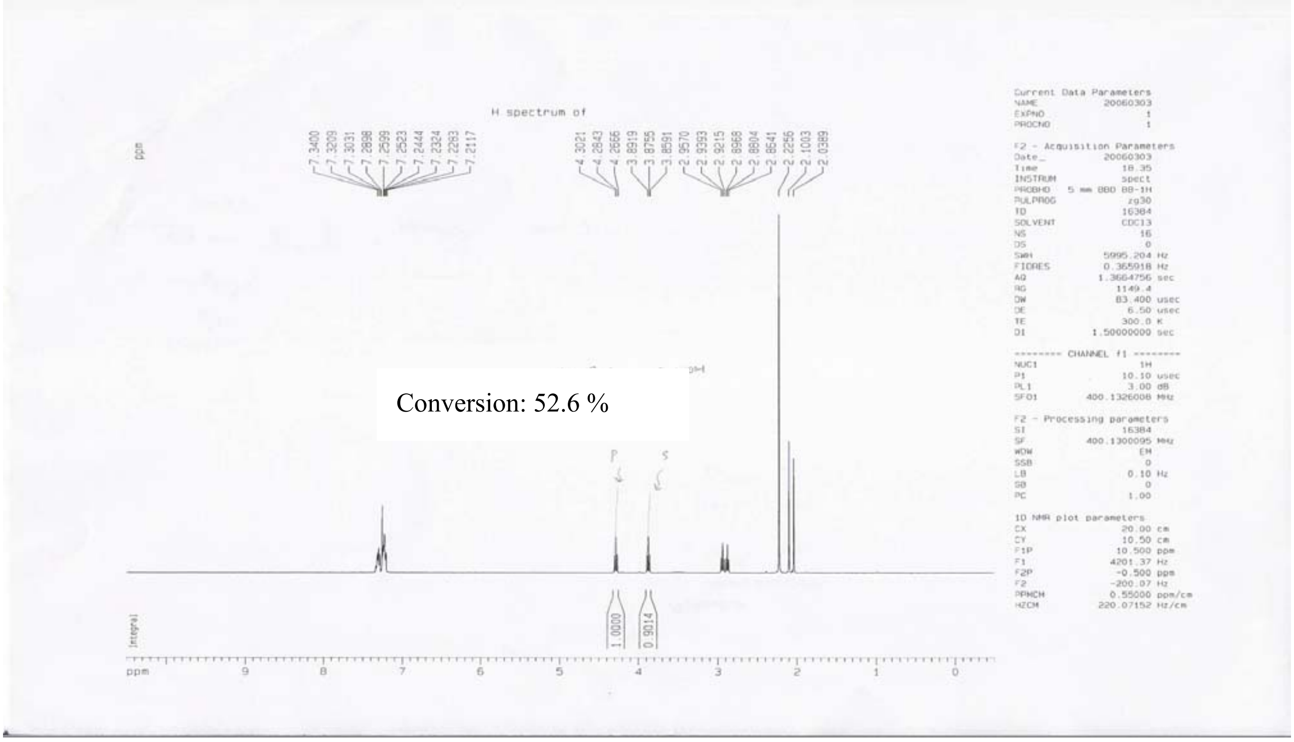
*** Ultrasonic sonicator**

***Reaction under UV light**



***Extraction of ester product from the ionic liquid with ether**

* Spectrogram of ^{1}H NMR spectroscopy



Conversion: 52.6 %

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RG                  1149.4
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======== CHANNEL f1 ========
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F2 - Processing parameters
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F2P                 -0.500 ppm
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PPMCM              0.55000 ppm/cm
HZCM             220.07152 Hz/cm
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$$\text{Conversion}= \frac{\text{Integration of product}}{\text{Total integration of starting material and product}} \times 100\%$$

評語

本作品具創意，且有環保的意義，使用 ionic liq.替代。H_2SO_4 促進皂化反應，其產率更高。但 ionic liq 的價格高，另方面反應速率慢，若在反應速率方面加以改善，並且回收的方便性加以改進，則本作品會更佳。