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Pyridinium saccharinate salts as efficient recyclable acylation catalyst: a new bridge between heterogeneous and homogeneous catalysis

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ABSTRACT

It is important to find a way for separation of concerned chemicals from product mixture after reaction, in order to avoid spreading harmful chemicals to society. The homogeneous nature of DMAP-catalyzed acylation still suffers from the problems of catalyst separation and/or residual DMAP contamination. DMAP causes acute dermal toxicity, whereas the corresponding DMAP salt exhibits only slight irritation to the skin. Very recently, we found that the DMAP saccharinate salt is also great recyclable catalyst, whose acylation of alcohols has been successfully and effectively carried out 10 times without loss in activity. This report covers our comprehensive studies on using the pyridinium saccharinate salts as efficient recyclable acylation catalysts including 4-*N*,*N*-dimethylaminopyridinium saccharinate (**A**), 4-(1-pyrrolidinyl) pyridinium saccharinate (**B**), 2-*N*,*N*-dimethylaminopyridinium saccharinate (**C**), and pyridinium saccharinate (**D**). Their structure and reactivity have been studied. The salts **A**, **C**, and **D** contain very interesting seven-membered synthon showing multiple H-bonding interactions for pair of pyridinium cation and saccharinate anion in the solid state. The salt **B** exhibits H-bonding interaction of N(sac) … H—N(py) in the solid state, instead of seven-membered synthon. The catalytic reactivity studies show that salts **A** and **B** are both very effective, with salt **B** even better in reactivity, and are both recyclable in the esterification of a variety of alcohols, under solvent-free and base-free conditions at room temperature.

1. Introduction

Homogeneous catalysis is a powerful tool in highly active and stereoselective organic transformations.[1] However, the majority of catalytic processes in industry are still conducted under heterogeneous conditions, since separation of the catalyst from product mixture is easier than under homogeneous conditions. Therefore, in addition to developing homogeneous catalysts that can be used at high substrate to catalyst ratio, efforts have also been made to provide the heterogeneous counterpart by fixing the catalysts to a solid support.[2] Recently, it has been reported that 4-(*N*,*N*-dimethylamino)pyridine (DMAP) is an effective homogeneous catalyst for the esterification[3] of alcohol with acid anhydride,[4] the ring-opening polymerization, the silylation of alcohol, etc.[5–7] The homogeneous nature of DMAP-catalyzed acylation still suffers from the problem of separation, i.e. and the problem of residual DMAP contamination. Furthermore, DMAP causes acute dermal toxicity,[8] whereas its salts were reportedly only slightly irritating upon the skin contact.[8,9] In order to avoid spreading harmful chemicals to the surroundings, it is important to find a recoverable DMAP type catalyst that could be easily separated from the product mixture, for example, by immobilizing DMAP onto solid supports.[10–12] A few immobilized systems have been reported, but they are not able to show effective catalytic activity with good recyclability at the same time. Lin et al.[12] used the silica nanosphere-supported DMAP to catalyze the acylation of alcohols. The support however, was in favor of support molecular weight as small as possible. Connon et al. reported a recyclable magnetic-nanoparticle-supported DMAP that can be used and recovered by an external magnet for a few times.[13,14] The fluorous methods[15] could offer a useful way to recover fluorous-tagged compounds from a reaction mixture.[16] Legros et al.[15] demonstrated a fluorine-containing system to recover the catalyst salt by addition of a non-polar solvent to precipitate the catalyst moiety.[17,18] However, the high cost of fluorous materials might be

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a concern. Very recently, we reported a new protocol concerning the recyclable catalyst **A** that is the salt of DMAP and saccharin. The DMAP saccharinate catalyzed acylation of alcohols was successfully and effectively carried out for more than 8 times without loss in catalytic activity. In this manuscript, we report our extended studies on the general use of pyridinium saccharinate salts as recyclable homogeneous catalyst. The pyridine-containing substrates used are 4-*N*,*N*-dimethylaminopyridine (**a**), 4-(1-pyrrolidinyl)pyridine (**b**), 2-*N*,*N*-dimethylaminopyridine (**c**), and pyridine (**d**). The corresponding pyridinium saccharinate salts[19] for **a**–**d** are 4-*N*,*N*-dimethylaminopyridinium saccharinate (**A**), 4-(1-pyrrolidinyl) pyridinium saccharinate (**B**), 2-*N*,*N*-Dimethylaminopyridinium saccharinate (**C**) and pyridinium saccharinate (**D**), with structures shown in Fig. 1. Two types of supramolecular interactions were observed, that of salts **A**, **C**, and **D** being in contrast to that of salt **B**. In the reactivity studies described below, we found that effect of the unique structure of salt **B** is seemingly correlated to the better catalytic reactivity among the salts **A**–**D**.

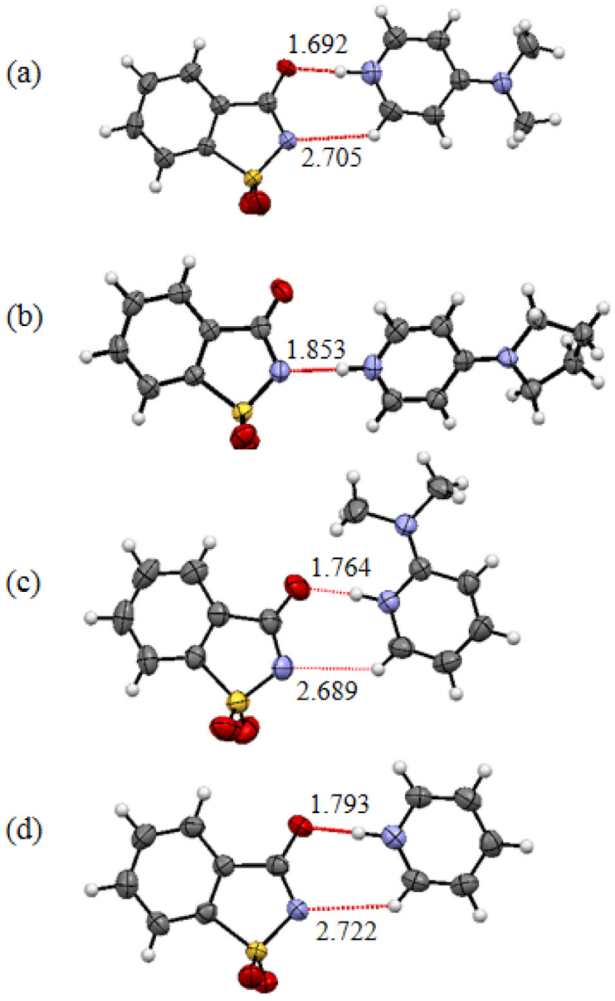


Fig. 1. The solid state cation–anion pair of the four salts: (a) 4-*N*,*N*-dimethylaminopyridinium saccharinate, **A**, (b) 4-(1-pyrrolidinyl)-pyridinium saccharinate, **B**, (c) 2-*N*,*N*-dimethylaminopyridinium saccharinate, **C**, and (d) pyridinium saccharinate (**D**). Color codes: C, black; N, blue; O, red; S, yellow, and H, white. Salts **A**, **C**, and **D** exhibit common seven-membered synthon, consisting of H-bonding interactions of O(sac) … H–N(py) and N(sac) … H–C(py), whereas salt **B** exhibits H-bonding interaction of N(sac) … H–N(py) instead of the seven-membered synthon.

2. Results and discussion

All of the pyridinium saccharinate salts **A**–**D** can easily be prepared from respective pyridine derivatives **a**–**d** and saccharin, with single crystals obtained by the diffusion crystallization from overlayering of a saturated methanolic solution with hexane. Preparations and structures are discussed first, followed by catalytic activity in acylation of the alcohol with acid anhydride.

2.1. Synthesis and structure

2.1.1. Preparation. As a typical example, the salt **B** was prepared simply by reacting **b** and saccharin in 1:1 M ratio at 60 °C. The salt **B** consists of a five-membered pyrrolidine at *para* position on pyridine ring as the *N*-containing electron donating group. The salt **A** and salt **C** consist of the dimethylamino group at *para* or *ortho* position on pyridine ring, respectively. And the salt **D** contains the parent pyridine. A comparison in structure and activity could be done among salts **A**–**D**. The salts **A**, **B**, and **D** were obtained in 95% yield, whereas salt **C** was obtained in 61% yield, attributable to the steric hindrance by *ortho* dimethylamino group on pyridine ring.

2.1.2. Structure. The four X-ray structures of salts **A**,[21] **B**, **C**, and **D**[20,22] are shown as ion-pairs in the Fig. 1a– d, respectively. The structures could be summarized that for this type of salts a highly probable synthon is from interaction between the paired, positively charged pyridinium cation and negatively charged saccharinate anion, with the cation–anion attraction reinforced by two H-bonding interactions embedded in a seven-membered ring. The crystal structure of parent pyridinium saccharinate (salt **D**) was a revisit at 100K in the current study with cell dimensions *a* 7.3166(3), *b* 12.8620(5), *c* 14.0641(5) Å, α 65.294(4), β 75.009(3), γ 78.375(3)o. Its seven-membered synthon could be seen a smooth interface between the plane of pyridinium cation and the plane of saccharinate anion, as demonstrated in Fig. 2a. The two reported structures of salt **D** were all in the same triclinic space group P-1, one with cell dimensions *a* 7.4677(7), *b* 12.9605(12), *c* 14.1895(13) Å, α 65.1760(10), β 74.752(2), γ 78.103(2)o at 292K,[22] and the other with cell dimensions *a* 7.4613(15), *b* 12.954(3), *c* 14.179(3) Å, α 65.251(2), β 74.747(3), γ 78.160(3)o at 298K.[20] When the temperature of X-ray intensity data changes from 298K, to 292K, eventually to 100K, the *R* value improves from 5.05%, to 4.50% and finally to 3.94%, and the estimated standard deviations of structural parameters also improves accordingly.

The synthon for pyridinium saccharinate salts serves as the primary stabilizing forces in the crystalline state. A proton transfer is noted, from the neutral saccharin to pyridine, and the nature of material is changed to charge-carrying pyridinium saccharinate system. The two H-bonding interactions are located at O(sac) … H–N(py), and N(sac) … H–C(py), where the former H-bonding parameters are O(sac) … N(py) 2.630 Å, O(sac) … H 1.663 Å, and ∠O(sac) … H–N(py) 178.1°; and the supportive N(sac) … H–C(py) H-bonding parameters are N(sac) … C(py) 3.349 Å, N(sac) … H 2.261 Å, and ∠N(sac) … H–C(py) 134.8°. The seven-membered synthon is planar. Shown in Fig. 2b is the plane defined by the seven-membered synthon skeleton that extends to the molecular plane of pyridinium and to the molecular plane of saccharinate, smoothly joining all the planes of salt **D**.

As briefly mentioned in the introduction, there is noted structure and reactivity relationship in this study. Salts **A**, **C**, and **D** exhibit in the solid state exactly the seven-membered synthon which has been viewed as resting state during the catalytic cycles of acylation in solution (see later). Alternatively in the solid state, salt **B** exhibits a H-bonding interaction of N(sac) … H–N(py), instead of the seven-membered synthon, as a result of the interplanar angle of 33.9° between pyridinium plane and the molecular plane of saccharinate (Fig. 3). This slightly twisted supramolecular structure of salt **B** is considered more energetic than a seven-membered synthon, in order to conform well to increased moment of inertia of C_2-symmetric pyrrolidinylpyridinium cation. Thus, it was believed that with additional resting state for salt **B** as catalyst in solution, salt **B** would be expected to perform better than salts **A**, **C** or **D**.

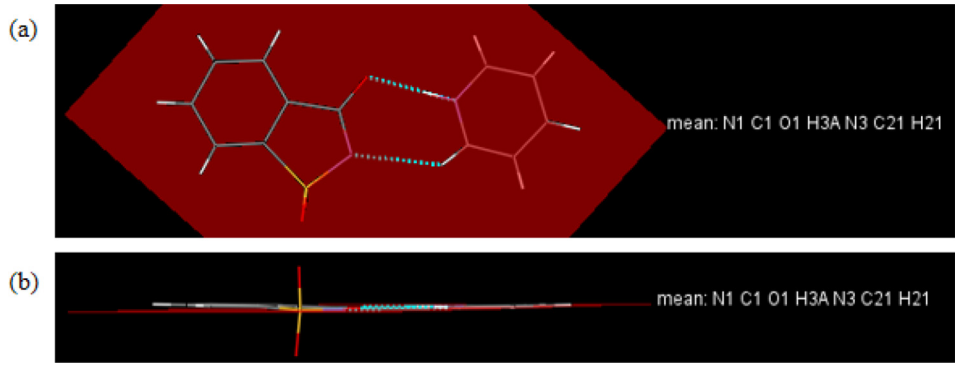


Fig. 2. (a) Top view and (b) rough side view of the synthon plane in salt **D**. Color codes: C, gray; N, blue; O, red; S, yellow, and H, white. Red shade indicates the least-squares plane defined by seven-membered synthon.

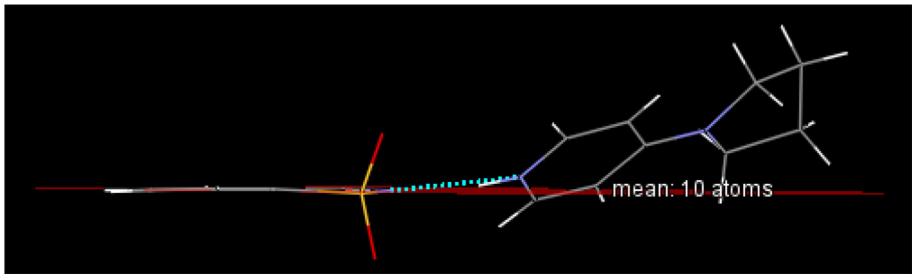


Fig. 3. Side view of the saccharinate molecular plane of salt **B**. Color codes: C, black; N, blue; O, red; S, yellow, and H, white. Red shade indicates the least-squares saccharinate molecular plane, without protons and two out-of-plane oxygens.

There are many published pyridinium saccharinate structures in the literature. A search on current version of Cambridge Structural Data Base revealed many crystal structures readily available for scrutiny on the synthon. All pyridinium saccharinate salts adopt the same seven-membered synthon, with the exception of one instance, namely, the half salt 5-methyl-2-(5-methylpyridin-2-yl)pyridinium saccharinate saccharin, showing hydrogen bonding interactions on N(sac) … H–N(py) and O(sac) … H–C(py) instead.[19]

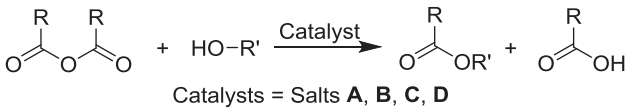
The ones adopting also the seven-membered synthon in literature are 1,2-bis(pyridinium-4-yl)ethane (saccharinate)$_2$, *trans*-1,2-bis(pyridinium-4-yl)ethene (saccharinate)$_2$,[23] 2-methylpyridinium saccharinate,[24] 4,4′-bipyridinium (saccharinate)$_2$, 4-picolinium saccharinate, and isonicotinamide saccharinate.[20]

There is presence of other weak interactions in salts **A**–**D** contributing to the stabilization in solid state, for instance the π–π stacking, C–H … π interaction,[25] and the H-bonding interactions on the –CO and –SO$_2$ groups with the neighboring hydrogen atoms. Salt **B** shows more short contacts attributable to C–H … π interactions. So does the above mentioned half salt 5-methyl-2-(5-methylpyridin-2-yl)pyridinium saccharinate saccharin. Both structures show similar H-bonding interaction of N(sac) … H–N(py).

The salts **A**–**D** dissolve in polar solvents, but precipitate from the non-polar ones.[19] We have made use of solubility of the salts and found that all four can be easily recovered for reuse. Given the strong binding interactions on cation–anion pair, we believe that the salts **A**–**D** exist in less polar organic solvents as solvated ion-pairs, likely without solvent molecules separating the cation–anion pair.

2.2. Catalysis on esterification

It has been known that the acylation of alcohol with acid anhydride is easily catalyzed by DMAP. The related conjugated acid pyridinium saccharinate was found to be active also in the catalytic acylation reaction. We extended the study to salts **A**–**D** (Scheme 1). Two acid anhydrides chosen to react with alcohols were (MeCO)$_2$O and (*i*PrCO)$_2$O in order to evaluate these salts on catalytic activity. For assessment of the catalytic acylation, many 2° alcohols and one 3° alcohol were tested. Table 1 gives the results by running the acylation reactions with 1 mol% loading of salt **A**–**D** as catalyst, without using any solvents or bases.



Scheme 1. Pyridinium saccharinate salt catalyzed acylation reaction of alcohol with acid anhydride.

Table 1
Results on esterification using salts **A**–**D** as catalyst

Entry	Catalyst	Alcohol	(RCO)$_2$O, (R=)	Temp, (°C)	Time, (h)	Yield,[a] (%)
1	**A**	1-Cyclohexanol	Me	25	2.5	99+
2	**A**	1-Cyclohexanol	iPr	25	2	99+
3	**B**	1-Cyclohexanol	Me	25	2	99+
4	**B**	1-Cyclohexanol	iPr	25	2	99+
5	**C**	1-Cyclohexanol	Me	25	24	98
6	**C**	1-Cyclohexanol	iPr	25	24	97
7	**D**	1-Cyclohexanol	Me	25	24	98
8	**D**	1-Cyclohexanol	iPr	25	24	98
9	**A**	2-Phenyl-2-propanol	Me	100	24	90
10	**A**	2-Phenyl-2-propanol	iPr	100	24	99+
11	**B**	2-Phenyl-2-propanol	Me	90	23	99
12	**B**	2-Phenyl-2-propanol	iPr	90	23	99+

[a] The 99+ means the yield is more than 99%.

When 1-cyclohexanol is the reactant, the acylation proceeds easily to completion in 2–2.5 h at room temperature employing salts **A** and **B** as catalyst, indicating that the catalysis is very facile (Table 1, entries 1–4). On the other hand, similar acylation employing salts **C** and **D** as catalyst takes 24 h to finish (Table 1, entries 5–8). For salts **A** and **B** as catalyst, the electron-donating dimethylamino group and pyrrolidinyl group, respectively, at *para* position on pyridine ring increase the rate by one order of magnitude, comparing to the result by the parent pyridinium salt **D**. Alternatively the salt **C** as catalyst exhibits a slowing-down of the reaction, attributed mainly to the steric hindrance the dimethylamino group at *ortho* position on pyridine ring. The *para* and *ortho* substitution on pyridine ring could also be justified in terms of intrinsic pKa parameter. The pKa value in aqueous solution for most basic site of pyridine is 5.23±0.10, that of 2-(dimethylamino) pyridine 7.04±0.10, and that of 4-(dimethylamino)pyridine (DMAP) 9.52±0.10. It is reasonable that DMAP is the most reactive one among the three. Similar reactivity for salts **A** and **B** was predicted on the basis of similar *pKa* values of salts **A** and **B**. Interestingly, the reactivity studies show that the salt **B** as catalyst was better in reactivity than the salt **A**, likely correlated to the difference of structural chemistry in the solid state and correspondingly the difference of resting state during the catalysis cycles.

We had also compared the catalytic activity of DMAP and that of salt **A**, using esterification of L-menthol with acid anhydrides as the model reaction, with results shown in Table 2. The data from Ishihara's work with DMAP as catalyst precursor[26] (Table 2, entries 3 and 4) and our own results with salt **A** as catalyst (Table 2, entries 1 and 2) gave very comparable acylation results.

Table 2
Comparison of catalytic activity of DMAP and salt **A**

Entry	Catalyst loading	Substrate	$(RCO)_2O$ (R=)	Temp, (°C)	Time (h)	Yield (%)
1	1 mol % salt **A**	L-Menthol	Me	25	8	97
2	1 mol % salt **A**	L-Menthol	iPr	25	8	98
3[a]	0.5 mol % DMAP	L-Menthol	Me	25	9	84
4[a]	0.5 mol % DMAP	L-Menthol	iPr	25	9	98

[a] The entries 3 and 4 are quoted from Ishihara's data,[26a] that we also repeated and had the same outcome.

Based on the results on Tables 1 and 2, the catalysis proceeds smoothly with salts **A** and **B** as catalyst and to a less degree with salts **C** and **D** as catalyst. The catalyst loading of salt **A** is slightly greater than the loading of DMAP only, yet the time to completion is faster for salt **A** as pre-catalyst than free DMAP only as pre-catalyst. The results from free DMAP-catalyzed acylation are comparable to those from salt **A**-catalyzed acylation. However we feel more important that salt **A** is safer to handle in the laboratory than free DMAP, and furthermore, the use of salt **A** has an advantage, namely, in catalyst recovering and reuse (see later).

*2.2.1. Salt **A**-catalyzed esterification.* The salt **A**-catalyzed esterification reactions have been discussed in our recent communication,[21] the summarized results here are for comparison with catalytic esterification by salts **B**–**D**. The salt **A** catalyzed esterification was carried out, under solvent-free and base-free conditions at room temperature (with the exception for esterification of 3° alcohol), and after completion of the reaction salt **A** catalyst was precipitated by adding hexane (or any other non-polar solvent) to the product mixture for recovery and reuse that were demonstrated for 10 runs. Besides acetic anhydride, the more sterically demanding isobutyric anhydride was run parallel-wise with good recyclability, also for 10 times.

Using salt **A** as catalyst, the 2° alcohols tested were 1-cyclohexanol, 1-phenyl ethanol, L-menthol, 1-cyclododecanol, and 4-nitrophenol, with satisfactory results both on reactivity and recyclability listed in Table 3, entries 1–10. The yields were all greater than or equal to 92% during the recycling experiments except in two cases with 87% at the last experiment. The bulky 3° alcohol, 2-phenyl-2-propanol, was difficult to acetylate or isobutyrate at room temperature. Its **A**-catalyzed esterification at 100 °C finished in 24 h and the recyclization could proceed for 10 times (Table 3, entries 11–12). It was also noticed that the heteroatom-containing (N atom) alcohol, 3-pyridyl methanol (entry 13), is rapidly esterified for 10 recycling runs without being influenced by the presence of heteroatom.

*2.2.2. Salt **B**-catalyzed esterification.*[26b] In view of the efficient results from salt **A**-catalyzed esterification reaction, we extended the scope of study by using analogous salt **B** as catalyst using the same acylation reactions between alcohol and acid anhydride. The salt **B** consisted of a *para* five-membered pyrrolidine on pyridine as the N-containing electron donating group. The salt was prepared by reacting equal molar **b** and saccharin at 60 °C to result in white solid crystalline materials in high yield.

The experimental results of salt **B** as acylation catalyst were recorded in Table 4. Similar to salt **A**, the salt **B** was a very effective, recyclable acylation catalyst for the esterification of 1-cyclohexanol with acetic anhydride as well as with isobutyric anhydride (Table 4, entries 1–2), which were successfully carried out under solvent-free and base-free condition at room temperature and both reactions were

Table 3
Salt **A**-catalyzed esterification of alcohols with anhydrides under solvent- and base-free conditions

Entry	Alcohol	$(RCO)_2O$ (R=)	T (°C)	T (h)	Yield[a] (%)									
1[b]	1-Cyclohexanol	Me	25	2.5	99+	99+	99+	97	97	97	98	94	93	87
2	1-Cyclohexanol	iPr	25	2	99+	99+	99+	99+	99+	99+	99	99	98	98
3	1-Phenyl ethanol	Me	25	2	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+
4	1-Phenyl ethanol	iPr	25	2	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+
5	L-Menthol	Me	25	8–12	97	96	96	96	95	92	95	98	92	87
6	L-Menthol	iPr	25	8–12	98	98	96	96	97	95	97	99	95	92
7	1-Cyclododecanol	Me	25	8	99	98	99	97	97	97	96	97	97	96
8	1-Cyclododecanol	iPr	25	8	95	95	95	95	94	94	95	95	94	94
9	4-Nitrophenol	Me	25	2–4	99+	99+	99+	98	99+	99+	96	96	96	96
10	4-Nitrophenol	iPr	25	2–4	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+
11	2-Phenyl-2-propanol	Me	100	24	90	90	88	85	88	88	88	88	85	80
12	2-Phenyl-2-propanol	iPr	100	24	99+	99+	99+	99	96	94	93	91	90	89
13	3-Pyridyl methanol	Me	25	0.5	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+

[a] 99+ means the yield is more than 99%.
[b] Rate law is ln[cyclohexanol]=−0.24t−0.58. (see Supplementary data D).

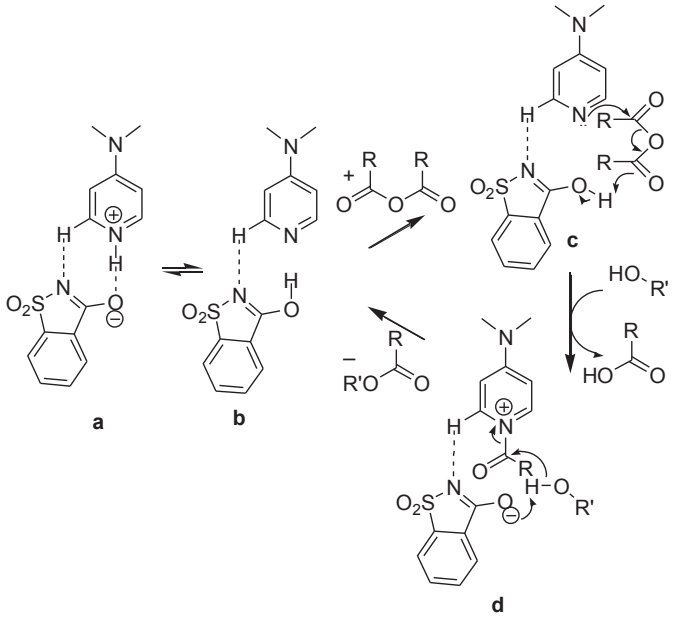
completed within 2 h. Salt **B** exhibited a solubility property the same as that of salt **A** and was easily precipitated by addition of hexane to the product mixture. Its recycling and reuse have been demonstrated 10 times, keeping yields all above 88% for either acetic anhydride or for sterically more hindered isobutyric anhydride with good recyclability. Furthermore, other 2° alcohols, i.e. 1-phenyl ethanol, L-menthol, and 1-cyclododecanol all proceeded easily to the recyclable acylation with salt **B** as shown in Table 4, entries 3–8. When the less nucleophilic 4-nitrophenol was used as substrate, the reaction completed in 2.5 h; and its recycling and reuse was also successfully repeated 10 times with a quantitative yield every run (Table 4, entries 9–10). As for the sterically hindered 2-phenyl-2-propanol, a 3° alcohol, the recycling experiments could also be effectively carried out at 90 °C for 10 times. The heteroatom-containing 3-pyridyl methanol could also be quickly esterified without being influenced by the heteroatom for 10 times. Overall, the salt **B** appeared to be an even better catalyst on acylation reaction of alcohol with acid anhydrides than salt **A**, in particular on the acylation of tertiary 2-phenyl-2-propanol (Table 4, entries 11–12), which requires only 90 °C and 23 h instead of 100 °C and 24 h (vide infra, Scheme 2).

*2.2.3. Salt **C**-catalyzed esterification.* The reaction of equal molar 2-(*N*,*N*-dimethylamino)pyridine and saccharin resulted in 61.4% yield of salt **C**, whose catalytic activity was also studied. The NMe_2 group at *ortho* position imposed a steric hindrance on acylation, and thus much longer time was required to reach completion. Shown in Table 5 entries 1–2 for example, the salt **C**-catalyzed esterification of 1-cyclohexanol with acetic anhydride and with isobutyric anhydride, respectively, took both 24 h at room temperature, with yields of 98% and 97%, respectively. The esterification of 1-phenyl ethanol exhibited similar results (Table 5 entries 3–4) whereas the esterification of 1° alcohol, the 3-phenyl propanol, was much faster and needed only 6–7 h to complete (Table 5 entries 5–6). At room temperature, without adding the catalyst salt **C**, the yield is around 20% which is significantly lower than those with the catalyst added. Because the catalytic activity of salt **C** was too much inferior to that of salts **A**–**B**, we decided that it won't gain meaningful advantage from extra recycling experiments with salt **C** as catalyst. Accordingly no recovery and reuse was attempted.

Table 4
Salt **B**-catalyzed esterification of alcohols with anhydrides under solvent- and base-free conditions

Entry	Reactant	$(RCO)_2O$ (R=)	T (°C)	t (h)	Yield[a] (%)									
1[b]	1-Cyclohexanol	Me	22	2	99+	99+	99+	99+	99+	98	98	95	93	88
2	1-Cyclohexanol	iPr	22	2	99+	99+	99+	99+	99+	99+	95	97	97	98
3	1-Phenyl ethanol	Me	22	1	99+	99+	99+	99+	99+	99+	94	94	89	89
4	1-Phenyl ethanol	iPr	22	1	99+	99+	99+	99+	99+	99+	99+	90	88	89
5	L-Menthol	Me	22	5	99	95	92	94	95	91	90	90	90	88
6	L-Menthol	iPr	22	5	99	99	91	91	90	91	88	87	85	84
7	1-Cyclododecanol	Me	22	6	92	92	92	92	90	91	91	91	90	90
8	1-Cyclododecanol	iPr	22	6	99	99	96	97	94	94	92	94	94	93
9	4-Nitrophenol	Me	22	2	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+
10	4-Nitrophenol	iPr	22	2	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+
11	2-Phenyl-2-propanol	Me	90	23	99	99	99	98	96	96	95	95	95	95
12	2-Phenyl-2-propanol	iPr	90	23	99	98	95	93	92	91	92	90	90	89
13	3-Pyridyl methanol	Me	22	0.5	99+	99+	99+	99+	99+	99+	99+	99+	99+	99+

[a] 99+ means the yield is more than 99%.
[b] Rate law is ln[cyclohexanol]=−0.35x−0.50. (see Supplementary data D).



Scheme 2. Proposed mechanism[27] of pyridinium saccharinate salt **A** catalyzed acylation reaction based on synthon connectivity as the resting state with O(sac) … H–N(py)/O(sac)-H … N(py) for propagation.

Table 5
Salt **C**-catalyzed esterification of alcohols with anhydrides under solvent- and base-free conditions

Entry	Reactant	$(RCO)_2O$ (R=)	T (°C)	t (h)	Yield[a] (%)
1	1-Cyclohexanol	Me	25	24	98 (49)
2	1-Cyclohexanol	iPr	25	24	97
3	1-Phenyl ethanol	Me	25	24	99 (17)
4	1-Phenyl ethanol	iPr	25	24	99
5	3-Phenyl propanol	Me	25	6	98 (19)
6	3-Phenyl propanol	iPr	25	7	96

[a] The numbers inside the parenthesis are the yields from the trials without adding the catalysts.

*2.2.4. Salt **D**-catalyzed esterification.* Prepared directly from reaction of parent pyridine and saccharin, salt **D** was also studied on its catalytic activity on esterification of alcohol with acid anhydride, as shown in Table 6. Relative to salts **A**–**B**, salt **D** showed much poorer results, which were expected, because of weaker basicity of **d** compared to **a** and **b**. For salts **A** and **B**, the NMe_2 group and the pyrrolidynyl group at *para* position on pyridine ring, respectively, donate electron density to the ring, whereas for salt **D** no such auxiliary donating group is available. Thus, the poor catalytic activity of salt **D**-catalyzed esterification was attributed to electronic effect. Shown in Table 6, the esterification reaction for the 2°

alcohols including 1-cyclohexanol, 1-phenyl ethanol, and L-menthol, took 24 h to finish at room temperature (Table 6, entries 1–2, 5–8).

Table 6
D-catalyzed esterification of alcohols with anhydrides under solvent- and base-free conditions

Entry	Reactant	$(RCO)_2O$; (R=)	T (°C)	t (h)	Yield[a] (%)
1	1-Cyclohexanol	Me	25	24	98 (49)
2	1-Cyclohexanol	iPr	25	24	98
3	1-Cyclohexanol	Me	60	8	97 (95)[b]
4	1-Cyclohexanol	iPr	60	8	95
5	1-Phenyl ethanol	Me	25	24	99 (17)
6	1-Phenyl ethanol	iPr	25	24	99
7	3-Phenyl propanol	Me	25	8	99 (29)
8	3-Phenyl propanol	iPr	25	8	98
9	L-Menthol	Me	100	24	91 (90)[b]
10	L-Menthol	iPr	100	24	88

[a] The numbers inside the parenthesis are the yields from the trials without adding the catalysts.
[b] At higher temperature (60 or 100 °C; entries 3&9), the catalytic activity from the catalyst shows only the very minor effect.

For the esterification of 1-cyclohexanol with acid anhydrides with salt **D** as catalyst, the reactions finished in 8 h if temperature was raised to 60 °C (Table 6, entries 3–4). With less steric influence the primary 3-phenyl propanol (Table 6, entries 7–8) could be acylated at room temperature in 8 h. The esterification of L-menthol with acid anhydrides took 24 h at 100 °C (Table 5, entries 9–10). Due to poor catalytic activity on esterification results, no attempts were made on recovery and reuse on salt **D**.

2.3. Mechanism of acylation of alcohols

As mentioned above, DMAP is an effective homogeneous catalyst for the esterification of alcohols. To overcome the major problem associated with the use of soluble catalysts, i. e. the recovery of the catalyst from the reaction medium, Ishihara et al. had immobilized the catalyst on a polymeric matrix by using polystyrene-supported DMAP. The catalyst loading was at the level of 5–10 mol%, with the residual polystyrene-supported DMAP carboxylate salt being recovered as residues from distillation of product mixture. This recovered precatalyst was reportedly reused more than three times.

The current method of recovery utilized the precipitation of the saccharinate salts from product mixture, by addition of hexane or other non-polar solvents to the soup and the saccharinate salts separated quantitatively, ready for reuse in next acylation reaction. The recovery and reuse were demonstrated for 10 runs with salts **A** and **B** as catalyst. We strongly favor to enter the catalytic cycle from the saccharinate salts side.

In order to improve on recovery and reuse of the catalyst, insights on mechanism as well as equilibria in reaction mixture are helpful. Following the original mechanism on DMAP catalyzed acylation of alcohol with acid anhydride, the rate-determining step is the reaction of *N*-acyl pyridinium carboxylate with the alcohol; free DMAP does not enter the kinetic equation directly.[26] The equilibria[21] involved are believed to be mainly the molecular processes on relocation of active proton between the reactant alcohol and the product carboxylic acid.

Given that the majority of pyridinium saccharinate structures reveals a seven-membered synthon in the solid state, and that collectively the strong–weak O(sac) … H–N(py) and N(sac) … H–C(py) hydrogen bonds become a robust recognition motif, we may reasonably assume that the presence of such a synthon is also in the solution state and use it as working hypothesis so that the pyridinium saccharinate are ion-pairs in solution. Thus, based on this ion-pairs concept, we think the mechanism is more likely as the one proposed below.

At the molecular level, taking advantage of the cation–anion pair, the pyridinium saccharinate catalyzed esterification reaction is consistent to a mechanism proposed in Scheme 2. The pyridinium saccharinate salt is an internally self-buffering system because the seven-membered synthon effectively interfaces more than one negative centers for one proton. The salt **B**, as derived from **b** and saccharine, is used for illustration: the pKa of acidic most proton of saccharine is 2.2 and the pKa of the basic most proton of pyrrolidinyl-pyridine (**b**) is 9.5. The isoelectronic point pI of salt **B** is then (2.2+9.5)/2=5.9, which is within reasonably range of pKa values of acetic acid and isobutyric acid, the by-products in the esterification of alcohols with acid anhydrides.

Shown in Scheme 2 the pyridinium saccharinate salt **A** stays in the static form of cation–anion and in the static form with neutral saccharine and pyridine, the latter being considered the more activated to react with acid anhydride and the form with ion pair serves as the resting. That is, the generation of transient DMAP in system is important for the catalytic activity, whereas the *N*-acyl pyridinium cation is also transient in the rate determining step that is followed by reaction with the alcohol substrate. Salts **A**, **C**, and **D** as catalyst, with their X-ray structures in mind, likely utilize pathway of Scheme 2. For salt **B**, the pathway of Scheme 2 is also reasonable. In addition, a pathway with N(sac) … H–N(py) as resting state may give an alternative route for salt **B**, also with its X-ray structure under consideration.

Search for pyridinium carboxylate structures in Cambridge Structural Data Base didn't reveal statistical importance on similar seven-membered synthon in that carboxylate replaces saccharinate. It cannot be ruled out however that the carboxylate anion exchanges positions with the saccharinate anion, to play a role during conversion of the acid anhydride to *N*-acyl cation and concurrently to carboxylic acid.

3. Conclusion

Four pyridinium saccharinate salts were prepared and their crystal structures studied. The structures all contain important H-bonding interactions between ion pair of pyridinium and saccharinate in the solid state. Salts **A**, **C**, and **D** showed the seven-membered synthon with embedded double H-bonding interactions whereas salt **B** exhibited only the N(sac) … H–N(py) H-bonding not the seven-membered synthon. The reactivity of salts **A**–**D** as catalyst on esterification has been studied. Salt **C** was a poor catalyst for esterification due to its steric hindrance and salt **D** without donating substituent on pyridine ring was also proved a poor catalyst. Salts **A** and **B**, whose kinetics have been studied, are very efficient recyclable catalysts for the acylation of a variety of 2° and 3° alcohols, and both salts could be recycled in the esterification reaction for 10 times without decreasing catalytic activity. From the kinetic studies, salt **B** turned out to be the best catalyst, even better than salt **A** in this esterification.

4. Experimental

4.1. General

Gas chromatographic/mass spectrometric data were obtained using an Agilent 6890 Series gas chromatograph with a series 5973 mass selective detector. The GC monitoring employed a HP 6890 GC using a 30 m×0.250 mm HP-1 capillary column with a 0.25 μm stationary phase film thickness. Infrared spectra were obtained on a Perkin Elmer RX I FT-IR Spectrometer. NMR spectra were recorded on Bruker AM 500 and 300 using 5 mm sample tubes. The residual

peaks of D_2O or $CDCl_3$ was used as the reference peaks for ^1H or ^{13}C NMR spectra. Elemental Analysis was done by the staff of the National Taiwan University Elemental Analysis Laboratory. The X-ray diffraction data of salts **A**–**D** were collected at 100 or 200K employing a Bruker (including Nonius BV) CCD diffractometer; the structure was solved by successive Fourier maps.

4.2. General procedure for the salt preparation

The 100 mL round bottomed flask was charged with pyridine derivatives (or pyridine) (4.09 mmol) and equimolar of saccharin (4.09 mmol, 500 mg) followed by the addition of 20 mL THF as solvent. Then the reaction mixture was set to react in THF, at ca. 60 °C for overnight. After the reaction, the solvent was removed by vacuum. The crude product was then obtained. Recrystallization proceeded with dissolution of crude product in methanol to form a saturated solution, to which a hexane overlayer (ca. 10 cm high) was added. Solvent diffusion over a period of a week at room temperature afforded white crystals of the desired salt.

4.3. Preparation of salt A[21]

The 100 mL round bottomed flask was charged with 4-(*N*,*N*-dimethylamino)pyridine (DMAP; 4.09 mmol, 500 mg) and equimolar of saccharin (4.09 mmol, 749.21 mg) followed by the addition of 20 mL THF as solvent. Then the reaction mixture was set to react in THF, at ca. 60 °C for overnight. After the reaction, the solvent was removed by vacuum. The crude product (1.24 g; yield=99%) was then obtained. Recrystallization proceeded with dissolution of crude product in methanol to form a saturated solution, to which a hexane overlayer (ca. 10 cm high) was added. Solvent diffusion over a period of a week at room temperature afforded white needle-shaped crystals of salt **A**.

Analytical data of salt **A**: Yield (purified): 95%, mp: 218.0 °C.

^1H NMR (500 MHz, D_2O) δ 7.90 (d, 2H, J=7.5 Hz, C_5H_4N–), 7.76–7.71 (m, 4H, C_6H_4–; Saccharin H), 6.72 (d, 2H, J=7.59 Hz, C_5H_4N–), 3.12 (s, 6H, CH_3); ^{13}C NMR (126 MHz, D_2O) δ 39.6, 107.0, 142.3, 157.6 (C's on the DMAP) 120.6, 123.9, 132.7, 133.6, 134.1, 138.3, 172.6 (C's on the Saccharin).

FTIR ν (cm^{-1}) 3077s (N–H), 1646s (C=O, stretch), 1542, 1443 m (pyridine), 1329, 1163, 1130, (R–SO_2–N), 1270s (N–CH_3).

EA: Calcd for $C_{14}H_{15}N_3O_3S$: C 55.07; H 4.95; N 13.76. Anal. Found: C 54.50; H 4.85; N 13.50.

X-ray study was detailed in Ref. 21.

Because the synthesis employed a general procedure described in the preparation of salt **A**, only salient amounts and yields are given for salts **B**–**D**.

4.4. Preparation of salt B

4-(1-Pyrrolidinyl)pyridine (4.09 mmol, 606.18 mg) and equimolar of saccharin (4.09 mmol, 749.21 mg) followed by the addition of 20 mL THF as solvent.

Yield (purified): 95%, white solid, mp: 184.5 °C.

^1H NMR (500 MHz, D_2O) δ 7.86 (d, 2H, J=7.3 Hz, C_5H_4N–), 7.83–7.70 (m, 4H, C_6H_4–; Saccharin H), 6.57 (d, 2H, J=7.8 Hz, C_5H_4N–), 3.39 (t, 4H, J=6.9 Hz, NCH_2–), 2.04 (m, 4H, CH_2–); ^{13}C NMR (126 MHz, D_2O) δ 24.0, 47.5, 106.6, 141.2, 153.9 (C's on the Pyrrolidine) 119.6, 123.0, 131.8, 132.7, 133.2, 137.2, 171.7 (C's on the Saccharin). FTIR ν (cm^{-1}) 3053 (N–H), 2866 (R–CH_2–R), 1650s (C=O, stretch), 1553s, 1450 m (pyridine), 1326, 1206, 1146s (R–SO_2–N), 1276s (N–CH_3).

EA: Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.68. Anal. Found: C, 57.65; H, 5.22; N, 12.68; S, 9.74.

X-ray crystallographic data of salt **B** (CCDC 892062): $C_{16}H_{17}N_3O_3S$, Mr 331.39, $P2_1/n$, a 13.4242(4), b 8.9063(3), I 13.6575(4) Å, β 112.260(2)°, V 1511.20(8) $Å^3$, Z=4, T=100.0(1)K, No of refln.=3088, GoF=1.111, R=2.99%, [I>2σ(I)].

4.5. Preparation of salt C

2-(*N*,*N*-Dimethylamino)pyridine (4.09 mmol, 500 mg) and equimolar of saccharin (4.09 mmol, 749.21 mg) followed by the addition of 20 mL THF as solvent.

Yield (purified): 61.4%, white solid, mp: 149.1 °C.

^1H NMR (500 MHz, D_2O) δ 7.76–7.72 (m, 2H, C_5H_4N–), 7.67–7.63 (m, 4H, C_6H_4–; Saccharin H), 6.90 (d, H, J=9.2 Hz, C_5H_4N–), 6.71 (t, H, J=6.7 Hz, C_5H_4N–), 3.07 (s, 6H, CH_3).

^{13}C NMR (126 MHz, D_2O) δ 38.5, 111.4, 111.8, 141.9, 143.0, 151.9 (C's on the DMAP) 120.2, 123.5, 132.3, 133.2, 133.7, 135.1, 172.1 (C's on the Saccharin).

FTIR ν (cm^{-1}) 3040 (N–H), 1646s (C=O, stretch), 1573s, 1456 m (pyridine), 1333, 1146s (R–SO_2–N), 1266s (N–CH_3).

EA: Calcd for $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76; S, 10.50. Anal. Found: C, 54.76; H, 4.85; N, 14.00; S, 10.89.

X-ray crystallographic data of salt **C** (CCDC 892061): $C_{14}H_{15}N_3O_3S$, Mr 305.35, $P2_1/c$, a 7.1952(4), b 8.4058(4), c 23.5390(11) Å, β 96.981(2), V 1413.12(12) $Å^3$, Z=4, T=200(2)K, No. of refln.=2480, GoF=0.951, R=3.90%, [I>2σ(I)].

4.6. Preparation of salt D

Pyridine (4.09 mmol, 323.11 mg) and equimolar of saccharin (4.09 mmol, 749.21 mg) followed by the addition of 20 mL THF as solvent.

Yield (purified): 95.2%, white solid, mp: 131.0 °C.

^1H NMR (500 MHz, D_2O) δ 8.78 (dd, 2H, J=5.5 Hz and J=1.4 Hz, C_5H_4N–), 8.60 (tt, H, J=7.8 Hz and J=1.8 Hz, C_5H_4N–), 8.06 (dd, 2H, J=7.8 Hz and J=6.9 Hz, C_5H_4N–), 7.88–7.80 (m, 4H, C_6H_4–; Saccharin H). ^{13}C NMR (126 MHz, D_2O) δ 126.7, 141.1, 146.4 (C's on the Pyridine) 119.7, 123.0, 131.5, 132.8, 133.2, 140.4, 171.5 (C's on the Saccharin).

FTIR ν (cm^{-1}) 3086 (N–H), 1630s (C=O, stretch), 1583, 1460 (pyridine), 1336s, 1173s, 1143 (R–SO_2–N).

EA: Calcd for $C_{12}H_{10}N_2O_3S$: C, 54.95; H, 3.84; N, 10.68; S, 12.23. Anal. Found: C, 54.44; H, 3.76; N, 10.81; S, 12.50.

X-ray crystallographic data of salt **D** (CCDC 1037131): $C_{12}H_{10}N_2O_3S$, Mr 262.28, *P-1*, a 7.3166(3), b 12.8620(5), c 14.0641(5) Å, α 65.294(4), β 75.009(3), γ 78.375(3), V 1154.85(8) $Å^3$, Z=4, T=100.0(1)K, No. of refln.=5624, GoF=1.031, R=3.94%, [I>2s(I)].

4.7. General procedure for the salt-catalyzed esterification

The alcohol (2 mmol) and the anhydride (2.2 mmol) were mixed in a 10 mL test tube and 1 mol % of salt **A** (0.02 mmol) was added. The tube was then capped (or under N_2 purge) and the reaction mixture was stirred at room temperature (except for 1-methylcyclopentanol at 60 °C). After a couple of hours the acid effluent was evaporated in vacuum. The residue was then allowed to cool to room temperature and the salt was precipitated by adding 2 mL hexane (or toluene). After filtration, salt was recovered, and then evaporating solvent from the filtrate afforded the crude ester product. The recovered salt was charged with the substrates, and the reaction mixture was then proceeded to the next run. The products were quantified with GC analysis by comparison to NMP as an internal standard. The products from the 1st run were further purified by column chromatography, and the isolated yields were compared with the GC/MS yields. They were all in good agreement.

All the salt-catalyzed esterification products listed in Tables are mostly known compounds. The products (Esters 1–15) have been checked by GC/MS, NMR spectrometer (mp if the product is a solid).

Esters 1–15 exhibited spectroscopic data exactly identical to those reported in the literature.[15,28–34]

4.7.1. (***a***)[15] ***Ester 1 (Cyclohexyl acetate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (m, H, OC*H*–), 2.01 (s, 3H, CH_3), 1.87–1.85 (m, 2H, C*H*–), 1.75–1.71 (m, 2H, C*H*–), 1.57–1.54 (m, 2H, CH_2–), 1.45–1.22 (m, 4H, CH_2–).

$C_6H_{11}OC(O)CH_3$, GC/MS (*m*/*z*; EI): 142 (M^+), 99 ($M^+-C_2H_3O$), 83 ($M^+-C_2H_3O_2$), 43 ($C_2H_3O^+$).

4.7.2. (***b***)[28] ***Ester 2 (Cyclohexyl isobutyrate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (m, H, OC*H*–), 2.46 (sept, H, *J*=6.8 Hz, O=CC*H*–), 1.83–1.78 (m, 2H, C*H*–), 1.72–1.68 (m, 2H, C*H*–), 1.53–1.49 (m, 2H, CH_2–), 1.44–1.23 (m, 4H, CH_2–), 1.11 (d, 6H, *J*=6.8 Hz, CH_3).

$C_6H_{11}OC(O)CH(CH_3)_2$, GC/MS (*m*/*z*; EI): 170 (M^+), 127 ($M^+-|-C_3H_7$), 99 ($M^+-C_4H_7O$), 83 ($M^+-C_4H_7O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).

4.7.3. (***c***)[29] ***Ester 3 (1-phenylethyl acetate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H, C_6H_5-), 7.27 (m, H, C_6H_5–), 5.88 (q, H, *J*=6.8 Hz, OC*H*–), 2.05 (s, 3H, CH_3), 1.53 (d, 3H, *J*=6.8 Hz, CH_3).

$PhCH(CH_3)OC(O)CH_3$, GC/MS (*m*/*z*; EI): 164 (M^+), 121 ($M^+-C_2H_3O$), 105 ($M^+-C_2H_3O_2$), 77 ($M^+-C_4H_7O_2$), 43 ($C_2H_3O^+$).

4.7.4. (***d***)[30] ***Ester 4 (1-phenylethyl isobutyrate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H, C_6H_5–), 7.27 (m, H, C_6H_5–), 5.87 (q, H, *J*=6.8 Hz, OC*H*–), 2.57 (sept, H, *J*=6.8 Hz, O=CC*H*–), 1.53 (d, 3H, *J*=6.8 Hz, CH_3), 1.19 (d, 3H, *J*=7.1 Hz, CH_3), 1.17 (d, 3H, *J*=7.1 Hz, CH_3).

$PhCH(CH_3)OC(O)CH(CH_3)_2$, GC/MS (*m*/*z*; EI): 192 (M^+), 121 ($M^+-C_4H_7O$), 105 ($M^+-C_4H_7O_2$), 77 ($M^+-|-C_6H_{11}O_2$), 43 ($C_3H_7^+$).

4.7.5. (***e***)[31] ***Ester 5 (2-isopropyl-5-methylcyclohexyl acetate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dt, H, *J*=4.3 Hz and 11.1 Hz, OC*H*–), 1.95 (s, 3H, CH_3), 1.92 (d, H, *J*=11.9 Hz, C*H*–), 1.79 (dsept, H, *J*=2.6 Hz and 6.8 Hz, C*H*–), 1.63–1.57 (m, 2H, CH_2–), 1.44–1.37 (m, H, C*H*–), 1.28 (tt, H, *J*=2.6 Hz and 11.1 Hz, C*H*–), 0.99 (dq, H, *J*=3.4 Hz and 9.4 Hz, C*H*–), 0.88 (q, H, *J*=11.1 Hz, C*H*–), 0.83 (d, 3H, *J*=3.4 Hz, CH_3), 0.82 (d, 3H, *J*=3.4 Hz, CH_3), 0.81 (m, H, C*H*–), 0.69 (d, 3H, *J*=7.7 Hz, CH_3).

2-$CH(CH_3)_2$-5-$CH_3C_6H_9OC(O)CH_3$, GC/MS (*m*/*z*; EI): 198 (M^+), 139 ($M^+-C_2H_3O_2$), 124 ($M^+-C_3H_6O_2$), 96 ($M^+-|-C_5H_{10}O_2$), 81 ($M^+-C_6H_{13}O_2$), 43 ($C_2H_3O^+$).

4.7.6. (***f***) ***Ester 6 (2-isopropyl-5-methylcyclohexyl isobutyrate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (m, H, OC*H*–), 2.43 (sept, H, *J*=6.8 Hz, O=CC*H*–), 1.89 (d, H, *J*=11.9 Hz, C*H*–), 1.81 (dsept, H, *J*=2.6 Hz and 6.8 Hz, C*H*–), 1.63–1.57 (m, 2H, CH_2–), 1.43–1.39 (m, H, C*H*–), 1.31 (tt, H, *J*=2.6 Hz and 11.1 Hz, C*H*–), 1.08 (d, 3H, *J*=3.4 Hz, CH_3), 1.07 (d, 3H, *J*=3.4 Hz, CH_3), 0.98 (dq, H, *J*=3.4 Hz and 9.4 Hz, C*H*–), 0.87 (q, H, *J*=11.1 Hz, C*H*–), 0.83 (d, 3H, *J*=3.4 Hz, CH_3), 0.81 (d, 3H, *J*=3.4 Hz, CH_3), 0.75 (m, H, C*H*–), 0.68 (d, 3H, *J*=6.8 Hz, CH_3).

2-$CH(CH_3)_2$-5-$CH_3C_6H_9OC(O)CH(CH_3)_2$, GC/MS (*m*/*z*; EI): 226 (M^+), 139 ($M^+-C_4H_7O_2$), 124 ($M^+-C_5H_{10}O_2$), 96 ($M^+-|-C_7H_{14}O_2$), 81 ($M^+-C_8H_{17}O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).

4.7.7. (***g***)[32] ***Ester 7 (cyclododecyl acetate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (m, H, OC*H*–), 2.04 (s, 3H, CH_3), 1.72 (hex, 2H, *J*=6.8 Hz, CH_2–), 1.52–1.29 (m, 20H, CH_2–).

$C_{12}H_{23}OC(O)CH_3$, GC/MS (*m*/*z*; EI): 226 (M^+), 167 ($M^+-C_2H_3O_2$), 43 ($C_2H_3O^+$).

4.7.8. (***h***)[33] ***Ester 8 (cyclododecyl isobutyrate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (m, H, OC*H*–), 2.51 (sept, H, *J*=6.8 Hz, O=CC*H*–), 1.71 (hex, 2H, *J*=6.8 Hz, CH_2–), 1.54–1.28 (m, 20H, CH_2–), 1.16 (d, 6H, *J*=6.8 Hz, CH_3).

$C_{12}H_{23}OC(O)CH(CH_3)_2$, GC/MS (*m*/*z*; EI): 254 (M^+), 211 ($M^+-|-C_3H_7$), 167 ($M^+-C_4H_7O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).

4.7.9. (***i***)[34] ***Ester 9 (4-nitrophenyl acetate)***: *pale yellow solid, m.p: 77 °C.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, 2H, *J*=8.7 Hz, C_6H_4–), 7.26 (d, 2H, *J*=8.7 Hz, C_6H_4–), 2.32 (s, 3H, CH_3).

4-$NO_2PhOC(O)CH_3$, GC/MS (*m*/*z*; EI): 181 (M^+), 138 ($M^+-C_2H_3O$), 122 ($M^+-C_2H_3O_2$), 92 ($M^+-C_2H_3NO_3$), 43 ($C_2H_3O^+$).

4.7.10. (***j***)[26] ***Ester 10 (4-nitrophenyl isobutyrate)***: *pale yellow solid, m.p: 39.4 °C.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 2H, *J*=8.6 Hz, C_6H_4–), 7.25 (d, 2H, *J*=8.6 Hz, C_6H_4–), 2.81 (sept, H, *J*=6.8 Hz, O=CC*H*–), 1.30 (d, 6H, *J*=6.8 Hz, CH_3).

4-$NO_2PhOC(O)CH(CH_3)_2$, GC/MS (*m*/*z*; EI): 209 (M^+), 138 ($M^+-C_4H_7O$), 122 ($M^+-C_4H_7O_2$), 92 ($M^+-C_2H_3NO_3$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).

4.7.11. (***k***)[26] ***Ester 11 (dimethylbenzyl acetate)***: *colorless liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 4H, C_6H_5–), 7.28 (t, H, *J*=6.8 Hz, C_6H_5–), 2.07 (s, 3H, CH_3), 1.82 (s, 6H, CH_3).

$PhCH(CH_3)_2OC(O)CH_3$, GC/MS (*m*/*z*; EI): 178 (M^+), 135 ($M^+-C_2H_3O$), 119 ($M^+-C_2H_3O_2$), 91 ($M^+-C_4H_7O_2$), 77 ($M^+-C_5H_9O_2$), 43 ($C_2H_3O^+$).

4.7.12. (***l***)[26] ***Ester 12 (dimethylbenzyl isobutyrate)***: *pale yellow solid, m.p: 72.4 °C.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 4H, C_6H_5–), 7.27 (t, H, *J*=6.8 Hz, C_6H_5–), 2.57 (sept, H, *J*=6.8 Hz, O=CC*H*–), 1.81 (s, 6H, CH_3), 1.20 (d, 6H, *J*=6.8 Hz, CH_3).

$PhCH(CH_3)_2OC(O)CH(CH_3)_2$, GC/MS (*m*/*z*; EI): 206 (M^+), 135 ($M^+-C_4H_7O$), 119 ($M^+-C_4H_7O_2$), 91 ($M^+-|-C_6H_{11}O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).

4.7.13. (***m***) ***Ester 13 (3-pyridinylmethyl acetate)***: *pale yellow liquid.* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, H, C_5H_4N–), 8.48 (d, H, *J*=4.3 Hz, C_5H_4N–), 7.60 (d, H, *J*=7.9 Hz, C_5H_4N–), 7.20 (dd, H, *J*=7.3 Hz and 4.9 Hz, C_5H_4N–), 5.02 (s, 2H, CH_2OC=O), 1.99 (s, 3H, O=CCH_3).

$C_5H_4NCH_2OCOCH_3$, GC/MS (*m*/*z*; EI): 151 (M^+), 108 ($M^+-C_2H_3O$), 92 ($M^+-C_2H_3O_2$), 78 ($M^+-C_3H_5O_2$), 43 ($C_2H_3O^+$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.073.

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