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Short Communication

Fluorous 4-*N*,*N*-dimethylaminopyridium iodide: Recyclable organocatalysts by precipitation for acylation reaction at room temperature

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ABSTRACT

A novel fluorous DMAP quaternary ammonium iodide salt organocatalyst was prepared. This fluorous organocatalyst was successfully employed to the acylation reaction at room temperature without the use of a stoichiometric amount of external base. It could be recovered 3 times from the reaction mixture by simple precipitation with excellent purity for direct reuse.

1. Introduction

Compared with the traditional metal-based catalyst, organocatalyst has drawn much attention, owing to its low toxicity, operational simplicity and high efficiency [1,2]. However, the major disadvantages of organocatalysts are high loading (up to 20 mol%) and difficulty of reusing. The recyclability of organocatalysts are of prime interest for the development of sustainable synthetic processes [3–5].

DMAP (4-*N*,*N*-Dimethylaminopyridine) is a very effective nucleophilic base catalyst for the acylation of alcohols with acid anhydrides and other related reactions [6–11]. Unfortunately, this powerful organocatalyst exhibit acute dermal toxicity [7]. To avoid this drawback, various recyclable DMAP have been prepared through immobilization on organic or inorganic supports [12].

Recently, fluorous technology has emerged as a new and powerful protocol to recover and reuse catalyst [13–18]. This strategy originally involved fluorous solvents [19] or silica gel [20], but the current trend tends toward simple solubility modulation of fluorous catalysts in conventional media, for recovery through precipitation [21–24]. Many fluorous compounds tagged with one or two "R_{f8}" and "R_{f10}" ponytail have little or no solubility in non-polar organic solvent such as octane and hexane [25]. The strategy of recycling catalyst through precipitation can be achieved by making organocatalyst bear a light fluorinated ponytail when using proper non-polar organic solvent as reaction media or as extraction reagent. Legros group reported the preparation of analogues of DMAP (**1**, Scheme 1) tagged with fluorous chains for the acylation reaction in 2008 [26]. Quite recently, they prepared fluorous carboxylate of DMAP (**2**, Scheme 1) as an active and recyclable acylation catalyst in the absence of Et_3N [27]. Herein, we report a novel fluorous DMAP quaternary ammonium salt (**3**, Scheme 1) as an efficient organocatalyst for the acylation reaction of alcohols with anhydrides at room temperature without the use of a stoichiometric amount of external base, such as Et_3N and *i*-Pr_2NEt.

2. Results and discussions

The fluorous DMAP quaternary ammonium iodide salts were prepared by simply mixing amine with perfluoroalkyl iodide [28]. The reaction of $R_{f8}I$ did not give the corresponding quaternary ammonium salts, and starting material was recovered (Scheme 2). Two fluorous DMAP quaternary ammonium solids **3a** ($R_f = C_6F_{13}C_2H_4$) and **3b** ($R_f = C_8F_{17}C_2H_4$) were obtained respectively from $R_{f6}CH_2CH_2I$, and $R_{f8}CH_2CH_2I$ perfluoroalkyl iodides, which have two methylene spacer avoiding excessive electronic and steric perturbations (Scheme 2). Based on the MS spectrometry, ^1H NMR, ^{13}C NMR and IR, it can be concluded that the fluorous 4-*N*,*N*-dimethylaminopyridine quaternary ammonium iodide salts were formed. Having the particular solubility of perfluorinated molecules, fluorous DMAP quaternary ammonium iodide salts **3a** and **3b** are different from DMAP and traditional quaternary ammonium iodide salts, and show no solubility in H_2O and AcOH. The fluorous DMAP salts have much less solubility in fluorous solvents (PFCs) such as perfluorohexane (C_6F_{14}, FC-72), perfluorooctane (C_8F_{18}, FC-77), and methoxy-nonafluorobutane ($C_4F_9OCH_3$, HFE-7100). They

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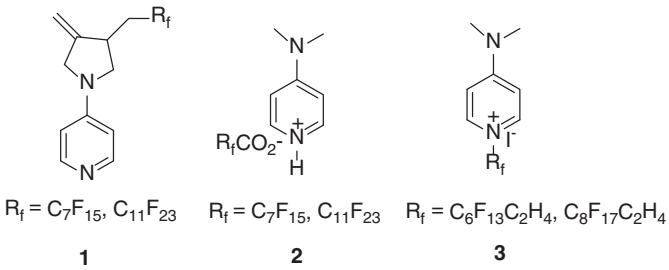
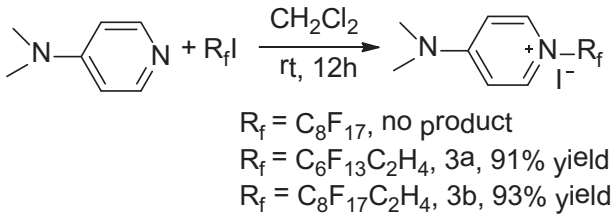


Scheme 1. Fluorous DMAPs and derivatives.



Scheme 2. Synthesis of fluorous DMAP iodide salts.

always appeared not to be soluble in non-polar solvents, such as hexane and octane. These fluorous salts could be solubilized in MeOH, EtOH and benzyl alcohol, which can offer an appropriate reaction medium for acylation of alcohol.

Initially, the reaction conditions for the acylation of benzyl alcohol and acetic anhydride were investigated (Table 1). The control experiment elucidated that only trace of acylation product could be obtained. DMAP/Et_3N and DMAP/*i*-Pr_2NEt systems (Entry 2, 3) afforded benzyl acetate in high yield in short time. DMAP itself, under auxiliary base- and solvent-free conditions, catalyzed the reaction to produce acylation product in 91% yield after 24 h (Entry 6). This might be attributed to the higher concentration, which leads to a polar reaction system [29,30]. It was found that 10 mol% catalyst loading is enough to promote the acylation at room temperature in neat condition without Et_3N (Entry 7, 8) [31].

Attempts were made to recycle the catalyst. When the reaction was finished, hexane was added to extract the organic compounds. Based on the ^{19}F NMR, no loss of fluorous DMAP to the organic extraction can be detected. The GC-MS of the organic phase showed that the reactions gave pure products. Importantly, reuse of the precipitated fluorous DMAP was equally effective without purification. For example, the yields of acylation using **3b** as catalyst from the first run to the third run were 98%, 97%, and 94%, respectively (Fig. 1). By calculating weight and detecting IR, ^{19}F NMR and ^{1}H NMR, we found that the catalyst was recovered in 93% yield and in 99% purity (Fig. 1). Iodide anion was proposed to play the key role in this system, which has been reported as catalyst for acylation reaction [32]. The free DMAP cannot be easy generated because ammonium salts of DMAP with an alkyl halide are highly stable. So, DMAP cation should not be a catalyst in this case.

To explore the generality and scope of **3b**-catalyzed acylation under auxiliary base- and solvent-free conditions, the reaction was examined with various alcohols and acetic anhydrides (Table 2). Acylations of primary and secondary alcohols proceeded well. Benzolic alcohols with various substitutions such as Me- and NO_2- and aliphatic alcohols gave the corresponding esters in above 90% yield. Secondary alcohols such as isopropyl alcohol and cyclohexanol reacted with acetic anhydride to get acylation product in 95% and 92% yields respectively. Finally, the **3b**-catalyzed acylation of benzyl alcohol with acetic anhydride was performed on a 10 g scale. After 24 h, hexane was used to extract product ester and acetic acid. The acetic acid was collected for experimental use. The catalyst was precipitated and fully recovered. The hexane phase was distilled to afford ester in 92% isolated yield.

3. Conclusions

In summary, a readily accessible and recyclable fluorous DMAP iodide organocatalyst has been developed for the acylation reaction of alcohols with anhydrides at room temperature. The reaction can be carried out under auxiliary base- and solvent-free conditions, and the fluorous catalyst can be recovered from the reaction mixture by simple precipitation. The strategy provides a choice for practical esterification.

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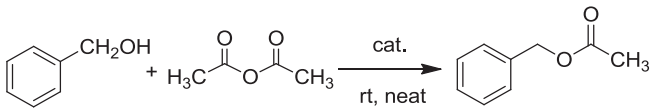
Table 1
Acylation of benzyl alcohol with acetic anhydride.[a]



Entry	Catalyst	Time (h)	Yield (%)[b]
1	–	32	4
2	10 mol% DMAP, 100 mol% Et_3N	1	99 (92)
3	10 mol% DMAP, 100 mol% *i*-Pr_2NEt	1	98
4	20 mol% DMAP	2	56
5	20 mol% DMAP	8	85
6	20 mol% DMAP	24	91 (84)
7	10 mol% **3a**	24	95, 93, 90
8	10 mol% **3b**	24	98 (91), 97, 94

[a] The reaction condition: benzyl alcohol, 1 mmol; acetic anhydride, 1.1 mmol.
[b] GC yield based on benzyl alcohol. Numbers in parentheses are isolated yields.

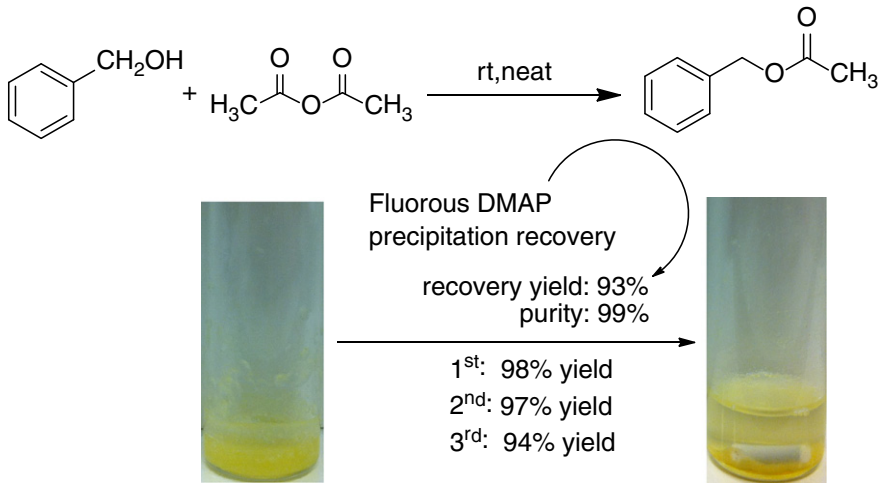
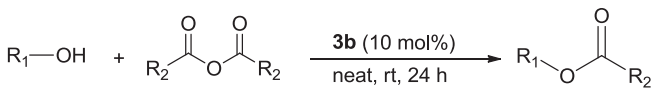


Fig. 1. Recycle of fluorous DMAP iodide salt in the acylation.

Table 2
Acylation of alcohols with acid anhydrides.[a]



Entry	R^1	R^2	Yield (%)[b]
1	$PhCH_2$	*i*-Pr	94 (89)
2	4-CH_3-$PhCH_2$	Me	96 (88)
3	4-CH_3-$PhCH_2$	*i*-Pr	93 (85)
4	4-NO_2-$PhCH_2$	Me	99 (93)
5	4-NO_2-$PhCH_2$	*i*-Pr	92 (86)
6	$CH_3(CH_2)_3$	Me	99 (92)
7	$CH_3(CH_2)_3$	*i*-Pr	96 (87)
8	$CH_3(CH_2)_7$	Me	92 (84)
9	*i*-Pr	Me	95 (87)
10	$(CH_2)_6$	Me	92 (81)
11	$(CH_2)_6$	*i*-Pr	96 (89)

[a] The reaction condition: alcohol, 1 mmol; acid anhydride, 1.1 mmol.
[b] GC yield based on benzyl alcohol. Numbers in parentheses are isolated yields.

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[28] Typical procedure for the preparation of fluorous DMAP **3b**: The DMAP (1.22 g, 10 mmol) was slowly added to a solution of $R_{f8}CH_2CH_2I$ (5.74 g, 10 mmol) in CH_2Cl_2. After being stirred for 12 h, the mixture was concentrated and then washed with *n*-hexane. After filtration, product was dried in vacuo at 50 °C for 8 h to give yellowlish solid (6.47 g, 93%). Melting point: 154–156 °C, ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.67–2.77 (m, 2H), 3.00 (s, 6H), 3.23–3.27 (m, 2H), 6.50 (s, 2H), 8.25 (s, 2H); ^{19}F NMR δ −60.6 (2 F), −80.7 (3 F), −113.2 (2 F), −120.9 (2 F), −121.8 (2 F), −122.0 (2 F), −122.6 (2 F), −126.1 (2 F); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.1, 148.8, 118.6–105.7 (m), 38.0, 35.4; IR υ 2933(–CH_2), 2359, 1649 (C–C), 1079–1197 (–CF_3 and –CF_2), 1055 (C–N cm^{-1}); MS (EI, 70 eV) m/z : 568.8 (M^+-I), MS (ACPI) m/z : 569.1 (M^+-I).
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[31] Typical procedure for fluorous DMAP **3b** catalyzed acylation: A sealed tube was charged with fluorous DMAP 3b (69.6 mg, 0.1 mmol), benzyl alcohol (108 mg, 1 mmol), and Ac_2O (113 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 24 h. Hexane (4 mL) was added, and the stirring was maintained for 10 min. After decantation, the hexane phase was removed, and the remaining catalyst (yellowish paste) can be reused for a further catalysis. The acylation product contained in the hexane phase was purified by distillation to afford 136 mg of benzyl acetate (91% yield).
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