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Fluorous analogues of DMAP (F-DMAP): Reusable organocatalysts for acylation reaction

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ABSTRACT

A short and facile preparation of analogues of DMAP (F-DMAPs) labelled with fluorous chains is reported. These catalysts efficiently promote the acylation of alcohols with anhydrides (Ac_2O, $(i\text{-}PrCO)_2O$) and can be partially recovered and reused. The effectiveness of F-DMAP is similar to that of DMAP.

1. Introduction

Since the pioneer work of Litvinenko and Kirichenko, followed by Steglich, in the late 1960s [1], DMAP (4-(dimethylamino)pyridine) has been widely used as organocatalyst for synthetic transformations [2]. One of the most striking effect of DMAP is exhibited in the acylation reaction of poorly reactive alcohols with carboxylic anhydrides for which catalytic amounts of this organocatalyst cause great rate accelerations [3,4]. However, due to its acute toxicity [5] the search for recyclable analogues is of great interest. For this purpose, various derivatives of DMAP have been supported on organic [6] as well as on inorganic supports [7], and used as recoverable catalysts [8]. In this connection, tagging DMAP with fluorous ponytails could represent a very attractive alternative to common supporting methods [9,10]. Indeed, fluorous compounds can often be easily removed from an organic mixture by various methods: liquid–liquid extraction [11], solid phase extraction (SPE) [12], or even precipitation [13]. Herein, we report the synthesis of fluorous analogues of DMAP (F-DMAP) and their application in the acylation reaction of alcohols with anhydrides.

2. Results and discussion

Many studies have been devoted to the structural effects of DMAP and its derivatives on their catalytic properties. From these reports, two major facts can be underlined: the lone pair of the amino moiety at C-4 of the pyridine ring plays a decisive role [3], and the sites C-2 have to be non-substituted [4]. Considering that fluoroalkyl groups are bulky and electron withdrawing, grafting the fluorous ponytails on the amino group with an adequate spacer seems to be the best design for efficient fluorous analogues of DMAP. It is generally admitted that a two- to three-methylene spacer avoids excessive electronic and steric perturbations, while keeping fluorophilicity properties [14]. Our first idea was thus to react 4-aminopyridine **1** with $C_6F_{13}(CH_2)_2I$, both commercially available (Scheme 1, path (a)).

However in the substrate **1**, the NH_2 moiety is poorly reactive while the nitrogen atom of the pyridine is more nucleophilic and a mixture of alkylated products was obtained. However, attempts to use selective protection methods remained also unsuccessful. We then turned to another strategy by using the 4-(diallylamino)pyridine **2** as an easily accessible starting material [15]: we reasoned that one perfluoroalkyl chain could be added onto both double bonds of **2** through a radical path (Scheme 1, path (b)) [16]. When placed in presence of perfluoroalkyl iodide (C_4F_9I or $C_8F_{17}I$) and sodium dithionite under basic conditions, the 4-(diallylamino)-pyridine **2** was completely converted as shown by NMR analyses [17]. Surprisingly, instead of the expected products resulting from

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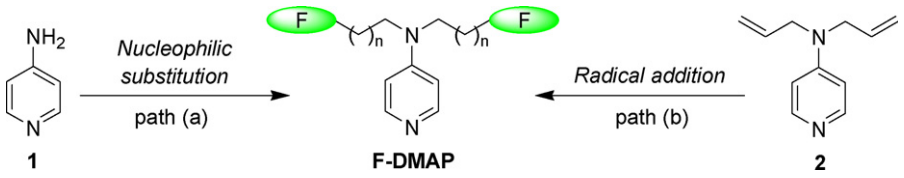
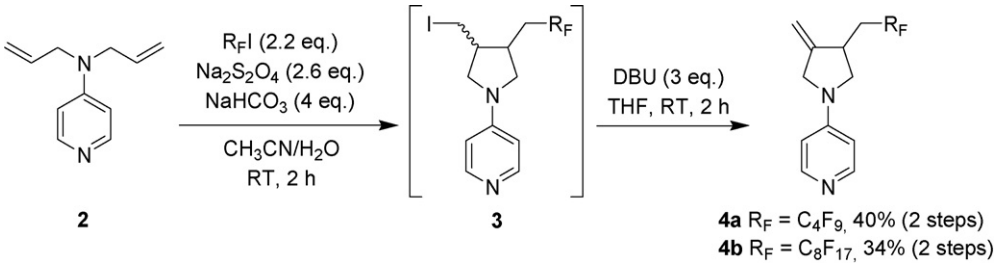


Scheme 1.



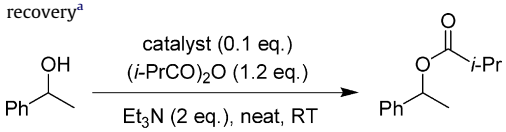
Scheme 2.

a di-addition of R_FI, the cyclic products **3** was formed. These latter probably come from the monoaddition of R_FI onto one of the double bond, and the resulting compound undergoes further cyclisation to afford the pyrrolidino derivative. The crude products **3a** and **3b** [18] are then submitted to dehydrohalogenation in presence of DBU [19], to yield F-DMAP **4a** and **4b** (40% and 34% yield, respectively; Scheme 2). While the obtained products **4a** and **4b** are structurally different from those initially designed, they fit with our requirements (site of grafting and spacer). Moreover, 4-pyrrolidinopyridine itself (PPY) is also known as a very effective acylation catalyst [20].

Having in hands our F-DMAPs **4a** and **4b**, we tested their potential as catalyst in the acylation of phenyl ethanol with the sterically hindered isobutyric anhydride under neat conditions [6a]. Results are presented in Table 1.

As expected from the structure of our compounds, 10 mol% of **4a** or **4b** is largely enough to promote the acylation in a very short reaction time: after only 15 min, more than 98% conversion were obtained (entries 1 and 4). Comparison with DMAP afforded similar results, while the conversion was extremely low without any catalyst (5% conversion after 15 min and almost no evolution after 1 h). Besides their intrinsic catalytic power the efficiency of F-DMAPs is also due to their partial miscibility in the reaction mixture, allowing the reaction to proceed almost under homogeneous conditions. The following point to be assessed was the recovery and recycling of F-DMAPs. Despite the acceptable fluorine content of our F-DMAP catalysts (%*F* = 44% for **4a**, and 55% for **4b**), they are completely insoluble in fluorous solvents (perfluoromethylcyclohexane, perfluorodecaline), probably due to their high polarity, precluding thus the use of liquid extraction for recovery

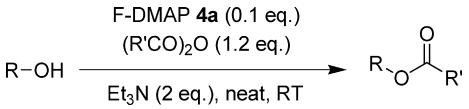
Table 1
Assessment of F-DMAPs **4** in the acylation of phenylethanol with $(i\text{-PrCO})_2O$ and recovery[a]

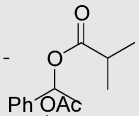
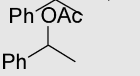
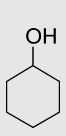
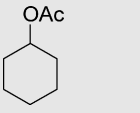
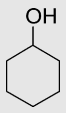
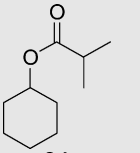
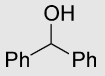
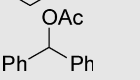
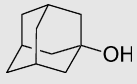
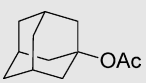


Entry	Catalyst	Run	Conversion (%)[b]
1	**4a**	1	>98
2		2	80
3		3	45
4	**4b**	1	>98
5		2	75
6		3	47
7	DMAP	–	>98
8	No catalyst	–	5

[a] Reactions performed on a 1-mmol scale of substrate.
[b] Monitored by GC. Only the acylation product was obtained.

Table 2
Acylation of alcohols with F-DMAP **4a** with isobutyric and acetic anhydrides[a]



Entry	Alcohol	R′	Time (h)	Product	Conversion (%)[b]	Yield (%)
1		*i*-Pr	0.4		>98	85
2		CH_3	0.4		>98	90
3		CH_3	0.4		>98	75
4		*i*-Pr	0.4		>98	82
5		CH_3	0.4		95	–
6[c]		CH_3	6.0		43	–

[a] Reactions performed on a 1-mmol scale of substrate.
[b] Monitored by GC. Only the acylation product was obtained.
[c] 2 eq. of Ac_2O and 3 eq. of Et_3N were used.

[21]. However, the addition of *n*-hexane to the reaction mixture caused a partial precipitation of the catalysts (*ca.* 60%). After removal of the hexane phase (containing the organic products), the remaining catalyst was reused. Unfortunately, the second run showed a significant drop in the reactivity for both catalysts (80% and 75% conversion with **4a** and **4b**, respectively), and even more at the third run (*ca.* 45%), as shown in entries 2–3 and 5–6.

Nevertheless F-DMAP **4a** was successfully used in the acylation of various alcohols (secondary and tertiary) with isobutyric and acetic anhydrides (Table 2). Like phenyl ethanol (entries 1 and 2), cyclohexanol (entries 3 and 4) and diphenyl methanol (entry 5) reacted remarkably fast with both anhydrides (15 min) to afford the corresponding esters. More sluggish is the acetylation of the tertiary alcohol 1-adamantanol with only 43% conversion after 6 h (entry 6). However, it is worth noting that it has been reported that the use of DMAP as catalyst for this later reaction gave similar results under closed reaction conditions (45% conversion after 5.2 h) [4a].

3. Conclusions

In summary, we have designed and synthesized fluorous analogues of DMAP (F-DMAPs). When used as catalysts to promote acylation reaction of alcohols with anhydrides, F-DMAPs exhibit an excellent effectiveness similar to that of the original DMAP. However, these catalysts are not yet conveniently recycled. This latter point could be improved by using fluorous silica gel for solid-phase extraction, or by increasing the fluorophilicity of the catalyst through the grafting of a second fluoroalkyl chain on the double bond. This work is currently in progress and will be reported in due course.

4. Experimental

4.1. Synthesis of F-DMAP 4a: typical procedure

A 250-mL flask was loaded with a solution of 4-(diallylamino)pyridine **2** [15] (1.0 g, 5.75 mmol) in a mixture of CH_3CN/H_2O (25:15 mL). To this solution, were successively added C_4F_9I (4.37 g, 12.64 mmol), $Na_2S_2O_4$ (2.6 g, 14.94 mmol) and $NaHCO_3$ (1.9 g, 23.0 mmol), and the mixture was vigorously stirred. After 2 h, brine was added (100 mL) to the reaction mixture, and it was extracted with AcOEt (3 × 200 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents were removed in vacuo. The crude residue **3a** (orange paste, 1.79 g) was then dissolved in THF (20 mL) and DBU (1.57 g, 10.35 mmol) was added. After stirring for 2 h, the reaction mixture was filtered and the solvent was eliminated in vacuo. The residue was then purified by flash chromatography over silica gel neutralized with Et_3N (CH_2Cl_2/MeOH, 85:15) to afford F-DMAP **4a** as a dark brown paste (0.95 g, 40% over 2 steps).

^{19}F NMR (acetone *d*-6, 188 MHz) δ −81.10 (tt, J = 3.2 Hz, J = 9.5 Hz, 3F), −112.7 (m, 2F), −124.0 (m, 2F), −125.7 (m, 2F); ^1H NMR (acetone *d*-6, 200 MHz) δ 3.26 (m, 4H), 4.02 (m, 3H), 5.25 (m, 2H), 6.55 (d, J = 6.3 Hz, 2H), 8.18 (d, J = 6.3 Hz, 2H); ^{13C}NMR (acetone *d*-6, 75 MHz) δ 34.17 (t, $^2J_{C-F}$ = 21 Hz, CH_2CF_2), 37.0 (CH), 53.1 (CH_2), 54.4 (CH_2), 108.7 (C=CH_2), 109.1 (CH), 106.5–125.6 (m, C_4F_9), 148.8 (C), 150.7 (CH), 153.7 (C); APCI *m*/*z* (rel. int.): 393 $[M+H]^+$ (100).

4.2. F-DMAP 4b

The same procedure was followed but starting from $C_8F_{17}I$ (12.64 mmol, 6.90 g). The product **4b** was obtained as a black paste (34% yield over 2 steps).

^{19}F NMR (acetone *d*-6, 188 MHz) δ −81.10 (tt, J = 2.0 Hz, J = 10.1 Hz, 3F), −112.5 (m, 2F), −121.8 (m, 6F), −122.5 (m, 2F), −123.0 (m, 2F), −126.2 (m, 2F); ^1H NMR (acetone *d*-6, 200 MHz) δ 3.28 (m, 4H), 4.10 (m, 3H), 5.25 (m, 2H), 6.55 (d, J = 6.3 Hz, 2H), 8.20 (d, J = 6.3 Hz, 2H); ^{13C}NMR (acetone *d*-6, 75 MHz) δ 34.18 (t, $^2J_{C-F}$ = 21 Hz, CH_2CF_2), 37.2 (CH), 53.1 (CH_2), 54.3 (CH_2), 108.7 (C=CH_2), 109.2 (CH), 106.0–128.0 (m, C_8F_{17}), 148.9 (C), 150.7 (CH), 153.8 (C); APCI *m*/*z* (rel. int.): 593 $[M+H]^+$ (100).

4.3. Acylation of phenyl ethanol with isobutyric anhydride catalysed by F-DMAP 4a: typical procedure

A test tube was charged with F-DMAP **4a** (39 mg, 0.1 mmol), and phenyl ethanol (122 mg, 1 mmol), Et_3N (202 mg, 2 mmol) and $(i\text{-PrCO})_2O$ (190 mg, 1.2 mmol) were successively added. After 15 min stirring, *n*-hexane was added to the reaction mixture (4 mL) and stirring was maintained for 10 min. After decantation, the hexane phase was removed, and the remaining catalyst (brown paste) can be reused for a further catalysis. The acylation product contained in the hexane phase was purified by chromatography over silica gel (cyclohexane/AcOEt, 90:10) to afford 163 mg of isobutyric acid 1-phenyl ethyl ester (85% yield).

^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (d, J = 6.9 Hz, 6H), 1.52 (d, J = 6.6, 3H), 2.56 (sept, J = 6.9 Hz, 1H), 5.87 (q, J = 6.6, 1H), 7.22–7.36 (m, 5H) [22].

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[18] The addition products **3a** and **3b** have not been isolated and fully characterized. Their structures have been assumed from that of dehydrohalogenation products **4a** and **4b**.
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