Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 22 Aug 2006.

To cite this article: Michael S. Wolfe (1997) N-Benzoyl-4-(dimethylamino)pyridinium Chloride: Isolation and Use for the Direct Benzoylation of Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:17, 2975-2984, DOI: 10.1080/00397919708005004

To link to this article: http://dx.doi.org/10.1080/00397919708005004

SYNTHETIC COMMUNICATIONS, 27(17), 2975-2984 (1997)

N-BENZOYL-4-(DIMETHYLAMINO)PYRIDINIUM CHLORIDE: ISOLATION AND USE FOR THE DIRECT BENZOYLATION OF ALCOHOLS

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Abstract. A simple method for the formation and isolation of *N*-benzoyl-4-(dimethylamino)pyridinium chloride is described. This reagent can be employed directly for the benzoylation of secondary and tertiary alcohols.

Dimethylaminopyridine (DMAP) is a common catalyst employed in the acylation of alcohols by acyl chlorides.[1] The *N*-acylpyridinium species **1** (scheme 1) is the reactive intermediate in this process,[2] and such species have been prepared and purified, usually using weak counterions (e.g., tetrafluoroborate).[3] During the course of optimizing conditions for the benzoylation of a hindered alcohol, we happened upon a simple, convenient procedure for the formation and isolation of

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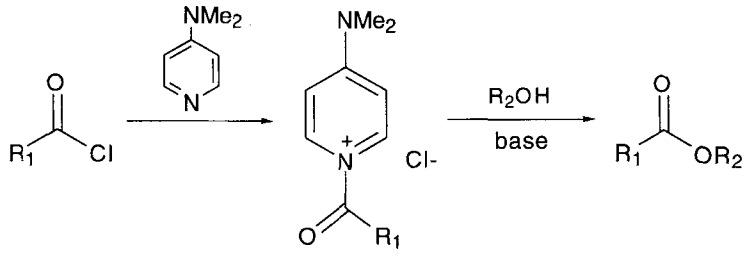
N-benzoyl-4-(dimethylamino)pyridinium chloride (**1**, R_1 = Ph). Herein, we report this procedure and the use of **1** for the direct benzoylation of secondary and tertiary alcohols.

Scheme 1

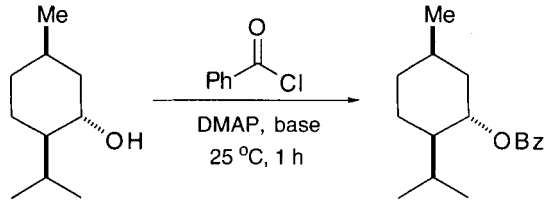


1

We found that excess triethylamine with 1.2 equivalents of benzoyl chloride and a full equivalent of DMAP allowed for the rapid benzoylation of isomenthol (table 1, entry 3). With no Et_3N (entry 1) or with one equivalent of Et_3N (entry 2), benzoylation did not occur. The use of a full equivalent of DMAP was essential for the rapid benzoylation (entries 4 and 5). Pyridine, typically used in benzoylation reactions via benzoyl chloride, was not nearly as effective as Et_3N (entry 6) and the polar aprotic acetonitrile was not as effective as a solvent as methylene chloride (entry 7).

When the benzoylation was attempted as in entry 3 only under more concentrated conditions, the reaction gave unpredictable results, with a white crystalline material forming within minutes. Further investigation revealed that this material would form even in the absence of an alcohol. Filtration and

Table 1. Effect of base, DMAP, and solvent on the benzoylation of isomenthol.



entry	equiv. base	equiv. DMAP	solvent	yield*
1	---	1.0	CH_2Cl_2	<2%
2	1.0 Et_3N	1.0	CH_2Cl_2	<2%
3	xs Et_3N	1.0	CH_2Cl_2	95%
4	xs Et_3N	---	CH_2Cl_2	<2%
5	xs Et_3N	0.1	CH_2Cl_2	<2%
6	xs pyridine	1.0	CH_2Cl_2	35%
7	xs Et_3N	1.0	AcN	81%

*Purified yield after silica gel chromatography.

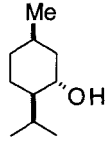
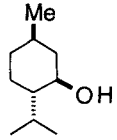
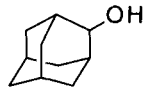
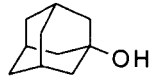
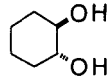
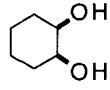
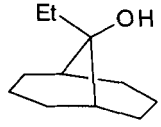
washing provided material that was spectroscopically consistent with 1 in 95% yield. Apparently, the only role Et_3N plays in the isolation of 1 is to drive its precipitation: 1 is formed just as readily in the absence of Et_3N, and THF can substitute for Et_3N to precipitate the product (see experimental section). It should be mentioned that while the chloride salts of such acylammonium compounds have been reported to be susceptible to thermal decomposition[3] and to be extremely

hygroscopic, we have found that if **1** is immediately dried under vacuum upon isolation, it can be readily handled for NMR analysis and for synthetic purposes (vide infra).

The ^{1}H- and ^{13}C-NMR spectra of **1** is consistent with the notion that its preferred solution conformation in $CDCl_3$ possesses a plane of symmetry perpendicular to the pyridinium ring: the two methyl groups are magnetically equivalent in both the ^{1}H- and ^{13}C-NMR spectra; also, the pyridinium C-2 and C-6 nuclei appear as a single peak, as do C-3 and C-5. Apparently, the carbonyl group is out of the plane of the pyridinium ring; this type of conformation has been observed in the x-ray crystal structure of the corresponding tetraphenylborate salt of **1**.[3]

When isomenthol was treated with 1.2 equivalents of **1** with excess Et_3N in methylene chloride for 1 h, the benzoylated product was isolated in 92% yield (table 2, entry 1), a yield comparable to that observed when **1** is generated under "in situ" condition (i.e., table 1, entry 3). This result both confirmed the structural assignment of **1** and demonstrated that this compound can be used directly for the benzoylation of alcohols. While isomenthol was readily benzoylated, menthol is apparently more sterically hindered and did not react under either set of conditions (entry 2). Likewise, the secondary alcohol 2-adamantanol was easily esterified (entry 3), while the tertiary alcohol 1-adamantanol did not react (entry 4). Both *trans*-1,2-cyclohexanediol (entry 5) and *cis*-1,2-cyclohexanediol (entry 6) were diesterified in high yield within

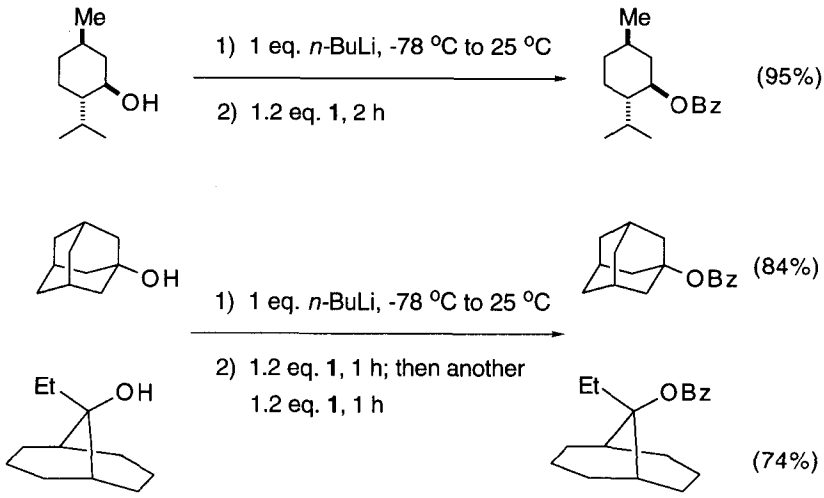
Table 2. Comparison of benzoylation of alcohols via **1** generated *in situ* or added directly.

Entry		In situ generation[a] (% yield[c])	Direct addition[b] (% yield[c])
1		95	92
2		N.R.	N.R.
3		91[d]	88[d]
4		N.R.	N.R.
5		93	93
6		99	98
7		N.R.	N.R.

[a] Conditions as in Table 1, entry 3. [b] 1.2 equiv. of **1** per hydroxyl group used instead of BzCl and DMAP. [c] Purified yield after chromatography. [d] Reaction time 2h.

1 hour, but the tertiary alcohol 9-ethyl[3.3.1]bicyclononan-9-ol was not reactive (entry 7).

Scheme 2



The unreactive alcohols (menthol, 1-adamantanol, 9-ethyl[3.3.1]bicyclononan-9-ol) underwent facile benzoylation by 1 if these alcohols were first converted to their corresponding lithium alkoxides (scheme 2). The two tertiary alcohols required the addition of another 1.2 equivalents of 1 to obtain a respectable yield. Nevertheless, this is notable since the benzoylation of hindered alcohols, particularly tertiary alcohols, has proven difficult, with special reagents[4,5] or high pressure[6] often being necessary. The yields in scheme 2 are comparable to those reported with these other reagents: benzoic anhydride and superbase $P(MeNCH_2CH_2)_3N$ together benzoylated menthol in 92% yield,[5] and benzoyl

trifluoromethanesulfonate likewise esterified 1-adamantanol in 89% yield.[4]

Benzoylpyridinium **1** readily hydrolyzes over the course of days if it is stored on the shelf. However, when stored dessicated at -20 °C, it displayed little sign of decomposition by ^{1}H-NMR after over one year. Indeed, it still benzoylated isomenthol as did freshly prepared **1** (table 2, entry 1) in identical yield (92%).

In summary, it appears from this study that isolated **1** offered no advantage over in situ generated **1** in benzoylating unhindered secondary alcohols (table 2); however, **1** may be used directly to benzoylate hindered secondary and tertiary alcohols after alkoxide formation (scheme 2). The use of isolated **1** may also prove advantageous in special circumstances. Investigators should be aware of the ready access and use of this reagent as a viable option.

Experimental Section

DMAP was purchased from Lancaster Synthesis, Ltd. All other materials purchased from Aldrich Chemical Co. These materials were used without further purification unless otherwise noted. CH_2Cl_2 was distilled from CaH and stored over 4Å molecular sieves, THF was freshly distilled from benzophenone ketyl, Et_3N was distilled and stored over KOH pellets, and benzoyl chloride was distilled prior to use. Flash chromatography performed using silica gel 60 (EM Science, 70-230 mesh, 63-200 microns). Infrared spectra were recorded

on a Perkin-Elmer 2000 FT-IR spectrophotometer. NMR spectra were obtained on a Bruker AM-300 FT-NMR. Chemical shifts are in ppm relative to tetramethylsilane. Elemental analysis performed at Desert Analytics (Tuscon, AZ). All reactions performed under anhydrous conditions using N_2.

N-benzoyl-4-(N,N-dimethylamino)pyridinium chloride (1). To a solution of DMAP (780 mg, 6.38 mmol) in 15 mL of CH_2Cl_2 was added dropwise benzoyl chloride (0.90 mL, 1.09 g, 7.75 mmol). After 20-30 min, 20 mL of THF was added slowly, during which time crystallization ensued. After another 15-20 min, the reaction was filtered under a cone of N_2, and the solid washed with hexanes. The white powder was immediately transferred to a dessicator and placed under vacuum: 1.57 g (94%). Material made in this manner was used for the direct benzoylation of alcohols as described below. Recrystallization from CH_2Cl_2/THF under dry conditions provided highly purified **1**. ^{1}H-NMR ($CDCl_3$): 3.43 (s, 6H), 7.40-7.65 (m, 7H), 8.35 (d, J = 8 Hz, 2H); ^{13}C-NMR ($CDCl_3$): 41.7, 108.7, 128.7, 129.2, 130.2, 134.6, 137.8, 158.2, 167.0.

General procedures for the benzoylation of alcohols.

Method A. In situ generation of 1. To a solution of DMAP (78 mg, 0.64 mmol) in 5 mL of CH_2Cl_2 was added 1.0 mL of Et_3N, benzoyl chloride (0.09 mL, 0.11g, 0.78 mmol), and finally 0.64 mmol of the alcohol. After 1-2 h, the reaction mixture was taken up into 60 mL of ether and washed with 3 x 25 mL of 1N HCl, 25 mL of saturated sodium bicarbonate, and 25 mL

of saturated sodium chloride. The ether layer was dried (Na_2SO_4), filtered, concentrated, and the residue passed through a silica gel column with hexane/ethyl acetate. Compounds were characterized by ^1H- and ^{13}C-NMR; all benzoyl ester products have been previously reported[4,5,7] except for that of 9-ethyl[3.3.1]bicyclononan-9-ol, characterized in full below.

Method B. Direct addition of 1. To a solution of **1** (202 mg, 0.78 mmol) in 5 mL of CH_2Cl_2 and 1.0 mL of Et_3N was added 0.64 mmol of the alcohol. After 1-2 h, the reaction was worked up as described in Method A.

Method C. Direct addition of 1 after alkoxide formation. To a -78 °C solution of the alcohol (0.64 mmol) in 5 mL of THF was added *n*-butyllithium (1.6 M in hexanes, 0.40 mL, 0.64 mmol). The reaction mixture was allowed to warm to room temperature whereupon a solution of **1** (202 mg, 0.768 mmol) in 5 mL of CH_2Cl_2 was added over the course of several minutes. In the case of the tertiary alcohols, another 202 mg of **1** in 5 mL of CH_2Cl_2 was added after 1 h. After 2 h total reaction time, the reaction mixture was worked up as described in Method A, only 2 x 25 mL additional washes with saturated sodium bicarbonate were included to ensure complete removal of benzoic acid.

9-ethyl[3.3.1]bicyclononan-9-ol benzoate. Formed according to Method C above as a clear colorless oil after silica gel chromatography. IR (neat): 2935, 2865, 1710, 1450, 1315, 1275, 1250, 1111, 942, 710 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.86 (t, J=

7.4 Hz, 3H), 1.50-2.15 (m, 12 H), 2.35 (q, J = 7.4 Hz, 2H), 2.55 (m, 2H), 7.40-7.60 (m, 3H), 8.07 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ 6.5, 20.4, 20.8, 24.7, 28.6, 28.8, 34.6, 88.5, 128.2, 129.4, 131.9, 132.3, 165.1. Anal cald. for $C_{18}H_{24}O_2$: C 79.37, H 8.88; found: C 79.16, H 8.89.

Acknowledgment. I thank Jennifer M. Smith for technical support for this study. This work was supported by Grant #IN-176-D from the American Cancer Society and through the American Association of Colleges of Pharmacy Grant Program for New Investigators.

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(Received in the USA 21 March 1997)