Benzoyl Trifluoromethanesulphonate. A Highly Efficient Benzoylating Agent for Sterically Hindered Hydroxy Groups

Masato Koreeda* and Lindsey Brown

Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109, U.S.A.

Reactions of benzoyl trifluoromethanesulphonate (BzOTf) with a variety of alcohols, including some with sterically hindered secondary and tertiary hydroxy groups, with phenolic compounds, and with 1,2-diols at low temperatures provide the corresponding benzoates in high yield.

The availability of an efficient procedure for the protection of the hydroxy group continues to be a major concern for those involved in the multi-step synthesis of complex natural products.[1] Among the many such protecting groups that are known, the benzoyl group has become increasingly important, due to its additional use in the determination of the absolute configuration of the original hydroxy compound. Among the most notable chiroptical applications in this area are in the exciton chirality c.d. method[2] with various types of benzoates, the sector analysis of secondary benzoates,[3] and the conformational analysis of allylic benzoates.[4] Besides the standard procedure for the benzoylation of the hydroxy group using benzoyl chloride in pyridine,[1] several more reactive benzoylating agents have been reported in the literature. These include benzoyl imidazole,[5] benzoyl cyanide,[6] heptafluoro-1-methylethyl phenyl ketone,[7] and benzoyl tetrazole.[8] However, none of these reagents are generally applicable to the benzoylation of tertiary or highly congested secondary hydroxy groups, as they require high temperatures and/or prolonged reaction times. Here we describe benzoyl trifluoromethanesulphonate (benzoyl triflate, BzOTf) as a highly efficient and versatile benzoylating agent of hydroxy groups, including those in sterically hindered secondary and tertiary alcohols, in phenols, and in 1,2-diols.

BzOTf (b.p. 92—94 °C, 2.2 mmHg) can be made in *ca.* 70% yield from benzoyl chloride and trifluoromethanesulphonic acid following the procedure of Effenberger and Epple.[9] The reagent, a colourless liquid, is extremely hygroscopic and darkens rapidly upon exposure to air, but can be stored at room temp. under dry nitrogen for several months without appreciable decomposition. While the reagent has been known in the literature since 1972,[9] its use has been limited primarily to that of a benzoylating agent of aromatic compounds.[10]

The benzoylation of relatively unhindered primary and secondary hydroxy groups with BzOTf proceeds smoothly at −78 °C in dry methylene chloride within several minutes, and the resulting benzoate is usually obtained in over 95% yield. It should be noted here, however, that some highly Lewis-acid sensitive functional groups such as acetals, ketals, and epoxides undergo rapid reaction with the reagent. Both acetals and

ketals provide clean deprotected carbonyl groups upon quenching with water. In contrast, epoxides generally yield a complicated mixture of products, originating from a carbonium ion intermediate, unless this intermediate can undergo a clean rearrangement, *e.g.*, treatment of 3β,4β-dihydroxy-5β, 6β-epoxycholestane (**1**) with 4.0 mol. equiv. of BzOTf at −78 °C produces the 4-keto steroid (**2**) [reaction (1)]. The product presumably arises from the carbonium ion generated *via* epoxide opening, followed by a hydride shift from C-4 to C-5.

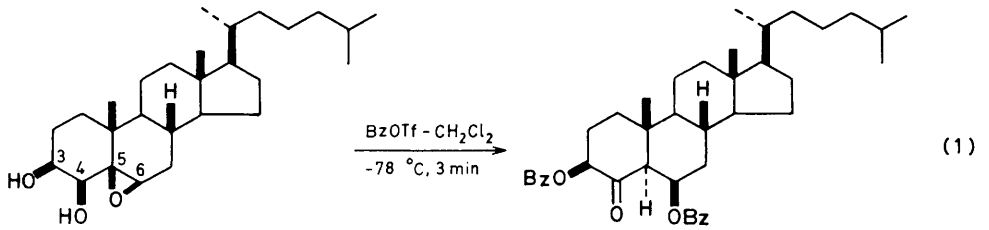
The results of the benzoylations of a number of compounds with sterically hindered secondary hydroxy groups, phenols, and groups of 1,2-diols, as well as tertiary alcohols, are summarized in Table 1. It should be pointed out that the addition of pyridine is essential for the benzoylation of tertiary alcohols. Also worth noting is that Friedel–Crafts type benzoylation is not a competing reaction with the phenolic compounds under these reaction conditions.

Typical experimental details are as follows for benzoylation of primary and secondary alcohols. To a 0.1 M solution of the alcohol in dry methylene chloride at −78 °C the appropriate amount of BzOTf is added *via* a syringe (see Table 1). When t.l.c. analysis indicates the reaction has reached completion, excess of the reagent is destroyed by addition of water (followed by aqueous work-up including dilution with ethyl acetate and washing with water, saturated sodium hydrogen carbonate, and then brine) or methanol (followed by filtration

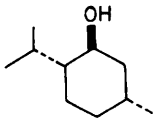
Table 1. Benzoylation of hindered hydroxy groups, phenol groups, and 1,2-diols.[a]

Alcohol	Equiv. of BzOTf per hydroxy group	Equiv. of pyridine per hydroxy group	Temp./°C (time)	Yield[b] %
(**3**)	3.0	—	−78 (1 h)	68
(**4**)	3.0	—	−78 (1 h)	77
(**5**)	5.3	—	−78 (2 h)	70
(**6**)	3.0	—	−78 (6 min)	84
(**7a**)	2.5	—	−78 (1 h)	72[c]
(**7b**)	2.5	—	−78 (1 h)	86
(**8**)	2.0	—	−78 (1.5 h)	63[d]
(**9**)	3.0	4.5	0 (30 min) then room temp. (1 h)	81
(**10**)	3.0	4.5	−78 (30 min) then room temp. (1 h)	89
cis-(**11**)	3.0	—	−78 (2.5 h)	92
trans-(**11**)	3.0	—	−78 (2.5 h)	86
(**12**)	2.0	3.5	−78 (30 min) then room temp. (1 h)	75

[a] All the reactions were carried out in methylene chloride under nitrogen. See text for general experimental procedure. [b] All yields are based on the isolated chromatographically pure material. The yields given herein are based on one or two runs and have not been optimized. All products gave satisfactory i.r., 360 MHz ^{1}H and 90.56 MHz ^{13}C n.m.r., and mass spectral data. [c] The C-3 monobenzoate was also isolated in 12% yield. [d] In addition, a mixture of 3,7- and 3,12-dibenzoates (35%) was obtained.



(1) (2), 89%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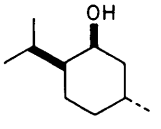
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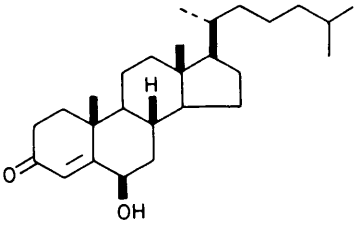
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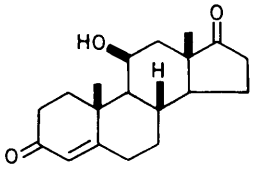
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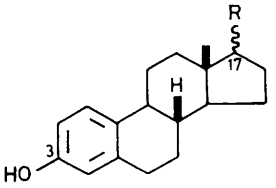
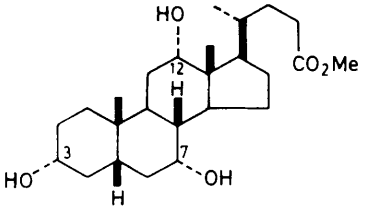

(7); a, R = β-OH
b, R = α-OH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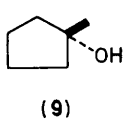
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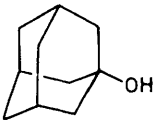
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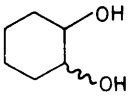
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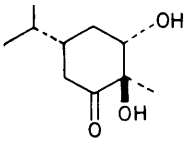
(12)

through Florisil). Chromatography yields the desired product. For benzoylation of tertiary alcohols the procedure is identical except for the addition of 1.5 equiv. of pyridine (relative to BzOTf) prior to cooling to −78 °C. After addition of BzOTf, the reaction is allowed to proceed at −78 °C for 30 min, then at room temp. for 1 h before quenching.

In conclusion, the use of readily accessible BzOTf at low temperatures provides a highly efficient and convenient means for the benzoylation of sterically hindered hydroxy groups. This method is particularly suited for complete benzoylation of polyhydroxylated natural products needed for chiroptical studies based on the exciton chirality c.d. method.

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