JOC*Note*

Synthesis of Benzyl Esters Using 2-Benzyloxy-1-methylpyridinium Triflate

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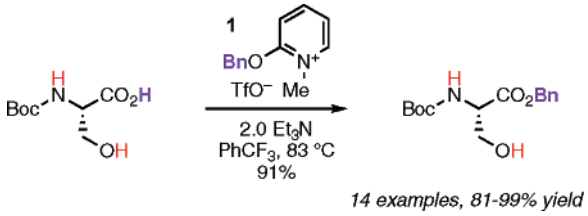
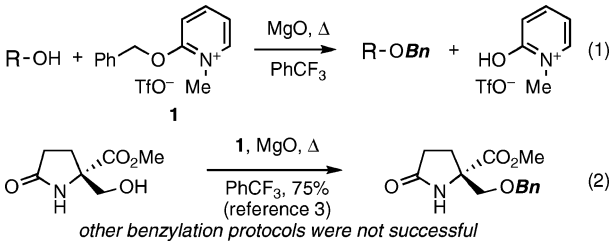


Triethylamine (Et_3N) mediates esterification reactions between the title reagent (**1**) and carboxylic acids. Alcohols, phenols, amides, and other sensitive functionality are not affected; a dual role for Et_3N as a promoter and a scavenger is postulated. Benzyl esters are obtained from substrates including amino acid and sugar derivatives.

2-Benzyloxy-1-methylpyridinium triflate[1] releases an electrophilic benzyl species upon warming. We have reported on this and related reagents[2] for alcohol etherification under mild and simple conditions (eq 1).



The title reagent is emerging as a superior method for the benzylation of alcohols. Triflate salt **1** is pre-activated, which precludes the need for strong acid or base in the reaction mixture. For example, Langlois recently described the synthesis of a benzyl ether using **1** on a substrate for which other common methods had failed (eq 2).[3]

Benzyloxypyridinium salt **1** acts as an *N*-alkyl variant of an activated benzyl trichloroacetimidate (i.e., **2a**, Figure 1). Like

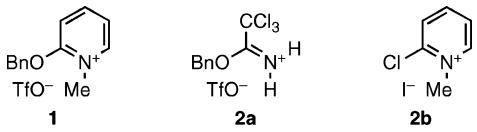
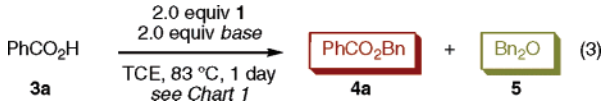


FIGURE 1. Benzyloxypyridinium salt **1**, triflic acid activated benzyl trichloroacetimidate (BTCA) **2a**, and Mukaiyama's reagent **2b**.

Mukaiyama's reagent[4] (**2b**, which influenced the design of **1**), **1** operates under nearly neutral conditions and is stable to routine storage and handling. Unlike **2b**, however, benzyloxypyridinium salt **1** does not activate carboxylic acids for acyl transfer reactions. Thus, **1** serves specifically as a benzyl transfer reagent.

This Note focuses on the use of **1** for preparing benzyl esters from carboxylic acids. The alkyl ester is a most popular choice for masking carboxylic acid groups in multistep synthesis.[5] Among common alkyl esters, benzyl esters offer the important advantage of cleavage through catalytic hydrogenolysis, in addition to hydrolysis under acidic or basic conditions.



To identify new conditions for the synthesis of benzyl esters, we began with an investigation into the simple conversion of benzoic acid into benzyl benzoate (eq 3) using 2.0 equiv[6] of **1** in trichloroethylene (TCE).[7]

As illustrated in Chart 1, an external base is not needed to promote the desired reaction. In fact, the omission of base is preferable to inclusion of magnesium oxide (MgO), which we found to be optimal for benzylation of alcohols.[1] The two most effective bases in our screening were potassium carbonate (K_2CO_3) and triethylamine (Et_3N). The highest estimated yield was obtained with K_2CO_3, whereas Et_3N completely suppressed formation of dibenzyl ether (Bn_2O).

The utility of Et_3N for the benzylation of acids using **1** stands in stark contrast to benzylation reactions of free alcohols, which are impeded by Et_3N or Hünig's base.[1] This distinction, *coupled with the complete suppression of* Bn_2O (Chart 1), suggests that Et_3N may be acting as both a weak base—to activate the carboxylic acid—and a phenylcarbenium scavenger, to block further reaction once the carboxylic acid has been consumed. We did not screen Hünig's base or any other (more expensive) trialkylamines in this study, as Et_3N left little room for improvement.

(1) (a) Poon, K. W. C.; Albiniak, P. A.; Dudley, G. B. *Org. Synth.* **2007**, *84*, 295−305. (b) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923−3927. (c) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 3142−3144.

(2) PMB transfer reagent: Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436−1437.

(3) Caubert, V.; Massé, J.; Retailleau, P.; Langlois, N. *Tetrahedron Lett.* **2007**, *48*, 381−384.

(4) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707−721.

(5) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2003.

(6) We typically employ 2.0 equiv of **1** to ensure complete conversion of the substrate under uniform conditions, although we have observed that 1.3−1.5 equiv of **1** is sufficient in many cases. For example, the isolated yield of benzyl benzoate using 1.3 equiv each of **1** and Et_3N was 93%.

(7) Our preferred solvent for benzylation reactions is trifluorotoluene ($PhCF_3$). We chose TCE for the initial screening of basic additives because (1) unlike $PhCF_3$, TCE solubilizes salt **1** at room temperature and (2) dichloromethane (DCM) and dichloroethane (DCE) were not optimal solvents for our previous studies. Due to significant environmental concerns related to the use of TCE, we continue to employ $PhCF_3$ for the majority of our efforts. $PhCF_3$, also known as benzotrifluoride or BTF, is frequently used industrially as a safer alternative to chlorinated solvents.

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CHART 1. Relative Efficiency of Various Bases for the Benzylation of Benzoic Acid According to Equation 3, as Estimated by ^{1}H NMR

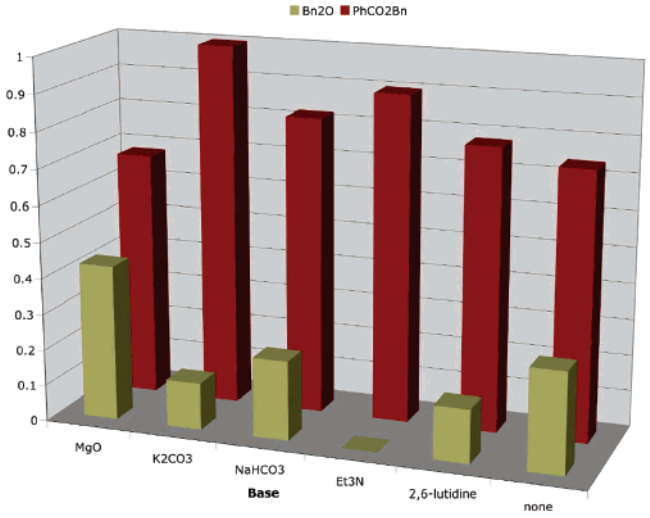
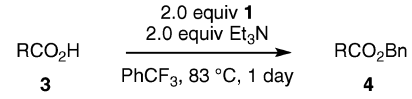
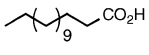
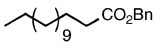
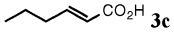
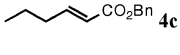
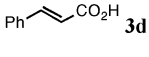
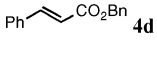
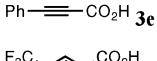
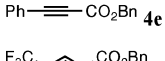
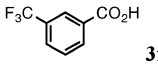
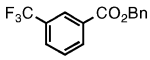
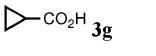
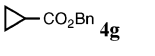
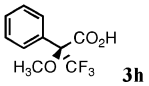
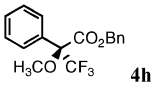


TABLE 1. Benzylation of Carboxylic Acids, Part 1[a]



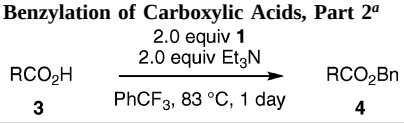
entry	RCO_2H (**3**)	RCO_2Bn (**4**)	Yield (%)
1	 **3b**	 **4b**	90
2	 **3c**	 **4c**	81
3	 **3d**	 **4d**	92
4	 **3e**	 **4e**	94
5	 **3f**	 **4f**	98
6	 **3g**	 **4g**	98
7	 **3h**	 **4h**	>99

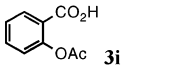
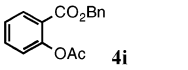
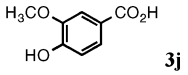
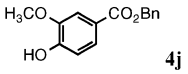
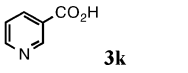
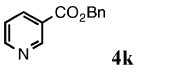
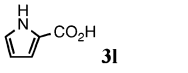
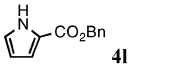
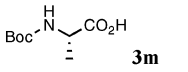
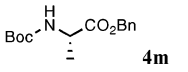
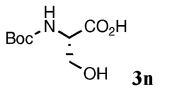
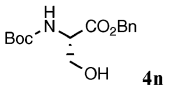
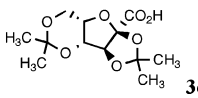
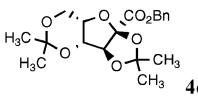
[a] Typical procedure: A mixture of carboxylic acid **3**, benzyl reagent **1** (2.0 equiv), Et_3N (2.0 equiv), and $PhCF_3$ was heated at 83 °C in a glass vial under argon for 1 day. See Supporting Information for details.

A simple collection of benzyl esters was prepared by mixing carboxylic acid substrates with 2.0 equiv each of **1** and Et_3N in $PhCF_3$[7] and then heating the resulting mixtures at 83 °C for 1 day (Table 1). A smaller excess of **1** may be employed if desired.[6] Alkyl, vinyl, alkynyl, and aryl carboxylic acids furnished the corresponding benzyl esters in good to excellent yields (81−98%, entries 1−5).[8] Cyclopropanecarboxylic acid was chosen as the alicyclic substrate to check for potential complications that might arise from the strained ring; the anticipated product was obtained in 98% yield (entry 6). Similarly, benzylation of Mosher's acid proceeded quantitatively to **4h** (entry 7), despite steric congestion at the α-carbon.

(8) Compare entry 3 (Table 1) with the reported benzylation of **3d** using benzyl trichloroacetimidate (BTCA) and $BF_3{\cdot}OEt_2$, which provide **4d** in only 60% yield: Kokotos, G.; Chiu, A. *Synthesis* **1997**, 168−170.

TABLE 2. Benzylation of Carboxylic Acids, Part 2[a]



entry	RCO_2H (**3**)	RCO_2Bn (**4**)	Yield (%)
1	 **3i**	 **4i**	92
2	 **3j**	 **4j**	91[b]
3	 **3k**	 **4k**	81[c]
4	 **3l**	 **4l**	86
5	 **3m**	 **4m**	85
6	 **3n**	 **4n**	91
7	 **3o**	 **4o**	>99

[a] Typical procedure: A mixture of carboxylic acid **3**, benzyl reagent **1** (2.0 equiv), Et_3N (2.0 equiv), and $PhCF_3$ was heated at 83 °C in a glass vial under argon for 1 day. See Supporting Information for details. [b] TCE used in place of $PhCF_3$. [c] DMF used in place of $PhCF_3$.

Substrates of greater complexity were then examined (Table 2). Benzylation of acetylsalicylic acid (aspirin, entry 1) and vanillic acid (entry 2)[9] illustrates compatibility with an acetate ester, aryl methyl ether, and free phenol. Nicotinic acid (entry 3) posed the greatest difficulty, perhaps due to poor solubility in $PhCF_3$ or TCE and/or competing N-alkylation on the pyridine ring. *N*,*N*-Dimethylformamide (DMF) provided a suitable reaction medium, and benzyl nicotinate was thus obtained in 81% yield. Conversely, benzyl esterification of pyrrole-2-carboxylic acid occurred under the standard conditions in 86% yield (entry 4).

We looked at two *N*-Boc-protected amino acids, alanine and serine. Boc-Ala-OBn was obtained in 85% yield (entry 5). Reaction with *N*-Boc-serine provided the benzyl *ester* product, Boc-Ser-OBn, in 91% yield (entry 6) with no evidence of competing benzyl *ether* formation or base-promoted elimination of the *β*-alcohol.[10,11] This result supports the idea that Et_3N acts both to promote reaction with the carboxylic acid and to suppress further reaction by quenching excess benzyl electrophiles. Benzylation of the monohydrate of (−)-2,3:4,6-di-*O*-isopropylidene-2-keto-L-gulonic acid (entry 7) proceeds in quantitative yield despite the presence of at least[12] 100 mol % of water.

Parallels can be drawn between **1** and benzyl imidates[8] or

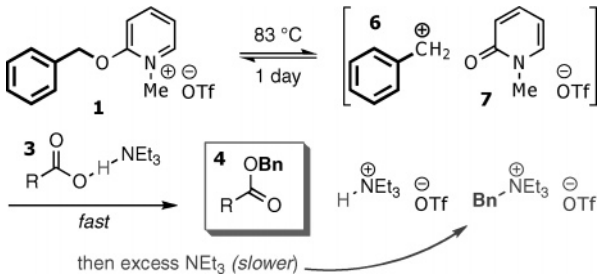
(9) Vanillic acid is poorly solubilized by $PhCF_3$, so TCE was employed.

(10) In contrast, treatment of **3n** with BTCA under reported conditions (see ref 8) resulted in general decomposition with no evidence of **4n**.

(11) We cannot exclude the possibility of base-promoted racemization events, as we have not measured the enantiomeric purity of any of the compounds reported in this paper.

(12) Anhydrous solvents, oven-dried glassware, and inert gas atmospheres were typically employed as part of routine experimental practice, but we took no special precautions in the storage and handling of salt **1** nor of the carboxylic acids, which are likely or known to be hygroscopic.

SCHEME 1. Proposed Mechanism for the Chemoselective Benzylation of Carboxylic Acids



isoureas[13] for the synthesis of benzyl esters, among which BTCA is commercially available and the most widely used. The major advantage of benzyloxypyridinium salt **1** over other imidate-type reagents is that **1** is pre-activated, whereas isoureas and imidates require activation from acidic protons.[14] 2-Benzyloxy-1-methylpyridinium triflate thus offers an immediate benefit for the benzylation of any acid-sensitive substrate. Oxypyridinium salt **1** is commercially available,[15] trivial to prepare,[1a] and stable indefinitely to storage.[1b]

This new protocol is attractive for derivatization of carboxylic acids, perhaps even as a convenient alternative to diazomethane. Although **1** was originally intended to address challenges associated with the synthesis of benzyl *ethers*, it is at least equally suitable for generating benzyl *esters*. As described above, benzylation of carboxylic acids proceeds in high yield and in the presence of alcohols, phenols, protected amines, acetals, and other functionality.

Taking into account previous mechanistic observations on the benzylation of alcohols,[1] including minor side products attributed to Friedel−Crafts-type benzylation of toluene using **1**,[1b,16] we propose that esterification reactions proceed as outlined in Scheme 1. Thermal activation of benzyloxypyridinium salt **1** provides a highly electrophilic species (**6**) that is quickly trapped by the carboxylate end of the acid−base complex **3**·NEt_3. Once the supply of complex **3**·NEt_3 is exhausted, the remaining **6** is quenched with excess triethylamine before it (**6**) can react with water, alcohols, or other functionality that may be present.

In conclusion, 2-benzyloxy-1-methylpyridinium triflate (**1**) reacts chemoselectively with carboxylic acids to provide the corresponding benzyl esters. The presumed byproducts of the reaction—pyridone **7**, Et_3N·HOTf, and $BnEt_3N^+$ TfO^-—are water soluble and are not observed after aqueous workup. As benzyl esters are among the most useful masking agents for carboxylic acids, especially amino acids, this convenient protocol will be useful for a wide range of chemical endeavors.

Experimental Section

Synthesis of Benzyl Esters. A mixture of pyridinium triflate **1** (2[6] equiv), NEt_3 (2 equiv), and carboxylic acid **3** (1 equiv) in solvent[7] (α,α,α-trifluorotoluene ($PhCF_3$), trichloroethylene (TCE), or dimethylformamide (DMF); 2 mL/mmol) was heated at 83 °C for 1 day. The resulting mixture was cooled to room temperature and then partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried ($MgSO_4$), filtered, concentrated under a vacuum, and purified on silica gel to yield benzyl ester **4**.

Benzoic Acid Benzyl Ester (4a) using 1.3 equiv of **1**. A mixture of pyridinium triflate **1** (149 mg, 0.43 mmol, 1.3 equiv), TCE (660 μL), NEt_3 (60 μL, 0.43 mmol, 1.3 equiv), and benzoic acid **(3a)** (40 mg, 0.33 mmol) was heated at 83 °C for 1 day. The reaction mixture was cooled to room temperature, diluted with H_2O (5 mL), and extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under a vacuum. The residue was purified by flash chromatography on silica gel (elution with 2:3 EtOAc/hexane) to give **4a** (65 mg, 93%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.11−8.08 (m, 2H), 7.60−7.55 (m, 1H), 7.47−7.33 (m, 7H), 5.38 (s, 2H).[17]

2-*tert*-Butoxycarbonylamino-3-hydroxy-propionic Acid Benzyl Ester (4n). A mixture of pyridinium triflate **(1)** (150 mg, 0.43 mmol), $PhCF_3$ (460 μL), NEt_3 (65 μL, 0.46 mmol), and *N*-Boc-serine **(3n)** (48 mg, 0.23 mmol) was heated at 83 °C for 1 day. Isolation and purification as above provided **4n** (61 mg, 91%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.47 (d, 1H, J = 6.8 Hz), 5.21 (s, 2H), 4.42 (bs, 1H), 3.98−3.88 (m, 2H), 2.34 (t, 1H, J = 5.9 Hz), 2.04 (s, 9H); ^{13}C NMR (75 MHz, CDCl3) δ 171.0, 156.0, 135.5, 128.8, 128.6, 128.4, 80.5, 67.6, 56.1, 28.3; IR (neat) 3371, 2977, 1716, 1506, 1455, 1068, 697 cm^{-1}; HRMS (ESI^+) calcd for $C_{15}H_{21}NO_5Na$ 318.1317, found 318.1301.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and copies of ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Nicolaou, K. C.; Yue, E. W.; Naniwa, Y.; De Riccardis, F.; Nadin, A.; Leresche, J. E.; La Greca, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2184−2187. (b) Review: Mathias, L. J. *Synthesis* **1979**, 561−576.

(14) Or Lewis acid reagents, which likely give rise to protic acid in situ.

(15) 2-Benzyloxy-1-methylpyridinium triflate [26189-59-3] is licensed, manufactured, and distributed by Sigma−Aldrich Chemical Co., catalog #679674. See (a) Dudley, G. B. Compounds and methods of arylmethylation (benzylation) as protection for alcohol groups. U. S. Patent Appl. 11/399,-300, 2006. (b) *ChemFiles* **2007**, *7* (3), 3.

(16) For Friedel−Crafts benzylation reactions using **1**, see: Albiniak, P. A.; Dudley, G. B. *Tetrahedron Lett.* **2007**, DOI: 10.1016/j.tetlet.2007.09.116.

(17) For full characterization data, see: Chen, C. T.; Munot, Y. S. *J. Org. Chem.* **2005**, *70*, 8625−8627.