Benzyl *N*-Phenyl-2,2,2-trifluoroacetimidate: A New and Stable Reagent for O-Benzylation

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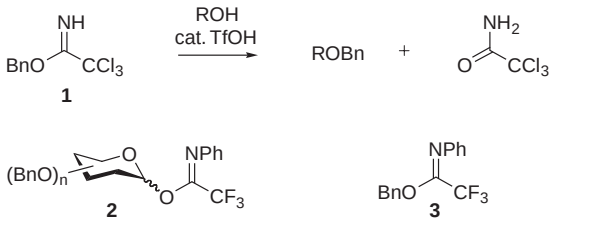
A new O-benzylation reagent, benzyl *N*-phenyl-2,2,2-trifluoroacetimidate, has been developed. It even reacts with sterically hindered alcohols and base-sensitive hydroxy esters to afford the corresponding benzyl ethers catalyzed by TMSOTf in 1,4-dioxane. This reagent was more stable than benzyl 2,2,2-trichloroacetimidate, a known benzylation reagent.

The benzyl group is one of the most indispensable protecting groups for a hydroxy group in organic synthesis, because its stability has been substantiated in numerous syntheses.[1] Among a variety of benzylations,[2] the Williamson ether synthesis, the reaction between metal alkoxides and benzyl halides, has been widely used in organic synthesis.[3] However, the alkaline reaction conditions limit the applicable substrates. Therefore, new methods for benzylation under non-basic conditions have been an important demand.

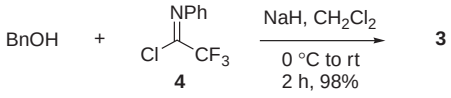
Benzyl trichloroacetimidate (**1**) is one of the reagents for benzylation under non-basic conditions (Scheme 1).[4] The reaction between **1** and a hydroxy group was catalyzed by triflic acid (TfOH) to afford benzyl ethers along with the release of trichloroacetamide.[4d,5] The trichloroacetimidate group was generally developed as a leaving group for glycosylations.[6] Recently, Yu and Tao reported a modified glycosyl imidate **2** that has *N*-phenyl-2,2,2-trifluoroacetimidate as a leaving group.[7] Thus, we expected that the *N*-phenyl-2,2,2-trifluoroacetimidate group could be diverted to a leaving group in the benzylation. We herein report a new reagent for benzylation, benzyl *N*-phenyl-2,2,2-trifluoroacetimidate (**3**), which is stable at room temperature for months and activated by acid-catalysts.

The new benzylation reagent **3** was prepared from benzyl alcohol and *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride (**4**)[8] in the presence of NaH (Scheme 2).[9] The use of neutral silica gel for the purification of **3** was important for its reproducible preparation. The compound **3** is a low viscosity liquid at 25 °C, and soluble in a wide variety of solvents.

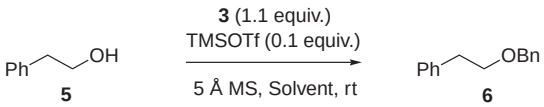
First, the optimal solvent was determined to be dimethoxyethane (DME) and 1,4-dioxane. During the investigations, 2-phenylethanol (**5**) and TMSOTf were the benzyl acceptor and the catalyst, respectively (Scheme 3). The examined solvents



Scheme 1. Benzyl trichloroacetimidate (**1**), Yu's glycosyl donor (**2**), and the new benzylation reagent **3**.



Scheme 2. Preparation of the new benzylation reagent **3**.



Scheme 3. Investigation of the optimal solvent.

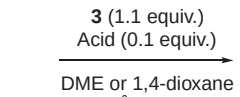
and resulting yields (in parentheses, %) of the corresponding benzyl ether **6** were as follows: CH_3CN (0), DMF (0), DMSO (0), Et_2O (24), THF (16), cyclopentylmethyl ether (trace), CH_2Cl_2 (24), DME (95), 1,4-dioxane (94), and toluene (14). Powdered 5 Å molecular sieves (MS) were added as a dehydrating agent to avoid the hydrolysis of **3** that induces the formations of benzyl alcohol and dibenzyl ether. The use of 4 Å MS decreased the reaction rate.

Next, the use of several Brønsted and Lewis acids was investigated as the catalyst (Table 1). The reactions were examined in DME and 1,4-dioxane. However, none of them afforded a better yield than with TMSOTf. In most cases, the use of 1,4-dioxane produced a better yield. In the investigations using Brønsted acids (Entries 1–4), the use of TfOH in 1,4-dioxane was effective. Among the Lewis acids, $Sn(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$ provided yields greater than 80% in 1,4-dioxane. The use of $BF_3 \cdot Et_2O$ was not effective in both of the solvents. Thus, the use of TMSOTf in 1,4-dioxane at rt was fixed as the standard condition for our further investigations.

The scope of the benzylation with **3** is as follows (Table 2). Although a reaction with phenol did not proceed (Entry 12), the reactions of the aliphatic secondary and tertiary alcohols proceeded smoothly (Entries 2–6). This method was also applicable to hydroxy esters (Entries 7–11) which benzylation is difficult under conventional basic conditions. No racemization occurred during the benzylation of ethyl (*S*)-mandelate (**14**). Thus, the non-basic O-benzylation with **3** would be expected to become an effective method in organic synthesis.

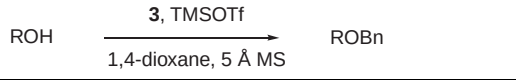
The typical procedure for the benzylation is as follows: to a stirred mixture of **3** (125 mg, 0.450 mmol), **5** (50.0 mg, 0.409 mmol), and 5 Å MS (50 mg) in 1,4-dioxane (4 mL) under an N_2 atmosphere, TMSOTf (9.1 mg, 0.041 mmol) was added. The reaction mixture was stirred for 30 min at rt, then quenched with Et_3N (30 mg). The mixture was filtered through a cotton-Celite pad to remove MS and evaporated. The resulting residue was purified by preparative TLC (stationary phase: silica-gel, eluant: 15/1 hexane/diethyl ether) to afford **6** (81.7 mg, 94%) as colorless oil.

Table 1. Benzylation of 2-phenylethanol with various acid catalysts



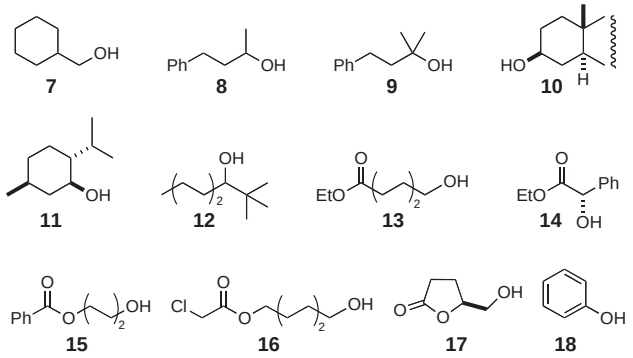
Entry	Acid	Solvent	Time /h	Yield /%
1	$HClO_4$	DME	1	52
2		1,4-dioxane	1	70
3	TfOH	DME	0.25	66
4		1,4-dioxane	0.25	88
5	$Sn(OTf)_2$	DME	0.5	68
6		1,4-dioxane	0.5	89
7	$Sc(OTf)_3$	DME	0.5	73
8		1,4-dioxane	1	83
9	$Yb(OTf)_3$	DME	1	trace
10		1,4-dioxane	1	83
11	$Cu(OTf)_2$	DME	2	27
12		1,4-dioxane	1	trace
13	$BF_3 \cdot Et_2O$	DME	—	N.R.
14		1,4-dioxane	—	N.R.

Table 2. Scope of the benzylation with **3**



Entry	ROH	Equiv. of **3**	Equiv. of cat.	Temp.	Time /h	Yield /%
1	**7**	1.5	0.3	rt	1	94
2	**8**	2.0	0.1	rt	2	92
3	**9**	5.0	0.2	rt	12	93
4	**10**[a]	1.1	0.1	rt	1.5	99
5	**11**	3.0	0.5	rt	13	95
6	**12**	2.0	0.3	60 °C	12	81
7	**13**	1.1	0.1	rt	0.5	91
8	**14**	2.0	0.1	60 °C	1.5	91
9	**15**	1.1	0.1	rt	0.5	95
10	**16**	1.5	0.1	60 °C	0.5	83
11	**17**	1.5	0.1	60 °C	1	73
12	**18**	1.1	0.1	rt	—	N.D.

a) (+)-Dihydrocholesterol.



In conclusion, **3** was developed as an O-benzylation reagent under non-basic conditions. The best result was obtained when TMSOTf catalyzed it in 1,4-dioxane. The reaction was effective even for the benzylation of hindered alcohols and base-sensitive hydroxy esters. The most remarkable feature of this reagent is its stability. Two months storage of neat **3** in air at rt produced no decomposition, and the 2-month-old **3** reacted as well as the fresh one with **5** to afford 94% yield of **6**; thus it is more stable than **1**.[10] Preparation of the 4-methoxybenzyl analog of **3** according to Scheme 2 was unsuccessful in our hands.

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9 The procedure for the preparation of **3** is as follows: To the stirred suspension of BnOH (2.34 g, 21.7 mmol) and **4** (5.00 g, 24.1 mmol) in CH_2Cl_2 (120 mL), NaH (964 mg, 24.1 mmol) was added at 0 °C. The mixture was stirred for 2 h at rt. After an addition of H_2O (0.1 mL), the mixture was evaporated and diluted with hexane (50 mL). The resulting mixture was filtered through a cotton-Celite pad, and the filtrate was evaporated. The resulting residue was purified by neutral silica-gel column chromatography (100 g of SiO_2: Silica Gel 60 N, pH 6.5–7.5, 40–50 μm, Kanto Chemical Co., Inc., hexane/Et_2O 50/1) to afford **3** (5.93 g, 98%) as pale yellow oil at rt, mp 19–20 °C; ^{1}H NMR (400 MHz in $CDCl_3$): δ 7.48–7.38 (m, 5H), 7.33 (dddd, $J = 7.3$, 6.7, 2.3, 2.3 Hz, 2H), 7.13 (ddd, $J = 7.6$, 7.3, 1.2 Hz, 2H), 6.85 (br d, $J = 8.0$ Hz, 2H), 5.34 (s, 2H); ^{13}C NMR (100 MHz in $CDCl_3$): δ 145.3 (q, $J_{C-C-F} = 34.3$ Hz), 144.5, 135.2, 128.9, 128.8, 128.7, 128.4, 124.1, 119.7, 116.4 (q, $J_{C-F} = 285.1$ Hz), 69.8.
10 The trichloroacetimidate **1** can be stored at 5 °C as solutions in hexane for periods of up to 2 months: see Ref. 4b.

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