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A Novel Acid-Catalyzed *O*-Benzylating Reagent with the Smallest Unit of Imidate Structure

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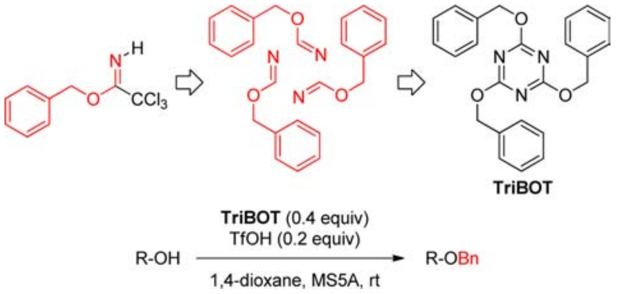
ABSTRACT



Formal trimerization of the smallest unit of benzyl imidate leads to 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT), which can be used as an acid-catalyzed *O*-benzylating reagent. The reaction of various functionalized alcohols with 0.4 equiv of TriBOT in the presence of trifluoromethanesulfonic acid afforded the benzyl ethers in good yields. TriBOT is an inexpensive stable crystalline solid with high atom economy.

The benzyl group is one of the most versatile protecting groups for hydroxy groups in organic synthesis.[1] Typically, the benzylation of alcohols is carried out using benzyl halide and a strong base such as NaH (Williamson ether synthesis); however, this method tends to fail or give lower yields when it is applied to alcohols possessing alkali-labile functionalities. Several methods[2] for benzylation occurring under acidic[2a−i] or nearly neutral conditions[2j−n] have been developed and can be applied to the benzylation of such alkali-labile alcohols. The most frequently used acid-catalyzed benzylating reagent is benzyl 2,2,2-trichloroacetimidate (BTCAI), which is activated by trifluoromethanesulfonic acid (TfOH) or trimethylsilyl trifluoromethanesulfonate (TMSOTf).[3] It can be used for the benzylation of β-hydroxy esters to afford the corresponding benzyl ethers without a retro-aldol reaction or β-elimination. However, there is still room for improvement in terms of stability (sensitive to moisture and heat),[4] usability (liquid), atom economy (additional trichloromethyl group), and cost. The development of a practical acid-catalyzed benzylating reagent that can solve the above-mentioned problems would be advantageous.

The conversion of imidate structure to the stable amide by protonation at the nitrogen of BTCAI seems to be a main driving force in benzylation. In addition, the trichloromethyl group as an electron-withdrawing group will enhance the reactivity of the imidate as a leaving group.

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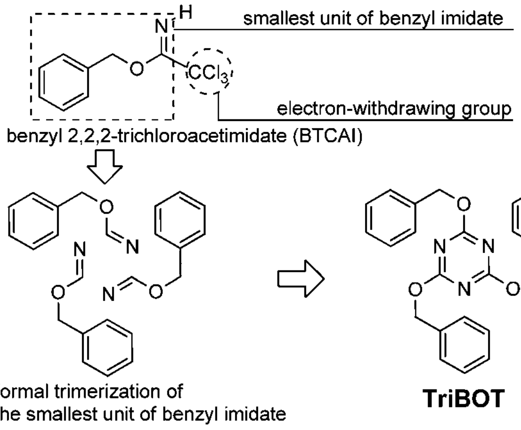
(4) BTCAI can be stored at 5 °C as a solution in hexane for periods of up to 2 months; see ref 3b.

10.1021/ol302222p

(a) Design of TriBOT



(b) Synthesis of TriBOT

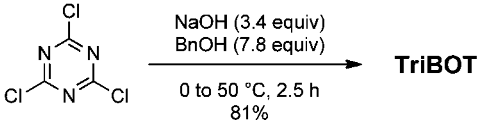


Figure 1. Design and synthesis of TriBOT.

For the development of a new acid-catalyzed benzylating reagent by exploiting the characteristics of imidate, we conceived the idea that the formal *trimerization of the smallest unit of benzyl imidate* leads to 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT, Figure 1a). This can be considered as the smallest benzyl imidate structure without any attachment. The π-electron-deficient triazine ring of TriBOT would function as an electron-withdrawing group corresponding to the trichloromethyl group of BTCAI. The molecular weight of the leaving group per one benzyl group of TriBOT is 3.8 times smaller than that of BTCAI (Table 1). TriBOT does not contain any halogen atoms. TriBOT is easily synthesized on a scale of several hundred grams from benzyl alcohol and cyanuric chloride in the presence of NaOH by the reported procedure[5a] as a stable, crystalline solid material at a low cost (Figure 1b). We did not observe any irritating or allergenic properties in our laboratory. Further, the final concomitant leaving group isocyanuric acid (vide infra) can be removed easily by filtration because it is weakly soluble in many organic solvents (AcOEt, ca. 0.13% (w/v); CH_2Cl_2, <0.1% (w/v)); and water, 0.2% (w/v). These features classify it as an eco-, and user-friendly reagent. TriBOT has been investigated for several applications,[5b−g] but has not been investigated as a benzylating reagent.[6] In this paper, we describe the development of TriBOT as a useful acid-catalyzed *O*-benzylating reagent.

Table 1. Comparison with BTCAI

	TriBOT	BTCAI
MW of leaving group per benzyl group	42.0	161.4
contained halogen atom	none	three chlorine
form	crystalline solid	liquid
stability	stable in air	sensitive to moisture and heat

Upon treatment of 3-phenylpropan-1-ol (**1a**) with TriBOT (0.6 equiv) and TfOH (0.2 equiv) in CH_2Cl_2 at room temperature, the benzylation of **1a** proceeded smoothly to form the corresponding benzyl ether **2a** in 67% yield (Table 2, entry 1). However, Friedel–Crafts benzylation products[7] and dibenzyl ether (Bn_2O), which was probably derived from residual moisture, were observed as byproducts. The use of 0.4 equiv of TriBOT marginally influenced the yield of **2a** (entry 2). While the reactions using acetonitrile, DMF, DMSO, AcOEt, toluene, and α,α,α-trifluorotoluene afforded **2a** in poor to moderate yields (entries 3–8), the reactions using ethereal solvents (diethyl ether (Et_2O), 1,2-dimethoxyethane (DME), and 1,4-dioxane, entries 9, 11, and 13) improved the yields, reducing the Friedel–Crafts products compared with that using CH_2Cl_2. When the reactions were conducted using 0.4 equiv of TriBOT, the yields of **2a** were greater than 90% when DME and 1,4-dioxane were used, except for Et_2O (entries 10, 12, and 14). Among these ethereal solvents, 1,4-dioxane was used for further examination because the solubility of TriBOT in it (ca. 1.2 M) is higher than that in others (Et_2O, <100 mM; DME, ca. 0.5 M). Moreover, when powdered molecular sieves 5A were added as a dehydrating agent to remove residual moisture, the yield of **2a** increased and the formation of Bn_2O decreased (entry 15). Among these reactions, the formation of a small amount of *N*-benzylisocyanuric acid (**3**)[8] was observed as a byproduct (30% yield based on TriBOT in the case of entry 15). Use of 0.35 equiv of TriBOT and the same amount of TfOH were effective for the suppression of the production of **3** (entry 16).

Upon treatment of **1a** with 0.35 equiv of TriBOT and the same amount of various acids, the reactions with TfOH and TMSOTf gave good yields (Table 3, entries 1 and 2), whereas the use of the other Brønsted and Lewis acids such as H_2SO_4, TsOH, and $BF_3 \cdot OEt_2$ afforded only poor yields (0–15%, entries 3–5). The recovered TriBOT indicates that

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(6) Intermolecular *O*- to *N*-rearrangement of benzyl group of TriBOT catalyzed by tetrabutylammonium iodide was investigated. Reynolds, G. F.; Nagel, C. J. M.; Larson, P. A. *J. Chem. Res., Synop.* **1982**, 310.

(7) Friedel–Crafts benzylation gave several compounds that could not be identified because each product is not isolated. The yields were calculated from integrated values of diarylmethylene peaks (3.92–4.10 ppm) of ^1H NMR as assuming that Friedel–Crafts benzylation was conducted only once on one substrate molecule.

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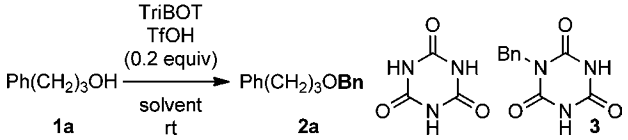
Table 2. Screening of Solvent Conditions and Equivalents of TriBOT



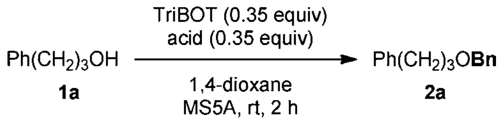
$$\underset{\mathbf{1a}}{\mathrm{Ph(CH_2)_3OH}} \xrightarrow[\text{solvent, rt}]{\text{TriBOT, TfOH (0.2 equiv)}} \underset{\mathbf{2a}}{\mathrm{Ph(CH_2)_3OBn}}$$

entry	solvent	TriBOT (equiv)	**2a**[a] (%)	Friedel–Crafts[a] (%)	Bn_2O[a] (%)
1	CH_2Cl_2	0.6	67	33	6
2		0.4	60	21	3
3	CH_3CN	0.6	13	0	0
4	DMF	0.6	0	0	0
5	DMSO	0.6	0	0	0
6	AcOEt	0.6	43	2	6
7	toluene	0.6	53	69[b]	4
8	$PhCF_3$	0.6	71	24	14
9	Et_2O	0.6	87	7	13
10		0.4	79	1	5
11	DME	0.6	92	0	16
12		0.4	92	1	5
13	1,4-dioxane	0.6	93	7	16
14		0.4	91	6	7
15		0.4[c]	94	5	4
16		0.35[c,d]	96	3	<1

[a] Yields (%) were determined by ^{1}H NMR based on **1a** using an internal standard. [b] Yield contains the benzylated solvent adducts yield. [c] Powdered molecular sieves 5A were added. [d] TfOH (0.35 equiv) was used.

these acids are not sufficiently strong to activate TriBOT efficiently.

Table 3. Benzylation of **1a** with Various Acid Catalysts



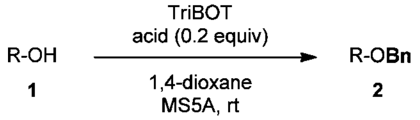
$$\underset{\mathbf{1a}}{\mathrm{Ph(CH_2)_3OH}} \xrightarrow[\text{1,4-dioxane, MS5A, rt, 2 h}]{\text{TriBOT (0.35 equiv), acid (0.35 equiv)}} \underset{\mathbf{2a}}{\mathrm{Ph(CH_2)_3OBn}}$$

entry	acid	**2a**[a] (%)	recovered **1a**[a] (%)	recovered TriBOT[b] (%)
1	TfOH	96	2	0
2	TMSOTf	90	3	0
3	H_2SO_4	5	52	86
4	$BF_3 \cdot OEt_2$	15	74	60
5	TsOH	0	76	91

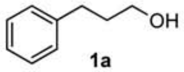
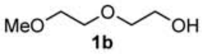
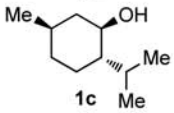
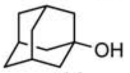
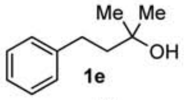
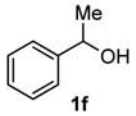
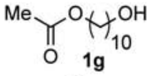
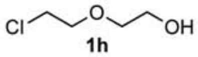
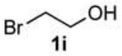
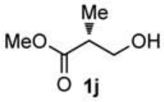
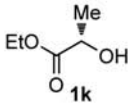
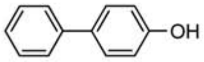
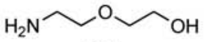
[a] Yields (%) were determined by ^{1}H NMR based on **1a** using an internal standard. [b] Yields (%) were determined by ^{1}H NMR based on TriBOT using an internal standard.

The scope and limitations of the substrates for the benzylation were investigated using TriBOT and a catalytic amount of TfOH (Table 4). Simple alcohols such as primary, secondary, and tertiary alcohols (**1a**–**d**, entries 1–4) provided the desired benzyl ethers **2a**–**d** in excellent yields. Tertiary alcohol **1e** and secondary benzyl alcohol **1f** (entries 5 and 6), which are prone to undergo an elimination reaction of the hydroxy group or the resulting benzyloxy group, provided good yields. Monoacetylated diol **1g** (entry 7) and halohydrins **1h** and **1i** (entries 8 and 9), which are not easily benzylated under standard basic conditions, gave excellent yields. The benzylation of β-hydroxy ester **1j** (entry 10), which is subject to acid- or

Table 4. Scope and Limitations of Various Alcohols for Benzylation Using TriBOT

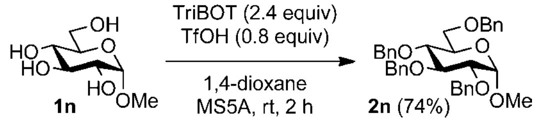


$$\underset{\mathbf{1}}{\text{R-OH}} \xrightarrow[\text{1,4-dioxane, MS5A, rt}]{\text{TriBOT, acid (0.2 equiv)}} \underset{\mathbf{2}}{\text{R-OBn}}$$

entry	substrate	TriBOT (equiv)	time	**2**[a] (%)
1	 **1a**	0.4	5 h	quant
2	 **1b**	0.4	5 h	95
3	 **1c**	0.4	5 h	90
4	 **1d**	0.4	5 h	86
5	 **1e**	1.05	70 min	72[b,c]
6	 **1f**	0.6	100 min	81[b]
7	 **1g**	0.4	5 h	89
8	 **1h**	0.4	7 h	quant
9	 **1i**	0.6	5 h	98
10	 **1j**	0.4	6 h	92
11	 **1k**	0.8	7 h	86
12	 **1l**	0.4	6 h	32
13	 **1m**	0.6	5 h	77[d]

[a] Isolated yield unless otherwise indicated. [b] Yields were calculated by ^{1}H NMR analysis from a mixture of the product and Bn_2O because a small amount of Bn_2O could not be removed from the product. [c] TfOH (0.35 equiv) was used. [d] TfOH (1.2 equiv) was used.

Scheme 1. Benzylation of Methyl α-D-Glucoside



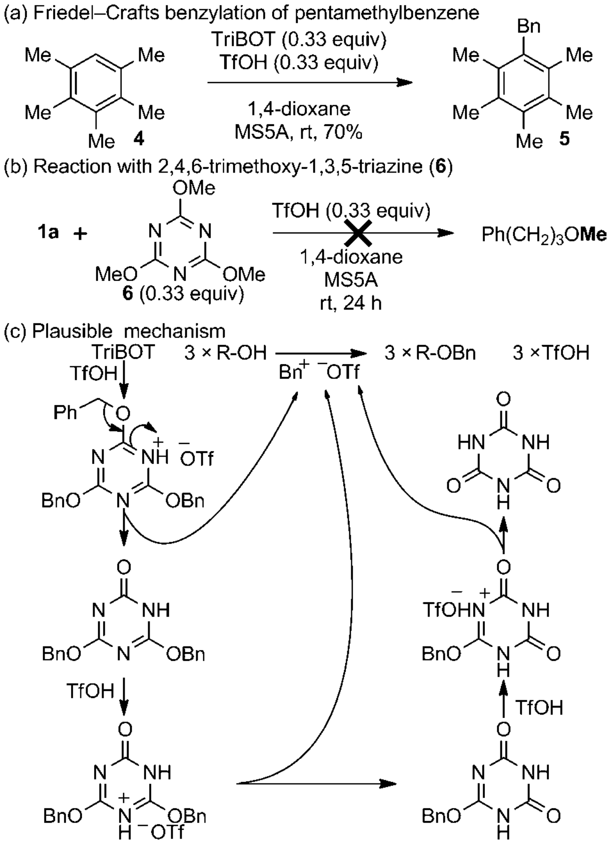


Figure 2. Reaction mechanism for benzylation using TriBOT.

base-catalyzed β-elimination, retro-aldol reaction, and racemization at the α-position to the carbonyl group, achieved a good yield without loss of enantiomeric purity. No racemization occurred during the benzylation of ethyl lactate **1k** (entry 11). The benzylation of phenol **1l** (entry 12) resulted in a moderate yield because competing Friedel–Crafts benzylation occurred at both the substrate and the product. The selective *O*-benzylation of amino alcohol **1m** (entry 13) was achieved using 1.2 equiv of TfOH to suppress the benzylation of amine by the formation of an ammonium salt.

It is worth noting that the reaction of methyl α-D-glucoside **1n** as a highly polar substrate afforded corresponding tetrabenzylated methyl α-D-glucoside **2n** in 74% yield (Scheme 1). The benzylation of highly polar substrates with BTCAI could not be conducted[3b,9] because the reaction is generally performed in nonpolar solvents (CH_2Cl_2/cyclohexane) to prevent rearrangement of BTCAI to *N*-benzyltrichloroacetamide. The benzylation of a sugar triol with BTCAI in DMSO resulted in a poor yield.[9]

When we conducted benzylation using pentamethylbenzene (**4**), which is used as a non-Lewis-basic cation scavenger,[10] benzylpentamethylbenzene (**5**) was obtained in a good yield (Figure 2a). This result indicates that a benzyl cation would be generated when the electron-deficient triazine ring of TriBOT is activated by protonation. On the other hand, 2,4,6-trimethoxy-1,3,5-triazine (**6**) was inert to **1a** under similar acidic conditions (Figure 2b), which indicates that the S_N2 reaction of alcohols to benzyl groups of activated TriBOT is unlikely to proceed because even the methyl group that generally undergoes S_N2 reaction faster than the benzyl group did not react.[11] These results can be rationalized by the following plausible mechanism (Figure 2c); TriBOT is protonated to form the benzyl cation which reacts with coexisting alcohols via an S_N1 mechanism to form benzyl ethers. The remaining two benzyl groups similarly react to form ethers.

In conclusion, regarding the 1,3,5-triazine as a trimeric structure of the smallest benzyl imidate unit, we have successfully found that TriBOT is a novel practical and useful acid-catalyzed *O*-benzylating reagent. Several advantages of TriBOT are as follows: (1) It can be easily synthesized on a large scale from inexpensive, commercially available benzyl alcohol and cyanuric chloride in one step. (2) It is a nonhygroscopic, stable, crystalline solid. It can be stored for 6 months at room temperature and handled in open to the air without any detectable decomposition. (3) The atom economy[12] of TriBOT is better than that of other traditional benzylating reagents[13] because the atoms of the leaving group per one benzyl group have only one carbon, nitrogen, and oxygen atom.

We now focus attention on the application of this concept to *p*-methoxybenzyl group and other alkyl groups. The results will be reported in due course.

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Supporting Information Available. Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Total molecular weight of reagents for introduction of 1 mol of benzyl group: 1/3 × TriBOT (399.44) + 0.2 × TfOH (150.08) = 163.16, BTCAI (252.52) + 0.2 × TfOH (150.08) = 282.54, BnBr (171.03) + Ag_2O (231.74) = 402.77, BnBr (171.03) + NaH (24.00) = 195.03.

The authors declare no competing financial interest.