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Study of the Reactivities of Acid-Catalyzed O-Benzylating Reagents Based on Structural Isomers of 1,3,5-Triazine

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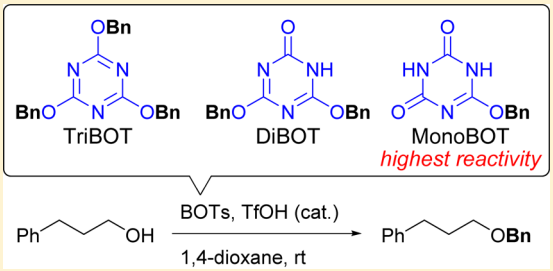
Supporting Information

ABSTRACT: We have demonstrated O-benzylating abilities of both 4,6-bis(benzyloxy)-1,3,5-triazin-2(1*H*)-one (DiBOT) and 6-(benzyloxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (MonoBOT), which have been previously suggested as reaction intermediates of the acid-catalyzed benzylation of 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT). We studied the effect on the reactivity of acid-catalyzed O-benzylation caused by the isomeric core triazine structures in these compounds by carrying out a kinetic study and estimating relative basicities using model compounds. Since MonoBOT showed superior reactivity, 1,3,5-triazine-2,4(1*H*,3*H*)-dione is a promising core structure for acid-catalyzed alkylating reagents.



Recently, we developed a novel acid-catalyzed benzylating reagent, 2,4,6-tris(benzyloxy)-1,3,5-triazine (TriBOT, Figure 1), which is an inexpensive stable crystalline solid with high atom economy.[1] TriBOT was designed based on the concept of the formal trimerization of the smallest unit of benzyl imidate. This concept has also been applied to acid-catalyzed *p*-methoxybenzylation.[2] Various alcohols react with TriBOT at room temperature, in the presence of an acid catalyst such as trifluoromethanesulfonic acid (TfOH), to afford the corresponding benzyl ethers.

Since all the three benzyl groups in TriBOT can be used for the reaction, and isocyanuric acid is formed as a coproduct, the reaction using TriBOT is considered to involve 4,6-bis(benzyloxy)-1,3,5-triazin-2(1*H*)-one (DiBOT)[3] and 6-(benzyloxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (MonoBOT) as reaction intermediates (Figure 1). Although the reactivities of the acid-catalyzed O-benzylation of DiBOT and MonoBOT have not been investigated, we presume that TriBOT, DiBOT, and MonoBOT (henceforth referred to as BOTs) are activated by protonation with TfOH to release a benzyl cation species, probably benzyl trifluoromethanesulfonate, via steps 1−3, respectively. These species react with alcohols to give the benzyl ethers and regenerate TfOH. The final O-benzylation step will be very fast at room temperature.[4] Therefore, the generation of the benzyl cation species from the protonated forms (PFs) of BOTs, whose concentrations in the reaction system depend on their basicities, is the rate-determining step in a series of reaction steps. The reaction rates of steps 1−3 as well as the basicities of BOTs are not expected to be mutually identical in view of the isomeric core structures of BOTs (1,3,5-triazine in TriBOT; 1,3,5-triazin-2(1*H*)-one in DiBOT; and 1,3,5-triazine-2,4(1*H*,3*H*)-dione in MonoBOT).[5]

Herein, we report the comparison of the reactivities of BOTs-based benzylating reagents in acid-catalyzed O-benzylation. This provides further mechanistic insights into the reaction of TriBOT and reveals the effect of the core structures of the benzylating reagents on acid-catalyzed O-benzylation.

DiBOT and MonoBOT were synthesized from 2,4-bis(benzyloxy)-6-chloro-1,3,5-triazine and 2-benzyloxy-4,6-dichloro-1,3,5-triazine in good yields (93% and 84%, respectively).[6] Both DiBOT and MonoBOT are crystalline solids and stable in air at room temperature.

To evaluate the O-benzylating abilities of DiBOT and MonoBOT by comparing them with that of TriBOT, we treated 3-phenylpropanol (**1**) with TriBOT (0.4 equiv), DiBOT (0.6 equiv), or MonoBOT (1.2 equiv) in the presence of TfOH (0.2 equiv). The mole equivalents of the benzyl group available for the reaction are identical (1.2 equiv) in these conditions. As a result, benzyl 3-phenylpropyl ether (**2**) was obtained at 95% yield with TriBOT (Table 1, entry 1), while relatively lower 85% yield with increased byproducts, *N*-benzylisocyanuric acid (**3**) and *N*,*N*′-dibenzylisocyanuric acid (**4**) (entry 2), was observed when using DiBOT. When MonoBOT was used, the reaction proceeded with an excellent 98% yield (entry 3). MonoBOT was therefore a promising benzylating reagent.

To observe the time course of the reaction intermediates and products of the acid-catalyzed O-benzylation with TriBOT, we monitored the reaction between alcohol **1** (200 mM) and TriBOT (80 mM) in the presence of a catalytic amount of TfOH (40 mM). As shown in Figure 2, DiBOT was observed to increase while TriBOT remained in the reaction mixture (0−90 min). After TriBOT disappeared completely, DiBOT began to decrease and finally disappeared (90−120 min). These

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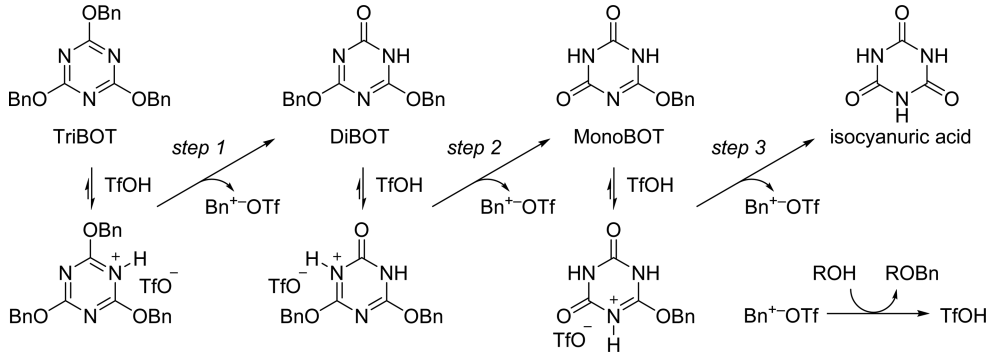
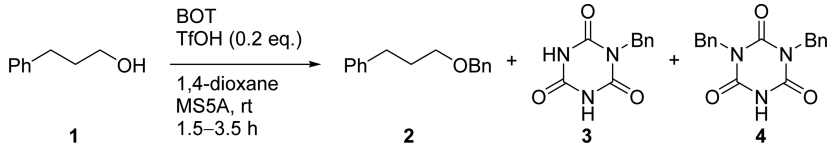


Figure 1. Acid-catalyzed O-benzylation with TriBOT.

Table 1. Acid-Catalyzed O-Benzylation of 1 with BOTs



entry	BOT (equiv)	time (h)	recovered **1** (%)[a]	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]
1	TriBOT (0.4)	3.5	4	95	29[b] (11)[c]	0[b] (0)[c]
2	DiBOT (0.6)	3	12	85	25[b] (15)[c]	6[b] (7)[c]
3	MonoBOT (1.2)	1.5	1	98	6[b] (7)[c]	1[b] (3)[c]

[a]Yields were calculated by ^{1}H NMR analysis using an internal standard. [b]Yields based on BOTs. [c]Yields based on the benzyl groups (total 1.2 equiv = 120%).

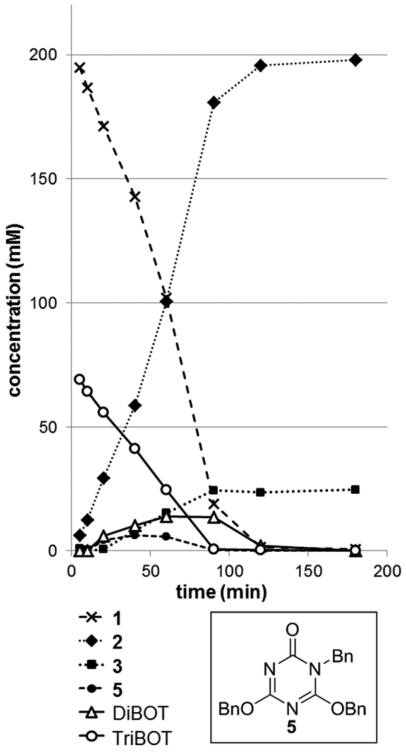


Figure 2. Time course of the reaction intermediates and products of the acid-catalyzed O-benzylation of **1** with TriBOT. The reaction was conducted in 1,4-dioxane at room temperature, and the concentration of each compound was determined by HPLC analysis.

results suggest that DiBOT was formed from TriBOT as a reaction intermediate. In contrast to DiBOT, MonoBOT could not be detected during the reaction, implying its high reactivity as observed in Table 1. Byproduct **3** seems to be formed via N-benzylated DiBOT (**5**) because **5** formed competitively in the early stage of the reaction and appeared earlier than **3**.

Since the benzyl cation species would be generated from the PFs of BOTs, the basicities of BOTs are meaningful factors in characterizing their reactivities as benzylating reagents. To estimate the relative basicities between BOTs, isocyanuric acid, and the alcohol, we conducted ^{1}H NMR analysis (NoD NMR) in competitive protonation among model compounds of BOTs (1.0 equiv, respectively) with TfOH (0.95 equiv) in 1,4-dioxane. The model compounds we employed were 2,4,6-trimethoxy-1,3,5-triazine (**6**), 4,6-bis(cyclohexylmethoxy)-1,3,5-triazin-2(1*H*)-one (**7**), 6-(3-phenylpropoxy)-1,3,5-triazine-2,4-(1*H*,3*H*)-dione (**8**), **3**, and *p*-bromobenzyl alcohol (**9**) for TriBOT, DiBOT, MonoBOT, isocyanuric acid, and the alcohol, respectively. These compounds were adopted because of their structural similarity, high solubility in 1,4-dioxane, inertness under acidic conditions and easy detection of NMR signals. When TfOH was added to a mixture composed of all the model compounds, only the methylene signal of **7** showed a downfield shift (Figure 3a,b), indicating that **7** is the most basic among all the model compounds. The downfield shift of the methyl signal of **6** and the relatively small downfield shift of the methylene signal of **8** were observed in the absence of **7** (Figure 3c). The only downfield shift of **8** (Figure 3d) in a mixture of **8**, **3**, and **9** shows that **8** has a stronger basicity than **3** and **9**. Thus, the order of the basicities is **7** > **6** ≈ **8** > **3** and **9**. On the basis of these model studies, it is presumed that BOTs are sufficiently more basic than isocyanuric acid and the alcohol in 1,4-dioxane, to give the corresponding PFs. Also, DiBOT is the most basic among the BOTs.

To estimate the reaction rate constants of each step in the acid-catalyzed O-benzylation of TriBOT (steps 1−3, Figure 1) individually, we measured the reaction rates of the acid-

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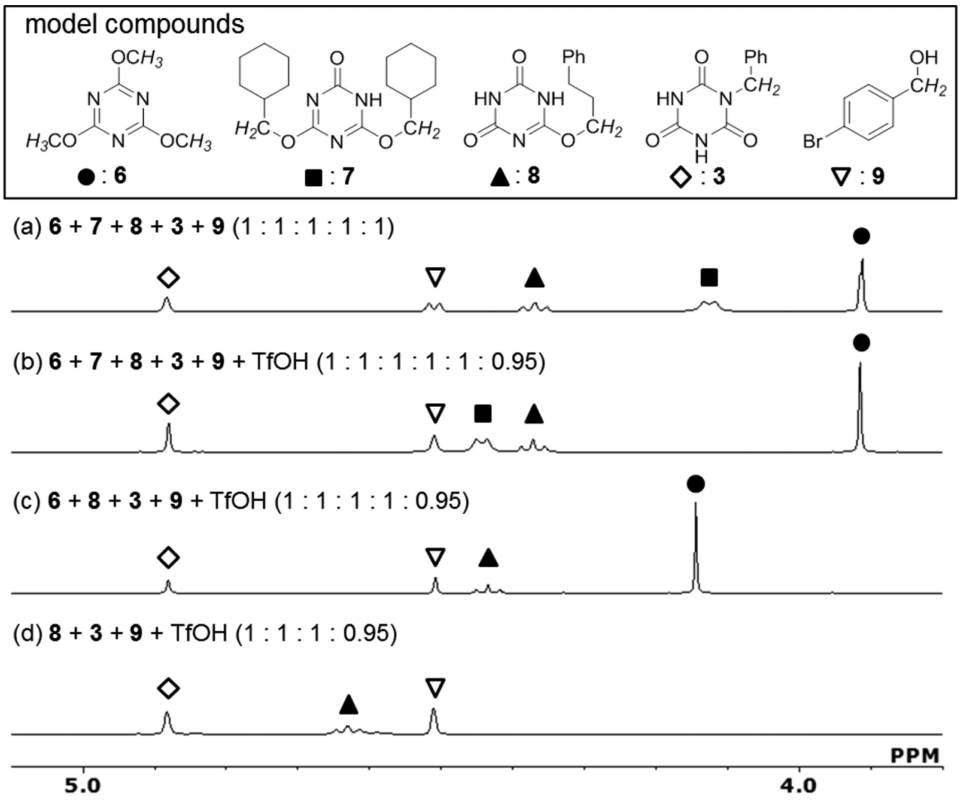

Figure 3. NMR spectroscopic analysis of competitive protonation among the model compounds.

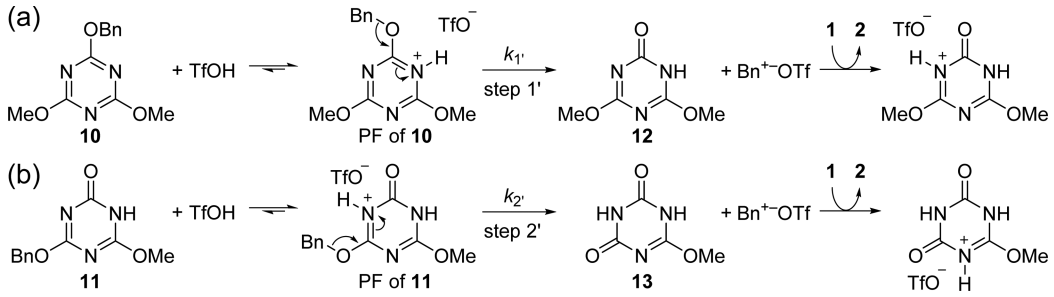

Figure 4. Acid-catalyzed O-benzylation with (a) **10** and (b) **11**.

catalyzed O-benzylation with 2-(benzyloxy)-4,6-dimethoxy-1,3,5-triazine (**10**), 4-(benzyloxy)-6-methoxy-1,3,5-triazin-2(1*H*)-one (**11**), and MonoBOT as shown in Figure 4. Compounds **10** and **11** are model compounds for TriBOT and DiBOT, respectively, whose benzyl group(s) is(are) partially replaced by a nonreactive methyl group(s). The reaction rate for the formation of **2** from these compounds can be compared under the same conditions because they all afford only 1 equiv of benzyl cation species. If the rate-limiting steps are the formation of the benzyl cation species from the PFs of **10**, **11**, and MonoBOT (steps 1′ and 2′ for **10** and **11** in Figure 4, respectively, and step 3 for MonoBOT in Figure 1), the reactions should follow first-order kinetics in the concentrations of their PFs. As a result, the reaction of **10** and **11** followed first-order kinetics in the estimated [PF] in the observed region with $k_{1'} = 16.5 \times 10^{-3}$ min^{-1} for **10** and $k_{2'} = 14.8 \times 10^{-3}$ min^{-1} for **11** at 25 °C (Figure S1 in the Supporting Information).[7,8] Unfortunately, the disappearance of MonoBOT was too fast to measure the rate constant (the residual MonoBOT was less than 3% at 5 min). Thus, the order of the rates for the formation of the benzyl cation species is MonoBOT > **10** ≈ **11**.

These results can be considered based on the relative free energies of **10**, **11**, MonoBOT, and their PFs. The higher the exothermicity of the formation of the leaving group, the faster the reaction will proceed. However, when the PF as a reactant is stable, the reaction will be slow. It is reported that the enthalpies of the sequential tautomerization reaction of cyanuric acid (2,4,6-trihydroxy-1,3,5-triazine) to 4,6-dihydroxy-1,3,5-triazin-2(1*H*)-one, 6-hydroxy-1,3,5-triazine-2,4-(1*H*,3*H*)-dione, and isocyanuric acid were calculated to be −4.0, −43.6, −68.2 kJ/mol (B3LYP/6-31++G(d,p) level of theory)[9a] and −1.9, −41.2, −66.1 kJ/mol (B3LYP/aug-cc-pVDZ level of theory)[9b] for each step, respectively. Owing to their structural similarity, the order of the exothermicities is presumed to be as follows: from MonoBOT to isocyanuric acid > from **11** to 6-(methoxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**13**) > from **10** to 4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one (**12**). In addition, on the basis of the study of the basicities of the model compounds, the order of stability of the PFs would be **11** > **10** ≈ MonoBOT. Thus, the fast reaction of MonoBOT can be attributed to the instability of the protonated MonoBOT and the high exothermicity of the formation of

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isocyanuric acid. It is interesting that **10** and **11** have the comparable rate constants. This indicate that steps 1′ and 2′ have similar activation energies despite the expected much higher exothermicity of the reaction of **11** to **13** than that of **10** to **12**. Although the origin of their comparable reactivities is not clear at present, the stability of the PF of **11** may contribute to some extent to increase in the activation energy.

In summary, acid-catalyzed O-benzylation proceeded with DiBOT and MonoBOT, which clearly indicates that they are reaction intermediates of TriBOT. We have studied the kinetics of acid-catalyzed O-benzylation and relative basicities using several compounds possessing 1,3,5-triazine; 1,3,5-triazin-2(1*H*)-one and 1,3,5-triazine-2,4(1*H*,3*H*)-dione structures, and shown the effect of the isomeric core structures of benzylating reagents on the reactivity of acid-catalyzed O-benzylation. We found that MonoBOT, which contains the 1,3,5-triazine-2,4(1*H*,3*H*)-dione structure, has a superior reactivity in acid-catalyzed O-benzylation. This characteristic heterocyclic structure contained in MonoBOT will be applied to the development of new acid-catalyzed alkylating reagents.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR spectra were recorded on 400 and 600 MHz spectrometers. Chemical shifts for ^{1}H NMR are reported in parts per million (δ) relative to tetramethylsilane as the internal standard. Coupling constant (J) are reported in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. ^{13}C NMR spectra were recorded on 100 and 150 MHz spectrometers. Chemical shifts for ^{13}C NMR are reported in parts per million (δ) relative to the solvent ($CDCl_3$, δ 77.16; DMSO-d_6, 39.52; acetone-d_6, 29.84). Analytical thin layer chromatography (TLC) was performed using glass plates precoated with 0.25 mm silica gel impregnated with a fluorescent indicator (254 nm). Flash chromatography was performed using silica gel (spherical, neutral, 40−100 mesh). TriBOT was prepared by the procedure reported in the literature.[1] Trifluoromethanesulfonic acid (>98.0% purity), dehydrated 1,4-dioxane, CH_2Cl_2, THF, and MeOH were purchased from commercial sources and used without further purification. Xylene was distilled over sodium before use. All reactions sensitive to oxygen or moisture were conducted under a nitrogen atmosphere. HPLC analysis was carried out using Mightysil RP-18Gp Aqua at a flow rate of 1.0 mL/min with UV detection at 254 nm. Concentrations of compounds were determined using calibration curves generated with *p*-nitrotoluene as an internal standard and samples with known concentrations.

General Procedure for O-Benzylation of 1 with BOTs. To a solution of **1** (40.1 μL, 0.30 mmol), DiBOT (55.7 mg, 0.18 mmol), and MS5A (7.5 mg) in 1,4-dioxane (1.50 mL) was added trifluoromethanesulfonic acid (5.3 μL, 0.060 mmol) at rt. After it stirred for 3 h, the reaction mixture was quenched with pyridine (24 μL, 0.30 mmol), concentrated under reduced pressure, and MeOH was added to the residue. The resulting mixture was filtered and concentrated under reduced pressure. The yields of **1**−**4** were determined using ^{1}H NMR measurements (CD_3OD) of the crude product, which contained (*E*)-*N*,*N*-dimethylcinnamamide as an internal standard. In the case of the reaction with MonoBOT, 2.60 mL of 1,4-dioxane was used as the reaction solvent.

HPLC Monitoring of O-Benzylation with TriBOT. To a solution of **1** (136 μL, 1.00 mmol), TriBOT (159.8 mg, 0.40 mmol), *p*-nitrotoluene (13.7 mg, 0.10 mmol), and MS5A (25.0 mg) in 1,4-dioxane (5.0 mL) was added trifluoromethanesulfonic acid (17.6 μL, 0.20 mmol) at rt. Aliquots (20 μL) were taken from the reaction mixture at intervals, diluted with pyridine solution (2.0 mM, 1.98 mL) in H_2O−MeCN (1:1), and filtered. HPLC analysis was performed using *p*-nitrotoluene as an internal standard. HPLC conditions: gradient of 0.1% TFA in H_2O (solvent A) and 0.1% TFA in MeCN (solvent B), 80% A + 20% B to 65% A + 35% B (0−10 min), 65% A + 35% B (10−20 min), 65% A + 35% B to 40% A + 60% B (20−25 min), 40% A + 60% B (25−40 min), 40% A + 60% B to 20% A + 80% B (40−45 min).

General Procedure for NMR Analysis in Competitive Protonation among the Model Compounds. 1,4-Dioxane (153 μL); 1,4-dioxane solutions of **6**, **8**, **3**, and **9** (60.0 μL of 0.10 M stock solution); **7** (150 μL of 0.040 M stock solution); and TfOH (57.0 μL of 0.10 M stock solution) were mixed in an NMR tube. A NoD NMR spectrum was recorded at 21 °C.

General Procedure for the Kinetic Study of O-Benzylation with 10, 11 and MonoBOT. To a solution of **10** (98.9 mg, 0.400 mmol), **11** (93.3 mg, 0.400 mmol) or MonoBOT (87.7 mg, 0.40 mmol), and **1** (54.5 μL, 0.400 mmol); *p*-nitrotoluene (16.5 mg, 0.120 mmol); and MS5A (20.0 mg) in 1,4-dioxane (4.0 mL) was added trifluoromethanesulfonic acid (33.4 μL, 0.381 mmol) at 25 ± 0.5 °C. Aliquots (40 μL) were taken from the reaction mixture at intervals, diluted with pyridine solution (4.0 mM, 2.0 mL) in H_2O−MeCN (1:1), and filtered. HPLC analysis was performed using *p*-nitrotoluene as an internal standard. HPLC conditions of the kinetic study with **10**: gradient of 80% H_2O + 20% MeCN to 65% H_2O + 35% MeCN (0−10 min), 65% H_2O + 35% MeCN to 30% H_2O + 70% MeCN (10−25 min), 30% H_2O + 70% MeCN to 10% H_2O + 90% MeCN (25−26 min). HPLC conditions of the kinetic study with **11** and MonoBOT: gradient of 0.1% TFA in H_2O (solvent A) and 0.1% TFA in MeCN (solvent B), 85% A + 15% B (0−5 min), 85% A + 15% B to 15% A + 85% B (5−15 min).

2,4-Bis(benzyloxy)-6-chloro-1,3,5-triazine.[10] To a solution of cyanuric chloride (92.2 mg, 0.500 mmol) and benzyl alcohol (156 μL, 1.50 mmol) in CH_2Cl_2 (1.0 mL) was added ethyldiisopropylamine (261 μL, 1.50 mmol) at −40 °C. After it stirred for 1.5 h, the mixture was allowed to warm to rt and stirred for 30 h. The mixture was washed with sat. aqueous NH_4Cl (2 mL) and brine (2 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 10:1) to afford title compound (156.6 mg, 96%) as colorless crystals. Mp 72−73 °C.

4,6-Bis(benzyloxy)-1,3,5-triazin-2(1*H*)-one (DiBOT).[3] To a solution of *N*-methylmorpholine (220 μL, 2.00 mmol) and acetic acid (57.2 μL, 1.00 mmol) in MeOH was added 2,4-bis(benzyloxy)-6-chloro-1,3,5-triazine (163.9 mg, 0.500 mmol) at 0 °C. After it stirred for 30 min, the mixture was allowed to warm to rt. After it stirred for an additional 1.5 h, acetic acid (57 μL, 1.0 mmol) was wadded. The mixture was concentrated under reduced pressure and $CHCl_3$ (5 mL) was added to the residue. The mixture was washed with 1 M aqueous HCl (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$−EtOAc, 4:1) to afford DiBOT (143.1 mg, 93%) as a white solid. Mp 170 °C (decomp.).

2-(Benzyloxy)-4,6-dichloro-1,3,5-triazine. To a solution of cyanuric chloride (7.38 g, 40.0 mmol) in CH_2Cl_2 (70.0 mL) was added a solution of benzyl alcohol (4.12 mL, 40.0 mmol) and ethyldiisopropylamine (7.70 mL, 44.0 mmol) in CH_2Cl_2 (35.0 mL) prepared in a flask at 0 °C. The residual benzyl alcohol and ethyldiisopropylamine in the flask were rinsed with CH_2Cl_2 (5.0 mL) into the mixture. After it stirred for 1 h, the mixture was allowed to warm to rt. After it stirred for an additional 1.5 h, the mixture was washed with 1 M aqueous HCl (110 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane−$CHCl_3$, 1:1) and recrystallization from hexane to afford title compound (9.45g, 92%) as colorless crystals. Mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.33 (m, 5H), 5.53 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 171.0, 133.8, 129.2, 128.9, 128.8, 71.9. Anal. Calcd for $C_{10}H_7Cl_2N_3O$: C, 46.90; H, 2.76; N, 16.41. Found: C, 47.13; H, 2.92; N, 16.32. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_8Cl_2N_3O$ 256.0044. Found: 256.0016. IR (KBr): 1541, 1508, 1429, 1362, 1300, 1255, 1057 cm^{-1}.

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6-(Benzyloxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (MonoBOT). To a biphasic solution of sodium acetate (2.051 g, 25.0 mmol) and *N*-methylmorpholine (110 μL, 1.00 mmol) in THF (10.0 mL) and H_2O (10.0 mL) was added 2-(benzyloxy)-4,6-dichloro-1,3,5-triazine (1.280 g, 5.00 mmol) at 0 °C. After it stirred for 1 h, the mixture was allowed to warm to rt. After it stirred for an additional 19 h, 1 M aqueous HCl (1.0 mL) was added to the mixture. After careful evaporation of THF, a precipitate was corrected and recrystallized from EtOH to afford MonoBOT (923.4 mg, 84%) as colorless crystals. Mp 200 °C (decomp); ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.24 (br s, 1H), 11.07 (br s, 1H), 7.48−7.34 (m, 5H), 5.35 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.3, 153.9 (br s), 135.1, 128.49, 128.45, 128.42, 69.2. Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.71; H, 4.12; N, 19.10. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{10}H_{10}N_3O_3$ 220.0722. Found: 220.0708. IR (KBr): 3076, 1751, 1736, 1684, 1577, 1313 cm^{-1}.

1-Benzyl-4,6-bis(benzyloxy)-1,3,5-triazin-2(1*H*)-one (5). To a mixture of DiBOT (154.7 mg, 0.500 mmol), cesium carbonate (177.2 mg, 0.544 mmol) and DMSO (1.0 mL) was added benzyl bromide (62.4 μL, 0.525 mmol) at rt. After it stirred for 30 min, the mixture was diluted with Et_2O (4 mL) and washed with H_2O (10 mL) and brine (4 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2−EtOAc, 19:1) to afford **5** (130.8 mg, 65%) as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.43 (m, 2H), 7.42−7.21 (m, 13H), 5.43 (s, 2H), 5.42 (s, 2H), 5.11 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.9, 163.1, 156.9, 135.5, 135.3, 133.7, 129.3, 128.91, 128.87, 128.85, 128.77, 128.7, 128.6, 128.2, 72.0, 70.5, 45.7. Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.54; H, 5.50; N, 10.44. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{24}H_{22}N_3O_3$ 400.1661. Found: 400.1685. IR ($CHCl_3$): 1705, 1603, 1533, 1423, 1348, 1176 cm^{-1}.

2,4,6-Trimethoxy-1,3,5-triazine (6).[1,11] To a suspension of $NaHCO_3$ (205.8 mg, 2.45 mmol) in MeOH (2.80 mL) was added cyanuric chloride (129.1 mg, 0.700 mmol) at rt. After it stirred for 2 h, the mixture was warmed to 50 °C. After it stirred an additional 22 h, the mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 1:1) to afford **6** (110.1 mg, 92%) as colorless crystals. Mp 143.6−144.6 °C.

2-Chloro-4,6-bis(cyclohexylmethoxy)-1,3,5-triazine. A solution of cyanuric chloride (2.634 g, 15.0 mmol), cyclohexylmethanol (4.59 mL, 37.5 mmol) and 1,10-phenanthroline (8.109 g, 45.0 mmol) in xylene (50.0 mL) was heated to reflux for 20 h. After it cooled to rt, the mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 30:1) followed by recrystallization from hexane to afford title compound (4.392 g, 86%) as colorless crystals. Mp 75.8−76.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.22 (d, *J* = 6.2 Hz, 4H), 1.89−1.63 (m, 12H), 1.34−1.13 (m, 6H), 1.12−0.99 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.6, 172.4, 74.5, 37.2, 29.8, 29.6, 26.4, 25.7. Anal. Calcd for $C_{17}H_{26}ClN_3O_2$: C, 60.08; H, 7.71; N, 12.36. Found: C, 60.35; H, 7.49; N, 12.28. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{17}H_{27}ClN_3O_2$ 340.1792. Found: 340.1820. IR (KBr): 2927, 2854, 1576, 1522, 1508, 1342, 1072, 1007 cm^{-1}.

4,6-Bis(cyclohexylmethoxy)-1,3,5-triazin-2(1*H*)-one (7). To a solution of acetic acid (46 μL, 0.80 mmol) and *N*-methylmorpholine (176 μL, 1.60 mmol) in MeOH (2.0 mL) was added 2-chloro-4,6-bis(cyclohexylmethoxy)-1,3,5-triazine (135.9 mg, 0.400 mmol) at 0 °C. After it stirred for 1.5 h, the mixture was allowed to warm to rt. After it stirred for an additional 1.5 h, 6 M aqueous HCl (0.13 mL) was added to the mixture and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2−MeOH, 30:1) to afford 7 (121.3 mg, 94%) as a white solid. Mp 200.2−202.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.16 (br s, 1H), 4.23 (d, *J* = 6.3 Hz, 4H), 1.90−1.63 (m, 12H), 1.32−1.12 (m, 6H), 1.06−0.93 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.1, 74.7, 36.9, 29.6, 26.4, 25.6. Anal. Calcd for $C_{17}H_{27}N_3O_3$: C, 63.53; H, 8.47; N, 13.07. Found: C, 63.45; H, 8.41; N, 13.13. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{17}H_{28}N_3O_3$ 322.2131. Found: 322.2145. IR (KBr): 2924, 2852, 1674, 1610, 1558, 1423, 1358, 1331 cm^{-1}.

2,4-Dichloro-6-(3-phenylpropoxy)-1,3,5-triazine. To a solution of cyanuric chloride (1.00 g, 5.42 mmol) and ethyldiisopropylamine (1.04 mL, 5.97 mmol) in CH_2Cl_2 was added **1** (739 μL, 5.42 mmol) at −20 °C. The mixture was stirred at −20 °C for 3 h, at 0 °C for 7 h, and at rt for 1 h. Ethyldiisopropylamine (378 μL, 2.17 mmol) was added at rt. After it stirred for an additional 6 h, the mixture was diluted with $CHCl_3$, washed with 1 M aqueous HCl (15 × 2 mL), and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 20:1) followed by recrystallization from hexane to afford title compound (1.07 g, 70%) as colorless crystals. Mp 53.6−54.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32−7.27 (m, 2H), 7.24−7.17 (m, 3H), 4.49 (t, *J* = 6.3 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.19−2.11 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.7, 171.2, 140.6, 128.7, 128.5, 126.4, 69.8, 31.8, 30.0. Anal. Calcd for $C_{12}H_{11}Cl_2N_3O$: C, 50.72; H, 3.90; N, 14.79. Found: C, 50.81; H, 4.00; N, 14.78. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{12}Cl_2N_3O$ 284.0357. Found: 284.0368. IR (KBr): 3030, 1541, 1506, 1308, 1255, 1038 cm^{-1}.

6-(3-Phenylpropoxy)-1,3,5-triazine-2,4(1*H*,3*H*)-dione (8). To a solution of sodium acetate (430.7 mg, 5.25 mmol) and *N*-methylmorpholine (38.5 μL, 0.35 mmol) in MeOH (17.5 mL) was added 2,4-dichloro-6-(3-phenylpropoxy)-1,3,5-triazine (497.2 mg, 1.75 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h, at rt for 13 h, and at 40 °C for 25 h. The mixture was concentrated under reduced pressure, and $CHCl_3$ was added to the residue. The mixture was washed with sat. aqueous NH_4Cl (20 mL), brine (20 mL), 1 M aqueous HCl (10 mL) and concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$−MeOH, 19:1) followed by recrystallization from hexane−THF to afford **8** (271.4 mg, 63%) as colorless crystals. Mp 200 °C (decomp.); ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.16 (br s, 1H), 11.01 (br s, 1H), 7.32−7.27 (m, 2H), 7.25−7.16 (m, 2H), 4.27 (t, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.02−1.94 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 161.4, 140.9, 128.4, 128.3, 125.9, 67.6, 31.0, 29.4. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.07; H, 5.25; N, 16.93. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{14}N_3O_3$ 248.1035. Found: 248.1033. IR (KBr): 3084, 2817, 1751, 1685, 1577, 1417, 1317 cm^{-1}.

2-(Benzyloxy)-4-chloro-6-methoxy-1,3,5-triazine. A solution of 2-(benzyloxy)-4,6-dichloro-1,3,5-triazine (200.0 mg, 0.781 mmol) and 1,10-phenanthroline (154.8 mg, 0.859 mmol) in MeOH (1.56 mL) was stirred at 50 °C for 7.5 h. After it cooled to rt, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (hexane−EtOAc, 4:1) to afford title compound (161.7 mg, 82%) as colorless crystals. Mp 64.9−66.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.42 (m, 2H), 7.42−7.31 (m, 3H), 5.48 (s, 2H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 172.7, 172.1, 134.7, 128.84, 128.76, 128.6, 70.8, 56.2. Anal. Calcd for $C_{11}H_{10}ClN_3O_2$: C, 52.50; H, 4.01; N, 16.70. Found: C, 52.63; H, 3.80; N, 16.75. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{11}H_{11}ClN_3O_2$ 252.0534. Found: 252.0515. IR (KBr): 1570, 1541, 1429, 1346, 1236, 1122 cm^{-1}.

2-(Benzyloxy)-4,6-dimethoxy-1,3,5-triazine (10). A solution of 2-(benzyloxy)-4-chloro-6-methoxy-1,3,5-triazine (200.0 mg, 0.795 mmol) and 1,10-phenanthroline (286.4 mg, 1.59 mmol) in MeOH (1.6 mL) was heated to reflux. After it stirred for 77 h, MeOH (1.6 mL) was added and the mixture was stirred at reflux for an additional 83 h. After the solution cooled to rt, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$−MeOH, 100:1) to afford **10** (113.3 mg, 58%) as colorless crystals. Mp 65.0−66.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.42 (m, 2H), 7.41−7.29 (m, 3H), 5.45 (s, 2H), 4.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 173.1, 135.5, 128.7, 128.6, 128.5, 70.0, 55.5. Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.15; H, 5.36; N, 16.88. HRMS (DART-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{12}H_{14}N_3O_3$ 248.1035. Found: 248.1023. IR (KBr): 2951, 1558, 1348, 1130 cm^{-1}.

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6-(Benzyloxy)-4-methoxy-1,3,5-triazin-2(1*H*)-one (11). To a solution of acetic acid (57.2 μL, 1.00 mmol) and *N*-methylmorpholine (220 μL, 2.00 mmol) in MeOH (2.50 mL) was added 2-(benzyloxy)-4-chloro-6-methoxy-1,3,5-triazine (128.5 mg, 0.500 mmol) at 0 °C. After it stirred for 30 min, the mixture was allowed to warm to rt and stir for an additional 1.5 h. Acetic acid (57 μL, 1.0 mmol) was added to the mixture and concentrated under reduced pressure. $CHCl_3$ (5 mL) was added to the residue, and the mixture was washed with 1 M aqueous HCl (5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$–EtOAc, 4:1) to afford **11** (104.1 mg, 89%) as colorless crystals. Mp 130 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.35 (br s, 1H), 7.48–7.31 (m, 5H), 5.46 (s, 2H), 4.04 (2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 134.4, 129.0, 128.9, 128.8, 71.0, 56.2. Anal. Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.45; H, 4.78; N, 17.95. HRMS (DART-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{12}N_3O_3$ 234.0879. Found: 234.0874. IR (KBr): 2962, 1684, 1610, 1576, 1471, 1362, 1325 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02059.

Kinetic study of O-benzylation with **10** and **11**, calibration curves for HPLC analysis, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(7) The reaction between **10**, **11**, or MonoBOT (100 mM, respectively) and alcohol **1** (100 mM) was conducted in the presence of TfOH (95 mM) in 1,4-dioxane at 25 °C (see Experimental Section). Since TfOH, which is a super acid (pK_a = −12 in H_2O, see below), would ionize completely in the reaction mixture, and **10** should be more basic than **1**, it is considered that $[\mathbf{10}]_0$ was 5 mM and the $[PF\ of\ \mathbf{10}]_0$ was 95 mM. The leaving group, 4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one (**12**), which is generated from the PF of **10** and would be sufficiently more basic than **10**, was protonated with regenerated TfOH and thus [**10**] was considered to be constantly 5 mM. Therefore, it is estimated that $[PF\ of\ \mathbf{10}] = [\mathbf{10}]_{obs} - 5$, where $[\mathbf{10}]_{obs}$ is the concentration of **10** observed in HPLC analysis, and represents the sum of [**10**] and the [PF of **10**]. For pK_a value of TfOH, see: Raamat, E.; Kaupmees, K.; Ovsjannikov, G.; Trummal, A.; Kütt, A.; Saame, J.; Koppel, I.; Kaljurand, I.; Lipping, L.; Rodima, T.; Pihl, V.; Koppel, I. A.; Leito, I. *J. Phys. Org. Chem.* **2013**, *26*, 162–170.

(8) The basicity of **11** would be sufficiently higher than that of **1** and the leaving group, 6-methoxy-1,3,5-triazine-2,4(1*H*,3*H*)-dione (**13**). For this reason, it is considered that $[\mathbf{11}]_0$ was 5 mM and the $[PF\ of\ \mathbf{11}]_0$ was 95 mM. Also, when the sum of [**11**] and the [PF of **11**] was 95 mM or less, [**11**] was virtually 0 mM because **11** was completely protonated by 95 mM of TfOH. Therefore, when the sum of [**11**] and the [PF of **11**] was 95 mM or less, it was estimated that $[PF\ of\ \mathbf{11}] = [\mathbf{11}]_{obs}$, where $[\mathbf{11}]_{obs}$ is the concentration of **11** observed in HPLC analysis, and represents the sum of [**11**] and the [PF of **11**].

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