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Development of Triazine-Based Benzylating Reagents Possessing t-Butyl Group on the Triazine Core: Thermally Controllable Reagents for the Initiation of Reaction

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Benzylating reagents, 4-(4,6-di-t-butyl-1,3,5-triazin-2-yl)-4-benzylmorpholinium triflate, and related derivatives have been developed. The reagents release benzyl triflate as a benzyl cation equivalent upon heating the solution to 40°C under neutral conditions. The O-benzylation of alcohols using a stoichiometric amount of these reagents afforded corresponding benzyl ethers in good to high yields. This was due to the presence of a bulky t-butyl group on the triazine ring of these reagents that prevents the consumption of benzyl triflate via a side reaction with a morpholinotriazine derivative.

Key words benzylating reagent; triazine; thermally controllable

The benzyl group is a protecting group for alcohols that is stable under strong acidic and basic conditions, and its deprotection is easily achieved via hydrogenolysis under mild conditions. Therefore, the benzyl group has been used for several organic synthetic reactions and various benzylation methods have been developed. Recently, we have developed several alkylating reagents based on the characteristics of 1,3,5-triazine. 2,4,6-Tris(benzyloxy)-1,3,5-triazine (TriBOT), 2,4,6-tris(p-methoxybenzyl)-1,3,5-triazine (TriBOT-PM), 6-((benzyl)oxy)-1,3,5-triazine-2,4(1H,3H)-dione (DPT-BM), 2,4,6-tris(t-butoxy)-1,3,5-triazine (TriAT- tBu), 2,4,6-tris(allyloxy)-1,3,5-triazine (TriAT-allyl), and N,N’-dimethylated 6-((benzyl)oxy)-1,3,5-triazine-2,4(1H,3H)-dione (DMBOT) achieve the alkylation of various alcohols in good to excellent yields in the presence of the triazine nitrogen owing to the high electrophilicity of BnOTf. Thus, an excess of DPT-BM (X-a) (>2.0 equiv.) is required to obtain benzyl ethers in good yields. Despite its salt property, the side reaction proceeds at the most nucleophilic site of the triazine nitrogen owing to the high electrophilicity of BnOTf. Therefore, the benzyl group has been used for hydrogenolysis under mild protection is easily achieved via a side reaction with a morpholinotriazine derivative.

Fig. 1 The Benzylation with DPT-BM (X-a) Proceeds under Nearly Neutral Conditions

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nitrogen atoms on the triazine ring might prevent the formation of \(N\)-benzyltriazinium compounds that correspond to \(Z-a\). In this paper, we report the development of a new benzylating reagent (\(X-b\)) that was designed by replacing the two phenoxy groups of DPT-BM (\(X-a\)) with a sterically bulky \(t\)-butyl group.

The benzylating reagent, \(X-b\), was prepared according to the procedure shown in Chart 1. The copper-catalyzed cross-coupling of \(t\)-butyl magnesium chloride with cyanuric chloride afforded 2,4-di-\(t\)-butyl-6-chloro-1,3,5-triazine (3), which was converted into 2,4-di-\(t\)-butyl-6-trifluoromethanesulfonyloxy-1,3,5-triazine (5) via 4,6-di-\(t\)-butyl-1,3,5-triazin-2(1\(H\))-one (4) using our original method.\(^{6,7,10,20}\) The treatment of 5 with \(N\)-benzylmorpholine in \(Et_2O\) afforded 4-(4,6-di-\(t\)-butyl-1,3,5-triazin-2-yl)-4-benzylmorpholinium triflate (\(X-b\)) as a precipitate in 89% yield.

To compare the benzylating ability of \(X-b\) with that of DPT-BM (\(X-a\)), the benzylation of \(1a\) was performed under the same condition shown in Table 1, entry 2. As a result, the reaction proceeded to afford \(2a\) in 93% yield, and the generation of the corresponding \(N\)-benzyltriazinium \(Z-b\) was not detected probably because the introduction of bulky \(t\)-butyl groups to the triazine ring prevented the \(Z-b\) formation (Table 1, entry 3). However, the completion of benzylation required a longer time than Table 1, entry 2. This would be because the liberation of the benzyl cation species, BnOTf, from \(X-b\) was slower than that from DPT-BM (\(X-a\)) due to the replacement of electron-withdrawing phenoxy groups with the electron-donating \(t\)-butyl groups, which would decrease the leaving ability of \(Y-b\). Heating at 40°C shortened the reaction time to 4 h and improved the yield to 93% (entry 4).

To accelerate the \(O\)-benzylation reaction with \(X-b\), we investigated the optimal conditions using primary alcohol, \(1b\), as a model alcohol (Table 2). Under the same condition as in Table 1, entry 3, the reaction was slow and required 56 h for its completion (entry 1). Despite the addition of a catalytic amount of triflic acid to activate \(X-b\), the reaction time could not be reduced (entry 2). When the reaction was conducted at 40°C, \(1b\) completely disappeared within 5 h, and product \(2b\) was afforded in 95% yield (entry 3). Moreover, the reaction at 60°C completed within 1 h (entry 4). Compared with entry 3, when the reaction was performed at a higher concentration, the yield of \(2b\) decreased and a longer reaction time was required (entry 5).\(^{21}\) The yield of \(2b\) decreased to 80% in CH₂Cl₂ (entry 6), whereas high yields were maintained in ethereal solvents such as 1,4-dioxane and diglyme (entries 7, 8).

We examined the scope and limitations of various alcohols for the benzylation using \(X-b\) at optimal conditions mentioned.
in the entries 3, 4 in Table 2. The results are summarized in Table 3. For comparison, the yields using DPT-BM (X-a) or Dudley reagent that were reported in the literature are also listed. The benzylation of simple primary alcohols, 1b and 1c, proceeded in high yields (entries 1, 2). Bulk secondary and tertiary alcohols, 1a and 1d–f, were converted into their corresponding benzyl ethers in >80% yields which are comparable to those using DPT-BM (X-a) (entries 3, 5, 7, 9). When the reaction temperature was increased to 60°C, the reactions completed within 1 h without a decrease of the yields (entries 4, 6, 8, 10). Base-labile alcohols, such as 1g and 1h, possessing a chloroalkyl or acetoxy group, provided benzyl ethers, 2g and 2h, in high yields (entries 11, 12). β-Hydroxyester 1i and 2-(trimethylsilyl)ethanol 1j, which are prone to decompose under acidic or basic conditions, were converted into products 2i and 2j, respectively, in good yields (entries 13, 14). No racemization was observed during the benzylation of 1i. The O-benzylolation of cholesterol 1k also afforded the corresponding ether 2k in good yields (entries 15, 16). Although tertiary alcohols, such as 1l and 1m, and their ethers (2l and 2m) are known to decompose under acidic or basic conditions, 2l and 2m were obtained without decomposition using approximately stoichiometric amount of X-b (entries 17–20). In particular, better yields were observed at 40°C, which is milder than the temperature used for Dudley reagent.

The formation of N-benzyltriazinium Z-b from X-b was not observed in all the reactions listed in Table 3. Therefore, we synthesized the benzylating reagents possessing a t-butyl and an alkoxy group on the triazine ring (X-c and X-d) to study the effect of t-butyl group on the formation of the corresponding N-benzyltriazinium (Z-c and Z-d). The benzylation of 1a using X-c or X-d resulted in the formation of 2a in higher yields compared with that obtained using DPT-BM (X-a), and it did not produce N-benzyltriazinium Z-c or Z-d (Table 1, entries 5, 6).

To compare the relative nucleophilicities of the morpholinotriazines Y, which are co-products produced from X and could undergo N-benzylization to form N-benzyltriazinium Z, crossover experiments were performed. A mixture of the equimolar amount of morpholinotriazines, Y-a, Y-c, and Y-d, was treated with the same amount of X-b, which is a source of benzyl cation species. As a result, N-benzyltriazinium, Z-a, Z-b, Z-c, and Z-d, were produced in a ratio of 94:0:4:2, respectively (Chart 2[A]). A similar reaction was conducted in the absence of Y-a because the relative nucleophilicities of Y-b, Y-c, and Y-d were ambiguous owing to the low yields of Z-b, Z-c, and Z-d, which result from the high nucleophilicity of Y-a. As a result, Z-b, Z-c, and Z-d were formed in a ratio of 0:77:23, respectively (Chart 2[B]). To conduct the reaction in the presence of one equivalent of Y-b, other benzylating reagents were used instead of X-b. The reaction employing DPT-BM (X-a) in the presence of Y-b, Y-c, and Y-d also produced a similar ratio of products as in reaction [A] (Chart 2[C]). When X-d was employed as the benzylating reagent in the presence of Y-b and Y-c, only a slight increase in Z-c was observed, and Z-b was not produced (Chart 2[D]). These experimental results clearly indicate that Y-b that possesses two t-butyl groups on the triazine ring does not react with a benzyl cation species at all.

As we previously reported, these results again indicate that the formation of Z proceeds intermolecularly between BnOTf and Y, and not via an intramolecular rearrangement. As expected, the introduction of a bulky t-butyl group into the triazine core caused a decrease in the rate of the N-benzylolation of Y; therefore, the O-benzylolation of alcohols produced high yields by using only 1.2 equiv. of X-b, X-c, or X-d.

We reported that DPT-BM (X-a) dissolved in CDCl 3 disappeared according to first-order kinetics, and the release of the benzyl cation species from DPT-BM (X-a) may occur via a nucleophilic attack to the N-benzyl group by the triflate counter anion (S2 reaction, Fig. 2). Thus, we conducted a kinetic study of the degradation of X-b, X-c, and X-d because the release rate of BnOTf from X should be affected by substituents on the triazine ring. As a result, all the reagents degraded according to first-order kinetics. The order of the first-order reaction rate constants, k of X, were determined to be DPT-BM (X-a)>X-d>X-c>X-b (Table 4). This result can be accounted for by the electronic effect of the substituents on the triazine ring. Based on the Hammett’s substituent constant, σα\text{\textscript{ar}}, the electron-withdrawing ability of the phenoxy group is larger than that of the methoxy group. In contrast, the t-butyl group has an electron-donating ability. The observed first-order rate constants of X are assumed to correlate with the leaving ability of Y altered by the substituents on the triazine. It has been reported that the Hammett equation is applicable to triazine derivatives using the sum of σm of two substituents on the tri-
Hammett plot for the degradation rate also provides a good linear relation (Fig. 3). The positive $\rho$ value (3.471) shows that electron-withdrawing groups stabilize the transition state by delocalization of the electron density increasing on the morpholine nitrogen. These results indicate that the reactivity of $X$ can be modulated by the inclusion of electron-donating or electron-withdrawing substituents on the triazine ring using the $\sigma_m$ as an indicator.

The low reactivity of $X_b$ is an advantage from an experimental point of view. The benzylation using DPT-BM ($X_a$) must be initiated by adding the reagent in the solid state to

Table 3. Benzylation of Several Alcohols Using $X_b$, and the Comparison of Benzylating Ability with Other Benzylating Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>temp. [°C]</th>
<th>time [h]</th>
<th>yield [%]$^a$</th>
<th>yield using other reagents [%]$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO</td>
<td>40</td>
<td>5</td>
<td>92</td>
<td>97$^b$</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>40</td>
<td>5</td>
<td>95$^e$</td>
<td>95$^{b,c}$</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>40</td>
<td>4</td>
<td>94</td>
<td>86$^f$</td>
</tr>
<tr>
<td>4</td>
<td>$2a$</td>
<td>60</td>
<td>0.5</td>
<td>91</td>
<td>86$^b$</td>
</tr>
<tr>
<td>5</td>
<td>$2d$</td>
<td>40</td>
<td>9</td>
<td>85</td>
<td>61$^e$ (85$^{b,d}$)</td>
</tr>
<tr>
<td>6</td>
<td>$2e$</td>
<td>60</td>
<td>1</td>
<td>81</td>
<td>61$^e$ (85$^{b,d}$)</td>
</tr>
<tr>
<td>7</td>
<td>$2f$</td>
<td>40</td>
<td>5.5</td>
<td>82</td>
<td>84$^f$</td>
</tr>
<tr>
<td>8</td>
<td>$2h$</td>
<td>40</td>
<td>5</td>
<td>89</td>
<td>90$^h$</td>
</tr>
<tr>
<td>9</td>
<td>$2i$</td>
<td>40</td>
<td>5</td>
<td>85</td>
<td>82$^b$</td>
</tr>
<tr>
<td>10</td>
<td>$2j$</td>
<td>40</td>
<td>17.5</td>
<td>82</td>
<td>n.d.$^{x,y}$</td>
</tr>
<tr>
<td>11</td>
<td>$2k$</td>
<td>60</td>
<td>1</td>
<td>72</td>
<td>78$^g$ (91$^{d,h}$)</td>
</tr>
<tr>
<td>12</td>
<td>$2l$</td>
<td>40</td>
<td>6</td>
<td>94</td>
<td>97$^b$</td>
</tr>
<tr>
<td>13</td>
<td>$2m$</td>
<td>40</td>
<td>5</td>
<td>85</td>
<td>82$^b$</td>
</tr>
<tr>
<td>14</td>
<td>TMS</td>
<td>40</td>
<td>17.5</td>
<td>82</td>
<td>n.d.$^{x,y}$</td>
</tr>
<tr>
<td>15</td>
<td>$2n$</td>
<td>60</td>
<td>1</td>
<td>87</td>
<td>n.d.$^{x,y}$</td>
</tr>
<tr>
<td>16</td>
<td>$2o$</td>
<td>40</td>
<td>3.5</td>
<td>65</td>
<td>44$^l$</td>
</tr>
<tr>
<td>17</td>
<td>$2p$</td>
<td>60</td>
<td>40</td>
<td>39</td>
<td>44$^l$</td>
</tr>
<tr>
<td>18</td>
<td>$2q$</td>
<td>40</td>
<td>5</td>
<td>73</td>
<td>59$^k$</td>
</tr>
</tbody>
</table>

$a$: Isolated yields. $b$: $X_a$ (2.0 equiv.), MgO (2.0 equiv.), DME (1.0 mol/L), r.t., 2 h.$^{11}$ $c$: The yield was determined by $^1$H-NMR analysis because a small amount of $Y_b$ could not be separated from $2e$. $d$: The yield was determined by $^1$H-NMR analysis because a small amount of $Bn_2O$ could not be separated from $2c$. $e$: $X_a$ (2.0 equiv.), MgO (2.0 equiv.), DME (1.0 mol/L), r.t., 4 h.$^{11}$ $f$: $X_a$ (3.0 equiv.), MgO (3.0 equiv.), DME (1.0 mol/L), r.t., 19 h.$^{11}$ $g$: $X_a$ (3.0 equiv.), MgO (3.0 equiv.), DME (1.0 mol/L), r.t., 7 h.$^{11}$ $h$: $X_a$ (3.0 equiv.), MgO (3.0 equiv.), DME (1.0 mol/L), r.t., 2 h.$^{11}$ $i$: Dudley reagent (2.0 equiv.), MgO (2.0 equiv.), PhCF$_3$ (0.1–0.5 mol/L), 83°C, 24 h.$^{14}$ $j$: The authors described that the yield was not determined because a small amount of $Bn_2O$ could not be separated from $2k$. $k$: Dudley reagent (2.0 equiv.), PhCF$_3$, 120°C (MW), 20 min.$^{17}$

In the case of these benzylation reagents, the Hammett plot for the degradation rate also provides a good linear relation (Fig. 3). The positive $\rho$ value (3.471) shows that electron-withdrawing groups stabilize the transition state by delocalization of the electron density increasing on the morpholine nitrogen. These results indicate that the reactivity of $X$ can be modulated by the inclusion of electron-donating or electron-withdrawing substituents on the triazine ring using the $\sigma_m$ as an indicator.

The low reactivity of $X_b$ is an advantage from an experimental point of view. The benzylation using DPT-BM ($X_a$) must be initiated by adding the reagent in the solid state to...
the alcohol solution under anhydrous conditions because DPT-
BM (X-a) rapidly decomposes when dissolved in a solvent. In
contrast, the benzylating reaction with X-b can be conducted
using a pre-prepared solution of X-b, which can be added to
a solution of reactants because X-b has a sufficient stability
to allow it to be dissolved in a solvent at room temperature.

a: These crossover experiments were performed in the presence of an equimolar amount of morpholinotriazines and a benzylating reagent. b: The product ratio was determined by 1H-NMR analysis.

Chart 2. The Crossover Experiments of Y in the Presence of Benzyl Cation Species
Therefore, the initiation and rate of benzylation reaction can be controlled by heating the reactant solution prepared at room temperature to an appropriate temperature.

In conclusion, we successfully developed a new benzylation reagent, X-b, by replacing the phenoxy groups on DPT-BM (X-a) with bulky t-butyl groups. The incorporation of two t-butyl groups into the triazine ring of the benzylating reagent inhibited the side reaction to form N-benzytriazinium Y-b because the morpholinotriazine Z-b cannot undergo reaction with BrONTF owing to the steric hindrance of the t-butyl groups. Hence, the O-benzylation of alcohols with a stoichiometric amount of X-b (1.2 equiv.) afforded benzyl ethers in good to high yields. A solution of X-b is stable, allowing its treatment at room temperature; however, the benzylation proceeds at 40°C. As a result of the kinetic study, the electronic effect of the substituents installed on the triazine ring affects the reactivity of the benzylating reagents. This result indicates that the leaving abilities of the morpholinotriazines correlate with the reactivity of the corresponding benzylating reagent and can be controlled by the substituents on the triazine core.

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**Conflict of Interest** The authors declare no conflict of interest.

**Supplementary Material** The online version of this article contains supplementary materials (detailed experimental procedure, physical data, and NMR spectra of isolated products).

**References and Notes**

21) The reason for the decrease in the reaction rate at a high concentration is unclear. As we previously reported in ref. 11, as the concentration of DPT-BM (X-a) increases, the degradation rate of DPT-BM (X-a) becomes slow. We assume that the benzylation with X-b at a high concentration exhibits a similar effect.
22) See supplementary materials for the synthesis of these morpholinotriazines.

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**Fig. 2.** The Generation of Benzyl Cation Species from DPT-BM (X-a).

**Fig. 3.** Hammett Plot for Degradation of the Benzylating Reagents X.

<table>
<thead>
<tr>
<th>X</th>
<th>$k 	imes 10^{-3}$ (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-a</td>
<td>35.5</td>
</tr>
<tr>
<td>X-b</td>
<td>0.1</td>
</tr>
<tr>
<td>X-c</td>
<td>2.5</td>
</tr>
<tr>
<td>X-d</td>
<td>5.0</td>
</tr>
</tbody>
</table>

$a$ The log($k 	imes 10^{-3}$), which is based on $k$ in Table 4, vs. the sum of $\sigma_m$ are shown in this plot. See the supporting information for details.