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Development of a Storable Triazinone-Based Reagent for *O*-*p*-Methoxybenzylation under Mild Heating Conditions

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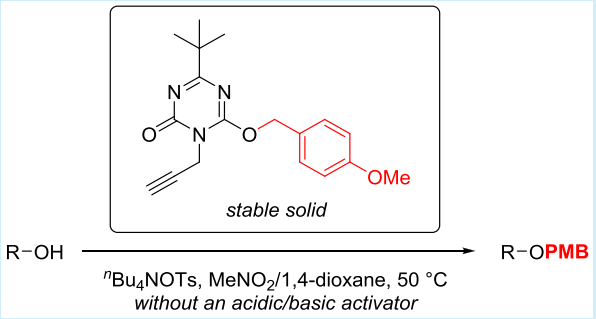
Supporting Information

ABSTRACT: A new triazinone-based reagent for *O*-*p*-methoxybenzylation has been developed. In spite of its stability in solid form, this reagent converts a free alcohol into the corresponding *p*-methoxybenzyl ether with mild heating (50−60 °C) in a solution. High functional group tolerance can be achieved because the reaction does not require the addition of an acidic or basic activator.



The *p*-methoxybenzyl (PMB) group is one of the most useful protecting groups for alcohols owing to the high stability of PMB ethers under a wide range of reaction conditions.[1] Unlike benzyl protection, the PMB group can be cleaved under mild oxidative or acidic conditions, and it thus enables selective transformation in multistep syntheses. PMB ethers are commonly prepared by Williamson ether synthesis by using PMB chloride (Figure 1) with a strong base such as

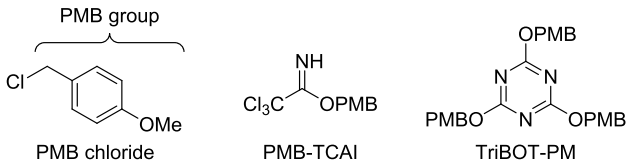


Figure 1. Reagents to convert alcohols into PMB ethers under basic or acidic conditions.

sodium hydride. However, this method is difficult to apply to alcohols with base-labile functionalities. Furthermore, the use of PMB chloride on a large scale is undesirable because it is not only a lachrymator but also a potentially hazardous chemical.[2] In fact, addition of a stabilizer (potassium or calcium carbonate) is required to prevent autocatalytic production of HCl gas, which may cause overpressurization and rupture of containers. To overcome the problems of PMB chloride, a number of *O*-*p*-methoxybenzylating reagents have been developed in the past few decades.[3−18] For example, PMB 2,2,2-trichloroacetimidate (PMB-TCAI, Figure 1) is widely used to introduce the PMB group under nonbasic conditions,[3] although the stability of this reagent is not satisfactory for long-term storage. In 2013, we reported 2,4,6-tris(*p*-methoxybenzyloxy)-1,3,5-triazine (TriBOT-PM, Figure 1) as a stable and easy-to-handle reagent for PMB ether synthesis.[4] However, these reagents require an activator such as a Brønsted/Lewis acid[3−15] or an electrophile[16−18] for the reaction. Because of this, the limitation of functional group compatibility is still inevitable. Although thermal *O*-*p*-methoxybenzylation with PMB-TCAI was found to proceed in the absence of an activator, the harsh reaction conditions (>100 °C, ∼24 h) would be problematic if the alcohol has sensitive functionalities.

We report herein a new, storable reagent for *O*-*p*-methoxybenzylation under mild heating conditions without the use of an activator. The synthesis of the new *p*-methoxybenzylating reagent **1** is shown in Scheme 1. The core structure 1,3,5-triazin-2(1*H*)-one, which was previously evaluated in our study on acid-catalyzed benzylating reagents,[19] achieved the compatibility between the reactivity and stability of **1**. On the basis of our previous findings, the substituents of **1** (the *tert*-butyl and *N*-propargyl groups) were rationally designed to suppress an *N*-alkylating side reaction that was occasionally observed in the reaction of triazine-based alkylating reagents.[4,20−24] The sterically bulky *tert*-butyl group on the triazine ring effectively reduced the *N*-benzylating side reaction caused by benzyl cation species.[25] In addition, the fixation of the heterocyclic core structure through the introduction of the *N*-substituent inhibited the side reaction that occurred via core structure isomerization during acid-

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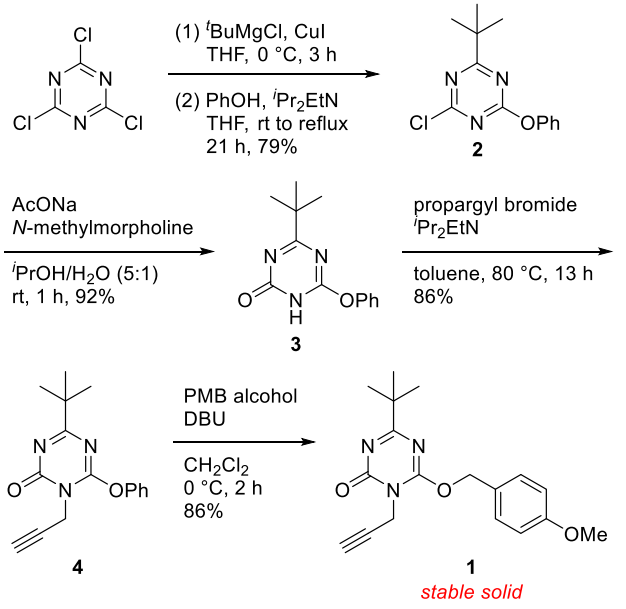
Scheme 1. Synthesis of the New *p*-Methoxybenzylating Reagent 1

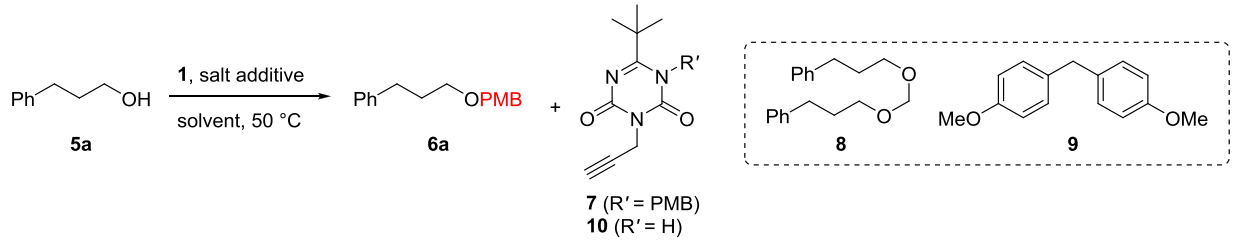


catalyzed *O*-benzylation.[26] The propargyl group was selected to be the *N*-substituent for **1**.[27]

As shown in Scheme 1, we synthesized **1** via intermediates **2**–**4** in 54% overall yield through selective and successive substitution of the three chlorides in 2,4,6-trichloro-1,3,5-triazine. The phenoxy group was used as a temporal substituent. Compound **1** was isolated as a stable solid and stored in a refrigerator (~5 °C) for up to 22 months. No detectable decomposition was observed after **1** was stored at room temperature (25–30 °C) under open air for 20 days (Figure S1).

Next, we carried out *O*-*p*-methoxybenzylation of 3-phenylpropanol (**5a**) by using 1.5 equiv of **1** (Table 1). The corresponding PMB ether **6a** was obtained upon heating them together at 50 °C for 4 h in $MeNO_2$ (entry 1). However, the yield was moderate (63%) because *N*-*p*-methoxybenzylated triazinedione **7** was formed competitively in 45% yield. $MeNO_2$ gave the best **6a**/**7** ratio among the solvents screened (Table S1). Because an iodide salt is often used in Williamson ether synthesis to facilitate the nucleophilic substitution,[1] we added tetra-*n*-butylammonium iodide ($^nBu_4NI$, 20 mol %) to the reaction mixture (entry 2). As a result, the yields of **6a** and **7** were changed (33% and 65%, respectively), indicating that the addition of a salt can affect the reaction selectivity. The bromide salt ($^nBu_4NBr$) gave a result similar to that with $^nBu_4NI$ (entries 2 versus 3), whereas the salts composed of trifluoromethanesulfonate and *p*-toluenesulfonate ($^nBu_4NOTf$, entry 4; $^nBu_4NOTs$, entry 5) afforded improved yields of **6a** (80% and 84%, respectively). An increased reaction concentration (from 0.4 to 0.6 M) further improved the yield (90%, entry 6). However, an increase in the salt amount (from 20 to 100 mol %) had no effect (entries 7 versus 6). The use of 1-ethyl-3-methylimidazolium methanesulfonate (emimOMs) also gave **6a** in 90% yield (entry 8). When the reaction was carried out by using **1** (2 equiv) with $^nBu_4NOTs$ (entry 9), we found **6a** (90%) along with small amounts of symmetric acetal **8** and bis(*p*-methoxyphenyl)methane (**9**) in the crude mixture. These byproducts suggested a side reaction between **6a** and a PMB cation species via a Friedel–Crafts type reaction pathway.[4,28] To suppress this side reaction, we conducted the reaction in the presence of ethereal solvents because the Friedel–Crafts-type side reactions were considerably inhibited by these solvents in our previous study of acid-catalyzed *O*-

Table 1. Conditions Screening for *O*-*p*-Methoxybenzylation of 5a with 1



entry	solvent	**1** (equiv)	salt additive (mol %)	concn (M)	time (h)	**6a**[a] (%)	**7**[a] (%)
1	$MeNO_2$	1.5	none	0.4	4	63	45
2	$MeNO_2$	1.5	$^nBu_4NI$ (20)	0.4	10	33	65
3	$MeNO_2$	1.5	$^nBu_4NBr$ (20)	0.4	10	35	65
4	$MeNO_2$	1.5	$^nBu_4NOTf$ (20)	0.4	5	80	26
5	$MeNO_2$	1.5	$^nBu_4NOTs$ (20)	0.4	5	84	25
6	$MeNO_2$	1.5	$^nBu_4NOTs$ (20)	0.6	5	90	23
7	$MeNO_2$	1.5	$^nBu_4NOTs$ (100)	0.6	5	90	22
8	$MeNO_2$	1.5	emimOMs (20)	0.6	5	90	29
9	$MeNO_2$	2.0	$^nBu_4NOTs$ (20)	0.6	7	90	41
10	$MeNO_2$/1,2-dimethoxyethane (4:1)	2.0	$^nBu_4NOTs$ (20)	0.6	7	88	29
11[b]	$MeNO_2$/1,4-dioxane (4:1)	2.0	$^nBu_4NOTs$ (20)	0.6	7	93 (90)[c]	43
12[d]	chlorobenzene	2.0	$^nBu_4NOTs$ (20)	1.0	2	86	37
13[d]	MeCN	2.0	$^nBu_4NOTs$ (20)	1.0	1.5	89	45

[a]Calculated from ^1H NMR spectroscopic analysis by using an internal standard, unless otherwise noted. [b]The reaction was carried out on a 0.3 mmol scale. [c]Isolated yield. [d]The reaction was carried out at 80 °C.

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benzylation.[20] Whereas with $MeNO_2$/1,2-dimethoxyethane (4:1) as the solvent, the reaction afforded **6a** in 88% yield (entry 10), the use of $MeNO_2$/1,4-dioxane (4:1) provided an improved result (93% yield based on ^1H NMR analysis, 90% isolated yield, entry 11). Under the reaction conditions of entry 11, coproducts **7** and **10** were isolated in 35% and 65% yield based on **1**, respectively. Additionally, the *p*-methoxybenzylation of **5a** in chlorobenzene and acetonitrile under modified conditions (1.0 M, 80 °C) gave satisfactory yields (entries 12 and 13, 86 and 89% yield, respectively).

As shown in Figure 2, we conducted the *O*-*p*-methoxybenzylation of alcohols **5b**–**g** under the reaction conditions of

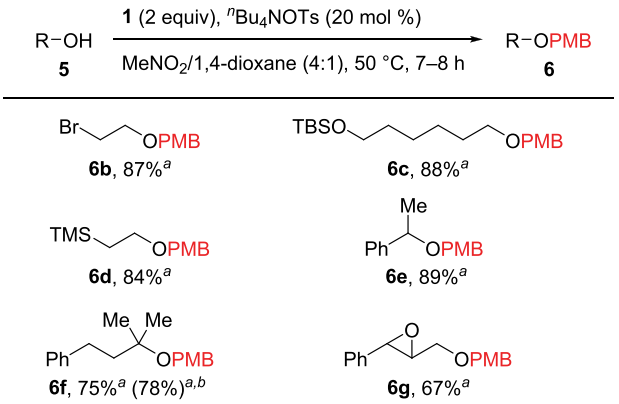
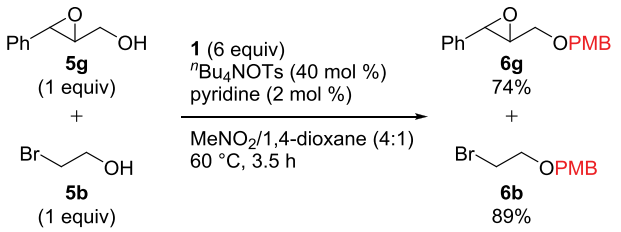


Figure 2. *O*-*p*-Methoxybenzylation of alcohols with sensitive functionalities by using **1**. (a) Isolated yields. (b) The reaction (7 h) was carried out with **1** (3 equiv).

entry 11 in Table 1. Since our purpose was to investigate the functional group tolerance, these known alcohols were selected although their *O*-*p*-methoxybenzylation reactions under appropriate conditions were reported individually. The reaction of 2-bromoethanol (**5b**), which is sensitive to bases and silver salts,[29] provided **6b** in 87% yield.[30] The *tert*-butyldimethylsilyl (TBS) group of the primary hydroxy group in **5c** survived during the *O*-*p*-methoxybenzylation to give **6c** in 88% yield.[7] The PMB ether of 2-(trimethylsilyl)ethanol (**5d**) was obtained in 84% yield despite the fact that **5d** can be decomposed via Peterson olefination under acidic or basic conditions.[4] Secondary alcohol **5e** provided the corresponding PMB ether **6e** in 89% yield, while tertiary alcohol **5f** afforded **6f** in 75% yield. The use of **1** (3 equiv) gave a slightly improved yield of **6f** (78%). The introduction of the PMB group into a highly acid-labile alcohol **5g** under acid-catalyzed conditions is known to be challenging.[30] It was reported that PMB ether **6g** was not obtained from **5g** under the standard conditions for *O*-*p*-methoxybenzylation with PMB-TCAI developed by Rai et al. [5 mol % $La(OTf)_3$, toluene, room temperature] because of the rapid decomposition of **5g**, whereas the use of boron trifluoride as a catalyst at low temperature provided **6g** only in 8% yield.[31] Product **6g** was obtained in 61% yield when the reaction was carried out with $La(OTf)_3$ at −78 °C in the presence of thioanisole. In contrast, our procedure with **1** afforded **6g** in 67% yield, which indicates the mildness of the reaction conditions. Furthermore, we found that the addition of a trace amount of pyridine was effective for this reaction (Table S2). As shown in Scheme 2, we carried out the *O*-*p*-methoxybenzylation of **5g** and **5b** together in one flask by using **1** in the presence of pyridine (2

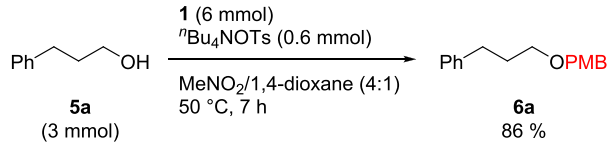
Scheme 2. *O*-*p*-Methoxybenzylation of 5g and 5b in One Flask with 1 in the Presence of a Trace Amount of Pyridine



mol %). As a result, **6g** and **6b** were obtained in 74% and 89% yield, respectively. This result is remarkable because all of the functionalities sensitive to acid, base, and silver salts in **5g** and **5b** were compatible under the reaction conditions.

As shown in Scheme 3, we carried out the synthesis of **6a** on a 3 mmol scale, which is 10 times larger than the reaction scale

Scheme 3. Synthesis of 6a with 1 on a 3 mmol Scale



of entry 11 in Table 1. As a result, **6a** was obtained in 86% yield, indicating the scalability of the *O*-*p*-methoxybenzylation with **1**.

The thermal behavior of **1** was studied by differential scanning calorimetry (DSC). Figure 3 shows the DSC curve

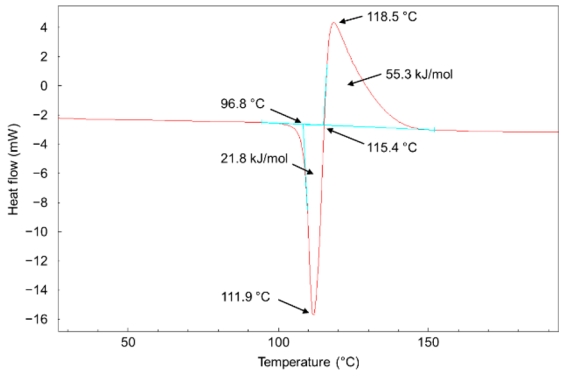


Figure 3. DSC curve for **1** at a heating rate of 10 °C/min.

for **1** at a heating rate of 10 °C/min. It was observed that the melting process (initiating at 96.8 °C, T_{min} = 111.9 °C) was immediately followed by an exothermal decomposition (initiating at 115.4 °C, T_{max} = 118.5 °C). Similar decompositions associated with melting were observed in some cases.[32,33] The melting enthalpy (21.8 kJ/mol) and the heat release of the decomposition reaction (55.3 kJ/mol) were determined for **1** by neglecting the superposition of the peaks.

To confirm the thermal decomposition of **1**, we heated **1** to 120 °C for 30 min without a solvent under a nitrogen atmosphere. No mass loss was observed after the heating, whereas we found that **1** was completely consumed and converted into **7** in 89% yield (determined by ^1H NMR analysis by using an internal standard), along with trace amounts of impurities including **10**.[34] Obviously, this O-to-N

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rearrangement reaction to form **7** produces no gas, and thus, **1** will have low risk for overpressurization of containers during storage, in contrast to PMB chloride.

As the PMB cation is more stable than the benzyl cation,[35] the reaction of **1** is likely to proceed via PMB cation species. This is supported by the formation of the Friedel–Crafts-type byproducts **8** and **9**. The plausible reaction mechanism is shown in Figure 4. Heating in a solution facilitates the ionization of **1** into intimate ion pair **11**, which can form *N*-PMB-rearranged product **7** despite the steric hindrance of the *tert*-butyl group. An alcohol reacts with **11** to afford the corresponding PMB ether and coproduct **10**. When $^{n}Bu_4NOTs$ is present in the reaction mixture, **11** would be separated by conversion into PMB *p*-toluenesulfonate[36] and $^{n}Bu_4N$ salt **12**. *O*-*p*-Methoxybenzylation of an alcohol with PMB *p*-toluenesulfonate provides the PMB ether, along with *p*-toluenesulfonic acid, which is captured by **12** to give **10** and regenerate $^{n}Bu_4NOTs$.

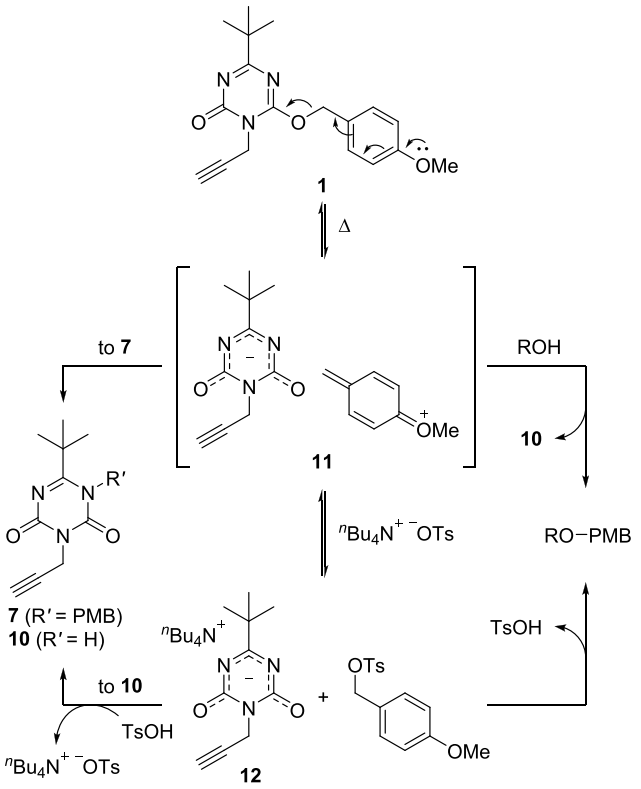

Figure 4. Plausible reaction mechanism for *O*-*p*-methoxybenzylation with **1**.

In conclusion, we have developed the *O*-*p*-methoxybenzylation of alcohols by using triazinone-based reagent **1**, which is stable to storage and can be handled in solid form. The *O*-*p*-methoxybenzylation with **1** proceeded without problems on a 3 mmol scale. DSC analysis with thermal decomposition study revealed that **1** decomposes to a rearranged product at around 115 °C. On the other hand, **1** is sufficiently reactive in solution under mild heating conditions (50–60 °C) to convert a free alcohol into the PMB ether. Therefore, **1** can be considered as a ready-to-use, synthetic PMB cation equivalent. The reaction of **1** was carried out with a neutral salt ($^{n}Bu_4NOTs$) but without an acidic, basic, or electrophilic activator, so it was compatible with sensitive functional groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00732.

Tables S1 and S2, experimental details, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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