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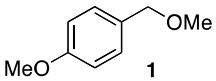
ABSTRACT

para-Methoxybenzyl methyl ether acts as an alkylating agent for thiols in the presence of trimethylsilyl trifluoromethanesulfonate and trialkylamine base in good yields (58-96%). Aryl ketones are alkylated under similar conditions, probably through an enol silane intermediate, also in high yields (67-95%). The active alkylating species is likely a *p*-methoxybenzyl cation.

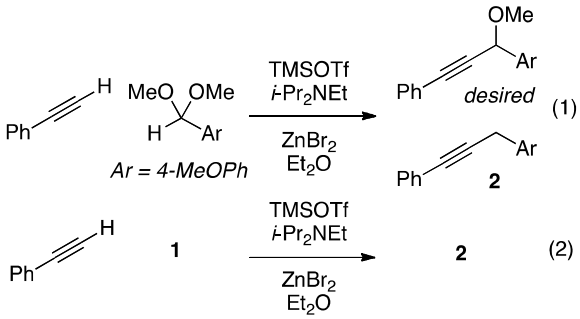
Keywords: *alkylation; methyl ethers; silyl triflates; enol silanes*

Alkylation of thiols and α-alkylation of carbonyl compounds is typically carried out by treatment of the substrate with a strong base and an alkyl halide. The efficiency of this process, however, is counterbalanced by the harsh reaction conditions, which often limit the substrate scope, and the notorious toxicity of common alkylating agents. Notable effort has been made to replace alkyl halides with alcohols, which may be activated under Brønsted or Lewis acidic conditions,[1,2] but to our knowledge the use of methyl ethers as alkylating agents is largely unexplored. Indeed, the stability of methyl ethers has led to their frequent use as protecting groups,[3] and they are generally regarded as inert except under extreme reaction conditions. Examples of methoxy substituents acting as leaving groups are extremely rare, despite pioneering efforts by Ranu and coworkers.[1a,4] Here, we report a mild and effective method for the activation of *para*-methoxybenzyl methyl ether (PMBME, **1**) by trimethylsilyl trifluoromethanesulfonate (TMSOTf), and the effective use of the resultant benzyl cation as an alkylating agent for thiols and aryl alkyl ketones.



1 *p*-methyoxybenzyl methyl ether (PMBME)

Previous work in our group has demonstrated that TMSOTf capably mediates the condensation of ketones with dimethyl acetals through a one-pot process, during which an enol silane generated in situ attacks an acetal activated by TMSOTf through extrusion of TMSOMe.[5] When we sought to employ catalytically generated zinc acetylides with acetal electrophiles, however, substrate scope was surprisingly poor.[6] Typically, the acetylide reactions were hampered by significant byproduct formation, especially in the case of anisaldehyde dimethyl acetal (eq 1). When isolated, the byproduct appeared to be deoxygenated alkylation product **2**. Because earlier work in our laboratory showed that dimethyl acetals may be reduced to methyl ethers in the presence of TMSOTf and *i*-Pr_2NEt,[3b] we replaced the dimethyl acetal in the reaction with independently synthesized *p*-methoxybenzyl methyl ether (**1**).[7] The same PMB-bearing byproduct was observed (eq 2).

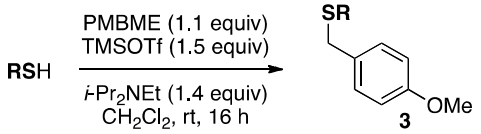


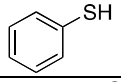
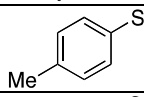
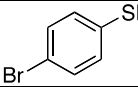
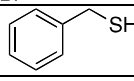
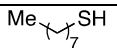
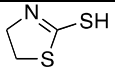
We hypothesized that PMBME acts as a vinylogous dimethyl acetal, which may generate a benzyl cation when treated with TMSOTf. Various attempts to alkylate zinc acetylides with PMBME failed to provide a reproducibly efficient reaction, however, because of competing terminal silylation of the zinc acetylide.[8] Nonetheless, the intriguing ability of PMBME to act as an alkylating agent led us to examine other nucleophiles that are compatible with TMSOTf. The use of silylated thiol nucleophiles in thioketalization reactions,[9] heteroconjugate additions,[10] and epoxide openings[11] is well established. Very recently, Baba et al. reported the indium-catalyzed alkylation of silylated thiols with alkyl acetates.[12] Accordingly, in situ generation of a silylated thiol in the presence of a benzyl cation appeared to be a prime opportunity to observe alkylation. Optimization studies suggested that the use of *i*Pr_2NEt and CH_2Cl_2 was optimal for efficient alkylation in the presence of TMSOTf (Table 1). The reaction performed well even when PMBME was the last reactant added to the mixture, which suggests that silylated thiols formed in situ are quite reactive with the putative cationic electrophile. The reaction was somewhat sensitive to the stoichiometry of PMBME. To wit, when greater than 1.1 equiv PMBME was present, byproduct generation often resulted from either overalkylation at sulfur or Friedel–Crafts alkylation of the aryl rings on the product.

A brief survey of the reaction scope revealed that aryl thiols are excellent substrates (entries 1-3). In the case of 4-bromothiophenol (entry 3), a larger excess of PMBME could be used without competing byproduct formation, which resulted in very high yield. Aliphatic thiols were more challenging. Although benzyl thiol underwent alkylation with moderate yield (entry 4), octanethiol did

not provide any thioether product under our reaction conditions (entry 5). Previous experience with aliphatic thiols in our group suggested that a stronger base might be necessary to activate octanethiol,[13] but replacement of trialkylamines with KO*t*-Bu under a variety of conditions did not result in an increase in yield.

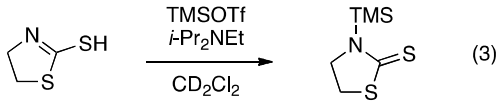
Table 1
Alkylation of thiols with PMBME



entry[a]	RSH	product	yield (%)[b]
1		**3a**	75
2		**3b**	89
3		**3c**	96[c]
4		**3d**	58
5		**3e**	ND[d]
6		**3f**	70[e]

[a]All reactions performed on 1.00 mmol scale in 5 mL CH_2Cl_2. [b]Isolated yield after chromatography. [c]Reaction performed with 1.5 equiv PMBME. [d]ND = not determined. [e]Reaction performed with 1.3 equiv TMSOTf and 1.2 equiv *i*Pr_2NEt.

When 2-mercaptothiazoline was subjected to the reaction conditions, it provided the *S*-alkylation adduct with no observed reactivity at the nitrogen center (entry 6), a result in accord with literature precedent[14] and in striking contrast to the highly regioselective *N*-acylation reactions of this substrate.[15] When TMSOTf, *i*Pr_2NEt, and 2-mercaptothiazoline were mixed in CD_2Cl_2, ^{13}C NMR spectroscopy showed the presence of a peak at 206 ppm. This resonance is consistent with the presence of a thiocarbonyl, which suggests that silylation of 2-mercaptothiazoline occurs primarily at nitrogen (eq 3). This *S*-silylation may prevent competitive *N*-alkylation when PMBME is included in the reaction mixture.

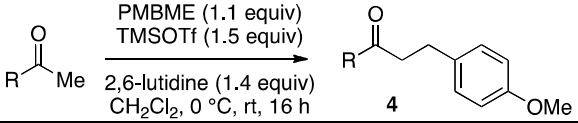


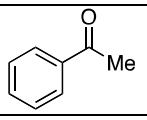
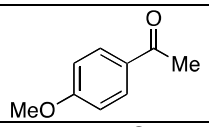
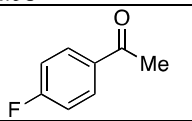
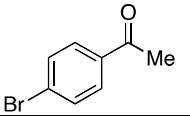
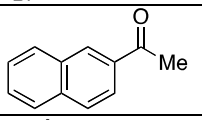
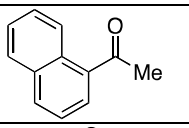
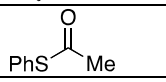
(3)

Encouraged by the ability of PMBME to act as an efficient alkylating agent for thiols, we moved on to aryl ketone pronucleophiles. These alkylation reactions require the in situ generation of enol silane nucleophiles through the action of trialkylamine base and TMSOTf, such that the silylating agent must play a role in the activation of both the nucleophile and the electrophile if alkylation is to occur. Previous work from our group suggested that enol silane generation would not be problematic,[5a,16] and we were gratified to observe high yields of the alkylation product for a variety of aryl ketones (Table 2). Again, the use of larger excesses of PMBME (e.g., 1.5 equiv) consistently generated byproducts derived from Friedel–Crafts alkylation of the desired product with excess PMBME.

A range of electron-rich and electron-poor acetophenone derivatives reacted smoothly, as did the more sterically encumbered acetonaphthones (Table 2, entries 1-6). Propiophenone appeared to be unreactive, but modest success was achieved with the thioester substrate *S*-phenyl thioacetate. The yield for thioester **4g** was reduced because of significant byproduct formation. Analysis of the byproduct showed that it was thiophenol alkylation adduct **3a**, presumably generated through deacylation of the thioester and subsequent attack of the thiolate-derived nucleophile upon the PMB cation.

Table 2
Alkylation of aryl ketones with PMBME



entry	RCOMe	product	yield[b]
1		**4a**	82
2		**4b**	67
3		**4c**	88
4		**4d**	92
5		**4e**	82
6		**4f**	75
7		**4g**	47[c]

[a]All reactions performed on 1.00 mmol scale in 5 mL CH_2Cl_2. [b]Isolated yield after chromatography. [c]Reaction performed with Et_3N instead *i*Pr_2NEt, and was stirred 1 h instead of 16 h. Major byproduct was thioether **3a**.

Despite the successes presented here, nucleophile scope for this reaction is somewhat narrow. Most notably, alcohol- and amine-based nucleophiles failed to produce appreciable yields of PMB-protected material, instead undergoing rapid silylation under our reaction conditions. Replacement of PMBME with related methyl ethers was disappointing. Both *m*-methoxybenzyl methyl ether and the unsubstituted benzyl methyl ether were unreactive, presumably because there was no properly positioned methoxy group to help stabilize the required cationic intermediate through conjugation.

Other electron-rich variants, including *o*-methoxybenzyl methyl ether and 2-furylmethyl methyl ether, rapidly decomposed when treated with TMSOTf. The promise of these in situ-generated benzyl cations is intriguing, however, and further studies that target other synthetic applications are underway.

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6. For a successful approach this strategy, see (a) Watson, M. P.; Maity, P. *Synlett* **2012**, *23*, 1705-1708. (b) Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 17142-17145.
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8. Rahaim, R. J.; Shaw, J. T. *J. Org. Chem.* **2008**, *73*, 2912-2915.
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