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COMMUNICATION

Microwave-assisted benzyl-transfer reactions of commercially available 2-benzyloxy-1-methylpyridinium triflate†

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Benzylation of alcohols and other substrates under thermal conditions translates smoothly from conventional heating into MW-assisted organic synthesis (MAOS). Reactions times are decreased from hours to minutes while good to excellent yields are maintained. MW heating should be considered for benzylation of high-value substrates using the title reagent.

Benzyl ethers and esters are ubiquitous for the protection of alcohols and carboxylic acids in chemical synthesis.[1] The benzyl group is inert to most common reaction conditions, yet it is susceptible to cleavage on command using a variety of mild protocols. The synthesis of benzyl ethers from alcohols has traditionally been accomplished under basic or acidic conditions (using benzyl bromide or trichloroacetimidate, respectively). We recently offered 2-benzyloxy-1-methylpyridinium triflate (**1**) as a complementary option using neutral, thermal conditions.[2]

The advantage of using **1**[3] for the benzylation of acid- and/or base-sensitive alcohols is clear from literature reports in which its unique effectiveness has been noted (Fig. 1).[4] As this reagent gains popularity, we considered it worthwhile to revisit our reagent development efforts in order to minimize certain disadvantages. Namely, the prolonged heating needed to activate the reagent can be detrimental to sensitive substrates, and the standard use of excess reagent increases costs and can increase the formation of by-products, most notably dibenzyl ether.[3b] We reasoned that these disadvantages could possibly by attenuated using rapid and efficient microwave (MW) heating;[5] reports of MW heating of ionic liquids[6] fuelled our optimism with respect to reactions involving **1**, an ionic reagent.

MW heating of organic reactions has been associated with reduced reaction times and, in many cases, higher chemical yields and fewer by-products, typically based on the ability of dedicated MW reactors to produce (and reproduce) heating profiles that are difficult to generate using conventional heating methods. The benefits of MW heating are most commonly observed in systems involving polar solvents and/or solutes, which convert incident MW radiation into heat more effectively than nonpolar solutes owing to higher loss tangents (tan δ) for polar molecules. Benzyl-transfer reactions of **1** meet these criteria, so we investigated a representative sample of diverse substrates using MW heating that we had previously examined using conventional heating. Specifically, we looked at primary and secondary alcohols, carboxylic acids, and electron-rich aromatic systems, all of which are good substrates for benzylation using **1**. We also tested the benzylation of tertiary alcohols and phenols, which have been problematic substrates. In all cases, MW-assisted benzylations were accomplished in comparable yield with dramatic reductions in reaction times, as described in the following paragraphs.

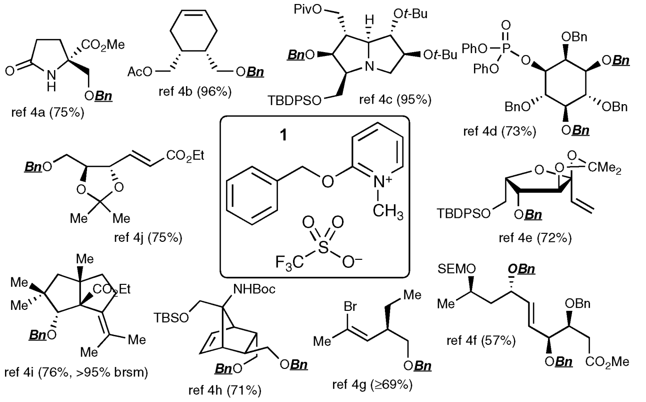

Fig. 1 2-Benzyloxy-1-methylpyridinium triflate (**1**), and benzyl ethers (O**B̲n̲**) optimally or uniquely prepared using **1** (yield in parentheses).

We first examined the benzylation of diethylene glycol, monomethyl ether (DEGME, **2a**, eqn (1)). Our original protocol, developed for maximum generality, involves heating at *ca.* 83 °C for 24 h in the presence of magnesium oxide (MgO, an acid scavenger).[3b] The sealed vessel capabilities of dedicated MW reactors make it convenient to heat reaction mixtures above the boiling point of the solvent ($PhCF_3$, b.p. 102 °C). After screening multiple sets of conditions, we settled on heating at 120 °C for 20 min. DEGME, like other primary alcohols, is an excellent substrate for benzylation, so one can reduce the stoichiometry of **1** and omit MgO as shown in eqn (1).[7]

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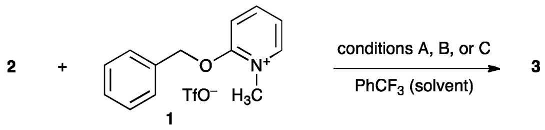
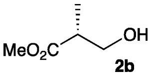
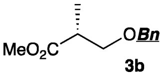
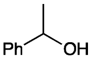
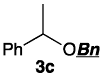
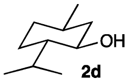
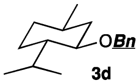
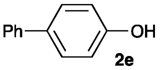
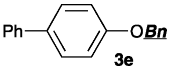
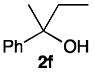
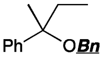
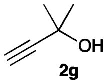
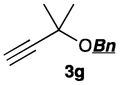
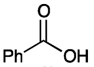
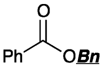
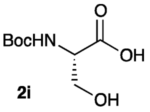
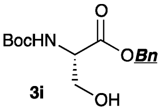
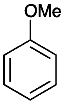
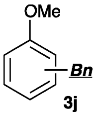
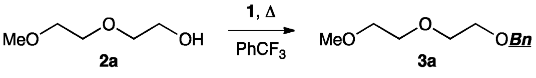
Table 1 Benzyl-transfer reactions of **1** with various alcohols, carboxylic acids, and other substrates under MW heating



Entry	Substrate	Conditions^a	Product	Yield^{b,h}
1^c	**2a**	A	**3a**	98% (93%)
2^c	 **2b**	A	 **3b**	98% (85%)
3	 **2c**	A	 **3c**	70%^{d} (83%)
4	 **2d**	A	 **3d**	70%^{d} 82%^{d,e} (88%)
5^f	 **2e**	A	 **3e**	56%^{d} (65%)
6^f	 **2f**	A	 **3f**	48%^{d}
7^f	 **2g**	A	 **3g**	59%
8	 **2h**	B	 **3h**	94% (93%)
9	 **2i**	B	 **3i**	98% (91%)
10	 **2j**	C	 **3j**	91%^{g} (90%)

^{a} Conditions A: 2.0 equiv **1**, 120 °C (MW), 20 min. Conditions B: 2.0 equiv **1**, 2.0 equiv Et_3N, 120 °C (MW), 20 min. Conditions C: 5.0 equiv **2j**, 1.0 equiv **1**, 120 °C (MW), 20 min. ^{b} Refers to isolated yield of pure products, unless otherwise indicated. ^{c} 1.2 equiv of **1**. ^{d} Yield estimated by ^{1}H NMR spectroscopy; product could not be separated from Bn_2O by-product. ^{e} 1.0 equiv of diethylene glycol, dimethyl ether (diglyme) added. ^{f} 2.0 equiv of MgO added. ^{g} *ca.* 60 : 40 mixture of regioisomers. ^{h} Yields in parentheses refer to benzylation using conditions reported earlier (ref. 2).



Original conditions (ref 3b) : 2.0 equiv **1**, 2.0 equiv MgO, 83 °C (oil bath), 24 h, 93%
MW-optimized conditions : 1.2 equiv **1**, 120 °C (MW), 20 min, >95%

(1)

MW benzylation of diverse substrates is recounted in Table 1. Primary alcohols DEGME (**2a**) and the Roche ester (**2b**, a core building block for polypropionate synthesis) are shown in entries 1 and 2. Roche esters **2b** and **3b** are prone to elimination under non-neutral conditions, so the high yield in entry 2 is noteworthy. For substrates other than primary alcohols, it was necessary to use two equivalents of **1** to achieve full conversion (entries 3–9).

Thus, MW-promoted benzylation of other substrate types—secondary and tertiary alcohol, phenol, carboxylic acid,[2c] and arene[2d]—occurred with yields comparable to previous reports but all within the shortened reaction time (entries 3–10). Note the selectivity for benzylation of a carboxylic acid in the presence of an alcohol (entry 9), as reported previously.[2c] Selective esterification using **1** provides a convenient alternative to the use of diazomethane for making alkyl esters. Non-polar benzyl ethers **3a–f** could not be separated from dibenzyl ether (Bn_2O, a common by-product in these reactions[2]), so the reaction yields are estimated by analysis of the ^{1}H NMR spectrum after silica gel chromatography (entries 3–6). Interestingly, the yield of **3d** was improved by including 1.0 equiv of diethylene glycol, dimethyl ether (entry 4). This additive had no effect on other experiments; the rationale behind the improved yield in entry 4 is unclear.

Considering the cost and high molecular weight of **1** compared to, for example, benzyl bromide, **1** is perhaps most attractive for the benzylation of complex, high-value substrates, such as key intermediates in multi-step synthesis research (*cf.* Fig. 1). Such efforts typically involve lab-scale experimentation, which coincidentally is also the arena in which MAOS has had the most impact (as opposed to chemical process or manufacturing-scale activities). Thus, MW heating protocols should be widely applicable for activating the title reagent (**1**).

Conclusions

MW-assisted benzylation reactions using 2-benzyloxy-1-methylpyridinium triflate (**1**) are reported. Representative substrates are benzylated upon heating either in an oil bath[2] or MW reactor, but MW experiments can be conducted conveniently at higher temperatures and at dramatically reduced reaction times. For those considering installing benzyl ethers onto high-value alcohols or carboxylic acids, we recommend using MW technology in the development of the optimal protocol.

Notes and references

1 P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, 4th ed., Wiley, Hoboken, New Jersey, 2007.

2 (*a*) K. W. C. Poon, S. E. House and G. B. Dudley, *Synlett*, 2005, 3142; (*b*) K. W. C. Poon and G. B. Dudley, *J. Org. Chem.*, 2006, **71**, 3923; (*c*) J. Tummatorn, P. A. Albiniak and G. B. Dudley, *J. Org. Chem.*, 2007, **72**, 8962; (*d*) P. A. Albiniak and G. B. Dudley, *Tetrahedron Lett.*, 2007, **48**, 8097.

3 (*a*) Dudley Benzylation Reagent, *In ChemFiles*, 2007, 7, p. 3; (*b*) K. W. C. Poon, P. A. Albiniak and G. B. Dudley, *Org. Synth.*, 2007, **84**, 295; (*c*) G. B. Dudley, 2-Benzyloxy-1-methylpyridinium trifluoromethanesulfonate, In *Electronic Encylopedia of Reagents for Organic Synthesis*, ed. L. Paquette, P. Fuchs, D. Crich, G. Molander, Wiley: Chichester10.1002/047084289X.rn00906, Posting Date: Sept. 15, 2008; (*d*) P. A. Albiniak and G. B. Dudley, *Synlett*, 2010, 841.

4 (*a*) V. Caubert, J. Massé, P. Retailleau and N. Langlois, *Tetrahedron Lett.*, 2007, **48**, 381; (*b*) J. P. Schmidt, S. Beltrán-Rodil, R. J. Cox, G. D. McAllister, M. Reid and R. J. K. Taylor, *Org. Lett.*, 2007, **9**, 4041; (*c*) S. Stecko, J. Solecka and M. Chmielewski, *Carbohydr. Res.*, 2009, **344**, 167; (*d*) C. M. Longo, Y. Wei, M. F. Roberts and S. J. Miller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4158; (*e*) D. Lo Re, F. Franco, F. Sánchez-Cantalejo and J. A. Tamayo, *Eur. J. Org. Chem.*, 2009, 1984; (*f*) M. Binanzer, G. Y. Fang and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2010, **49**, 4264; (*g*) M. A. McGowan, C. P. Stevenson, M. A. Schiffler and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2010, **49**, 6147; (*h*) G. M. Chinigo, A. Breder and E. M. Carreira, *Org. Lett.*, 2011, **13**, 78; (*i*) D. F. Taber and C. G. Nelson, *J. Org. Chem.*, 2011, **76**, 1874; (*j*) T. Tomioka, Y. Yabe, T. Takahashi and T. K. Simmons, *J. Org. Chem.*, 2011, **76**, 4669.

5 C. O. Kappe, D. Dallinger and S. S. Murphree, *Practical Microwave Synthesis for Organic Chemists. Strategies, Instruments, and Protocols*, Wiley-VCH, Weinheim, 2009.

6 R. Martínez-Palou, *Mol. Divers.*, 2010, **14**, 3.

7 One can reproduce these conditions under conventional heating by immersing a resealable reaction vessel in a pre-heated oil bath, but this protocol provides lower yield (89%) and is less convenient than using the dedicated MW reactor.