Tetrahedron Letters 54 (2013) 5118–5121

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

p-Methoxybenzyl-*N*-phenyl-2,2,2-trifluoroacetimidate: a versatile reagent for mild acid catalyzed etherification

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ARTICLE INFO

Article history:
Received 12 June 2013
Revised 3 July 2013
Accepted 9 July 2013
Available online 18 July 2013

Keywords:
p-Methoxybenzylation
Acid catalyzed etherification
Rare earth metal triflate
Regioselective etherification

ABSTRACT

PMB-NPTFA **1a** is a new month bench stable and powerful reagent for the formation of PMB ethers. Several alcohols were protected in high yields and short reaction times, using low reagent loading and small catalytic amounts of $Bi(OTf)_3$. The mild conditions of the reaction confer a good orthogonality to acid- and base-sensitive protecting groups.

Among the substituted benzyl type protecting groups, *p*-methoxybenzyl (PMB) ethers occupy a central position due to their orthogonality to benzyl ether (Bn) and their stability under basic, nucleophilic, and mildly acidic conditions.[1] They are commonly obtained from corresponding alcohol using PMBCl, in the presence of bases (NaH or Ag_2CO_3),[2] or *N*-(4-methoxybenzyl)-*o*-benzenedisulfonimide and NaH.[3] However, such basic conditions are not compatible with compounds prone to racemization or β-elimination and/or by alkali-labile protecting groups such as acetate or benzoate. Therefore, reagents allowing the preparation of PMB ethers under acid-catalyzed or even neutral conditions have been developed: (i) PMB-trichloroacetimidate **1b** (PMB-TCA);[4] (ii) PMB-trifluoroacetimidate;[5] (iii) pyridinium or tetrazole based reagent such as 2-(PMB)-3-nitropyridine,[6] PMB-2-pyridylthiocarbonate,[7] 5-PMBthio-1-phenyl-1*H*-tetrazole,[8] 2-(PMB)-4-methylquinoline;[9] (iv) PMB-4-pentenyl ether.[10] However, although good results have been reported with these reagents, none of them have reached the status of general reagent for the preparation of PMB ethers.

In the last decade, glycoside donors activated by a *N*-phenyl-2,2,2-trifluoroacetimidate (NPTFA) moiety have found extensive use in glycosylation reactions.[11] However there is, to our knowledge, no report on the use of *p*-methoxybenzyl-*N*-phenyl-2,2,2-trifluoroacetimidate **1a** (PMB-NPTFA) for the preparation of PMB ethers. The reported instability of benzyl-*N*-phenyl-2,2,2-trifluoroacetimidate reagent (Bn-NPTFA) may have discouraged attempts to prepare imidate **1a**.[12] We were thus pleased to find that PMB-NPTFA **1a** could be conveniently prepared from *p*-methoxybenzyl alcohol and *N*-phenyl-2,2,2-trifluoroacetimidoyl chloride[13] in the presence of NaH (Scheme 1) and easily isolated in 89% yield by simple extractive work up followed by crystallization. Interestingly, in crystalline form, PMB-NPTFA **1a** proved to be month bench stable, easy to handle, and soluble in a large variety of solvents.

The catalytic potential of $Bi(OTf)_3$ and rare earth metal triflates ($M(OTf)_3$) as versatile Lewis acids for several types of organic reactions is well documented.[14] $Yb(OTf)_3$, $Sc(OTf)_3$, and $La(OTf)_3$ have been shown to catalyze etherification reactions with PMB-TCA **1b**,[4f] while $Bi(OTf)_3$ and $Yb(OTf)_3$ were shown to promote glycosylation with NPTFA activated glycoside donors.[11] This prompted us to test whether $Bi(OTf)_3$ or $M(OTf)_3$ could also catalyze the etherification of alcohols with the PMB-NPTFA **1a**.

In order to test the ability of various $M(OTf)_3$ to promote etherification with reagent **1a**, the primary alcohol **2**[15] was used as a model. The first reactions were performed in DCM in the presence of 1.2 equiv **1a** and 4 Å molecular sieves (MS). $Sm(OTf)_3$ and $Nd(OTf)_3$ (5 mol %) proved to be the less efficient catalysts, leading to less than 25% yield after 1 h reaction at rt (Table 1, entries 1 and 2). In comparison, $Yb(OTf)_3$ and $Bi(OTf)_3$ (3 mol %) led to nearly quantitative yields after 1 h at 10 °C (entries 6 and 7), while In and Sc triflates showed intermediate reactivity (entries 4 and 5). However when $Nd(OTf)_3$ loading and reaction time were increased, the PMB ether **3** was formed in 98% yield (entry 3). Thus, all $M(OTf)_3$ tested proved to be able to catalyze the etherification of primary alcohol **2** with PMB-NPTFA **1a** in good yield and short reaction time, while the choice of the catalyst allows modulating the reaction rate. Due to its high reactivity and commercial availability in anhydrous form, $Bi(OTf)_3$ was selected as the catalyst

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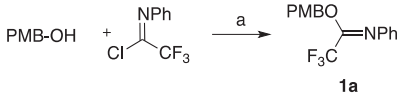
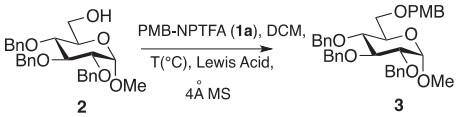
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.066



a. NaH, DCM, 0°C to rt, 2h, 89% by crystallization

Scheme 1. Preparation of PMB-NPTFA **1a**.

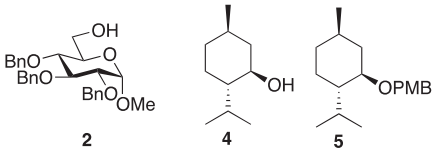
Table 1
Reaction of alcohol **2** and PMB-NPTFA **1a** with catalytic amounts of rare earth metal or bismuth triflates



Entry	Catalyst	(mol %)	*T* (°C)	Time (h)	Yield[a] (%)
1	$Sm(OTf)_3$	5	rt	1	25
2	$Nd(OTf)_3$	5	rt	1	15
3	$Nd(OTf)_3$	10	rt	3	98
4	$In(OTf)_3$	3	10	1	79
5	$Sc(OTf)_3$	3	10	1	83
6	$Yb(OTf)_3$	3	10	1	93
7	$Bi(OTf)_3$	3	10	1	93

Reaction conditions: PMB-NPTFA **1a** (1.2 equiv), [ROH] = 0.1 mol L^{-1}.
[a] Yields were determined using ^1H NMR of the crude reaction mixtures.

Table 2
Influence of solvent and MS nature on the $Bi(OTf)_3$ catalyzed etherification with PMB-NPTFA **1a**



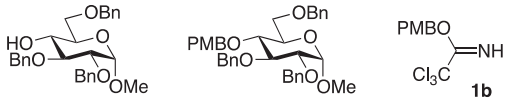
Entry	Alcohol	Solvent	MS	Time	Yield[a] (%)
1	**2**	DCM	4 Å[b]	1 h	92
2	**2**	DCM	AW300[c]	1 h	76
3	**2**	Toluene	4 Å[b]	1 h	98
4	**2**	Toluene	AW300[c]	1 h	80
5	**4**	DCM	4 Å[b]	2 h	52
6	**4**	Toluene	4 Å[b]	15 min	81

Reaction conditions: PMB-NPTFA **1a** (1.3 equiv), $Bi(OTf)_3$ (3 mol %), [ROH] = 0.1 mol L^{-1}, rt.
[a] Isolated yields.
[b] Conventional 4 Å MS.
[c] AW300 (4 Å acid-washed MS).

for further evaluation of the scope and limitations of the use of imidate **1a** for the preparation of PMB ethers.

Toluene and acid-washed MS have been reported to have beneficial effect on glycoside acetimidates or PMB-TCA **1b** activation leading to enhancement of reaction rates.[4f,14a,16] Thus, we next examined the influence of solvent and MS nature on the outcome of the reaction. In order to determine whether primary and secondary alcohols would react in the same way, alcohols **2** and **4** were both used as substrates with **1a** (1.3 equiv), $Bi(OTf)_3$ (3 mol %), either in DCM or toluene and with conventional or acid washed 4 Å MS (AW300). Primary alcohol **2** reacted faster in DCM than secondary alcohol **4** (Table 2, entries 1 and 5). Gratifyingly, with the later substrate, we observed an impressive increase in the reaction rate when DCM was replaced by toluene (entries 5 and 6). Indeed, with toluene as the solvent, ether **5** was isolated in 81% yield after only 15 min reaction at rt.[17] In contrast to the results reported with NPTFA glycoside donors[14a,16] and irrespective of the solvent used,

Table 3
Formation of PMB ethers: comparison between PMB-NPTFA **1a** and PMB-TCA **1b**



Entry	Alcohols	Reagent	PMB ether	Yield (%)
1	**2**	PMB-TCA **1b**	**3**	92[a]
2	**2**	PMB-NPTFA **1a**	**3**	98[b]
3	**6**	PMB-TCA **1b**	**7**	90[a]
4	**6**	PMB-NPTFA **1a**	**7**	95[b]

Reaction conditions: **1a** or **1b** (1.3 equiv), $Bi(OTf)_3$ (3 mol %), conventional 4 Å MS, [ROH] = 0.1 mol L^{-1}, toluene, rt.
[a] PMB ethers **3** and **7** were contaminated by TCA-NH_2, even after two purifications by flash-chromatography. Respective PMB ethers and TCA-NH_2 amounts were estimated using ^1H NMR.
[b] Isolated yields.

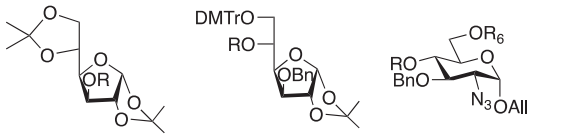
the replacement of conventional 4 Å MS by AW300 had a detrimental effect on the formation of PMB ether **3** (entries 2 and 4 vs 1 and 3). Partial decomposition of PMB-NPTFA **1a** was observed when AW300 was used, suggesting that the proton scavenging capacity of conventional 4 Å MS is beneficial to the reaction.

Next, to determine if the new PMB-NPTFA reagent **1a** offered an added value over the previously described PMB-TCA **1b**,[4d–g] we investigated the etherification of primary and secondary alcohols **2** and **6**[15] with either imidates **1a** or **1b**. If both reagents allowed reaching full conversion of both substrates, consistently higher isolated yields were obtained with **1a** (Table 3). Indeed, when **1b** was used, two purifications by chromatography on silica gel were not sufficient to obtain ethers **3** and **7** exempt of residual trichloroacetamide by product. In contrast, the low polarity of the UV active *N*-phenyl-2,2,2-trifluoroacetamide produced in the reaction with PMB-NPTFA **1a**, greatly facilitated the isolation of PMB ethers **3** and **7** in pure form after a single flash-chromatography.

Then to probe the compatibility of the optimized etherification procedure with acid labile protecting groups, acetonide **8**, dimethoxytrityl derivative **10,** and *N*-Boc amino-acid **18**[18] were used as substrates. As shown in Table 4, entries 1 and 6, 1,2-*O*-isopropylidene and *N*-Boc moieties proved to be fully stable under the reaction conditions, leading to the corresponding PMB ethers in respective 77% and 92% isolated yields.[19] With the DMTr ether **10**, the reaction was quenched after 4 h giving compound **11** in 50% yield along with 45% of unreacted **10** (entry 2), indicating that DMTr ethers are also stable under the reaction conditions. Not surprisingly, benzyl and allyl ethers were fully stable as shown by the isolation of ether **13** in 80% yield (entry 3). Gratifyingly, the base sensitive substrates **14** and **16**, containing respectively an acetate or a uronate moiety, were converted in their respective PMB ethers in good yields as expected (entries 4 and 5). Taken together, these data demonstrate the versatility and broad substrate compatibility of $Bi(OTf)_3$ catalyzed etherification reaction with imidate **1a**.

Finally, we used 1,2-diol furanose **20a** and 1,3-diol pyranose **22a**, to evaluate the potentiality of PMB-NPTFA **1a** for regioselective etherification of primary versus secondary alcohols. A first set of experiments was performed on diol **20a** ($Bi(OTf)_3$, 3 mol %) and, as expected, the primary position reacted faster, leading to 6-*O*-PMB ether **20b**[20] in the highest proportions (Table 5, entries 1 and 4). Depending on the reaction conditions, various proportions of 5-*O*-PMB regioisomer **20c**[20] and 5,6-di-*O*-PMB ether **20d** were formed: changing DCM to toluene resulted in a small increase from 12% to 16% of the 5-*O*-PMB ether **20c** along with the enhancement of the proportion for **20b** from 56% to 62% (entries 1 and 3). Such result suggested that toluene favored the mono etherification on diol **20a**. Lowering the temperature from −10° to −40° reduced

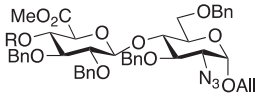
Table 4
Formation of PMB ethers: stability of various protecting groups



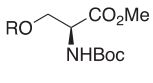
8 R = H
9 R = PMB

10 R = H
11 R = PMB

12 R = H, R_6 = OBn
13 R = PMB, R_6 = OBn
14 R = H, R_6 = OAc
15 R = PMB, R_6 = OAc



16 R = H
17 R = PMB



18 R = H
19 R = PMB

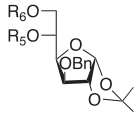
Entry	Substrate	PMB ether	Time	Yield[a] (%)
1	**8**	**9**	30 min	77
2	**10**	**11**	4 h	50[b]
3	**12**	**13**	24 h	80[c]
4	**14**	**15**	24 h	76[c]
5	**16**	**17**	5 h	76[d]
6	**18**	**19**	30 min	92

[a] Reaction conditions: **1a** (1.3 equiv), $Bi(OTf)_3$ (3 mol %), [ROH] = 0.1 mol L^{-1}, toluene, rt, isolated yields.
[b] The reaction did not reach completion; no degradation was observed.
[c] Up to 10 mol % of $Bi(OTf)_3$ loading and 0.9 equiv of **1a** added to speed up the reaction.
[d] 0.9 equiv of **1a** added after 2.5 h stirring.

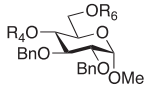
the reaction rates as expected without affecting the global yield and the proportion of the different regioisomers (entries 1–4). Gratifyingly, when the reaction was performed in DCM at −40 °C on the 1,3-diol **22a**, the 6-*O*-PMB ether **22b**[20] was obtained in 71% isolated yield. With this substrate, DCM proved to be much superior to toluene as the solvent (entries 6 and 7) by decreasing the formation of both 4-*O*-PMB regioisomer **22c**[20] and 4,6-di-*O*-PMB ether **22d**. Such results are in accordance with our observation that the reaction rates of reagent **1a** with primary alcohol **2** are similar in DCM and toluene, whereas etherification of secondary alcohol **4** is much slower in DCM than in toluene (Table 2). As mentioned above (Table 1), the reaction rate of reactions with PMB-NPTFA **1a** can be modulated by the catalytic activity of the $M(OTf)_3$ used. We thus tested whether the reduced catalytic power of $Nd(OTf)_3$ or $Sm(OTf)_3$ could be used to enhance the regioselectivity of the reaction for primary alcohols (Table 5, entries 5 and 8–11). As expected, the reaction rates were dramatically reduced, but no real improvement in the isolated yields of 6-*O*-PMB ether **20b** and **22b**[20] were observed. Taken together these results showed that good to medium regioselectivity could be obtained for reactions with reagent **1a**.

In summary, $Bi(OTf)_3$ catalyzed reaction of various primary or secondary alcohols with PMB-NPTFA affords the corresponding PMB ethers in high yields and short reaction times. Besides being remarkably stable and easy to handle, the amide by-product of PMB-NPTFA is non polar and UV active and thus much easier to remove than the trichloroacetamide released when using PMB-TCA. The PMB-NPTFA reagent should thus find many

Table 5
Regioselectivity of etherification reactions with PMB-NPTFA **1a**



20a R_5 = R_6 = H
20b R_5 = H, R_6 = PMB
20c R_5 = PMB, R_6 = H
20d R_5 = R_6 = PMB



22a R_4 = R_6 = H
22b R_4 = H, R_6 = PMB
22c R_4 = PMB, R_6 = H
22d R_4 = R_6 = PMB

Entry	Substrate	**1a** (equiv)	Catalyst	Solvent	*T* (°C)	Time	Yield[a] (%)	6-*O*-PMB[b]		4 or 5-*O*-PMB[b]		4,6 or 5,6-di-*O*-PMB[b]	
1		1.15	$Bi(OTf)_3$	DCM	−10	20 min	84		56		12		32
2		1.15	$Bi(OTf)_3$	DCM	−40	40 min	82		54		14		32
3	**20a**	1.20	$Bi(OTf)_3$	Toluene	−10	20 min	89	**20b**	62	**20c**	16	**20d**	22
4		1.15	$Bi(OTf)_3$	Toluene	−40	25 min	85		60		18		22
5		1.10	$Nd(OTf)_3$	Toluene	rt	24 h	70		59		12		29
6		1.15	$Bi(OTf)_3$	DCM	−40	40 min	95		71		14		15
7		1.15	$Bi(OTf)_3$	Toluene	−40	25 min	85		54		20		26
8	**22a**	1.05	$Nd(OTf)_3$	DCM	rt	22 h	73	**22b**	70	**22c**	16	**22d**	14
9		1.10	$Nd(OTf)_3$	Toluene	−40	72 h	91		64		15		21
10		1.05	$Sm(OTf)_3$	DCM	0	2 h	86		67		11		22
11		1.05	$Sm(OTf)_3$	Toluene	0	2 h	85		60		24		16

Reaction conditions: catalyst (3 mol %), [ROH] 0.1 mol L^{-1}, 4 Å MS.
[a] Global yield.
[b] (%) Proportions of mono and bis-etherified sugars.

applications for the preparation of PMB ethers under non basic conditions.

Acknowledgment

This work was supported by Paris Sud University and CNRS.

Supplementary data

Supplementary data associated (these data include experimental procedures and spectral/analytical data for key intermediates and products) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.066.

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19. *p*-Methoxybenzylidene is also stable under the reaction conditions. Results not shown.
20. After acetylation of the isolated products, unambiguous assignment of the etherified positions were performed by ^{1}H NMR analysis: a downfield shift of H-5 signal from 4.20–4.08 to 5.31 ppm was observed upon conversion of **20b** to **21b**; from 3.72–3.58 to 5.05 ppm for H-4 when **22b** was converted to **23b**; from 3.94–3.84 to 4.28 and 4.12 ppm for H-6a and H-6b in the conversion of **20c** to **21c** and from 3.73–3.48 to 4.26 and 4.20 ppm for H-6a, H-6b when **22c** was converted to **23c**. See Supplementary data for details.