Simple and efficient method for protection of hydroxyl groups as 4-methoxybenzyl ethers

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SUPPORTING INFORMATION

1. General procedure for the preparation of 4-Methoxybenzyl N-allyl thiocarbamate (2) (Scheme 1)

4-Methoxybenzyl N-allyl thiocarbamate (**2**) was prepared according to procedure of alcohol thiocarbamates preparation in microwave reactor. A solution of corresponding alcohol (138 mg, 1 mmol) in toluene was stirred at room temperature for 20 min in the presence of 4 Å micronized molecular sieves (10 mg). Suitable base (**Table 1**) and N-allyl isothiocyanate (0.39 ml, 4 mmol) were added and subsequently reaction mixture was exposed to microwave irradiation (2W) for 1 h at a temperature of 50°C. Reaction progress was monitored by TLC (toluene/EtOAc 8/1). Afterward, the reaction mixture was filtered and washed with brine (2x3 ml), dried (MgSO₄) and the solvent was evaporated. The crude product was purified by column chromatography on silica gel eluting EtOAc/hexane (1/18). Fractions containing the product were combined, and solvent was removed to afford corresponding alcohol N-allyl thiocarbamate.

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Scheme 1.

Table 1. Suitable base using to synthesis of alcohol N-allyl-thiocarbamate

Entry	Base	Equivalent (mmol)
1.	K ₂ CO ₃	1.5
2.	iPr ₂ NEt	1
3.	BEMP	0.01
4.	DBU	0.15

4-Methoxybenzyl N-allyl thiocarbamate (2) Yield: 94%; yellow oil; 7.29-7.33 (2H, m, *o*-Ph), 6.87 - 6.91 (2H, m, *m*-Ph), 6.40 (1H, br.s, NH), 5.80-5.91 (1H, 2dt, *J* 10.2Hz, *J* 17.1Hz, *J* 5.8Hz ^{1'}CH₂^{2'}CH^{3'}CH₂), 5.45 (2H, ps, CH₂Ph), 5.15 - 5.20 (2H, m, ^{1'}CH₂^{2'}CH^{3'}CH₂), 4.17-4.21 (2H, tt, *J* 5.8Hz, *J* 3.05Hz, *J* 1.52Hz, ^{1'}CH₂^{2'}CH^{3'}CH₂), 3.80 (3H, s, PhOMe); d_C (100.6 MHz, CDCl₃) 190.12, 159.60, 132.48, 130.18, 128.66, 117.43, 113.80, 71.82, 55.17, 47.54; HRMS (ESI- MS): calcd for C₁₂H₁₅NO₂S: 260.0721 [M+Na]⁺; found: 260.0709 .

2. General procedure for the Reaction of various types of alcohols (Scheme 2)

A solution of alcohol (1 mmol) in methyl chloride (1.5 ml) was stirred at room temperature for 20 min. in the presence of molecular sieves (4 Å, 50 mg). After 20 min. the mixture was stirred at -25°C temperature for 10 min. 4-methoxybenzyl N-allyl thiocarbamate (2 mmol) in methylene chloride (1.5 ml) was stirred in second flask at -25 °C. *N*-Bromosuccinimide (NBS) (2 mmol) and Et₄N⁺Tf⁻l (2mmol) were dissolved in methyl chloride (1.5 ml) were in third flask and this mixture was also cooled down at -25°C. Cooled flasks were then connected and TfOH (0,01mmol) in methylene chloride (0,5 ml) was added to the mixture. The reaction was completed (TLC, 3:1 hexane/ethyl acetate) in 6 minutes. The reaction mixture was neutralized with Et₃N (0,05 mmol), filtered and washed with brine (1x3ml). The solution was dried (MgSO₄) and evaporated. The crude product was purified by column chromatography (hexane/ethyl acetate 25/1 v/v).

Scheme 2.

1-Methoxy-4-(pentyloxy)benzene (4a)¹ Yield: 83%; colorless oil; d_H (400 MHz CDCl₃) 7.26 (2H, d, *J* 8.3Hz, *o*-Ph), 6.89 (2H,d, *J* 8.3Hz, *m*-Ph), 4.33 (2H, s, CH₂Ph) 3.79 (3H, s, PhOMe), 3.70 (2H, m, OCH₂(CH₂)₃Me), 1.59-1.54 (2H, m, OCH₂CH₂(CH₂)₂Me), 1.3-1.21 (4H, m, O(CH₂)₂(CH₂)₂Me), 0.87-0.84 (3H, m, O(CH₂)₂(CH₂)₂Me); d_C (100.6 MHz, CDCl₃) 159.0, 130.7, 129.1, 113.6, 72.4, 70.1, 55.2, 29.4, 28.3, 22.5, 14.0.; HMRS (EI): calcd for C₁₃H₂₀O: 208.1463 [M]⁺; found: 208.1457. ¹H, ¹³C NMR and HMRS spectra were identical with those in the literature¹.

1-(tert-Butoxymethyl)-4-methoxybenzene (4b)¹ Yield: 80%; colorless oil; d_H (400 MHz $CDCl_3$) 7.25 (2H, d, J 8.3Hz, o -Ph), 6.85 (2H, d, J 8.3Hz, m -Ph), 4.38 (2H, s, CH₂Ph) 3.79 (3H, s, PhOMe), 1.29 (9H, s, OC(CH₃)₃); d_C (100.6 MHz, $CDCl_3$) 158.8, 131.9, 128.9, 113.7, 73.2, 63.7, 55.3, 27.7.; HMRS (EI): calcd for $C_{12}H_{18}O$: 194.1306 $[M]^+$; found: 194.1297. 1H , ^{13}C NMR and HMRS spectra were identical with those in the literature¹.

Reference:

1. Cuenca, A. B.; Mancha, G.; Asensio, G.; Medio-Simon, M. Chemistry A European Journal "Water Compatible Gold(III)-Catalysed Synthesis of Unsymmetrical Ethers from Alcohols", **2008**, 14, 1518.

4-Methoxybenzyl allyl ether (4c)² Yield: 70%; colorless oil; d_H (400 MHz $CDCl_3$) 7.27 (2H, d, J 8.7 Hz, o -Ph), 6.87 (2H, d, J 8.7 Hz, m -Ph), 5.95-5.90 (1H, m, OCH₂CHCH₂) 5.32-5.18 (2H, m, OCH₂CHCH₂), 4.54 (2H, s, CH₂Ph), 4.01 (2H, d, J 5.7 Hz, OCH₂CHCH₂), 3.81 (3H, s, PhOMe); d_C (100.6 MHz, $CDCl_3$) 159.10, 134.79, 130.30, 129.23, 116.86, 113.67, 71.67, 70.75, 55.12.; HRMS (EI): calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994; found 178.0993. 1H , ^{13}C NMR and HMRS spectra were identical with those in the literature².

References:

2. Harada, N.; Nishikata, T.; Nagashima, H. Tetrahedron, „Vinyl polymerization versus [1,3] O to C rearrangement in the ruthenium-catalyzed reactions of vinyl ethers with hydrosilanes" **2012**, 68, 3243

Cholesteryl (4-methoxybenzyl) ether (4d)³ Yield: 80%; colorless oil d_H (400 MHz $CDCl_3$) 7.26 (2H, d, J 8.4 Hz, o -Ph), 6.86 (2H, d, J 8.4Hz, m -Ph), 4.49 (2H, s, CH₂Ph), 3.80 (3H, s, PhOMe), 3.42 – 3.50 (2H, m, cholesterol), 1.40 – 2.40 (21H, m, cholesterol), 1.33 – 1.38 (3H, m, cholesterol), 1.10 – 1.30 (6H, m, cholesterol), 0.99 (3H, s, cholesterol), 0.92 – 0.98 (2H, m, cholesterol), 0.87 (3H, s, cholesterol), 0.67 (3H, s, cholesterol); d_C (100.6 MHz, $CDCl_3$)

159.0, 141.0, 131.1, 129.2 (2C), 121.5, 113.8 (2C), 78.3, 69.6, 56.8, 56.2, 55.3, 50.2, 42.3, 39.8, 39.5, 39.2, 37.3, 36.9, 36.2, 35.8, 32.0, 31.9, 28.5, 28.3, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.7, 11.9. ^1H and ^{13}C NMR spectra were identical with those in the literature ³.

References:

- Jung, M. E.; Koch, P. *Tetrahedron Letters*, " *Mild, selective deprotection of PMB ethers with triflic acid/1,3-dimethoxybenzene*", **2011**, 52, 6051.

(±)-2-(4-Methoxyphenylmethoxymethyl) oxirane (4e)⁴ Yield: 81%; colorless oil; d_{H} (400 MHz CDCl_3) 7.27 (2H, d, J 8.3 Hz, *o*-Ph), 6.87 (2H, d, J 8.3 Hz, *m*-Ph), 4.52 (2H, dd, J 11.7 Hz, J 7.81 Hz, CH₂Ph), 3.82 (3H, s, PhOMe), 3.72 (1H, dd, J 11.48 Hz, J 2.93 Hz, CH₂OCHCH₂), 3.41 (1H, dd, J 11.48 Hz, J 5.86 Hz, CH₂OCHCH₂O), 3.20-3.15 (1H, m, CH₂OCHCH₂O), 2.81 (1H, t, J 4.39 Hz, J 9.28 Hz, CH₂OCHCH₂O), 2.61 (1H, m, CH₂OCHCH₂O); d_{C} (100.6 MHz, CDCl_3) 159.1, 129.8, 129.3, 113.6, 72.8, 70.4, 55.1, 50.7, 44.; MS m/z (EI) 194 ($[\text{M}]^+$, 100%), 163 ($[\text{M}-\text{OMe}]^+$, 6), 122 (69), 78 (22); Found: 194.0950, $[\text{C}_{11}\text{H}_{14}\text{O}_3]^+$ requires 194.0943. ^1H , ^{13}C NMR and HMRS spectra were identical with those in the literature ⁴.

References:

- Walker, Louise F.; Bourghida, A.; Connolly, S.; Wills, M. *Journal of the Chemical Society, Perkin Transactions I*, "Synthesis of 2,5-dihydrofurans via alkylidene carbene insertion reactions", **2002**, 965.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-(4-methoxybenzyl)- α -D-glucofuranose (4f) Yield: 78% d_{H} (400 MHz CDCl_3) 7.28 (2H, dd, J 6.8 Hz *o*-Ph), 6.88 (2H, dd, J 6 Hz, *m*-Ph), 5.89 (1H, d, J 3.6 Hz, H-1 α), 4.54-4.64 (2H, t, J 11.9 Hz, CH₂Ph), 4.44-4.45 (1H, dd, J 3.6 Hz, H-2), 4.30-4.40 (2H, m, H-3, H-5), 3.98-4.18 (3H, m, H-4, H-6, H-6'), 3.82 (3H, s, PhOMe), 1.32, 1.39,

1.50, 1.58 (12H, 4s, 2x(CH₃)₂C); d_C (100.6 MHz, CDCl₃) 159.4, 129.7, 129.3, 113.8, 111.8, 108.9, 105.3, 82.7, 81.3(3), 81.3(1), 73.0, 72.1, 67.4, 55.3, 26.8(4), 26.7(7), 26.3, 25.5.; HRMS (EI): m/z: calcd for C₂₀H₂₈O₇: 380.1835, found 380.1829 [M⁺]. ¹H, ¹³C NMR and HMRS spectra were identical with those in the literature.^{5,6}

References:

5. Dang, H.-S.; Roberts B. P. Journal of the Chemical Society, Perkin Transactions I, " *Deoxygenation of tertiary and secondary alcohols ROH by thiol-catalysed radical-chain redox decomposition of derivatives ROCH₂X to give RH and XCHO*" **2002**, 1161.
6. Kurita, T.; Hattori, K.; Seki, S.; Mizumoto, T.; Aoki, F.; Yamada, Y.; Ikawa, K.; Maegawa, T.; Monguchi, Y.; Sajiki, H.; Chemistry A European Journal, " *Efficient and Convenient Heterogeneous Palladium-Catalyzed Regioselective Deuteration at the Benzylic Position*", **2008**, 14, 664.

1,2:3,4-Di-O-isopropylidene-6-O-(4-metoksybenzylo)-α-D-galactopyranose (4g) ⁷ Yield: 81 d_H (400 MHz CDCl₃) 7.26 (2H, dd, , *J* 6.2 Hz *o*-PhOMe), 6.86 (2H, dd, *J* 6.2 Hz *m*-PhOMe), 5.54 (1H, d, *J* 3.5 Hz, H-1), 4.58(1H, dd, *J* 3.5 Hz, *J* 2.2 Hz, H-3), 4.49 (2H, dd, *J* 12 Hz, CH₂Ph), 4.30-4.32 (1H, dd, *J* 2.2 Hz, H-2), 4.25-4.29 (1H, m, H-4), 3.90-4.00 (1H m, , H-5), 3.80 (3H, s, OMe), 3.57-3.66 (2H, m, H-6, H-6'), 1.33, 1.34, 1.44, 1.53 (12H, 4s, 2x(Me)₂C); d_C (100.6 MHz, CDCl₃) 159.2, 131.3, 130.5, 129.4, 114.4, 113.8, 109.2, 96.4, 73.0, 71.2, 70.6, 68.6, 66.9, 55.3, 26.0, 24.5.; HRMS: calcd for C₂₀H₂₇O₇ 379.175679, found 379.176152. ¹H, ¹³C NMR and HMRS spectra were identical with those in the literature ⁷.

Reference:

7. Sharma, G. V. M.; Mahalingam, A.K. J. Org. Chem.” *A Facile Conversion of Alcohols into p-Methoxybenzyl Ethers (PMB-ethers) Using p-Methoxybenzyl Alcohol–Yb(OTf)₃*”, **1999**, 64, 8943.

Methyl-2,3,4-tri-O-benzoilo-6-O-(4-metoksybenzylo)- α -D-glucopyranoside (4h)⁸ Yield: 85 d_H (400 MHz CDCl₃) 7.85-7.98 (6H, m, o-PhCO), 7.48-7.52 (3H, m, p-Ph-C=O), 7.25-7.42 (6H, m, m-PhCO), 7.18 (2H, dd, J 7.5 Hz, o-PhOMe), 6.73 (2H, dd, J 7,1 Hz, m-PhOMe), 6.11 (1H, t, J 9.6 Hz, H-3), 5.64 (1H, t, J 9 Hz, H-4), 5.29-5.54 (2H, m, H-1, H-2), 4.54 (2H, dd, J 11.6 Hz CH₂PhOMe), 4.23-4.19 (1H, m, H-5), 3.72 (3H, s, PhOMe), 3.65-3.63 (2H, m, H-6, H-6'), 3.49 (3H, s, OMe); d_C (100.6 MHz, CDCl₃) 165.8, 161.2, 133.2, 129.9, 129.4, 128.4, 128.2, 113.7, 97.2, 73.3, 72.2, 70.71, 69.5, 68.9, 68.1, 55.6, 55.2. MS m/z (%) 649.6 (80) [M+Na]⁺. ¹H and ¹³C NMR spectra were identical with those in the literature ⁸.

References:

8. Miranda, P. O.; Brouard, I.; Padron, J. I.; Bermejo J. *Tetrahedron Letters*, ” *Ferric chloride: a mild and versatile reagent for the formation of 1,6-anhydro glucopyranoses*”, **2003**, 44, 3931.

Methyl-2,3-di-O-benzyl-6-O-tert-butyldimethylsilyl-4-O-(4-methoxybenzylo)- α -D-glucopyranoside (4i)⁹ Yield: 84%; colorless oil; d_H (400 MHz CDCl₃) 7.33-7.26 (10H, m, benzyl), 7.10 (2H, d, J 8.4Hz, o- Ph), 6.84 (2H, d, J 8.4Hz, m- Ph), 5.03 (1H, d, J=11.6 Hz, CH₂Ph), 4.72 (1H, d, J=11.6 Hz, CH₂Ph), 4.66 (1H, d, J=12 Hz, CH₂Ph), 4.55 (1H, d, J=3.6 Hz, H-1), 4.56 (1H, d, J=12 Hz, CH₂Ph), 3.86-3.65 (8H, m, CH₂Ph, PhOMe, H-2, H-3, H-4) 3.53-5.52 (2H, m, H-5, H-6), 3.46 (1H, dd, J 4.0 Hz, J 9.6 Hz, H-6'), 3.37 (3H s, OMe), 0.88, 0.05, 0.04 (3s, 15H, t-BuMe₂Si); d_C (100.6 MHz, CDCl₃) 159.8, 138.1, 129.2, 128.4, 128.2, 127.8, 127.3, 97.5, 81.7, 80.8, 77.3, 76.7, 75.0, 73.2, 62.6, 53.0, 55.9, 25.9, 18.1, -5.01,

-5.36.; ESI HRMS: Calcd for $C_{35}H_{48}O_7^- NaSi$: 631.3062; found: m/z 631.3070 $[M+Na]^+$. 1H , ^{13}C NMR and HMRS spectra were identical with those in the literature ⁹.

References:

9. Borsuk, K.; Kazimierski, A.; Solecka, J.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. *Carbohydrate Res.* „Stereocontrolled formation of oxacephams from carbohydrates”, **2002**, 337, 2005.