# Noncatalytic selective 6-*O*-acetylation of methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside with acetic acid and acetic anhydride

*Y. E. Tsvetkov, M. L. Gening, and N. E. Nifantiev*★

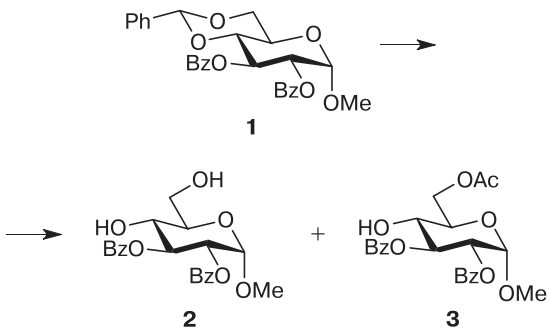
*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (499) 135 8784. E-mail: nen@ioc.ac.ru*

Noncatalytic acetylation of methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside with acetic acid or acetic anhydride proceeds regioselectively at the primary hydroxyl group and affords methyl 6-*O*-acetyl-2,3-di-*O*-benzoyl-α-D-glucopyranoside in good yield. The possibility of 6-*O*-acetylation should be taken into account when removing a 4,6-*O*-benzylidene protecting group with aqueous acetic acid at elevated temperature.

**Key words:** acetic acid, acetic anhydride, methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside, selective 6-*O*-acetylation.

The benzylidene group is widely used in synthetic organic chemistry for protection of 1,2- and 1,3-diols, including protection of hydroxy groups at the C(4) and C (6) atoms in hexopyranosides.[1] The 4,6-*O*-benzylidene group is usually removed by acid hydrolysis using dilute strong acids (sulfuric, hydrochloric, *p*-toluenesulfonic acid, *etc.*)[1,2] or aqueous acetic acid upon heating.[1,3—5] The advantage of the latter reagent is the simplicity of the reaction mixture work-up, which consists in evaporation. We also used the hydrolysis of benzylidene derivative **1** (see Ref. 6) with 80% aqueous AcOH to obtain 4,6-diol **2** (Scheme 1).

**Scheme 1**




**Reagents and conditions:** 80% aq. AcOH, 50 °C, 48 h.

The reaction gave diol **2** in 80% yield, as well as a product with higher chromatographic mobility, which, according to the NMR spectra, was 6-acetate **3** (10% yield). Therefore, aqueous AcOH at elevated temperatures is capable of acetylating the primary hydroxy group in 4,6-diol **2**.

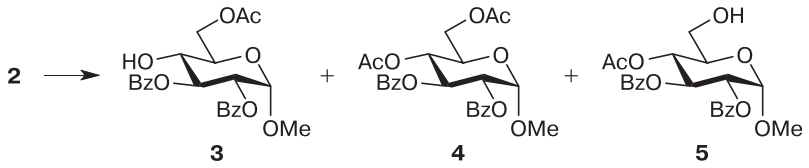
Considering this result, we studied the possibility of noncatalytic selective 6-*O*-acetylation of diol **2** with acetic acid, since our further goal was to obtain 6-acetate **3**. This compound is supposed to be used for the introduction of an azide group at the C(4) atom with the formation of 4-azido-4-deoxygalactose derivative,[7] a precursor for the synthesis of containing 4-amino-4-deoxygalactose moiety analogs of cyclic oligosaccharides obtained earlier,[8] as well as oligomeric blockers of bacterial adhesins,[9] ion channels,[10,11] and other molecular systems.[12] In addition, glucose derivatives selectively acetylated at the O(6) atom, similar to compound **3**, are convenient blocks for the assembly of β-(1→6)-linear[13] and β-(1→3),(1→6)-branched[14,15] oligoglucosides corresponding to the fragments of β-glucans of the cell wall of fungi[16,17] of the genera *Candida*, *Aspergillus*, and others.

Preliminary experiments showed that aqueous AcOH (70—90%) at 80 °C in fact selectively acetylates diol **2** with the formation of compound **3** as the main product. TLC of the reaction mixture showed also the presence of minor amounts of 4,6-diacetate **4** and 4-acetate **5** (Scheme 2). The conversion degree of the starting diol **2** and the reaction selectivity were practically independent of the concentration of AcOH used.

However, the low reaction rate (the degree of conversion of **2** after 90 h was 75—80%) did not allow us to consider the reaction with aqueous AcOH as a preparative method for selective 6-*O*-acetylation. Therefore, further we studied acetylation of **2** with anhydrous AcOH. The reaction of **2** with glacial AcOH at 100 °C for 36 h gave

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2228—2230, November, 2020.

**Scheme 2**




**Reagents and conditions:** AcOH, 100 °C, 36 h or $Ac_2O$, 60 °C, 15 h or $Ac_2O$, pyridine, $CH_2Cl_2$, 0 → 20 °C.

good yield of 6-acetate **3** (72%), as well as compounds **4** and **5** in 15 and 6% yields, respectively. Thus, the reaction with anhydrous AcOH showed a sufficiently high regioselectivity, which makes it suitable for 6-*O*-acetylation of 4,6-diols of the compound **2** type.

Acetic anhydride in the presence of basic or acidic catalysts[18,19], both homogeneous and heterogeneous, is one of the most commonly used reagents in the acetylation reaction. We studied the acetylation of diol **2** with acetic anhydride in the absence of catalysts. The reaction of **2** with $Ac_2O$ at 60 °C for 15 h gave 6-acetate **3** and diacetate **4** in 83 and 15% yields, respectively. Carrying out this reaction at 50 °C for 22 h leads to a slight decrease in the yield of diacetate **4** (12%), while the yield of **3** remains unchanged (83%). TLC showed that 4-acetate **5** is formed in trace amounts in both cases.

For comparison, we carried out acetylation of **2** with 1.3 equiv of $Ac_2O$ in the presence of 2 equiv. of pyridine at 0 → 20 °C. This reaction turned out to be less regioselective than the described above noncatalytic acetylation with AcOH or $Ac_2O$. As a result, 6-acetate **3**, 4,6-diacetate **4**, and 4-acetate **5** were isolated in 64, 21, and 9% yields, respectively.

To sum up, acetic acid and acetic anhydride in the absence of catalysts selectively acetylate the primary hydroxy group in methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside, giving the corresponding 6-acetate in good yield. The possibility of acetylation of C(6) hydroxy group should be taken into account when removing the 4,6-*O*-benzylidene group with aqueous acetic acid at elevated temperatures.

The efficiency of acetic acid and, in particular, acetic anhydride as reagents for selective 6-*O*-acetylation is superior to that of many reagents described in the literature, such as, for example, 1-acetoxybenzotriazole,[20,21] 1-acetylimidazole,[22] and acetyl chloride in the presence of pyridine[23] or 2,4,6-collidine.[24] Only in a few cases (acetyl chloride in the presence of basic alumina[18] and acetic anhydride in the presence of 4 Å molecular sieves[19]) higher yields (~90%) of the products of selective 6-*O*-acetylation were achieved for substrates of similar structure.

## Experimental

Thin layer chromatography was performed on Kieselgel 60 F254 silica gel plates (Merck), compounds were detected in UV light or by spraying with a solution of orcinol (orcinol (180 mg) in a mixture of water (85 mL), 85% phosphoric acid (10 mL), and 95% ethanol (5 mL)), followed by heating at ~150 °C. Column chromatography was performed on Silica gel 60 (40—63 μm, Merck). Optical rotation was measured on a JASCO P-2000 digital polarimeter (Japan) at 20—25 °C. NMR spectra were recorded at 25 °C on a Bruker Avance 600 spectrometer in deuterochloroform ($CDCl_3$). Residual non-deuterated $CHCl_3$ ($\delta_H$ 7.27) was used as an internal standard for $^1H$ NMR spectra, the signal of $CDCl_3$ ($\delta_C$ 77.0) was used as a reference for $^{13}C$ NMR spectra. The signal assignment was carried out using 2D COSY and HSQC correlation NMR spectroscopy. The electrospray ionization (ESI) high resolution mass spectrum was recorded on a Bruker micrOTOF II instrument. Acetic acid of reagent grade distilled over potassium permanganate was used for acetylation.

**Synthesis of compounds 2 and 3.** A suspension of benzylidene derivative **1** (3.90 g, 7.95 mmol) in 80% aq. AcOH (20 mL) was stirred at 50 °C for 48 h (after ~30 h the reaction mixture became homogeneous), AcOH was evaporated and coevaporated with toluene (3×30 mL). The residue was chromatographed (toluene—EtOAc (4 : 1), then toluene—acetone (4 : 1→3 : 1)) to obtain diol **2** (2.56 g, 80%) and 6-acetate **3** (0.37 g, 10%).

**Methyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside (2).** A colorless foam, $R_f$ = 0.17 (toluene—EtOAc, 3 : 2), $[\alpha]_D$ +146 (*c* 1, EtOH) (Ref. 4: +155 (*c* 1, EtOH)). $^1H$ NMR (600 MHz, $CDCl_3$), δ: 7.99—7.32 (m, 10 H, Ar); 5.77 (t, 1 H, H(3), *J* = 9.7 Hz); 5.22 (dd, 1 H, H(2), $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 10.1 Hz); 5.13 (d, 1 H, H(1), $J_{1,2}$ = 3.6 Hz); 4.00—3.91 (m, 3 H, H(4), 2 H(6)); 3.89—3.84 (m, 1 H, H(5)); 3.43 (s, 3 H, $CH_3O$). $^{13}C$ NMR (150 MHz, $CDCl_3$), δ: 167.3, 166.0 (Ph<u>C</u>O), 133.4, 129.9, 129.8, 128.4 (Ar), 97.1 (C(1)), 74.1 (C(3)), 71.6 (C(2)), 71.3 (C(5)), 69.8 (C(4)), 62.0 (C(6)), 55.4 ($CH_3O$).

**Methyl 6-*O*-acetyl-2,3-di-*O*-benzoyl-α-D-glucopyranoside (3).** A colorless syrup, $R_f$ = 0.62 (toluene—EtOAc, 3 : 2), $[\alpha]_D$ +134 (*c* 1, $CHCl_3$) (Ref. 25: $[\alpha]_D$ +150.8 (*c* 1.2, $CHCl_3$)). $^1H$ NMR (600 MHz, $CDCl_3$), δ: 8.01—7.34 (m, 10 H, Ar); 5.76 (t, 1 H, H(3), *J* = 9.7 Hz); 5.27 (dd, 1 H, H(2), $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 10.1 Hz); 5.13 (d, 1 H, H(1), $J_{1,2}$ = 3.6 Hz); 4.54 (dd, 1 H, H(6a), $J_{6a,5}$ = 4.6 Hz, $J_{6a,6b}$ = 12.3 Hz); 4.40 (dd, 1 H, H(6b), $J_{6b,5}$ = 2.4 Hz, $J_{6b,6a}$ = 12.3 Hz); 4.02—3.97 (m, 1 H, H(5)); 3.82 (t, 1 H, H(4), *J* = 9.5 Hz); 3.44 (s, 3 H, $CH_3O$); 2.16 (s, 3 H, $CH_3CO$). $^{13}C$ NMR (150 MHz, $CDCl_3$), δ: 171.4 ($CH_3\underline{C}O$), 167.3, 165.9 (Ph<u>C</u>O), 133.4, 133.3, 129.8, 128.4 (Ar), 97.1 (C(1)), 73.8 (C(3)), 71.2 (C(2)), 69.7 (C(5)), 69.5 (C(4)), 62.9 (C(6)), 55.4 ($CH_3O$), 20.8 ($\underline{C}H_3CO$). The NMR spectroscopy data for compound **3** are in good agreement with the data reported in the work.[25]

**Synthesis of compounds 3, 4, and 5. Method *A*.** A solution of diol **2** (134 mg, 0.33 mmol) in glacial AcOH (2.5 mL) was heated at 100 °C for 36 h, AcOH was evaporated and coevapo-

rated with toluene (3×5 mL). The residue was chromatographed (toluene—EtOAc, 85 : 15 → 80 : 20 → 70 : 30) to obtain 6-acetate **3** (106 mg, 72%) identical to that described above, diacetate **4** (25 mg, 15%), and 4-acetate **5** (9 mg, 6%).

**Methyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzoyl-α-D-glucopyranoside (4).** A colorless syrup, $R_f$ = 0.69 (toluene—EtOAc, 3 : 2), $[\alpha]_D$ +132 (*c* 1, $CHCl_3$) (Ref. 25: $[\alpha]_D$ +127.9 (*c* 1, $CHCl_3$)). $^1$H NMR (600 MHz, $CDCl_3$), δ: 7.98—7.34 (m, 10 H, Ar); 5.99—5.92 (m, 1 H, H(3)); 5.35 (t, 1 H, H(4), *J* = 10.1 Hz); 5.23—5.18 (m, 2 H, H(1), H(2)); 4.34 (dd, 1 H, H(6a), $J_{6a,5}$ = = 4.6 Hz, $J_{6a,6b}$ = 12.3 Hz); 4.18 (dd, 1 H, H(6b), $J_{6b,5}$ = 2.2 Hz, $J_{6b,6a}$ = 12.3 Hz); 4.16—4.11 (m, 1 H, H(5)); 3.44 (s, 3 H, $CH_3O$); 2.14, 1.95 (both s, 6 H, 2 $CH_3CO$). $^{13}$C NMR (150 MHz, $CDCl_3$), δ: 170.7, 169.5 (2 $CH_3\underline{C}O$), 165.8 (Ph$\underline{C}$O), 133.4, 133.3, 129.9, 129,7, 128.4 (Ar), 97.0 (C(1)), 71.8 (C(2)), 70.5 (C(3)), 68.3 (C(4)), 67.4 (C(5)), 62.0 (C(6)), 55.6 ($CH_3O$), 20.8, 20.5 (2 $\underline{C}H_3CO$). The NMR spectroscopy data for compound **4** are in good agreement with the data reported in the work.[26]

**Methyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-α-D-glucopyranoside (5).** A colorless syrup, $R_f$ = 0.34 (toluene—EtOAc, 3 : 2), $[\alpha]_D$ +144 (*c* 1, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$), δ: 7.99—7.35 (m, 10 H, Ar); 6.03 (t, 1 H, H(3), *J* = 9.6 Hz); 5.30 (t, 1 H, H(4), *J* = 9.9 Hz); 5.22 (d, 1 H, H(1), $J_{1,2}$ = 3.6 Hz); 5.19 (dd, 1 H, H(2), $J_{2,3}$ = 9.6 Hz); 3.96—3.91 (m, 1 H, H(5)); 3.80 (dd, 1 H, H(6a), $J_{6a,5}$ = 2.2 Hz, $J_{6a,6b}$ = 12.7 Hz); 3.69 (dd, 1 H, H(6b), $J_{6b,5}$ = 4.1 Hz, $J_{6b,6a}$ = 12.7 Hz); 3.45 (s, 3 H, $CH_3O$); 2.00 (s, 3 H, $CH_3CO$). $^{13}$C NMR (150 MHz, $CDCl_3$), δ: 170.6 ($CH_3\underline{C}O$), 166.1, 165.5 (2 Ph$\underline{C}$O), 133.4, 133.3, 129.9, 129.7, 128.4 (Ar), 97.0 (C(1)), 72.0 (C(2)), 70.2 (C(3)), 69.5 (C(5)), 68.8 (C(4)), 61.1 (C(6)), 55.6 ($CH_3O$), 20.6 ($\underline{C}H_3CO$). MS (ESI), found *m/z*: 467.1304 $[M + Na]^+$; calculated for $C_{23}H_{24}NaO_9$ 467.1313.

**Method *B*.** A solution of diol **2** (152 mg, 0.38 mmol) in $Ac_2O$ (3 mL) was heated at 60 °C for 15 h, $Ac_2O$ was evaporated and coevaporated with toluene (3×5 mL). Column chromatography of the residue (toluene—EtOAc, 85 : 15 → 80 : 20) gave 6-acetate **3** (140 mg, 83%) and diacetate **4** (27 mg, 15%) identical to those described above.

**Method *C*.** Pyridine (64 μL, 0.68 mmol) and $Ac_2O$ (42 μL, 0.44 mmol) were added to a solution of diol **2** (137 mg, 0.34 mmol) in $CH_2Cl_2$ (3 mL) cooled with ice. The mixture was stirred at 4 °C for 2 h, then the temperature was raised to ambient within 3 h. After 16 h, MeOH (50 μL) was added, the reaction mixture was diluted with chloroform (50 mL), washed with 1 *M* HCl and water, and concentrated. Column chromatography of the residue (toluene—EtOAc, 85 : 15 → 80 : 20 → 70 : 30) gave 6-acetate **3** (96 mg, 64%), 4,6-diacetate **4** (35 mg, 21%), and 4-acetate **5** (13 mg, 9%) identical to those described above.

This work was financially supported by the Russian Science Foundation (Project No. 19-43-02023).

## References

1. T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons, Inc., New York, 1999, p. 217.
2. P. J. Kocieński, *Protecting Groups*, 3rd ed., Georg Thieme Verlag, Stuttgart, 2005, p. 137.
3. E. B. Rodriguez, R. V. Stick, *Austr. J. Chem.*, 1990, **43**, 665.
4. M. von Itzstein, I. D. Jenkins, *J. Chem. Soc., Perkin Trans. 1*, 1986, 437.
5. P.-E. Jansson, J. Lindberg, G. Widmalm, *Acta Chem. Scand.*, 1993, **47**, 711.
6. R. W. Jeanloz, D. A. Jeanloz, *J. Am. Chem. Soc.*, 1957, **79**, 2579.
7. S. Wu, L. Yang, W. Sun, L. Si, S. Xiao, Q. Wang, L. Dechoux, S. Thorimbert, M. Sollogoub, D. Zhou, Y. Zhang, *Eur. J. Med. Chem.*, 2017, **130**, 308.
8. M. L. Gening, D. V. Titov, A. A. Grachev, A. G. Gerbst, O. N. Yudina, A. S. Shashkov, A. O. Chizhov, Y. E. Tsvetkov, N. E. Nifantiev, *Eur. J. Org. Chem.*, 2010, 2465.
9. M. L. Gening, D. V. Titov, S. Cecioni, A. Audfray, A. G. Gerbst, Y. E. Tsvetkov, V. B. Krylov, A. Imberty, N. E. Nifantiev, S. Vidal, *Chem. Eur. J.*, 2013, **19**, 9272.
10. T. Saha, A. Roy, M. L. Gening, D. V. Titov, A. G. Gerbst, Y. E. Tsvetkov, N. E. Nifantiev, P. Talukdar, *Chem. Commun.*, 2014, **50**, 5514.
11. A. Roy, T. Saha, M. L. Gening, D. V. Titov, A. G. Gerbst, Y. E. Tsvetkov, N. E. Nifantiev, P. Talukdar, *Chem. Eur. J.*, 2015, **21**, 17445.
12. V. P. Ananikov, D. B. Eremin, S. A. Yakukhnov, A. D. Dilman, V. V. Levin, M. P. Egorov, S. S. Karlov, L. M. Kustov, A. L. Tarasov, A. A. Greish, A. A. Shesterkina, A. M. Sakharov, Z. N. Nysenko, A. B. Sheremetev, A. Yu. Stakheev, I. S. Mashkovsky, A. Yu. Sukhorukov, S. L. Ioffe, A. O. Terent´ev, V. A. Vil´, Y. V. Tomilov, R. A. Novikov, S. G. Zlotin, A. S. Kucherenko, N. E. Ustyuzhanina, V. B. Krylov, Y. E. Tsvetkov, M. L. Gening, N. E. Nifantiev, *Mendeleev Commun.*, 2017, **27**, 425.
13. D. V. Yashunsky, A. A. Karelin, Y. E. Tsvetkov, N. E. Nifantiev, *Carbohydr. Res.*, 2018, **455**, 18.
14. D. V. Yashunsky, Y. E. Tsvetkov, N. E. Nifantiev, *Russ. Chem. Bull.*, 2015, **64**, 2922.
15. D. V. Yashunsky, Y. E. Tsvetkov, N. E. Nifantiev, *Carbohydr. Res.*, 2016, **436**, 25.
16. Yu. E. Tsvetkov, E. A. Khatuntseva, D. V. Yashunsky, N. E. Nifantiev, *Russ. Chem. Bull.*, 2015, **64**, 990.
17. A. A. Karelin, Y. E. Tsvetkov, N. E. Nifantiev, *Russ. Chem. Rev.*, 2017, **86**, 1073.
18. P. Tiwari, A. K. Misra, *Carbohydr. Res.*, 2006, **341**, 339 and references cited therein.
19. M. Adinolfi, G. Barone, A. Iadonisi, M. Schiattarella, *Tetrahedron Lett.*, 2003, **44**, 4661 and references cited therein.
20. L. Greffe, M. T. Jensen, F. Chang-Pi-Hin, S. Fruchard, M. J. O´Donohue, B. Svensson, H. Driguez, *Chem. Eur. J.*, 2002, **8**, 5447.
21. H.-M. Chen, S. G. Withers, *Carbohydr. Res.*, 2018, **467**, 33.
22. M. G. Tilbrook, R. V. Stick, S. J. Williams, *Aust. J. Chem.*, 1999, **52**, 885.
23. Q.-W. Liu, H.-C. Bin, J.-S. Yang, *Org. Lett.*, 2013, **15**, 3974.
24. S. Singh, Z. Su, M. Grossutti, F.-I. Auzanneau, *Carbohydr. Res.*, 2014, **390**, 50.
25. T. Ziegler, M. Vollmer, S. Oberhoffner, E. Eckhardt, *Liebigs Ann. Chem.*, 1993, 255.
26. K.-i. Sato, N. Kubo, R. Takada, S. Sakuma, *Bull. Chem. Soc. Jpn*, 1993, **66**, 1156.

*Received June 15, 2020;*
*in revised form July 16, 2020;*
*accepted July 27, 2020*