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Note

# Improved anomeric selectivity for the aroylation of sugars

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**Abstract**—By manipulating the solvent and using bulky TMEDA as a base, good yields and improved anomeric selectivities were obtained for the aroylation of D-glucose over similar esterifications using pyridine. The reaction has been extended to mannose and the β-anomer of pergalloylated mannose was predominantly obtained in one step by direct aroylation of the parent sugar.


*Keywords*: Aroylation; Galloylation; Carbohydrate esterification; Anomeric esters; TMEDA

Although the aroylation of alcohols is a basic and well-studied subject, the development of synthetic methods for the selective aroylation of sugars is of great importance, especially when these methods are stereoselective with respect to the anomeric centre. Unfortunately, the known methods for direct aroylation of sugars normally lead to a mixture of anomers where the kinetic isomer is predominant,[1,2] making the obtention of the other anomer in important quantities a challenge.[3,4] Natural β-penta-*O*-galloyl glucose (β-PGG) is believed to be responsible for the genesis of ellagitannins.[5,6] The ready availability of both anomers could help in the search for more powerful antiviral or anticancer therapeutic agents.[7–9] We have found that by changing the solvent and base in the reaction of galloylation, it was possible to obtain protected PGGs with an anomeric excess superior to 85%.

As a general rule, aroylation of alcohols involves their treatment by an aroylating agent in the presence of a base such as pyridine, triethylamine and/or 4-DMAP.[10] More recently,[11] a new method for the benzoylation of alcohols has been described using TMEDA as a base, which gave the expected benzoates in excellent yields. This method has been extended to other acyl halides, allowing the obtention of alkoxycarbonates[12] or protected gallates.[13]

A classical benzoylation of D-glucose in pyridine[2] (Table 1, entry 1) led predominantly to the β anomer, implying that the β-glucopyranose form had been selectively aroylated. The result was similar with the more hindered tri-*O*-methylgalloyl chloride (**2**) and the reaction led to the same proportion of anomers (entry 4). In an attempt to obtain the β-PGG with a better anomeric excess, we have replaced pyridine with TMEDA, expecting that the bulky intermediate **4**[11,14–16] (Fig. 1) suspected to be formed between the acyl halide and the base, would react preferentially at the least hindered equatorial anomeric hydroxyl to give the expected β-anomer of D-glucose (Scheme 1).[4,17,18]

As expected (entries 3, 5, 6 and 12), the use of TMEDA led preferentially to the kinetic product. Contrarily to previously published studies,[11] we have

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**Table 1.** Aroylation of glucose (yields not optimised)

| Entry | Solvent | G′Cl (equiv) | Base (equiv)[a] | Yield (%) | α:β |
|---|---|---|---|---|---|
| 1[2] | — | **1** | Pyridine | — | 39:61 |
| 2 | $CH_2Cl_2$ | **1** (8) | Pyridine | 86 | 70:30 |
| 3 | $CH_2Cl_2$ | **1** (8) | TMEDA (8) | 80 | 31:69 |
| 4 | — | **2** (8) | Pyridine | 13 | 39:61 |
| 5 | $CH_2Cl_2$ | **2** (5) | TMEDA (1) | 9 | 16:84 |
| 6 | $CH_2Cl_2$ | **2** (5) | TMEDA (5) | 24 | 14:86 |
| 7 | THF | **2** (5) | TMEDA (5) | 41 | 32:68 |
| 8 | $CH_2Cl_2$ | **2** (5) | TMEDA (5) | 45 | 23:77 |
| 9 | Toluene | **2** (5) | TMEDA (5) | 20 | 32:68 |
| 10 | $CH_3CN$ | **2** (5) | TMEDA (5) | 22 | 42:58 |
| 11 | THF:$CH_2Cl_2$ (1:2) | **2** (5) | TMEDA (5) | 29 | 24:76 |
| 12 | $CH_2Cl_2$ | **2** (8) | TMEDA (8) | 70 | 14:86 |
| 13 | $CH_2Cl_2$ | **2** (8) | TMEDA (8) | 54 | 35:65 |
| 14 | $CH_2Cl_2$ | **2** (8) | Pyridine | 60 | 86:14 |
| 15 | THF | **2** (8) | TMEDA (8) | 52 | 12:88 |
| 16 | $CH_3CN$ | **2** (8) | TMEDA (8) | 86 | 34:66 |
| 17 | $CH_2Cl_2$ | **3** (8) | TMEDA (8) | 61 | 0:100 |

[a] Pyridine:$CH_2Cl_2$, 1:2 for entries 2, 8, 13 and 14.

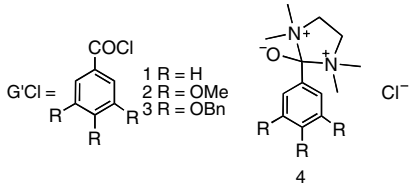
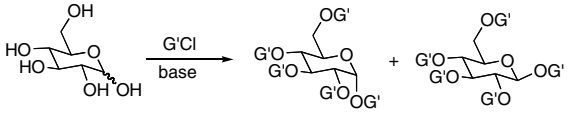



**Figure 1.** Aroylating reagents used in this work.



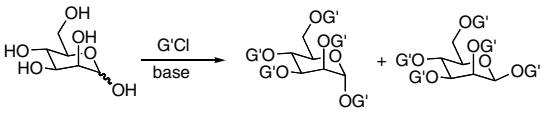

**Scheme 1.**

found that the amount of base was very important for the galloylation reaction (Table 1). The yield of the reaction was effectively higher when the number of equiv of TMEDA was the same as for the tri-*O*-methylgalloyl chloride **2** (entries 5, 6 and 12; 10 and 16). The best yields of aroylation were obtained by adding 1.6 equiv of chloride per hydroxyl group, and the same quantity of base (entries 12–16).

The importance of the solvent on the anomeric selectivity of the esterifications is also noteworthy (entries 6–16). Actually, the use of dry acetonitrile provided the best yields (entry 16), but it was with dry dichloromethane (entries 5, 6 and 12) or tetrahydrofuran (entry 15) that the β-selectivity was the most pronounced. The addition of pyridine to dichloromethane (ratio 1/2, entries 8 and 13) tended to decrease the proportion of protected β-PGG in favour of its α anomer. We also noticed (entry 4) that the use of pyridine only gave a low (13%) yield with a ratio α : β of about 1 to 1.5. Surprisingly, use of dichloromethane as cosolvent with pyridine (entries 2 and 14) inverted the anomeric selectivity and the α anomer was obtained as the predominant product from the reaction of glucose with **2**, yielding 86% of α-PGG (entry 14).

Knowing that the β-anomer must be the kinetic product of the reaction of aroylation,[4] we have then been able to deduce more aspects of the mechanism of aroylation in the presence or absence of TMEDA. As we have seen before, the amount of base strongly influences the overall yield. This fact is consistent with the formation of the reactive complex **4**. Following the model described by Bols and Hanson,[19] we can infer that the rate of mutarotation in dichloromethane or tetrahydrofuran compared with the rate of aroylation by **4**, favoured the β-O-aroylated compound, or that the base (TMEDA) was a better catalyst for mutarotation than pyridine. The bulky reagent **4** inhibited the reaction with the α-hydroxyl. The use of an aroylating agent such as **2**, with its particular electron availability may enhance the stability of the intermediate **4**. The *N*-acylpyridinium halide, which was probably formed on mixing the chloride reagent and pyridine[20] is probably responsible for the obtention of the other anomer predominantly.

In order to show that the hindering of the aroylating agent plays a crucial role in the reaction of aroylation,[4] we have run the reactions in the presence of a similar but larger aroylating agent than **2**, namely tri-*O*-benzyl galloylchloride **3** (Table 1, entry 17). In this case, the combined effects of the formation of the intermediate type **4** and its hindrance turned the reaction totally selective and we isolated only the kinetic β-anomer. This result can be compared with the one reported in the literature,[21] where the obtention of the same products by direct galloylation in the presence of DCC had led to a nearly equimolar (33:42) α/β mixture.




**Scheme 2.**

We have then extended this study to the galloylation of mannose (*C*-2 epimer of glucose) (Scheme 2, Table 2, entries 2–6) and have obtained the expected compounds with good to very good yields. The classical benzoylation[2] of mannose in pyridine afforded mainly the α-anomer (entry 1). The addition of dichloromethane as solvent increased the ratio in favour of the β-anomer (entry 2), whereas substitution of pyridine by TMEDA gave predominantly the β-anomeric form (entry 3).

We have thus managed to obtain with good diastereoselectivity the β-form of the pentakis-(*O*-trimethoxygalloyl)mannose (entry 4) by using TMEDA. The formation of the equatorial anomer was probably due to the kinetic anomeric effect.[4]

In conclusion, we have demonstrated that several factors affect the anomeric selectivity of the aroylation of sugars. We also describe a direct method for the galloylation of sugars where the anomeric stereoselectivity can be controlled by varying the acyl chloride (bulkyness, electron availability), the solvent and the base. The obtention of the challenging β-mannopyranoside as the predominant product from D-mannose by a cheap, nontoxic and direct method of aroylation has been realised.

## 1. Experimental

### 1.1. General methods

Reagents and solvents were purified before use. Flash chromatography was performed on silica gel from Macherey-Nagel (Kieselgel 60 M). Compounds were visualised with a soln of 30% $H_2SO_4$ in EtOH and heating, or under UV light. Optical rotations were measured at 20 °C on a Perkin–Elmer 241 polarimeter (1 dm cell). Melting points were determined on a Büchi 530 apparatus and are not corrected. Anhydrous $MgSO_4$ was used to dry organic extracts. $^1$H NMR spectra were recorded on a Bruker AMX-400 apparatus ($^1$H at 400 MHz and $^{13}$C at 100 MHz) in $CDCl_3$ with chemical shift values ($\delta$) in ppm downfield from tetramethylsilane. Elemental analyses were performed by the IST analytical services in Lisbon using a combustion apparatus.

### 1.2. Typical procedure for the galloylation reactions

To a soln of TMEDA (0.34 mL; 2.24 mmol; 8 equiv) in dry solvent (5 mL) was added D-glucose (50 mg; 0.28 mmol) and tri-*O*-methylgalloyl chloride (517 mg; 2.24 mmol; 8 equiv) dissolved in dry solvent (5 mL). The reaction mixture was refluxed for 24 h under an inert atmosphere. After cooling, it was quenched with a phosphate buffer solution pH 7, extracted with $CH_2Cl_2$ ($3\times20$ mL), and the organic phase washed with brine and water, dried and concentrated. Purification of the crude product by preparative chromatography afforded the pure (4:1:1 $Et_2O$–$CH_2Cl_2$–hexane) α- and β-pentakis(*O*-trimethoxygalloyl)-D-glucoses, or a mixture of the two whose ratio have been determined by $^1$H NMR spectra and/or HPLC.

### 1.3. 1,2,3,4,6-Pentakis[-*O*-(3,4,5-trimethoxybenzoyl)]-α,β-D-glucopyranose

Purification by preparative chromatography (2:1:1 $Et_2O$–$CH_2Cl_2$–hexane) led to the two anomers.

α-*Anomer*: mp 96–97 °C. $[\alpha]_D$ +81.2 (*c* 0.8, $CH_2Cl_2$). IR data (KBr): $\nu_{max}$ 1731.6 (C=O). $^1$H NMR data (400 MHz, $CDCl_3$): 7.41 (s, 2H, Gall-H), 7.29 (s, 2H, Gall-H), 7.14 (s, 4H, Gall-H), 7.11 (s, 2H, Gall-H), 6.77 (d, $J_{1,2}$ 3.2 Hz, 1H, H-1), 6.26 (t, *J* 10.0–10.4 Hz, 1H, H-3), 5.75 (t, *J* 10.0–10.4 Hz, 1H, H-4), 5.56 (dd, $J_{1,2}$ 3.6, $J_{2,3}$ 10.0 Hz, 1H, H-2), 4.77 (dd, $J_{5,6b}$ 2.6 Hz, 1H, H-6b), 4.67–4.63 (m, 1H, H-5), 4.40 (dd, $J_{5,6a}$ 5.4, $J_{6a,6b}$ 12.2 Hz, 1H, H-6a), 3.94, 3.93, 3.89, 3.85, 3.83, 3.82, 3.71 (7s, 45H, $OCH_3$). $^{13}$C NMR data (100 MHz, $CDCl_3$): $\delta$ 165.59, 164.98, 164.82, 163.87, (C=O), 153.16, 152.84 (Gall-C-3 and Gall-C-5), 143.28, 142.86, 142.75, 142.65, 142.45 (Gall-C-4), 124.34, 123.77, 123.53, 123.41, 123.30 (Gall-C-1), 107.38, 107.04, 106.91 (Gall-C-2 and Gall-C-6), 90.29 (C-1), 70.72 (C-2), 70.52 (C-3 and C-5), 69.18 (C-4), 62.85 (C-6), 60.94, 60.80, 56.32, 56.10, 56.04, 55.88 ($OCH_3$). Anal. Calcd for $C_{56}H_{62}O_{26}$: C, 58.43; H, 5.43. Found: C, 58.25; H, 5.49.

**Table 2.** Aroylation of mannose

| Entry | Solvent | G′Cl (equiv) | Base (equiv) | Yield (%) | α:β |
|---|---|---|---|---|---|
| 1 | — | **1** | Pyridine | 95 | 86:14 |
| 2 | $CH_2Cl_2$ | **1** (8) | Pyridine | 87 | 64:36 |
| 3 | $CH_2Cl_2$ | **1** (8) | TMEDA (8) | 87 | 44:56 |
| 4 | $CH_2Cl_2$ | **2** (8) | TMEDA (8) | 88 | 20:80 |
| 5 | $CH_2Cl_2$ | **2** (8) | Pyridine | 77 | 34:66 |
| 6 | $CH_2Cl_2$ | **2** (10) | Pyridine | 91 | 52:48 |

β-*Anomer*: mp 99–100 °C. $[\alpha]_D$ +18.91 (*c* 0.6, $CH_2Cl_2$). IR data (KBr): $\nu_{max}$ 1728.7 (C=O). $^1H$ NMR data (400 MHz, $CDCl_3$): $\delta$ 7.33, 7.31, 7.17, 7.16, 7.11 (5s, 10H, Gall-H), 6.22 (d, $J_{1,2}$ 8.4 Hz, 1H, H-1), 6.03 (t, 1H, H-3), 5.81 (dd, $J_{1,2}$ 8.4, $J_{2,3}$ 9.6 Hz, 1H, H-2), 5.74 (t, *J* 9.2–9.6 Hz, 1H, H-4), 4.81 (d, $J_{6a,6b}$ 12.2 Hz, 1H, H-6b), 4.39–4.46 (m, 2H, H-5 and H-6a), 3.92, 3.91, 3.90, 3.88, 3.87, 3.86, 3.85, 3.84, (8s, 45H, $OCH_3$). $^{13}C$ NMR data (100 MHz, $CDCl_3$): $\delta$ 165.63, 165.48, 165.01, 164.91, 164.17, (C=O), 152.95, 152.88, 152.81 (Gall-C-3 and Gall-C-5), 143.03, 142.78, 142.65, 142.40, (Gall-C-4), 124.42, 123.45, 123.38, 123.12, (Gall-C-1), 107.32, 107.04, 106.94 (Gall-C-2 and Gall-C-6), 92.84 (C-1), 73.16 (C-5), 72.89 (C-3), 71.08 (C-2), 69.62 (C-4), 63.06 (C-6), 60.77, 56.07, 56.00 ($OCH_3$). Anal. Calcd for $C_{56}H_{62}O_{26}$: C, 58.43; H, 5.43. Found: C, 58.40; H, 5.38.

### 1.4. 1,2,3,4-Pentakis-[*O*-(3,4,5-trimethoxybenzoyl)]-α,β-D-mannopyranoses

α-*Anomer*: mp 94–95 °C. $[\alpha]_D$ −35.56 (*c* 1.0, $CH_2Cl_2$). IR data (KBr): $\nu_{max}$ 1729.1 (C=O); $^1H$ NMR data (400 MHz, $CDCl_3$): 7.41, 7.33, 7.24, 7.13, 7.06, (5s, 10H, Gall-H), 6.54 (s, 1H, H-1), 6.07 (t, *J* 10.0 Hz, 1H, H-4), 5.97 (dd, $J_{2,3}$ 2.6, $J_{3,4}$ 10.2 Hz, 1H, H-3), 5.88 (d, $J_{1,2}$ 1.6 Hz, 1H, H-2), 4.70 (dd, $J_{5,6b}$ 1.6 Hz, 1H, H-6b), 4.59–4.63 (m, 1H, H-5), 4.47 (dd, $J_{5,6a}$ 5.4, $J_{6a,6b}$ 12.2 Hz, 1H, H-6a), 3.97, 3.95, 3.94, 3.92, 3.92, 3.88, 3.88, 3.84, 3.83, 3.80, 3.80, 3.79, 3.76, 3.65 (14s, 45H, $OCH_3$). $^{13}C$ NMR data (100 MHz, $CDCl_3$): $\delta$ 165.56, 165.09, 164.95, 164.77, 163.42 (C=O), 153.16, 153.13, 152.84, 152.76 (Gall-C-3 and Gall-C-5), 143.47, 143.04, 142.90, 142.59, 142.44 (Gall-C-4), 124.33, 123.65, 123.55, 123.36 (Gall-C-1), 107.57, 107.35, 107.10, 107.02, 106.86 (Gall-C-2 and Gall-C-6), 91.60 (C-1), 71.00 (C-5), 69.86 (C-3), 69.75 (C-2), 66.84 (C-4), 63.09 (C-6), 60.96, 60.87, 60.78, 56.42, 56.14, 56.09, 55.94, 55.73 ($OCH_3$). Anal. Calcd for $C_{56}H_{62}O_{26}$: C, 58.43; H, 5.43. Found: C, 58.29; H, 5.56.

β-*Anomer*: mp 90–91 °C. $[\alpha]_D$ −65.14 (*c* 1.0, $CH_2Cl_2$). IR data (KBr): $\nu_{max}$ 1728.3 (C=O). $^1H$ NMR data (400 MHz, $CDCl_3$): $\delta$ 7.39, 7.26, 7.14, 7.13, 7.08 (5s, 10H, Gall-H), 6.36 (s, 1H, H-1), 6.05 (d, $J_{1,2}$ 2.8 Hz, 1H, H-2), 6.00 (t, $J_{4,5}$ 9.6 Hz, 1H, H-4), 5.74 (dd, $J_{2,3}$ 3.2, $J_{3,4}$ 9.8 Hz, 1H, H-3), 4.80 (d, $J_{6a,6b}$ 9.2 Hz, 1H, H-6), 4.47–4.40 (m, 2H, H-5 and H-6a), 3.88, 3.85, 3.83, 3.81, 3.80, 3.78, 3.77, 3.65, 3.63 (9s, 45H, $OCH_3$). $^{13}C$ NMR data (100 MHz, $CDCl_3$): $\delta$ 165.34, 164.94, 164.69, 163.22 (C=O), 152.97, 152.68, 152.62, 152.57 (Gall-C-3 and Gall-C-5), 142.78, 142.71, 142.66, 14.43, 142.14 (Gall-C-4), 124.21, 123.78, 123.29, 122.95 (Gall-C-1), 107.17, 106.96,106.83,106.75, 106.70 (Gall-C-2 and Gall-C-6), 90.85 (C-1), 72.67 (C-5), 71.33 (C-3), 69.74 (C-2), 67.14 (C-4), 63.19 (C-6), 60.64, 60.54, 55.89, 55.76, 55.52 ($OCH_3$). Anal. Calcd for $C_{56}H_{62}O_{26}$: C, 58.43; H, 5.43. Found: C, 57.95; H, 5.53.

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