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Note

Microwave-assisted glycosylation for the synthesis of glycopeptides

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Abstract—An efficient one-step synthesis of *O*-linked glycosylamino acids is described. This methodology converts commercially available peracetylated mono- and disaccharides activated by cheap and environmentally safe $FeCl_3$ under microwave irradiation with Fmoc-Ser-OBn to the corresponding β-glycosides in short reaction times and moderate yields.

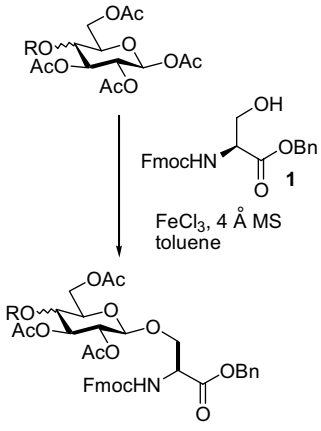
Keywords: Glycopeptides; Microwave activation; *O*-Glycosylation

Some functional glycoproteins are expressed on tumour cell surfaces,[1] for example, T–F (Thomson–Friedenreich),[2] and sialyl-Tn.[3] Vaccines containing these structures, usually as carbohydrate–protein conjugates, have been shown to induce specific antitumour cell antibody responses in mice and patients.[4] Thus, much efforts have been devoted to establish easy and efficient methods for glycopeptide synthesis.[5,6]

For the synthesis of glycopeptides, very efficient glycosylation procedures have been achieved.[7] The common approach uses a glycosyl donor with a leaving group at the anomeric centre, which is activated with a promoter to yield an oxocarbenium ion susceptible to nucleophilic attack by a glycosyl acceptor. Recently, Carvalho et al. reported on the mercuric bromide-promoted glycosylation of Fmoc-Ser-OBn with 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride.[8] The glycosylation of Fmoc-Ser-OH with β-glucose pentaacetate in dichloromethane under $BF_3{\cdot}OEt_2$ promotion has been reported previously in yields from 30% to 37% and reaction times from 2 to 18 h.[9] The glycosylation reactions described require multi-step reactions for the synthesis of the glycosyl donor and/or heavy-metal reagents such as AgOTf, $HgBr_2$ and $HgCN_2$ for the activation. Long reaction times are often required and low yields are observed. Thus, we were interested in the efficient direct β-glycosylation of Fmoc-Ser-OBn, which could be useful for glycopeptide synthesis on solid supports.

$FeCl_3$ has been reported to promote the β-glycosylation of alcohols with β peracetylated glycosides.[10]

Hence, $FeCl_3$ was used as Lewis acid initially under reflux conditions in toluene to activate galactose pentaacetate **2** in the presence of Fmoc-Ser-OBn **1**, which subsequently formed the O-linked β-galactosyl-serine derivate **3**[11] (Scheme 1). Under these conditions, many side products were observed. The optimal temperature with respect to activation and side products was 45 °C. The initial in situ activation of the anomeric acetyl



Scheme 1.

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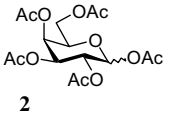
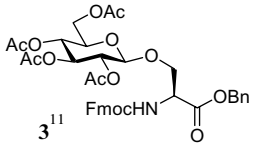
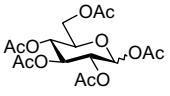
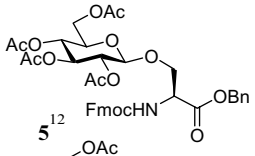
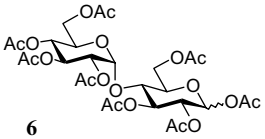
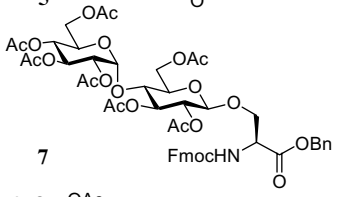
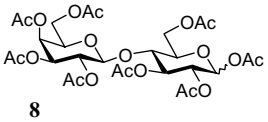
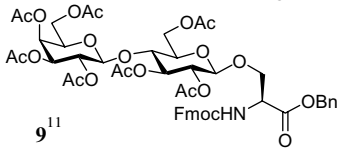
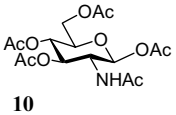
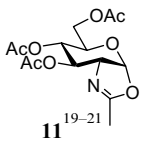
group with $FeCl_3$ was observed by TLC, indicating that the addition rather than activation was problematic. After 15 h reaction time, no starting material of **2** was left. We also observed that only the β-anomers of **2**, **4**, **6** and **8** reacted to the corresponding glycosylamino acids **3**,[11] **5**,[12] **7** and **9**,[11] respectively.

However, increase in the amount of acetylated sugar did not increase the glycopeptide formation neither under reflux conditions, nor in the presence of additional and different Lewis acid catalysts ($AlMe_3$, $TiCl_4$). Thus, it appears that steric hindrance to the nucleophilic attack of the serine derivative **1** caused the low yields and long reaction times. Microwave-assisted synthesis has demonstrated that steric problems could be overcome.[13] This approach has been shown to greatly increase yields in many reactions, such as in the open vessel Diels–Alder reaction. Encouraged by these previous studies, we used microwave irradiation in the following experiments. The glycosylation of Fmoc-Ser-OBn **1** in the presence of $FeCl_3$ (1.0 equiv), toluene or acetonitrile was successfully carried out in open vessels under microwave conditions in a microwave oven (200 W), which led to the disappearance of the starting materials after 4 min and to the generation of the corresponding glycosylated Fmoc-Ser-OBn compounds as the major products. The per-*O*-acetylated galactose **2**, glucose **4**, maltose **6** and lactose **8** derivatives were subjected to these conditions to study the reaction scope (Table 1). These products were purified by silica gel column chromatography, and their ^1H NMR spectra confirmed the β-configuration of the newly formed glycosidic linkage (i.e. maltose, H-1: δ 4.45, $J_{1,2}$ 7.7 Hz). We were thus able to prepare *N*-9-fluorenylmethoxycarbonyl-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl]-L-serine benzylester **9** from per-*O*-acetylated lactose in 54% yield. Preparation of **9** has been compared to the literature method, which requires three steps and results in an overall yield of 9%, including the synthesis of 3,6,2′,3′,4′,6′-hexa-*O*-acetyl-1,2-*O*-(1-cyanoethylidene)-α-D-lactose.[11]

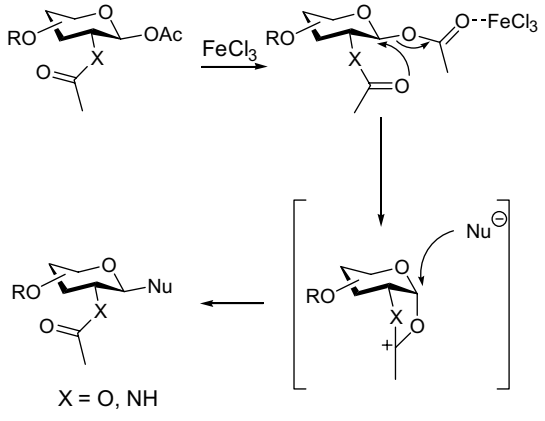
We were unable to activate the α-anomers of galactose **2**, glucose **4** and cellobiose peracetates under the same conditions. In a mixture of α- and β-glucose peracetate (1:1) **4**, only the β-anomer of **4** reacted, the α-anomer of **4** being re-isolated. A simple control experiment showed the importance of microwave heating. When an anomeric mixture of **4** in toluene was heated at 110 °C for 15 h in an oil bath with $FeCl_3$ and **1**, only 20% conversion to the glycopeptide **5** was observed after work up. In contrast the analogue microwave experiment in an open vessel yielded **7** in 51% in 4 min with a maximum temperature of 68 °C. Lukasiewcz et al. reported recently the microwave-assisted oxidation of aromatic molecules into the corresponding aryl ketones,

Table 1. $FeCl_3$-mediated glycosylation of Fmoc-Ser-OBn **1**

Donor		Product	Microwave		Conventional	
			Time (min)	α/β (yield %)	Time (min)	α/β (yield %)
 **2**	**2β**	 **3**[11]	4	0:1 (52)	720	0:1 (31)
	2α		4	0:0 (0)	300	0:0 (0)
 **4**	**4β**	 **5**[12]	2 × 4	0:1 (61)	720	0:1 (22)
	4α		4	0:0 (0)	300	0:0 (0)
 **6**	**6β**	 **7**	4	0:1 (52)	720	0:1 (10)
	6α		4	0:0 (0)	300	0:0 (0)
 **8**	**8β**	 **9**[11]	2 × 4	0:1 (54)	720	0:1 (16)
	8α		4	0:0 (0)	300	0:0 (0)
 **10**	**10β**	 **11**[19–21]	2 × 4	1:0 (85)	—	—

quinones or lactones by Magtrieve™, a magnetically retrievable oxidant based on tetravalent chromium dioxide (CrO_2).[14] They observed, that the temperature of Magtrieve™ surface was higher than the boiling point of toluene, but boiling was not detected at all. This means that in heterogeneous systems (like $FeCl_3$/toluene) the temperature of the solid may be higher than the bulk temperature of the reaction mixture. The higher temperature of the solid could be responsible for the higher reaction rates and yields of the product, which would not be possible under conventional conditions in an oil bath.

It is believed that β-glycosylation proceeds via neighbouring group participation by an acyl group at *O*-2 of the donor, as described by *Lemieux*.[15] The initially formed oxocarbenium ion is in equilibrium with the more stable acyloxonium ion formed by participation of the acyl group.[16] A solvent of low polarity like toluene favours the acyloxonium ion probably by inefficient solvatation of the oxocarbenium ion.[17] Nucleophilic ring opening of the acyl carbon results in the beta-configurated glycoside (Scheme 2). However, formation of orthoesters, often described in literature as a serious side reaction, was not observed. An explanation could be that the positive charge of the acyloxonium ion is stabilised by the vicinal acetate, which would favour the thermodynamic controlled attack of the alcohol at C-1 in a *trans*-selective manner. Higher temperature has been reported to support this suggested mechanism.[17] We also found, that 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose **10** reacted very efficient with $FeCl_3$ in $CHCl_3$ under microwave irradiation in 85% yield to 2-methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline **11**, which opens a wide repertoire of further reactions with glycosyl acceptors, primary or secondary hydroxy groups, azides and serine derivatives.[18] However, in the presence of **1** we were unable to react oxazoline **11** direct to the corresponding β-*O*-GlcNAc-Ser under $FeCl_3$ promotion and microwave conditions.



Scheme 2.

In conclusion, we have shown that glycosyltransfer reactions of peracetylated mono- and disaccharides with peptides can be substantially facilitated by microwave heating. The reaction times are shortened from 5–10 h to 4 min, the yields are improved and the environmentally safe promotor $FeCl_3$ can replace heavy metals like AgOTf, $HgBr_2$ and $HgCN_2$ or $BF_3{\cdot}OEt_2$. This is the first report about the use of microwave heating in the glycosylation of amino acids.

The β-anomeric selectivity of the starting acetylated sugars provides the potential for separation and discrimination of donor substrates for multi-component and multi-step reactions. Additionally, the glycosidation method may be also applicable to solid phase glycopeptide synthesis containing vulnerable peptide sequences.

1. Experimental

1.1. General

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of Ar. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. $CHCl_3$ and toluene were distilled from CaH_2 under Ar. External reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available plates, precoated with a 0.25 mm layer of silica containing a fluorescent indicator (E. Merck) and compounds were sprayed with anisaldehyde reagent followed by heating. Organic layers were dried over $MgSO_4$ unless stated otherwise. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Petroleum ether refers to the fraction with bp 40–60 °C. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless stated otherwise, using a Bruker AM-400 instrument, operating at 400 MHz for ^1H and at 100 MHz for ^{13}C. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C (central of triplet) 77.0] or CH_3OH [δ_H 3.35, δ_C (central of septet) 49.0]. Melting points were determined on a Melt-Temp 2 microscope. Electrospray-ionisation mass spectra (ESIMS) were recorded with a Finnigan MAT 8340 on samples suspended in MeOH. IR spectra in pressed KBr discs were recorded on a Bio-Rad FTS-25 spectrometer. Optical rotation values were measured with a Dr. Kernchen sucromat polarimeter.

1.2. *N*-9-Fluorenylmethoxycarbonyl-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-L-serine benzyl ester 3

A soln of **2** (40.0 mg, 102 μmol, 1.0 equiv), Fmoc-Ser-OBn **1** (42.0 mg, 101 μmol, 1.0 equiv), 4 Å molecular

sieves (25 mg) in toluene (1 mL) and $FeCl_3$ (17.0 mg, 102 μmol, 1.0 equiv) was reacted 4 min in a microwave oven (200 W). The reaction mixture was filtered, the molecular sieves washed with $CHCl_3$ and directly applied to column chromatography (4:1 diethyl ether–petroleum ether), which provided **3** as a foamy solid (40.0 mg, 54 μmol, 52%). $[\alpha]_D$ +0.2 (*c* 1.0, $CHCl_3$), lit.[11] $[\alpha]_D$ −1.2 (*c* 1.0, $CHCl_3$); R_f 0.40 (4:1 diethyl ether–petroleum ether); IR (cm^{-1}): 1159, 1263, 1455, 1738, 2868, 2928, 2956, 3463; ^1H and ^{13}C NMR spectra data are in accordance with lit.[11] ESIMS: $[M+Na]^+$ calcd for $C_{39}H_{41}NO_{14}[Na]^+$ 770.2425, found *m/z* 770.2434.

1.3. *N*-9-Fluorenylmethoxycarbonyl-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-L-serine benzyl ester 5

Coupling of **4** (40.0 mg, 102 μmol, 1.0 equiv) and **1** (42.0 mg, 101 μmol, 1.0 equiv) as described in the preparation of **3** gave **5** as a foamy solid (46.0 mg, 62 μmol, 61%); $[\alpha]_D$ +2.6 (*c* 1.0, $CHCl_3$); R_f 0.39 (4:1 diethyl ether–petroleum ether); IR (cm^{-1}): 1167, 1255, 1459, 1742, 2887, 2946, 3487; ^1H and ^{13}C NMR spectra data are in accordance with lit.[12] ESIMS: *m/z* 770.1 100%, $[M+Na^+]$.

1.4. *N*-9-Fluorenylmethoxycarbonyl-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyl]-L-serine benzylester 7

Coupling of **6** (50.0 mg, 74 μmol, 1.0 equiv) and **1** (31.0 mg, 74 μmol, 1.0 equiv) as described in the preparation of **3** gave **7** as a foamy solid (40.0 mg, 39 μmol, 52%); mp: 121 °C; $[\alpha]_D$ +45.0 (*c* 1.0, $CHCl_3$); R_f 0.29 (4:1 diethyl ether–petroleum ether); IR (cm^{-1}): 1159, 1255, 1459, 1734, 2864, 2936, 2960, 3471; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* 7.5 Hz, 2H, Aryl–H), 7.61 (d, *J* 7.40 Hz, 2H, Aryl–H), 7.19–7.42 (m, 9H, Aryl–H), 5.65 (d, $J_{N,H}$ 8.1 Hz, 1H, N-H), 5.40 (d, $J_{1'',2''}$ 3.7 Hz, 1H, H-1″), 5.39 (dd, $J_{3',4''}$ 9.9, $J_{2'',3''}$ 10.5 Hz, 1H, H-3″), 5.23 (t, $J_{2'',3'} = J_{3',4'}$ 9.2 Hz, 1H, H-3′), 5.19 (s, 2H, OCH_2Bn), 5.07 (t, $J_{3',4''}$ 9.9 Hz, 1H, H-4″), 4.87 (dd, $J_{1'',2''}$ 3.7, $J_{2'',3''}$ 10.5, 1H, H-2″), 4.77 (t, $J_{1'',2'}$ 8.1 Hz, 1H, H-2′), 4.45 (d, $J_{1'',2'}$ 8.1 Hz, 1H, H-1′), 4.36–4.54 (m, 4H, Aryl–CH–CH_a–O, 2-H, H_2-6′), 4.21–4.29 (m, 3H, H-3_a, H-$6''_a$, C*H*CH_2–), 4.12 (dd, *J* 12.2, 4.3 Hz, 1H, Aryl–CH–CH_b–O), 4.04 (dd, $J_{6a'',6b''}$ 2.2, $J_{5'',6''}$ 12.6 Hz, 1H, H-$6''_b$), 3.95 (m, 2H, H-5″, H-4′), 3.88 (dd, $J_{3a,3b}$ 3.2, $J_{3b,2}$ 10.8 Hz, 1H, H-3_b), 3.47 (m, 1H, H-5′), 2.10, 2.09, 2.06, 2.03, 2.01, 1.98 (6s, 21H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.49, 170.47, 170.38, 170.11, 169.90, 169.56 (seven ester CO), 169.38 (C-1), 155.82 (NH*C*OO), 143. 76, 143.62, 141.30 (four aromatic quaternary carbons Fmoc), 135.11 (quaternary aromatic carbon CH_2Ph), 128.23, 128.52, 128.60 (five tertiary aromatic carbons CH_2Ph), 120.00, 124.98, 125.09, 127.09, 127.75 (eight tertiary aromatic carbons Fmoc), 100.59 (C-1′), 95.56 (C-1″), 75.11 (C-3′), 72.48 (C-4′), 72.15 (C-5′), 71.97 (C-2′), 69.99 (C-2″), 69.63 (C-3), 69.28 (C-3″), 68.52 (C-5″), 67.97 (C-4″), 67.56 (CH_2Ph), 67.08 (CH_2Fmoc), 62.59 (C-6′), 61.43 (C-6″), 54.45 (C-2), 47.11 (CHFmoc), 26.88, 20.86, 20.72, 20.63, 20.55, 20.47 (7 C*C*H_3). MS (ESI): *m/z* $[M+Na]^+$ calcd for $[C_{51}H_{57}NO_{22}]Na^+$ 1058.3270, found *m/z* 1058.3273.

1.5. *N*-9-Fluorenylmethoxycarbonyl-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl]-L-serine benzylester 9

Coupling of **8** (50.0 mg, 74 μmol, 1.0 equiv) and **1** (31.0 mg, 74 μmol, 1.0 equiv) as described in the preparation of **3** gave **9** as a foamy solid (41.0 mg, 40 μmol, 54%); $[\alpha]_D$ +6.6 (*c* 1.0, $CHCl_3$), lit.[11] $[\alpha]_D$ −0.8 (*c* 1.0, $CHCl_3$); R_f 0.13 (4:1 diethyl ether–petroleum ether); IR (cm^{-1}): 1159, 1263, 1455, 1730, 2872, 2932, 2964, 3431; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* 7.4, 2.3 Hz, 2H, Aryl–H), 7.61 (d, *J* 7.4 Hz, 2H, Aryl–H), 7.31–7.43 (m, 9H, Aryl–H), 5.63 (d, $J_{N,H}$ 8.1 Hz, 1H, N–H), 5.34 (dd, $J_{3',4''}$ 3.5, $J_{4'',5''}$ 1.0 Hz, 1H, H-4″), 5.19 (m, 2H, H-6″), 5.15–5.17 (d, $J_{3',4'} = J_{4',5'}$ 9.1 Hz, 1H, H-4′), 5.16 (d, $J_{1'',2'}$ 9.1 Hz, 1H, H-1′), 5.09–5.14 (dd, $J_{2'',3''}$ 10.4, $J_{1'',2''}$ 7.8 Hz, 1H, H-2″), 4.94–4.97 (dd, $J_{2'',3''}$ 10.4 $J_{3',4''}$ 3.5 Hz, 1H, H-3″), 4.84–4.88 (dt, $J_{5'',6''}$ 8.2, $J_{4'',5''}$ 1.0 Hz, 1H, H-5″), 4.70 (s, 2H, CH_2OBn), 4.47 (m, 2H, H_2-6′), 4.44 (d, $J_{1'',2''}$ 7.8 Hz, 1H, H-1″), 4.20–4.28 (m, 2H, H-3_a, Fmoc-CH), 4.03–4.15 (m, 4H, H-3′, 2-H, Fmoc-CH_2), 3.84–3.87 (m, 1H, H_b-3), 3.73–3.78 (t, $J_{1'',2'} = J_{2'',3'}$ 9.1, 1H, H-2′), 3.48–3.52 (m, 1H, H-5′), 2.15, 2.07, 2.06, 2.05, 1.99, 1.97 (7s, 21H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170. 64, 170.43, 170.36, 170.00, 169.87, 169.37 (eight ester CO, C-1), 156.15 (NH*C*OO), 143.94, 141.61, 140.91, 140.53 (four aromatic quaternary carbons Fmoc), 135.42 (quaternary aromatic carbon CH_2Ph), 128.48, 128.82, 127.28 (five tertiary aromatic carbons CH_2Ph), 128.93, 128.86, 128.09, 127.94, 127.42, 125.31, 120.36 (eight tertiary aromatic carbons Fmoc), 101.36 (C-1″), 101.21 (C-1′), 76.38 (C-2′), 73.02 (C-5′), 72.87 (C-4′), 71.81 (C-5″), 71.28 (C-3″), 61.76 (CH_2Fmoc), 69.86 (C-3), 69.40 (C-2″), 67.87 (C-6″), 67.44 (C-6′), 66.92 (C-4″), 65.66 (CH_2Bn), 62.19 (C-3′), 61.13 (C-2), 47.42 (CHFmoc), 29.99, 22.98, 22.98, 21.08, 20.93, 20.80 (7 C*C*H_3). ESIMS: *m/z* 1058.3 100%, $[M+Na^+]$.

1.6. 2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline 11[19–21]

A soln of **10** (100.0 mg, 256 μmol, 1.0 equiv), 4 Å molecular sieves (25 mg) in $CHCl_3$ (10 mL) and $FeCl_3$ (60.0 mg, 353 μmol, 1.4 equiv) was reacted 2 × 4 min in a microwave oven (200 W). The reaction mixture was filtered, the molecular sieves washed with $CHCl_3$ and

directly applied to column chromatography (20:1 $CHCl_3$–MeOH), which provided **11** as a colourless solid (71.7 mg, 217 μmol, 85%). The ^1H NMR[20] spectrum data was in accordance with lit. $[\alpha]_D$ +15.0 (*c* 1.0, $CHCl_3$), lit.[21] $[\alpha]_D$ +16.3 (*c* 1.0, $CHCl_3$); R_f 0.30 (20:1 $CHCl_3$–MeOH).

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