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Tetrahedron Letters 47 (2006) 307–310
Tetrahedron Letters

$HClO_4$–SiO_2 catalyzed glycosylation using sugar trichloroacetimidates as glycosyl donors

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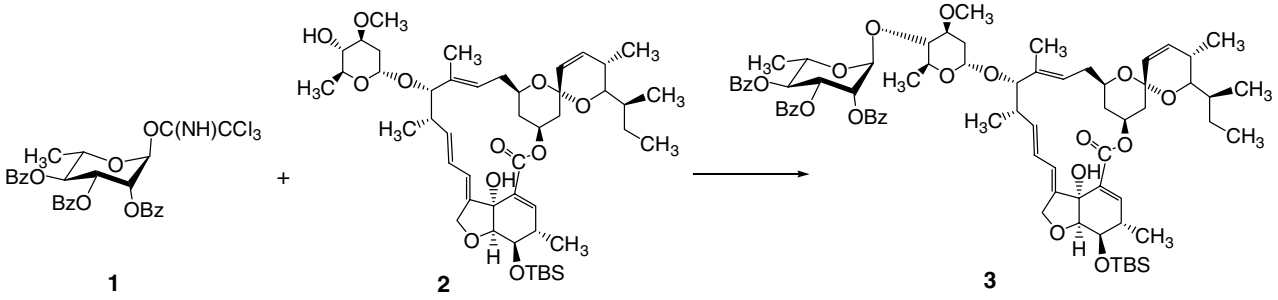
Received 11 October 2005; accepted 3 November 2005
Available online 21 November 2005

Abstract—Silica-supported perchloric acid ($HClO_4$–SiO_2) has been used as an efficient promoter, as a replacement of TMSOTf, in various glycosylation reactions using sugar trichloroacetimidates as glycosyl donors. Operational simplicity, economic considerations, high yield, short reaction time and low toxicity were the key features associated with this protocol.

In synthetic carbohydrate chemistry, trichloroacetimidates have become the most widely used glycosyl donors.[1] They can be easily prepared by a base-catalyzed reaction of a lactol with trichloroacetonitrile. In standard glycosylation reactions using trichloroacetimidate donors, a catalytic amount of Lewis acid promoter, such as trimethylsilyl triflate (TMSOTf) or boron trifluoride etherate ($BF_3{\cdot}Et_2O$), is most commonly used.[2–5] *O*-Trichloroacetimidates exhibit outstanding donor properties in terms of ease of formation, stability, reactivity, general applicability, and usually result in high product yield. In addition to TMSOTf and $BF_3{\cdot}Et_2O$, other promoters, including TESOTf, AgOTf, TsOH, TfOH, and $Sn(OTf)_2$, have been occasionally utilized to activate trichloroacetimidates.[6–9]

In our efforts to synthesize avermectin B_{1a} analogues, we discovered that AgOTf was a more efficient catalyst than TMSOTf or $BF_3{\cdot}Et_2O$ for trichloroacetimidate glycosyl donors.[10] However, AgOTf is expensive, moisture and light sensitive, and discommodious to handle. Recently, $HClO_4$–SiO_2 has been introduced as a catalyst for acetylation,[11,12] Ferrier rearrangement,[13,14] acetylation,[15] and chemo-selective de-isopropylidenation



Scheme 1. Reagents and conditions: $HClO_4$–SiO_2, CH_2Cl_2, 0 °C, 98%.

Keywords: Glycosylations; Carbohydrates; Synthesis; Perchloric acid on silica.
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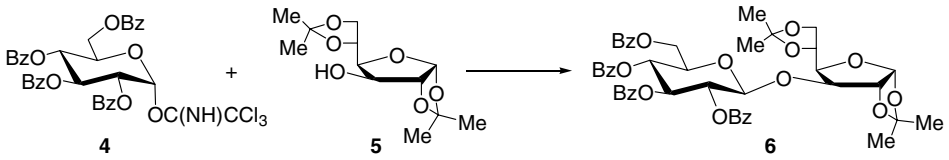
doi:10.1016/j.tetlet.2005.11.025

Table 1. Optimization of the amount of $HClO_4$–SiO_2 used in the protocol[a]



Entry	Molar ratio (donor:$HClO_4$–SiO_2)	Reaction time (min)	Yield (%)
1	100:1.5	>120	<10[b]
2	100:3	60	>75
3	100:6	30	>75
4	100:9	<20	<30[c]

[a] The reactions were carried out in CH_2Cl_2 at 0 °C.
[b] No improvement after the first 30 min.
[c] Donor decomposed quickly.

and de-tritylation.[16] Curious about whether this immobilized acid could be used in glycosylation, we tried to condense trichloroacetimidate **1**[17] and lactone **2**[18] using $HClO_4$–SiO_2 as catalyst (Scheme 1). We were excited to find that the desired product **3** was obtained in 98% yield. We report herein the application of $HClO_4$–SiO_2 catalyzed glycosylation in a number of examples, using trichloroacetimidates as glycosyl donors.

The amount of $HClO_4$–SiO_2 used in the glycosylation was optimized in the glycosylation of acceptor **5** with donor **4** (Table 1). Optimal results were obtained using a molar ratio (donor:promoter $HClO_4$–SiO_2) of 100:3 to 100:6. We were also pleased to observe that this glycosylation reaction could be carried out smoothly at the 100 g scale (of donor), resulting in a 77% isolated yield of disaccharide product **6**. The same reaction using TMSOTf as a promoter resulted in a 56% yield.[19] The main by-product of this reaction, generated from acetal migration in **5**, was significantly reduced under $HClO_4$–SiO_2 catalysis. The efficacy of reused $HClO_4$–SiO_2 catalyst was tested with catalyst recycled from the large-scale synthesis of **6**. When applied to the condensation of **4** and **5**, under conditions described in entry 3 of Table 1, a significantly lower yield of **6** (<35%) was obtained.

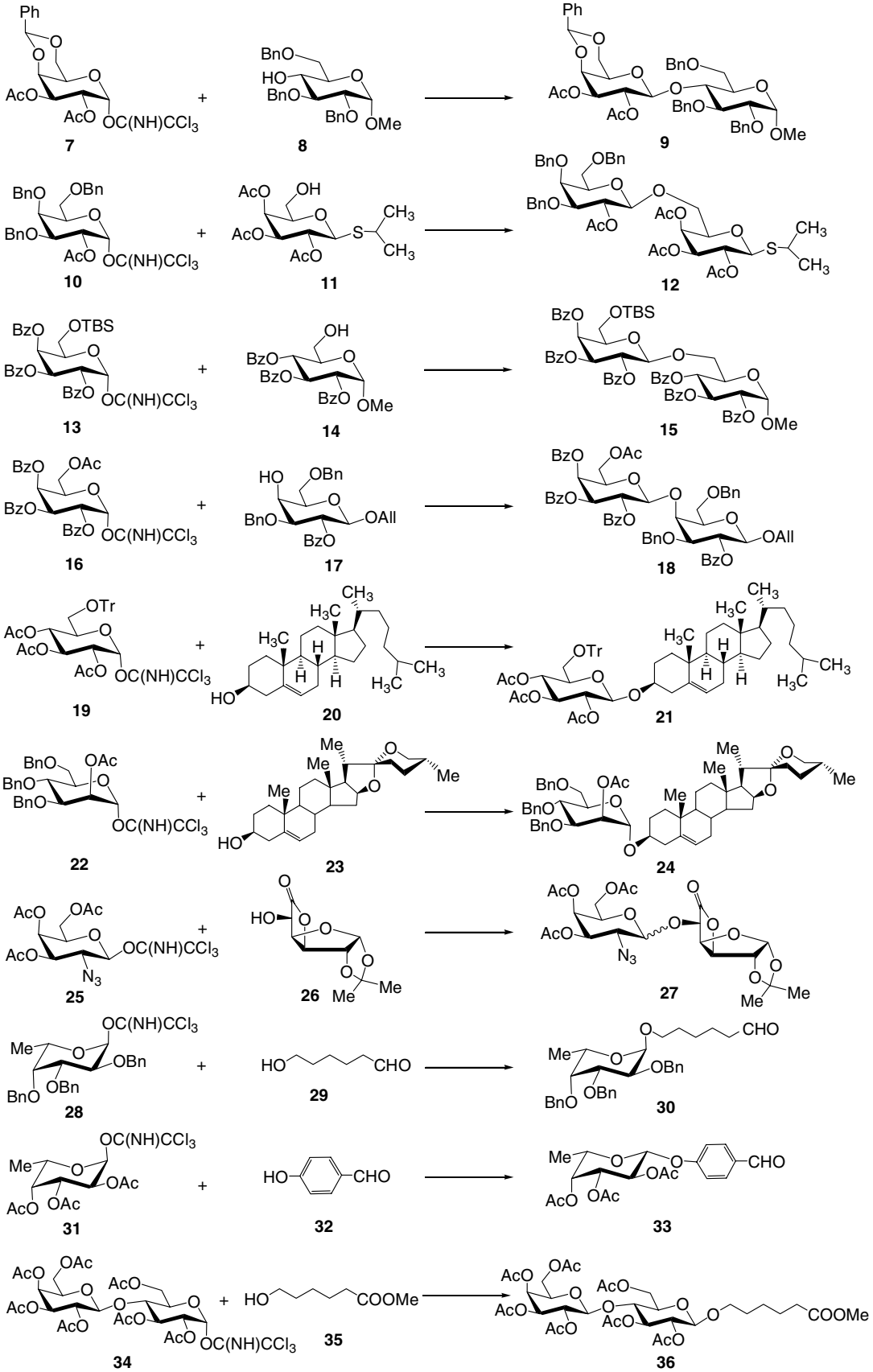
Next, the scope of this promoter was assessed to establish whether it could be widely used in glycosylation reactions (Scheme 2). All of the reactions examined proceeded smoothly under normal glycosylation procedures and the products were obtained in good to excellent yields. Moreover, no workup was required beyond the mere filtration of the catalyst, followed by chromatographic purification. A variety of hydroxyl protecting groups such as isopropylidene (**5**), benzylidene (**7**), TBS (**13**), Bz (**16**), All (**17**), Tr (**19**), Bn (**22**, **28**), Ac (**31**), and other functional groups as lactone (**2**, **26**), aldehyde (**29**, **32**), azide (**25**) and thioglycoside (**11**) were found to be compatible under these glycosylation conditions. More impressively, the yields for trityl-containing product **21** (85%), fucosyl **30** (89%), **33** (80%), and lactosyl **36** (84%) were significantly improved using $HClO_4$–SiO_2. These reactions gave unsatisfactory yields (30–50%) using TMSOTf as catalyst in our previous studies.[20]

The $HClO_4$–SiO_2 catalyst can be easily prepared from the readily available $HClO_4$ and silica gel (100–200 mesh). Typically, 1.1 g of $HClO_4$ (a 70% aqueous solution) and 20 g of SiO_2 were suspended in Et_2O (80 mL) for 1 h at rt. The mixture was concentrated and the residue was heated at 110 °C for 2 h to furnish $HClO_4$–SiO_2 as a free flowing powder (1 g contains 0.37 mmol $HClO_4$). A general procedure for $HClO_4$–SiO_2 catalyzed glycosylation is described as follows: To a solution of trichloroacetimidate donor (1.0 mmol) and alcohol acceptor (0.95 mmol) in dry CH_2Cl_2 (5–8 mL) at 0 °C is added $HClO_4$–SiO_2 (3–6%, mol ratio based on donor). The mixture is stirred under these conditions for about 10–60 min, and the reaction is monitored for completion by TLC analysis. The mixture is filtered, the silica washed with dichloromethane, and the combined organic phase concentrated under reduced pressure. The residue is then purified by silica gel column chromatography to obtain a pure product.

In summary, we have demonstrated that the $HClO_4$–SiO_2 promoted glycosylation of various trichloroacetimidate donors are highly efficient reactions. The mild reaction conditions, experimental simplicity, low cost, excellent yields and their environmentally benign nature are major advantages of this new approach. A large number of functional groups used for protecting group manipulation remained unaffected, and the side reactions such as migration and degradation in coupling reactions were suppressed. We expect that this protocol will find a general application in organic synthesis.

Acknowledgements

This work was supported by National Basic Research Program of China (2003CB415001), NNSF of China (project 30330690), and NIH of the US (HL62244).



Scheme 2. Reagents and reaction conditions: $HClO_4$–SiO_2, CH_2Cl_2, 0 °C; 88% for **9**; 90% for **12**; 92% for **15**; 81% for **18**; 83% for **21**; 90% for **24**; 78% for **27** as an α,β mixture (α:β = 2:1); 89% for **30**; 80% for **33**; 84% for **36**.

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18. Compound **2** was obtained from the avermectin B_{1a} hydrolysis (1% H_2SO_4 in isopropyl alcohol), followed by selective silylation (TBSCl, Im, DMF).
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20. All new compounds gave satisfactory ^{1}H NMR and MALDI-TOF MS data. **3**: $[\alpha]_D^{20}$ −63 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.13–0.14 (m, 6H, 2CH_3), 0.78–0.95 (m, 19H), 1.22–1.35 (m, 3H), 1.34–1.36 (m, 6H, H-6^{I}, 6^{II}), 1.48–1.53 (m, 4H, H-14a,20a), 1.57–1.60 (m, 4H), 1.79–1.83 (m, 4H), 2.02–2.06 (m, 1H, H-20e), 2.24–2.30 (m, 4H), 2.52–2.60 (m, 1H, H-12), 3.30–3.35 (t, 1H, $J = 9.1$ Hz), 3.39–3.41 (m, 1H), 3.47–3.52 (m, 4H), 3.72–3.80 (m, 1H), 3.84–3.94 (m, 2H), 3.97–4.0 (m, 2H), 4.07 (s, 1H), 4.27–4.31 (m, 1H), 4.44–4.45 (m, 1H), 4.63–4.68 (m, 2H, H-8a), 4.81 (d, 1H, $J = 3.5$ Hz, H-1^{I}), 5.0–5.08 (m, 1H, H-3), 5.33–5.42 (m, 2H, H-15, H-19), 5.46 (d, 1H, $J = 1.6$ Hz, H-1^{II}), 5.52–5.57 (dd, 1H, $J = 2.5$, 9.9 Hz, H-23), 5.69 (t, 1H, $J = 9.8$ Hz, H-4^{I}), 5.74–5.88 (m, 6H, H-9, 10, 11, 22, 2^{II}, 3^{II}), 7.25–8.12 (m, 15H). **9**: $[\alpha]_D^{20}$ +66 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.04, 2.06 (2s, 2 × 3H, 2Ac), 3.06 (s, 1H), 3.37 (s, 3H, OCH_3), 3.48–3.52 (m, 1H), 3.60–3.64 (m, 2H), 3.80–3.90 (m, 4H), 4.17 (m, 1H), 4.23 (d, 1H, $J = 3.6$ Hz, H-4^{I}), 4.43 (d, 1H, $J = 12.0$ Hz, one proton of PhCH_2), 4.52 (d, 1H, $J =$ 8.0 Hz, H-1^{I}), 4.57 (d, 1H, $J = 3.6$ Hz, H-1), 4.63, 4.74 (2 d, 2H, $J = 12.0$ Hz, PhCH_2), 4.68 (dd, 1H, $J =$ 3.6, 10.0 Hz, H-3^{I}), 4.78–4.82 (m, 2H, PhCH_2), 5.10 (d, 1H, $J = 12.0$ Hz, one proton of PhCH_2), 5.30 (dd, 1H, $J = 8.0$, 10.0 Hz, H-2^{I}), 5.45 (s, 1H), 7.19–7.45 (m, 20H). **12**: $[\alpha]_D^{20}$ +25 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 6H, $J = 7.0$ Hz, CH(CH_3)$_2$), 1.96, 2.00, 2.04, 2.10 (4s, 12H, 4Ac), 3.14–3.18 (m, 1H), 3.47 (dd, 1H, $J = 2.4$, 10.0 Hz, H-3′), 3.54–3.62 (m, 3H), 3.69–3.72 (m, 2H), 3.82–3.84 (m, 1H), 3.94 (d, 1H, $J = 2.4$ Hz, H-4′), 4.36 (d, 1H, $J = 8.0$ Hz, H-1), 4.42, 4.45, 4.48, 4.57, 4.65, 4.92 (6d, 12H, $J = 12.0$ Hz, 3 PhCH_2), 4.52 (d, 1H, $J = 10.0$ Hz, H-1′), 5.01 (dd, 1H, $J = 3.3$, 10.0 Hz, H-3), 5.18 (t, 1H, $J = 10.0$ Hz, H-2′), 5.33 (dd, 1H, $J = 8.0$, 10 Hz, H-2), 5.38 (d, 1H, $J = 3.3$ Hz, H-4), 7.26–7.35 (m, 15H, Ph). **15**: $[\alpha]_D^{20}$+71 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.08, −0.07 (2s, 6H, 2CH_3), 0.79 (s, 9H), 3.01 (s, 3H, OCH_3), 3.70–3.85 (m, 4H), 4.10 (dd, 1H, $J = 1.7$, 11.2 Hz), 4.20–4.23 (m, 1 H), 4.89 (d, 1H, $J = 8.0$ Hz, H-1′), 4.90 (d, 1H, $J = 3.5$ Hz, H-1), 5.10 (dd, 1H, $J = 3.5$, 10.0 Hz, H-2), 5.33 (t, 1H, $J = 10.0$ Hz), 5.44–5.51 (m, 2H), 5.86 (t, 1H, $J = 10.0$ Hz), 6.06 (t, 1H, $J = 10.0$ Hz), 7.25–8.00 (m, 30H). **21**: $[\alpha]_D^{20}$ +52 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (s, 3H), 0.80–0.90 (m, 14H), 0.95–1.00 (m, 3H), 1.05–1.13 (m, 6H), 1.24–1.41 (m, 8H), 1.48–1.57 (m, 3H), 1.68–1.72 (m, 5H), 1.74–1.92 (m, 1H), 1.96–2.0 (m, 5H), 2.03–2.07 (m, 4H), 2.22–2.26 (m, 2H), 3.05–3.09 (dd, 1H, $J = 5.1$, 10.4 Hz, H-6a), 3.18–3.21 (dd, 1H, $J = 2.1$, 10.4 Hz, H-6b), 3.51–3.60 (m, 2H, H-5, H-3 of cholesterol), 4.58 (d, 1H, $J =$ 8.1 Hz, H-1), 4.99–5.03 (m, 1H, H-2), 5.09–5.16 (m, 2H, H-3, H-4), 5.36 (d, 1H, $J = 4.1$ Hz), 7.19–7.45 (m, 15H). **30**: $[\alpha]_D^{20}$ −56 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, 3H, $J = 6.5$ Hz, H-6), 1.38–1.43 (m, 2H), 1.54–1.68 (m, 4H), 2.30–2.38 (m, 2H), 3.26–3.32 (m, 1H, one proton of OCH_2), 3.54–3.61 (m, 1H, H-5), 3.64–3.70 (m, 1H, one proton of OCH_2), 3.86 (t, 1H, $J = 6.9$ Hz, H-3), 4.07 (dd, 1H, $J = 4.2$, 6.9 Hz, H-2), 4.14 (t, 1H, $J = 6.9$ Hz, H-4), 4.54–4.78 (m, 6H, 3PhCH_2), 4.87 (d, 1H, $J = 4.2$ Hz, H-1), 7.26–7.36 (m, 15H), 9.72 (s, 1H, C*H*O). **33**: $[\alpha]_D^{20}$ +33 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, 3H, $J = 6.5$ Hz, H-6), 2.03, 2.06, 2.20 (3s, 9H, 3CH_3CO), 4.02–4.04 (m, 1H, H-5), 5.14 (dd, 1H, $J = 3.4$, 10.0 Hz, H-3), 5.18 (d, 1H, $J = 8.0$ Hz, H-1), 5.33 (d, 1H, $J = 3.4$ Hz, H-4), 5.50 (dd, 1H, $J = 8.0$, 10.0 Hz, H-2), 7.11 (d, 2H, $J = 8.6$ Hz, *Ph*), 7.85 (d, 2H, $J = 8.6$ Hz, *Ph*), 9.92 (s, 1H, C*H*O). **36**: $[\alpha]_D^{20}$ +46 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34–1.36 (m, 2H), 1.54–1.64 (m, 4H), 1.96, 2.03, 2.04, 2.05, 2.06, 2.12, 2.15 (7s, 7 × 3H, 7CH_3CO), 2.30 (t, 2H, $J = 7.4$ Hz), 3.44–3.46 (m, 1H), 3.47–3.60 (m, 1H), 3.66 (s, 3H, OCH_3), 3.76–3.88 (m, 3H), 4.05–4.14 (m, 3H), 4.44 (d, 1H, $J = 8.0$ Hz), 4.47 (d, 1H, $J = 8.0$ Hz), 4.48–4.50 (m, 1H), 4.88 (dd, 1H, $J = 8.0$, 10.0 Hz), 4.95 (dd, 1H, $J = 3.4$, 10.0 Hz), 5.10 (dd, 1H, $J = 8.0$, 10.0 Hz), 5.20 (t, 1H, $J = 9.5$ Hz), 5.34 (d, 1H, $J = 3.1$ Hz).