2,4,6-Tri-*tert*-butylpyrimidine (TTBP): A Cost Effective, Readily Available Alternative to the Hindered Base 2,6-Di-*tert*-butylpyridine and its 4-Substituted Derivatives in Glycosylation and Other Reactions

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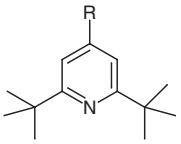
Received 4 October 2000

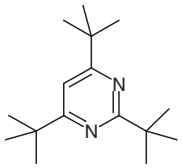
Abstract: It is reported that 2,4,6-tri-*tert*-butylpyrimidine (TTBP), a highly sterically hindered base available through an efficient, cost-effective one pot sequence, is a replacement for 2,6-di-*tert*-butylpyridine and its 4-substituted analogs in glycosylation reactions and in the formation of vinyl triflates.

Key words: glycosylations, carbohydrates, non-nucleophilic base, pyrimidines, triflates

2,6-Di-*tert*-butylpyridine (**1**) was introduced by Brown and Kanner[1] as a mild base capable of distinguishing between Brønsted and Lewis acids.[1] Subsequently 2,4,6-tri-*tert*-butylpyridine (**2**) and 2,6-di-*tert*-butyl-4-methylpyridine (**3**) have also been described, and all three bases and polymer-bound versions thereof,[2] have been extensively employed as non-nucleophilic bases in a broad variety of contexts[3] including glycosylation reactions,[4,5] and the formation of vinyl triflates.[6–9] Kahne and coworkers exploited the inability of these bases to form amine-borane complexes, as noted originally by Brown,[1] by conducting glycosylations in the presence of **3** and BF_3, so avoiding the formation of orthoesters seen in the absence of the Lewis acid.[10] In this laboratory we have made extensive use of **3** in our various β-mannosylation sequences,[11–14] but, in applying this chemistry to the synthesis of higher oligosaccharides on larger scales have been confronted by the irksome but real issue of cost. In effect **1**, **2** and **3** as purchased from the usual chemical supply houses are expensive (>$12/g in the year 2000) even when purchased in 25g lots. Syntheses of these bases making use of multiple, one-pot or sequential additions of *tert*-butylmetal reagents to pyridine or substituted pyridines, with rearomatization, necessitate the use of large excesses of the nucleophile so rendering them less than optimal for scale up as well as inefficient.[1,15–18] The various syntheses involving the formation of the corresponding *tert*-butylated pyrylium ions followed by treatment with ammonia are attractive but nevertheless require multiple steps or give only moderate yields.[19,20] The most direct of these approaches is Stang's[21] but even this only allows for the production of ~65 g batches of **3** and only reduces the cost to an estimated $9.4/g. Bates' synthesis of **3**,[22] the condensation of dilithio isobutylene with two equivalents of pivalonitrile, is low yielding and does not appear to be scalable. We now report that 2,4,6-tri-*tert*-butylpyrimidine (TTBP, **4**) serves as an admirable replacement for **1**–**3** in a range of glycosylations, and in the formation of enol triflates, and, moreover, that it can be produced in 90 g batches in a one-pot process that brings the cost down to approximately $4.3/g.



1: R = H
2: R = *tert*-Bu
3: R = Me



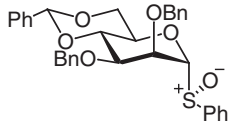
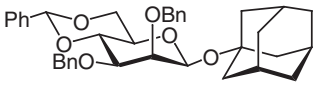
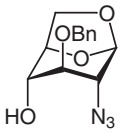
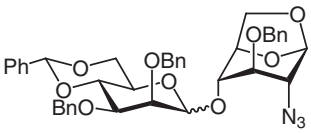
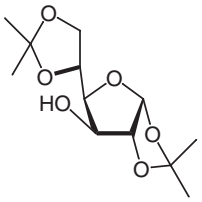
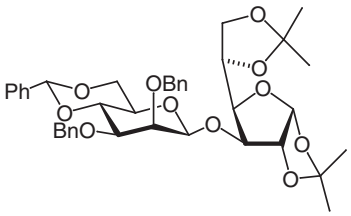
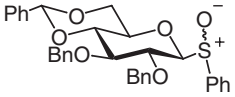
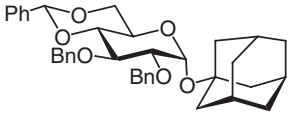
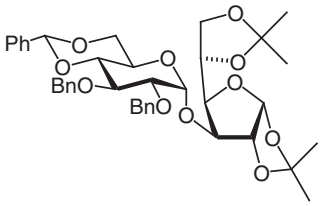
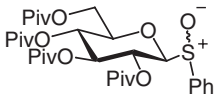
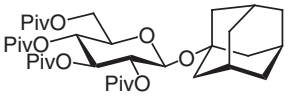
4

TTBP (**4**) was first prepared in modest yield by van der Plas and Koudijs, by Minisci-type homolytic alkylation of pyrimidine.[23] A much improved synthesis was later described by García Martínez, Hanack and coworkers involving the condensation of pinacolone with two equivalents of pivalonitrile, mediated by triflic anhydride.[24] We have found that this sequence may be readily scaled to provide 90g batches in a one-pot, chromatography-free sequence. The poor nucleophilicity of **4** was apparent to van der Plas and Koudijs who noted that no reaction took place on exposure to bromine and to peracids.[23] These authors also determined a pK_a of 1.02 for **4** in 50% aqueous ethanol,[23] which is considerably smaller than those of 3.58, 4.02 and 4.41 for **1**, **2** and **3**, respectively, in the same solvent.[1,25] Although **4** is thus a very mild base, it was thought that it would still be more than sufficient to neutralize triflic acid, the byproduct in the type of glycosylations studied here, in enol triflate formation, and in the whole multitude of reactions for which triflic anhydride[26] is used as reagent.

In the event, a series of glycosidic couplings (Table) were conducted by the sulfoxide method[5,12] and the results found to be in every way comparable to identical reactions previously carried out with **3** as base in our laboratory.[12,27] These include β-selective mannosylations,[12] α-selective glucosylations,[27] standard β-selective glucosylations with neighboring group participation,[5,12] and high yielding couplings to *tert*-alcohols.[12]

Although we have not carried out extensive investigations, it is obvious that the replacement of **1**–**3** by the new base **4** is not limited to the sulfoxide glycosylation meth-

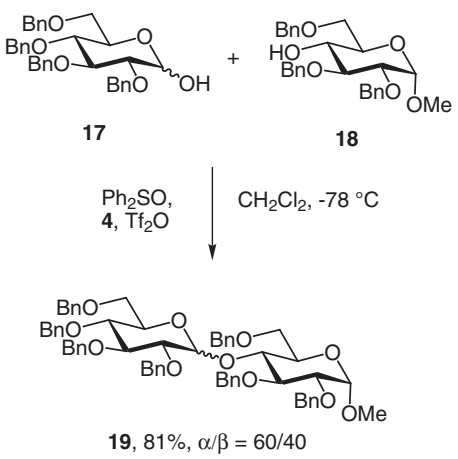
Table Sulfoxide Glycosylations in the Presence of **4**

Entry	Donor	Acceptor	Product	Yield (%)	Ratio (α/β)
1	 **5**	 **6**	 **7**	82	β only
2	**5**	 **8**	 **9**	76	~1/5
3	**5**	 **10**	 **11**	90	β only
4	 **12**	**6**	 **13**	78	α only
5	**12**	**10**	 **14**	79	α only
6	 **15**	 **6**	 **16**	73	β only

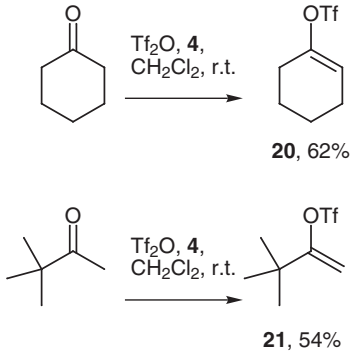
od. By way of a further example we have, nevertheless, applied **4** in Gin's[28,29] dehydrative glycosylation sequence (Scheme 1), when the yield and selectivity were again comparable to the original.

Finally, as an illustration that **4** will find application as a replacement for **1**–**3** outside the field of carbohydrate chemistry, we have employed it as base in the synthesis of two vinyl triflates previously prepared by Stang[30] and others[31] using **3** (Scheme 2). Yet again the yields were comparable and even superior to those reported in the original papers.

In closing we return to the synthesis of **4** and also to several of its features, aside from cost, which render it a very attractive replacement for **1**–**3**. The synthesis of **4** that we have employed here is developed from a literature procedure,[24] which recommended stirring of pivalonitrile, pinacolone, and triflic anhydride at room temperature for 18 h, after which extractive work up and chromatography was reported to give a 92% yield. In our hands, retaining the



Scheme 1



Scheme 2

same ratios of reactants and solvent, we find that the reaction is far from complete after 18 hours with both the conversion of pinacolone to its enol triflate and the reaction of the enol triflate with the nitrile incomplete. Our observations are consistent with those of Hargrove and Stang who found that pinacolone was only converted in approximately 60% yield to its enol triflate after 60 h.[30] It is entirely probable that the rate of reaction in the original protocol was accelerated by an undetermined catalyst. Until such a time as this is verified we simply find it convenient, and recommend, that the reaction be monitored by removal of aliquots and not quenched until complete. The pyridines **1**–**3** are low melting solids and sublime readily on attempted drying under only moderate vacuum (~1 mm Hg) at room temperature. The pyrimidine **4** on the other hand is nicely crystalline and, while certainly susceptible to sublimation, does so much less readily than **1**–**3**. Pyridines **1**–**3** are hygroscopic and discolor rapidly on exposure to air and light, whereas **4**, in the several months that we have had samples in the laboratory, does not appear to suffer from these inconveniences. All in all, the storage and handling of the crystalline **4** combine to make it a very user-friendly alternative to the popular hindered pyridines.

All glycosyl donors (**5**,[12] **12**,[27] **15**,[32] and **17**[33]) and acceptors (**6**, **8**,[34] **10**, and **18**[35]) were prepared as previously described or were commercially available. All glycosides (**7**,[12] **9**,[12] **11**,[12] **13**,[27] **14**,[27] **16**,[12] and **19**[29]) gave spectral data fully consistent with those previously reported in the literature.

Large Scale Synthesis of TTBP (4)

A solution of pinacolone (65.7 mL, 0.52 mol) in CH_2Cl_2 (100 mL) was slowly added to a solution containing Tf_2O (100.8 mL, 0.60 mol) and trimethylacetonitrile (125 mL, 1.10 mol) in CH_2Cl_2 (350 mL) at 20 °C under argon. After stirring for 5 d, additional trimethylacetonitrile (20 mL, 0.18 mol) was added. The reaction mixture was stirred for a further 24 h then quenched by the addition of sat aq $NaHCO_3$ solution, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was crystallized from MeOH to give TTBP as a white solid (91.0 g, 70%); mp 77–78 °C (Lit.[24] mp 76–77 °C).

^{1}H NMR ($CDCl_3$): δ = 1.33 (18 H, s, 6 × CH_3), 1.39 (9 H, s, 3 × CH_3), 7.03 (1 H, s, ArH).

^{13}C NMR ($CDCl_3$): δ = 29.8 (6 × CH_3), 29.9 (3 × CH_3), 37.8 and 39.7 (3 × *C*CH_3), 107.3 (ArCH), 175.1 and 176.6 (3 × ArC).

Sulfoxide Coupling Using TTBP (4); General Procedure (Table)

Tf_2O (0.033 mL, 0.20 mmol) was added to a stirred solution of the sulfoxide (0.18 mmol), TTBP (0.11 g, 0.44 mmol) and activated powdered molecular sieves (3 Å) in CH_2Cl_2 (3 mL), at −60 °C under argon. After stirring for 5 min at −60 °C, a solution of the acceptor (0.36 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred for a further 5 min at −60 °C, then quenched by the addition of MeOH, filtered, washed with sat aq $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated under reduced pressure. The glycosides were isolated by chromatography on silica gel.

Vinyl Triflates Using TTBP (4); General Procedure (Scheme 2)

To a stirred solution of the ketone (30 mmol) and TTBP (8.19 g, 33 mmol) in CH_2Cl_2 (150 mL) was added Tf_2O (5.24 mL, 32 mmol). The reaction mixture was left to stir at r.t. under argon (the progress of the reaction was monitored by ^{1}H NMR). Once complete, the solvent was removed under reduced pressure, the residue diluted with hexanes (100 mL) and filtered to remove the tri-*tert*-butylpyrimidine triflate. The filtrate was washed with cold 1 M HCl, brine, dried (K_2CO_3) and concentrated under reduced pressure. The vinyl triflate was isolated by distillation under reduced pressure.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (19) by Dehydrative Glycosylation with TTBP as Base

To a stirred solution of **17**[33] (0.187 mmol), diphenyl sulfoxide (0.525 mmol), and powdered molecular sieves (3 Å) in a mixture of toluene and CH_2Cl_2 (3:1, 7.5 mL) at −78 °C was added Tf_2O (0.044 mL, 0.258 mmol). The reaction mixture was stirred at this temperature for 10 min, and then at −40 °C for 1 h. TTBP (232 mg, 0.94 mmol) and a solution of **18**[35] (0.300 mmol) in toluene (2 mL) were added sequentially at −40 °C. The solution was stirred at this temperature for 30 min, then at 0 °C for 25 min, and finally at 25 °C for 4 h before the addition of excess Et_3N (0.19 mL, 1.34 mmol). The reaction was diluted with CH_2Cl_2, washed with sat aq $NaHCO_3$ solution, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The two anomers of **19** were isolated by chromatography (5% THF in toluene) on silica gel with spectral data consistent with that reported in the literature.[29]

Acknowledgement

We thank the NIHGMS (GM 57335) for partial support of this work.

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Article Identifier:
1437-210X,E;2001,0,02,0323,0326,ftx,en;C03000SS.pdf