

# A study of polymer-supported bases for the solution phase synthesis of glycosyl trichloroacetimidates

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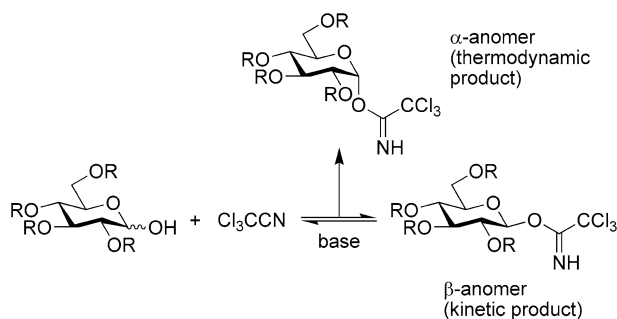
Received 17 December 2004; revised 8 February 2005; accepted 9 February 2005

**Abstract**—Polystyrene-supported strong organic bases are highly efficient reagents for the solution-phase synthesis of glycosyl trichloroacetimidates, affording quantitative yields of pure products in short reaction times after simple filtration and evaporation. Although efficiency of the different bases varies with substrate structure, polymer-bound 1,8-diazabicyclo[5.4.0]undec-7-ene was found to give the best results for all the substrates tested.

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To foster advances in the emerging field of glycomics,<sup>1</sup> the development of improved synthetic tools for the efficient and facile assembly of complex oligosaccharides and glycoconjugates is mandatory. In spite of recent accomplishments in solid-phase<sup>2</sup> and enzymatic methods,<sup>3</sup> the synthesis of complex oligosaccharides is still a very challenging undertaking. In recent years, new solution-phase techniques have been developed to ease reaction work-up and product isolation, avoiding the pitfalls of solid-phase approaches. These techniques include the use of soluble polymer-supported methods,<sup>4</sup> lipophilic,<sup>5</sup> or fluorophilic<sup>6</sup> protecting groups, tagging methods for post-synthesis purification using scavenging resins,<sup>7</sup> solid-phase capture–release strategies,<sup>8</sup> sequential one-pot glycosylations,<sup>9</sup> and polymer-bound reagents<sup>10</sup> and catalysts.<sup>11</sup>

Glycosyl trichloroacetimidates are very efficient and widely used glycosylating reagents, which are readily prepared by base-promoted addition of an anomeric hydroxyl group to trichloroacetonitrile using either inorganic (e.g., NaH, K<sub>2</sub>CO<sub>3</sub>, or Cs<sub>2</sub>CO<sub>3</sub>) or organic (e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene) bases (Scheme 1).<sup>12</sup> Careful chromatographic purification of crude trichloroacetimidates is usually necessary to remove all traces of base that could interfere with the subsequent acid-catalyzed glycosylation step. However, purification is often



Scheme 1.

impaired by the acid lability of these glycosyl donors. As part of a project aimed at the development of practical procedures for the solution synthesis of oligosaccharides using polymer-supported reagents, we have studied the preparation of a series of glycosyl trichloroacetimidates of common hexoses in the presence of different supported bases.<sup>13,14</sup>

The set of bases<sup>15</sup> and partially protected hexoses included in this study are shown in Figure 1. Reactions were performed at room temperature under mild magnetic stirring in an air atmosphere. After the specified time, the reaction mixture was filtered, the resin was rinsed with CH<sub>2</sub>Cl<sub>2</sub> and the solvent (and excess Cl<sub>3</sub>CCN) was removed at reduced pressure. The crude was analyzed by <sup>1</sup>H NMR.

Each supported base was assayed with all substrates in three different solvents: CH<sub>2</sub>Cl<sub>2</sub>, THF, and toluene.

**Keywords:** Carbohydrates; Solid-supported reagents; Glycosylation.

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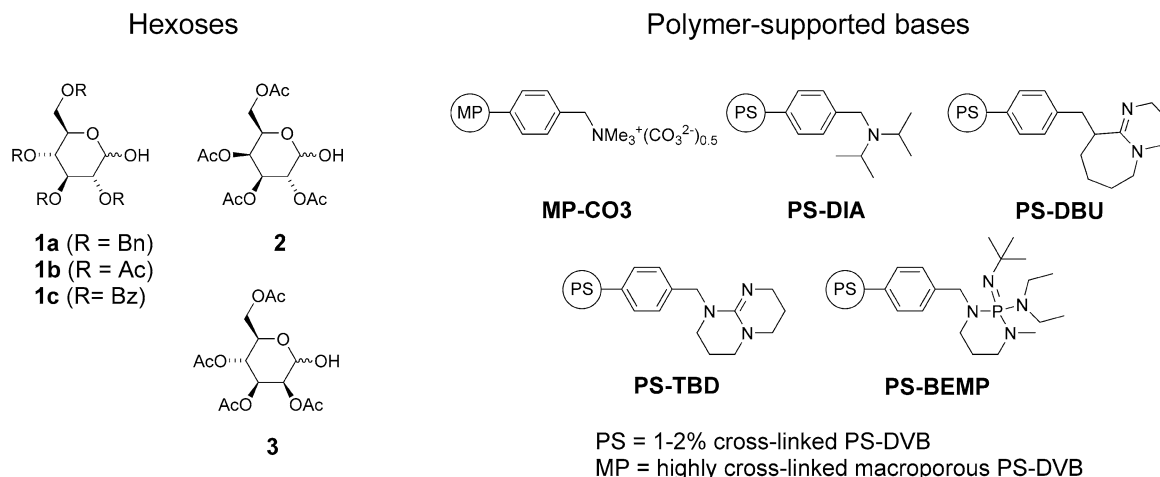


Figure 1.

The results obtained using this general procedure are presented in Table 1.

Taking 2,3,4,6-tetra-*O*-benzyl- $\alpha$ -D-glucopyranose (**1a**) as a reference substrate, the performance of the different bases roughly follows the trend expected on the basis of relative base strengths (Table 1, entries 1–3 and 6).<sup>16</sup> Of the solvents tested, CH<sub>2</sub>Cl<sub>2</sub> gives the best results and THF performs poorly in general (Table 1, entries 6–8). With regards to the bases tested, only PS-DBU and PS-BEMP efficiently promote the reaction on all substrates tested using a limited amount of base ( $\leq 1$  equiv). PS-DIA is a poor base for this reaction affording very low yields (<10%, Table 1, entries 2 and 11) of product even after extended reaction times

(>24 h). MP-CO3 is only efficient for acyl-substituted hexoses (Table 1, entries 9, 10, 14, 17, and 21), what can be attributed to the increased acidity of the anomeric hydroxyl of these substrates due to the electron withdrawing effect of the acyl groups. With the exception of the D-mannopyranose derivative **3**, anomeric mixtures of glycosyl trichloroacetimidates are usually obtained. As observed under homogeneous conditions,<sup>12</sup> prolonged reaction times, stronger bases, or electron withdrawing groups on the hexose favor formation of increased amounts of the thermodynamically more stable  $\alpha$ -imide, in many cases being the exclusive product (see Scheme 1). In the case of acyl-substituted hexoses, best results are often obtained adding the base last (method B). Use of larger amounts of base gives faster

**Table 1.** Preparation of glycosyl trichloroacetimidates from hexoses **1–3** using the polymer-supported bases shown in Figure 1, under different reaction conditions

| Entry | Hexose    | Base (equiv)  | Cl <sub>3</sub> CCN (equiv) | Solvent                         | Method <sup>a</sup> | Time (h) | Yield (%) ( $\alpha/\beta$ ratio) <sup>b</sup> |
|-------|-----------|---------------|-----------------------------|---------------------------------|---------------------|----------|--|
| 1     | <b>1a</b> | MP-CO3 (1.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | A                   | 22       | <10  |
| 2     |           | PS-DIA (1.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | A                   | 30       | N.R.   |
| 3     |           | PS-DBU (1.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | A                   | 3.5      | >99 (1:1)                                      |
| 4     |           | PS-DBU (1.0)  | 5.0                         | Toluene                         | A                   | 15       | >99 (2:3)                                      |
| 5     |           | PS-TBD (1.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | A                   | 25       | 20 (3:2)                                       |
| 6     |           | PS-BEMP (1.0) | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | A                   | 5.5      | >99 (3:2)                                      |
| 7     |           | PS-BEMP (1.5) | 5.0                         | Toluene                         | A                   | 4.5      | 28 (1:1)                                       |
| 8     |           | PS-BEMP (1.5) | 5.0                         | THF                             | A                   | 25       | N.R.   |
| 9     | <b>1b</b> | MP-CO3 (1.0)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 5        | 94 (4:1)                                       |
| 10    |           | MP-CO3 (0.5)  | 5.0                         | Toluene                         | A                   | 3.5      | >99 (1:0)                                      |
| 11    |           | PS-DIA (1.0)  | 5.5                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 36       | <10  |
| 12    |           | PS-DBU (0.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.5      | >99 (1:0)                                      |
| 13    | <b>1c</b> | PS-BEMP (0.5) | 3.5                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.7      | >99 (1:0)                                      |
| 14    |           | MP-CO3 (1.0)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 4.5      | >99 (9:1)                                      |
| 15    |           | PS-DBU (0.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.1      | >99 (1:0)                                      |
| 16    |           | PS-BEMP (1.0) | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.5      | >99 (1:0)                                      |
| 17    | <b>2</b>  | MP-CO3 (1.0)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 3.5      | >99 (7:3)                                      |
| 18    |           | PS-DBU (0.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.5      | >99 (9:1)                                      |
| 19    |           | PS-TBD (1.0)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.5      | >99 (4:1)                                      |
| 20    |           | PS-BEMP (0.5) | 3.5                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.5      | >99 (9:1)                                      |
| 21    | <b>3</b>  | MP-CO3 (0.5)  | 3.5                         | CH <sub>2</sub> Cl <sub>2</sub> | A                   | 1.7      | >99 (1:0)                                      |
| 22    |           | PS-DBU (0.5)  | 5.0                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 1.1      | >99 (1:0)                                      |
| 23    |           | PS-TBD (0.5)  | 3.5                         | CH <sub>2</sub> Cl <sub>2</sub> | B                   | 2.2      | >99 (1:0)                                      |

<sup>a</sup> Method A: Cl<sub>3</sub>CCN was added dropwise to a suspension of hexose and base in the corresponding solvent. Method B: base was added in one portion to a solution of hexose and Cl<sub>3</sub>CCN in the corresponding solvent.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis.

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