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## Iodonium Ion generated *in situ* from *N*-Iodosuccinimide and Trifluoromethanesulphonic Acid promotes Direct Linkage of 'Disarmed' Pent-4-enyl Glycosides

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*N*-lodosuccinimide and trifluoromethanesulphonic acid provide a powerful source of iodonium ion which allows 'disarmed' pent-4-enyl glycosides that normally respond sluggishly to iodonium dicollidine perchlorate, to react rapidly and to exhibit stereodirection *via* neighbouring group participation of C-2 esters.

Recent studies in our laboratory have revealed that pent-4enyl glycosides (NPGs) are novel substrates for a variety of reactions occurring at the anomeric centre of sugars, including (a) chemoselective deprotection under neutral conditions,<sup>1</sup> and (b) direct saccharide coupling.<sup>2b</sup> The attractiveness of these substrates is enhanced by the fact that they can be 'armed' or 'disarmed' because of the effect that C-2 substituents have on the rate of oxidative deglycosidation.<sup>2b</sup> Thus, the reaction of the 'armed' ether (1) with the 'disarmed' ester (2) gives only the cross product (4a), there being no evidence of the product of self-coupling, (3), nor of a trisaccharide arising from further reaction of (4a) with alcohol (2). However, conversion of the 'disarmed' ester (4a) into the 'armed' ether (4b) now facilitates the further stage of coupling to give (5) (Scheme 1).

However, there were three interrelated aspects that compromised the effectiveness of NPGs for oligosaccharide syntheses. Firstly, the disadvantage for disarmed species [*e.g.*, (2)] was that NPGs would have to sacrifice the efficient stereocontrolled formation of *trans*-1,2-glycosides, which is a hallmark of C-2 esters.<sup>3</sup> Secondly, change from disarmed to armed status involved juggling of protecting groups, thereby

## Table 1. NIS/TfOH promoted reactions.<sup>a</sup>



<sup>a</sup> Typical reaction procedure: the pent-4-enyl glycoside (1 equiv.) and alcohol donoi (1.1 equiv.) were dissolved in dry  $CH_2Cl_2$  under argon, and pulverised activated molecular sieves (4A) were added. N-Iodosuccinimide (2.5 equiv.) was added and a saturated solution of trifluoromethanesulphonic acid in  $CH_2Cl_2$  (*ca.* 0.15 M) was added dropwise until TLC indicated that the glycoside had all been consumed. (The reaction is virtually instantaneous). Work-up with saturated bicarbonate and 10% sodium thiosulphate solutions followed by flash chromatography afforded the products. <sup>b</sup> Bz = benzoyl. <sup>c</sup> TBDMS = Bu<sup>t</sup>Me<sub>2</sub>Si.





compounding an already major concern of oligosaccharide synthesis. Thirdly, iodonium dicollidine perchlorate  $[I(coll)_2ClO_4]$ ,<sup>4</sup> although an excellent halonium ion source,<sup>2</sup> is not commercially available, and toxic and expensive silver salts are used in its preparation. In addition, the liberated collidine sometimes caused side reactions.

We therefore launched a search for a promoter which would not require silver salts, was non-toxic, and was more convenient to utilize. *N*-Iodosuccinimide (NIS) by itself gave no advantage over NBS. The additional requirement for a non-nucleophilic, non-basic counterion (to replace  $ClO_4^-$ ) led us to examine trifluoromethanesulphonate. Eventually it emerged that the combination of *N*-iodosuccinimide and trifluoromethanesulphonic acid (NIS/TfOH) provided a ready, inexpensive, potent source of iodonium ion,† thereby overcoming the third problem above (Table 1).

It was further discovered that NIS/TfOH functioned well with C-2 acylated NPGs, such as (2) and (4a). Thus, as indicated in entries 1—4 (Table 1), the mannoside (6) and glucoside (7) reacted smoothly with the primary and secondary alcohols of (13) and (14) to give the disaccharides (18)—(21) in acceptable yields and at acceptable rates. The absence of *cis*-1,2-coupled products was evidence of efficient neighbouring group participation by the C-2 esters in these reactions.

The generation of iodonium ions from NIS/TfOH can be interpreted as involving protonation of the imide carbonyl in the first step (Scheme 2), hence, a logical concern was the compatibility with sugars bearing acid labile protecting groups. The result in entry 5 (Table 1) shows that the acid sensitive 2-deoxy sugar (8) and the acetalated reactant (15) may be coupled safely, as judged by the formation of (22). An even more stringent test is shown in entry 6 which also demonstrates the generality of NIS/TfOH as an iodinating agent. Thus, the reaction of the exceedingly acid sensitive hex-2-enopyranoside (9)<sup>6</sup> gave the cyclic carbonate (23), a process that had been accomplished previously in our laboratory using iodonium dicollidine perchlorate.<sup>7</sup>

The appreciable difference in reaction rates of (1) and (2) which inspired the 'armed' and 'disarmed' experiments<sup>2b</sup> is an innate property of these substrates and can still be exploited in spite of the fact that the reactions were complete within the time required to run the TLC. This is exemplified in entry 7 where reaction of (10) and (16) gave (24) only. Similarly, the higher reactivity of the *ortho* ester (11) ensured that the product from reaction with (17) was (25) (entry 8).

The final example in entry 9 shows that thioglycosides, such as (12), can also be activated<sup>8</sup> by this promoter, as judged by the formation of (26).

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 $<sup>\</sup>dagger$  Previously, N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) have been treated with acids to generate halonium ions for aromatic halogenation.<sup>5</sup>