Pure Appl. Chem., Vol. 84, No. 1, pp. 1–10, 2012.
http://dx.doi.org/10.1351/PAC-CON-11-08-04

The I_2/Et_3SiH system: A versatile combination with multiple applications in carbohydrate chemistry*

Matteo Adinolfi, Alfonso Iadonisi‡, Antonello Pastore, and Silvia Valerio

Department of Organic Chemistry and Biochemistry, University of Naples "Federico II", Via Cinthia 4, I-80126, Naples, Italy

Abstract: In this contribution, a brief survey of the multiple synthetic opportunities offered by the I_2/Et_3SiH combined system is presented. Both reagents are cheap and easy to handle, and their combination allows HI to be quickly formed in situ. A suitable stoichiometry of the mixture can be addressed to a set of very useful transformations of carbohydrate chemistry ranging from glycosidation reactions to functional group manipulation of sugars.

Keywords: carbohydrates; organic synthesis; protecting groups.

INTRODUCTION

Owing to their high functionalization, sugars are difficult compounds to be synthetically manipulated, and their employment in organic synthesis is often associated with long multistep schemes required for setting the right profile of functional groups in each residue. Additionally, oligosaccharide synthesis is still the object of intense investigation, and the functionalization of each saccharide building block plays a fundamental role in tuning several parameters such as the donor/acceptor reactivity and the regio- and stereocontrol of glycosidations [1]. Despite the remarkable progress in the development of straightforward procedures for both the rapid functional differentiation of sugars [2] and the oligosaccharide assembly [1], the request of ever more practical procedures is still an issue of high interest. Indeed, most advanced procedures devised for these tasks still suffer from practical drawbacks such as the recourse to unstable reagents, lengthy reactions, use of expensive stoichiometric reagents, etc.

In this regard, this contribution is focused on the numerous synthetic opportunities offered by the I_2/Et_3SiH combined system in synthetic carbohydrate chemistry. Both reagents are of practical interest as they are easily handled and storable, and upon mixing they quickly generate HI and Et_3SiI in situ by a process that can occur under anhydrous conditions [3]. As will be shown, a different stoichiometric combination of the reagents can be addressed to varied applications in carbohydrate chemistry ranging from glycosidations to functional group elaboration of sugars.

Besides our contributions, the combined use of I_2 and Et_3SiH is not frequently reported in the literature; in some applications these reagents are employed in combination with further catalysts, for example, in the hydroiodination of alkenes and alkynes [4] and in the anomeric iodination of sugars [5]. In the absence of other co-reagents, I_2 and Et_3SiH have been reported to promote the reductive Ferrier

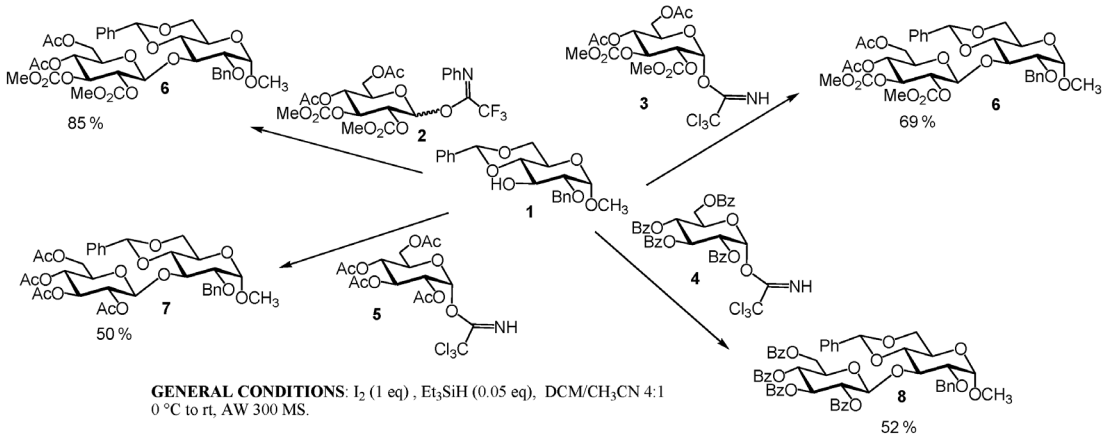
Pure Appl. Chem. **84**, 1–106 (2012). A collection of invited papers based on presentations at the 16th European Carbohydrate Symposium (Eurocarb-16), Sorrento, Italy, 3–7 July 2011.
‡Corresponding author

rearrangement of glycals [6], the Friedel–Crafts cyclization of aryl-substituted propargyl alcohols [7], the reductive opening of benzylidene acetals [8], and the reduction of an aromatic formyl substituent to a methyl group [9].

RESULTS AND DISCUSSION

Use of the I_2/Et_3SiH system as a glycosidation promoter

Our first contribution on the I_2/Et_3SiH system stemmed from an attempt to extend the scope of iodine as a glycosidation promoter after Field and co-workers had reported some examples of armed glycosyl donors (including a tetra-O-benzylated glycosyl trichloroacetimidate) activated by stoichiometric iodine [10]. This effort led to a protocol for the activation of the less reactive disarmed glycosyl imidates that relies on a combined activation system composed of stoichiometric iodine and catalytic triethylsilane (Scheme 1) [11]. Interestingly, the use of catalytic amounts of both reagents was not effective for the reaction to occur, suggesting that the sole HI cannot catalyze the reaction at a practical rate. The reaction outcome was critically dependent on the nature of the solvent, the best results being achieved in 4:1 dichloromethane/acetonitrile. The nature of drying agents had a critical role too; the use of commercially available acid-washed molecular sieves (AW 300 MS) did indeed prevent the shutdown of the catalytic cycle that was instead observed in the presence of normal 4Å molecular sieves.



Scheme 1 Activation of disarmed trihaloacetimidates by I_2 (stoich) and Et_3SiH (cat).

Interestingly, in the coupling with the selected model acceptor **1**, we observed an especially good performance of the *N*-phenyltrifluoroacetimidate donor **2**. This class of donors had been proposed just a few months before in a paper by Yu [12], and in the following years numerous contributions have confirmed its usefulness [13] as well as its possible complementarity with standard trichloroacetimidates [1].

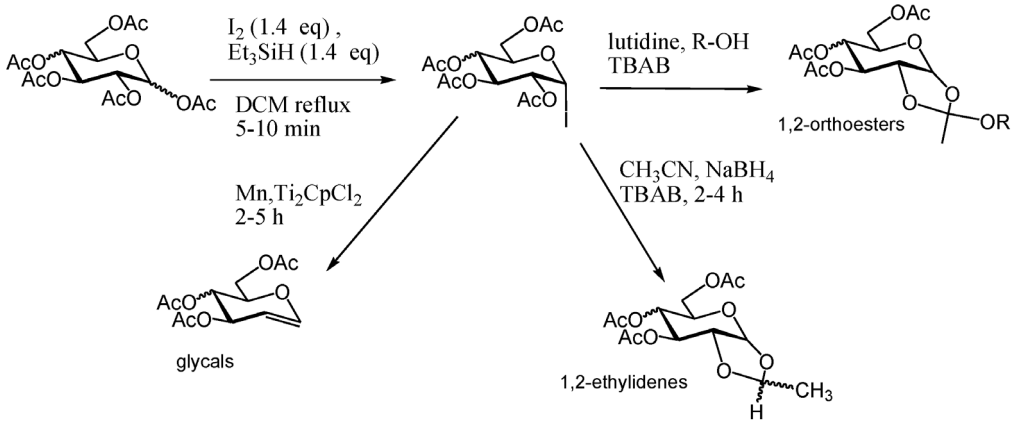
Another interesting result of that investigation lies in the higher yields obtained from donors **2** and **3** (equipped with an unusual methoxycarbonyl group as a participating functionality) than when using donors **4** and **5**, protected with conventional acetyl and benzoyl groups. In our experience, this trend was often found reproducible under a variety of activation conditions for imidate donors, especially when mild conditions were contemplated [14].

Gratifyingly, some years later, Tanaka, Takahashi, and co-workers developed a very useful application of the analogous stoichiometric combination even in the activation of highly armed glycosyl donors. In particular, they achieved a highly selective synthesis of β-glycosides of 2,6-di-deoxy sugars

by activating the corresponding trichloroacetimidate donors at very low temperatures in toluene; the wide scope of the procedure was demonstrated with the application to a large number of compounds, including very demanding targets [15].

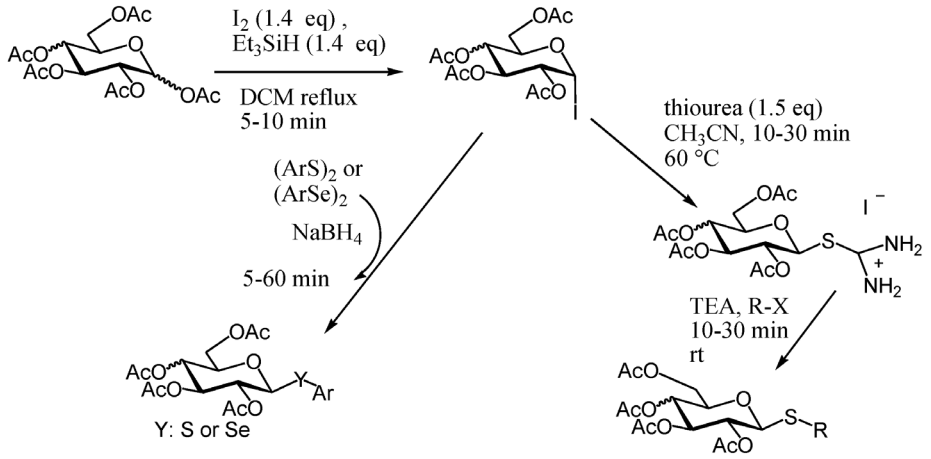
Synthesis of glycosyl iodides and synthetic elaborations thereof

In a subsequent investigation, the use of a different stoichiometric combination of I_2 and Et_3SiH was addressed toward alternative useful transformations of carbohydrate chemistry. Remarkably, per-O-acetylated sugars can be smoothly converted into the corresponding glycosyl iodides upon exposure to a moderate excess of both reagents (1.4 equiv each) in refluxing dichloromethane (Scheme 2) [16]. The reaction takes very short times (5–10 min), and the outcome is independent of the anomeric composition of the starting material (with just an exception being found to date with the *N*-Troc glucosamine precursor [17]). This approach can be considered a useful alternative to the use of iodotrimethylsilane (TMSI, sensitive reagent) [18], or the combined propandithiol/I_2 [19] and hexamethyldisilane/I_2 [20] systems. Glycosyl iodides generated with I_2/Et_3SiH are obtained after a simple extractive work-up just contaminated by inert nonsaccharidic triethylsilylated side-products; the resulting crude mixtures can thereby be directly submitted to further elaborations typically applied to glycosyl bromides. For example, 1,2-orthoesters, glycals, and ethylidenes can be readily accessed via glycosyl iodides thus obtained [16]. In some cases, the extractive work-up following the anomeric iodination can be even suppressed; for example, 1,2-orthoesters can be accessed by simply adding the requisite reagents to the iodination mixture (one-pot procedure), whereas the ethylidenation step can be carried out by just replacing the solvent of the iodination step (dichloromethane) with acetonitrile. All these methodologies are generally effective in terms of yields, and, not unexpectedly, glycosyl iodides often reacted in shorter times than the brominated counterparts under otherwise identical reaction conditions.



Scheme 2 Straightforward access to glycosyl iodides and direct conversion to 1,2-orthoesters, ethylidenes, and glycals.

The ready access to glycosyl iodides and their high reactivity elicited the development of other useful synthetic schemes in carbohydrate chemistry. Practically important applications are the streamlined approaches for the synthesis of alkyl-, aryl thioglycosides, and selenoaryl glycosides (Scheme 3) [21]. Alkyl thioglycosides are readily obtained from crude iodides through the generation of the corresponding thiouronium intermediate and its direct treatment, in a one-pot fashion, with a mild base as triethylamine (TEA) and the suitable alkylating agent (Scheme 3). Alternatively, direct exposure of crude glycosyl iodides (from the extractive work-up) to the appropriate phenyl chalcogenide (easily



Scheme 3 Straightforward access to thioaryl-, selenoaryl-, and thioalkylglycosides via glycosyl iodides.

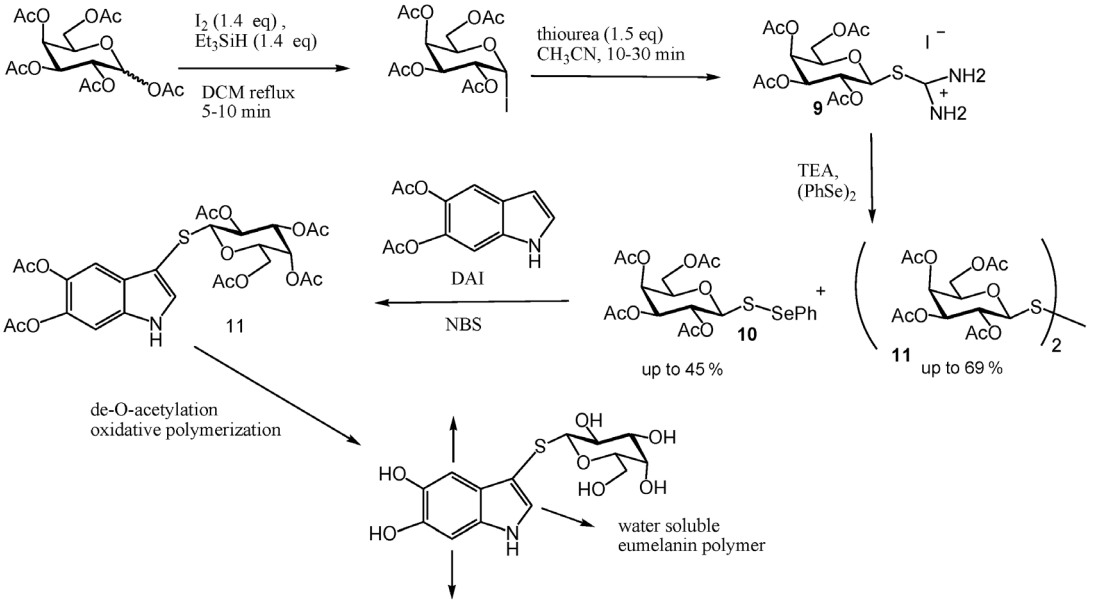
generated in situ under reductive conditions) led to the smooth generation of phenylthio- and phenylselenoglycosides (Scheme 3).

Interestingly, the thioalkylation step can also be used to attach functionalized chains, and this chemistry was recently employed by Comegna et al. for the streamlined synthesis of aminoethyl thioglycosides useful for the assembly of glycosylated peptoids via a solid-phase approach [22]. Another application was also described with the preparation of suitable intermediates for oligosaccharide synthesis [23].

The scheme of thioglycosidation has been more recently adapted to the generation of phenylselenyl thioglycosides, a class of compounds recently introduced by Davis and co-workers for the direct thioglycosidation of proteins through the generation of a disulfide linkage with cysteine residues [24]. The S–Se linkage can be generated on addition of phenyl diselenide and TEA to the reaction vessel where the glycosyl thiouronium intermediate **9** has been formed (Scheme 4) [25]. Experiments conducted by changing the equivalents of $(PhSe)_2$ in this step indicated that overall yields of phenylseleno sulfide **10** are always moderate (never exceeding 45 %); on the other hand, an advantage of the scheme is that this product can be purified with a single chromatography and without isolation of any intermediate.

Application of this synthetic sequence always led to the generation of the corresponding symmetrical disulfide **11** as the main byproduct (Scheme 4), and a suitable adjustment of the reaction conditions allowed this latter product to be obtained in a synthetically useful yield. In particular, treatment of the thiouronium intermediate **9** with excess TEA (4 equiv) and a catalytic amount of phenyl diselenide (3 %) for an hour at 50 °C yielded the galactosyl disulfide **11** in a good overall yield (69 % from the per-O-acetylated precursor) [26]. The product was obtained with a large predominance of the β-disulfide, owing to the preferential generation of a 1,2-*trans* product in the anomeric thio-functionalization step [21]. The catalytic role played by phenyl diselenide suggests that the S–Se intermediate **10** is amenable to nucleophilic attack by the glycosyl thiolate as this latter is gradually generated in situ from the thiouronium precursor. The phenylselenolate leaving group is then quickly re-oxidized under air to the corresponding diselenide useful in turn for the regeneration of the S–Se reactive intermediate **9**. Interestingly, this mechanism presents some similarities with that of some selenoenzymes promoting the synthesis of disulfides [27].

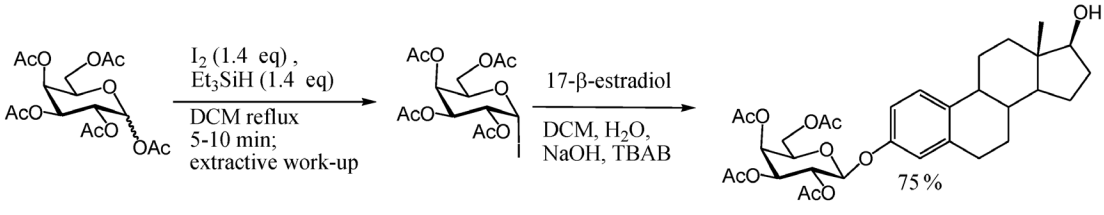
The S–Se intermediates like **10** turned out to be useful thioglycosylation agents in the presence of *N*-bromosuccinimide (NBS), to yield 3-thioglycosylated derivatives of DAI (5,6-di-acetoxy indole) [25] (Scheme 4). De-O-acetylation and oxidative polymerization of these products led to a novel class



Scheme 4. Straightforward access to (phenylselenyl)thioglycosides and their application to the synthesis of water-soluble eumelanin polymers.

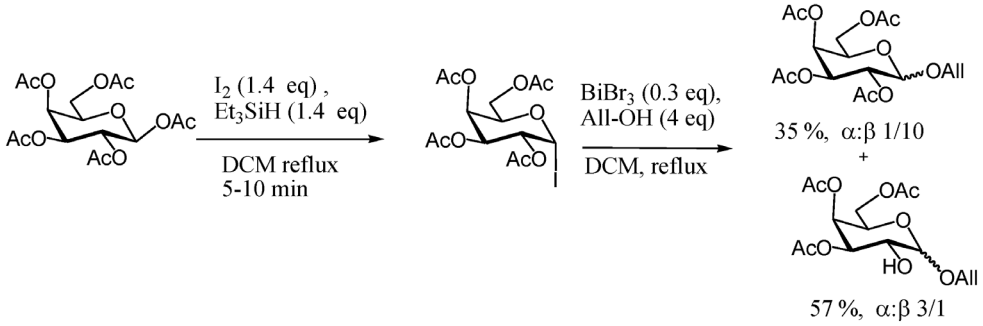
of glycoconjugates, the water-soluble thioglycosylated eumlanin polymers that offer a useful model for investigating the properties of natural eumelanins. Indeed, these latter are important biopolymers because thry are responsible for the black color of human skin, hair, and eyes, but their investigation is very difficult because of the insolubility in any solvent.

Another synthetically useful application of crude glycosyl iodides points to their possible role as glycosyl donors. Indeed, several contributions by other groups have emphasized that glycosyl iodides can be activated by stoichiometric promoters, including applications on demanding oligosaccharide targets [28]. Alternatively, glycosyl iodides can be activated by halide [29] and phosphine oxide [30] catalysis, or undergo a direct substitution process with suitable nucleophiles [31]. The crude iodides generated from the I_2/Et_3SiH system proved reactive enough for the selective glycosidation of the phenol position of 17-β-estradiol under basic two-phase conditions (Scheme 5) [17]. Yields were critically dependent on the nature of the saccharidic precursors, owing to a competitive process elimination providing 1,2-acetoxy glycals. In particular, best results were obtained from galacosyl and *N*-Troc aminoglucosyl iodides as the donors.



Scheme 5 Selective phenyl O-glycosidation of 17-β-estradiol using glycosyl iodides as the donors.

The rapid synthesis of per-O-acetylated glycosyl iodides recently offered another interesting opportunity for the fast access to useful saccharidic building blocks. In particular, the activation of glycosyl iodides with sub-stoichiometric amounts of $BiBr_3$ in the presence of allyl alcohol resulted in the generation of the corresponding allyl glycoside along with a product allylated at the anomeric position and free at O-2 (Scheme 6) [32]. The latter product often predominated, and therefore the procedure was useful for the quick generation of saccharidic building blocks bearing a synthetically versatile allyl group at the anomeric position and a free alcoholic functionality at C-2, the other positions maintaining the initial protection. Interestingly, all of the allyl glycosides thus obtained (either fully protected or free at O-2) were generally characterized as anomeric mixtures. Yields of the 2-O-deprotetcted allyl glycosides were strongly dependent on the nature of the precursor; synthetically useful results were recorded from *gluco*-, *galacto*-, *lacto*-configured precursors, whereas disappointing results were obtained from mannose and 6-deoxy sugar precursors (these latter essentially yielded fully protected allyl glycosides). Some mechanistic experiment indicated that the reaction might proceed via the slow generation of a 1,2-orthoester intermediate that then evolves to the allyl glycosides. In addition, there is evidence that the allyl moiety initially incorporated into the orthoester intermediate is not necessarily transferred to the anomeric position of the same molecule.



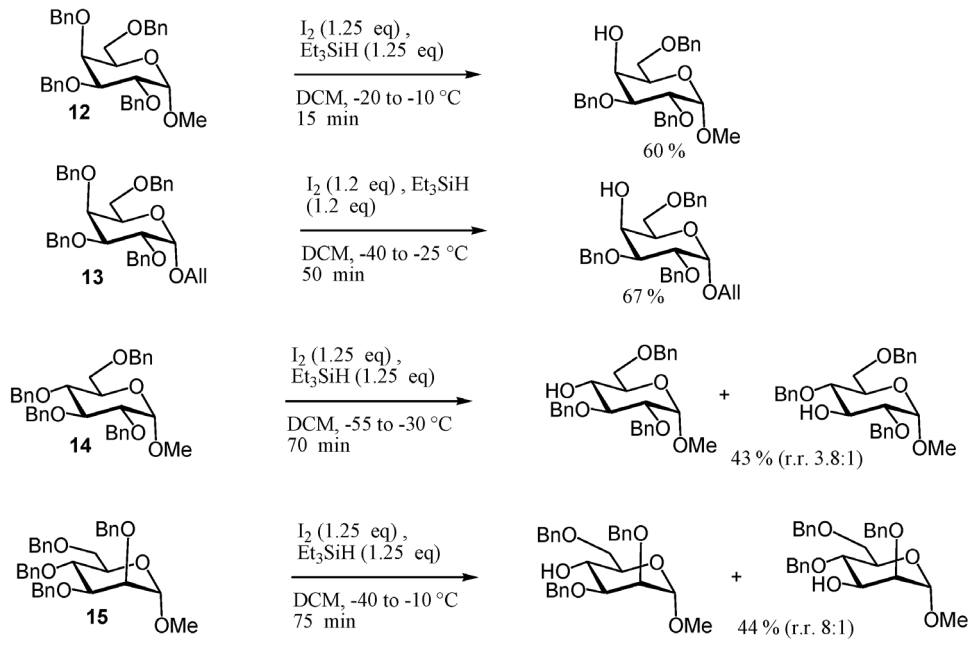
Scheme 6 Straightforward synthesis of allyl glycosides deprotected at O-2.

Other applications in protecting groups chemistry

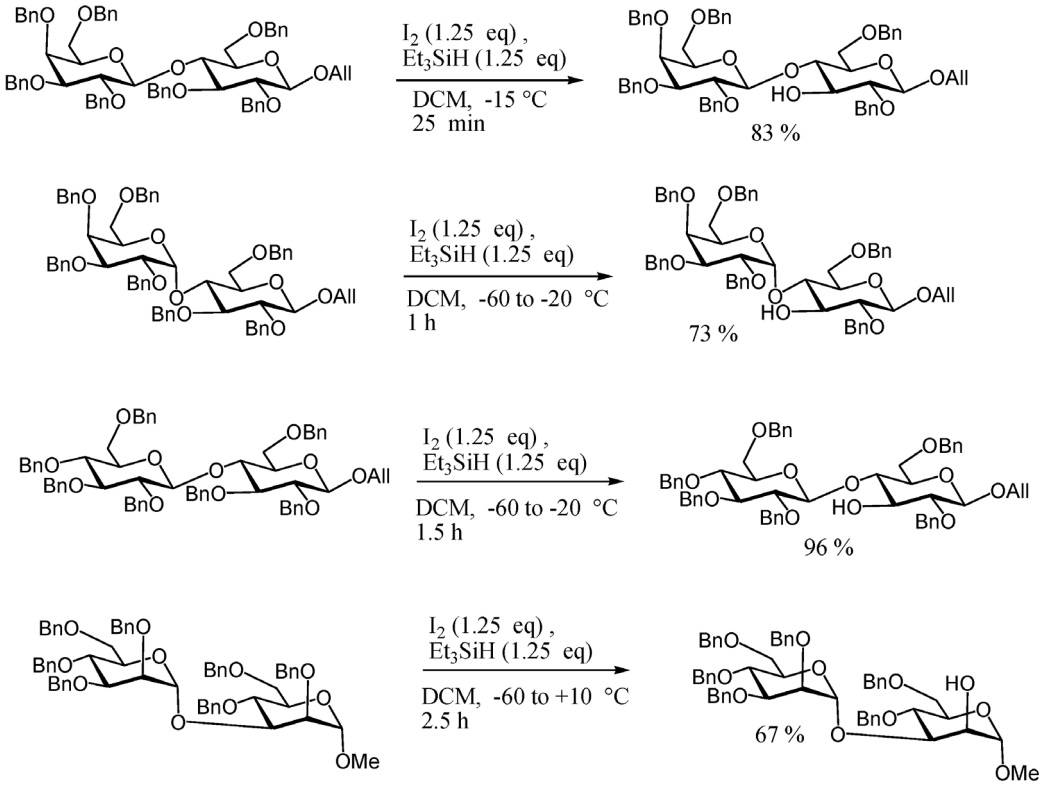
Besides the application of glycosyl iodide intermediates in the streamlined access to a very wide range of useful building blocks and glycoconjugates, the I_2/Et_3SiH system proved very useful in other deprotection procedures. Some years ago, the combination of I_2 (ca. 0.4 equiv) and Et_3SiH (0.05 equiv) in MeOH was employed to remove the benzylidene protecting group from methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene α-glucopyranoside, minimizing the undesired processes of de-O-acetylation and acetyl migration observed with other hydrolytic systems [33].

More recently, an especially relevant application was disclosed with the regioselective deprotection of highly O-benzylated substrates [34]. Exposure of a range of 2,3,4,6-tetra-O-benzylated glycosides to a slight excess of both reagents in dichloromethane at low temperature resulted in the preferential benzyl removal at position 4 (Scheme 7). Regioselectivity was especially high when starting from *galacto* precursors **12** and **13**, whereas the corresponding *gluco*- and *manno*-precursors (**14** and **15**, respectively) yielded minor amounts of the inseparable 3-OH regioisomer. Very interestingly, the versatile allyl protecting group survived unaffected under these conditions.

Very remarkably, application of the procedure to per-O-benzylated disaccharides provided especially high yields of a single mono de-O-benzylated product (Scheme 8), despite the larger number of potential competitive events. Inspection of the results reveals a well-defined regioselectivity trend for all the examined substrates with the deprotection occurring on the reducing saccharidic terminus at a



Scheme 7 Regioselective de-O-benzylation of tetra-O-benzylated monosaccharides.



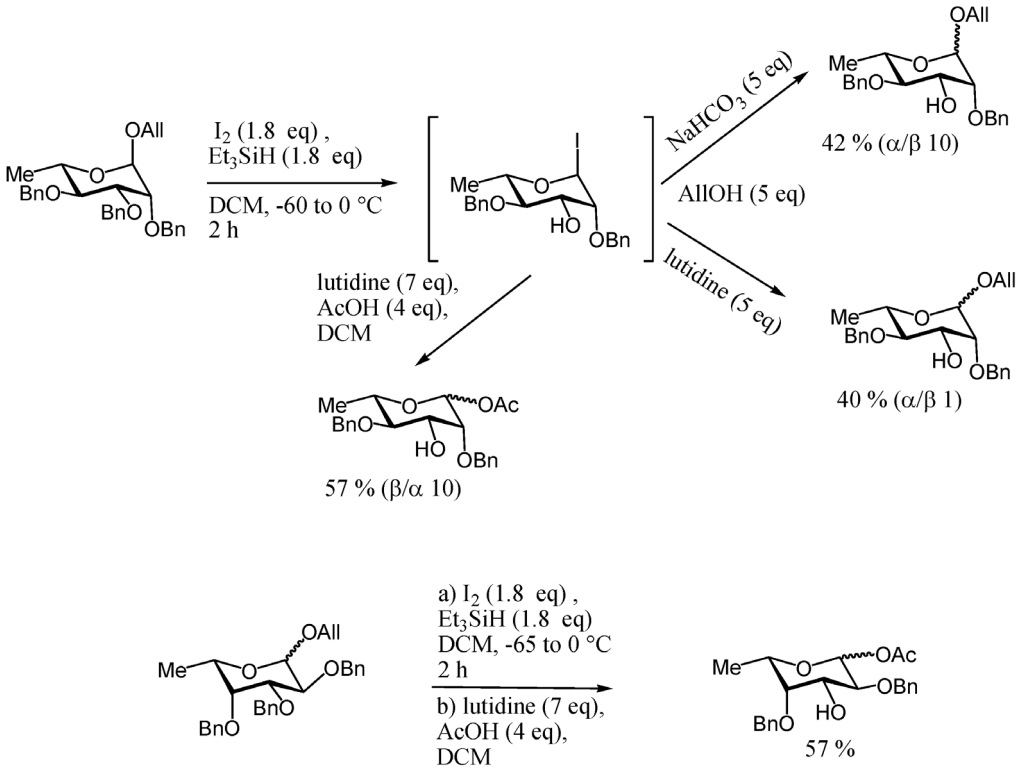
Scheme 8 Highly regioselective de-O-benzylation of epta-O-benzylated disaccharides.

secondary carbinol site flanking the glycosidation attachment site. Interestingly, in the case of the 3-O-linked mannose disaccharide (Scheme 8, last example), the axially oriented benzyl group at O-2 is preferentially removed.

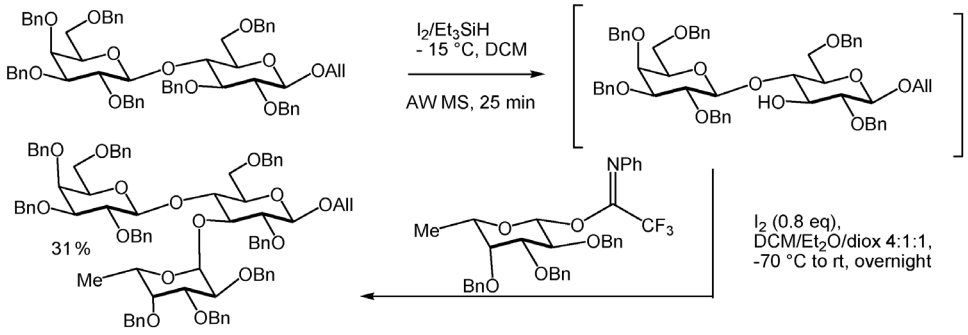
Collectively, all data highlight the unusual regioselectivity of this procedure, which favors the removal of especially encumbered benzyl groups. In addition, some mechanistic investigation indicated HI (and not Et_3SiI) as the actual promoter of the deprotection. Thus, the reaction likely occurs via an initial fast (and reversible) HI-promoted protonation of the benzyloxy group followed by the nucleophilic attack of the nearby iodide anion to the benzyloxonium site. The resulting transfer of the benzyl group (with formation of benzyl iodide as the byproduct) might be kinetically favored with a crowded neighborhood owing to the release of steric strain.

Another interesting result of this procedure was observed on anomerically reactive substrates such as 6-deoxy sugar glycosides or tetra-O-benzylated β-hexopyranosides. In these cases, the anomeric iodination was a faster process than de-O-benzylation at any site, and then a higher amount of both I_2 and Et_3SiH was needed for achieving a concomitant deprotection (Scheme 9). The in situ generated partially protected glycosyl iodides were found too reactive to be isolated; nonetheless, they could be easily converted into useful and workable building blocks under suitable quenching conditions (Scheme 9).

As shown in examples of Scheme 9, the initial allyl aglycon can be either re-attached or even replaced by an acetyl group in dependence on the quenching procedure. Also relevant is the preferential deprotection at O-3 for highly O-benzylated 6-deoxy sugar derivatives rather than at O-4 (see Scheme 7). In addition to the wide scope of the procedure for a well-differentiated set of saccharidic precursors, the protocol lends itself to incorporation into sequential one-pot schemes. An interesting



Scheme 9 Regioselective de-O-benzylation and concomitant anomeric modification of 6-deoxy sugar precursors.



Scheme 10 One-pot synthesis of a trisaccharide via sequential de-O-benzylation/glycosidation.

application of this idea was represented by the synthesis of a Lewis X mimic starting from fully protected precursors, as illustrated in Scheme 10.

CONCLUSION

In this communication, we have shown the multiple synthetic opportunities offered by the I_2/Et_3SiH combined system in carbohydrate chemistry. The reactivity of this reagent is mainly associated with the easy and fast generation in situ of HI. Easy manipulation and storage of these reagents as well as the operational simplicity of many of the developed protocols are expected to elicit in the future new useful procedures for the streamlined preparation of valuable "building blocks". More in general, the reagent is expected to offer new opportunities in organic synthesis, as also suggested by very recent contributions in the literature.

ACKNOWLEDGMENTS

We thank all coauthors in the references who contributed to expanding the scope of the title reagent. We acknowledge the support from the Italian Ministry of University (MIUR), the University of Naples "Federico II" ("Programma Faro"), and facilities of the "Centro Interdipartimentale di Metodologie Chimico-Fisiche dell'Università di Napoli".

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