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AN EFFICIENT THIOGLYCOSIDE-MEDIATED FORMATION OF α-GLYCOSIDIC LINKAGES PROMOTED BY IODONIUM DICOLLIDINE PERCHLORATE

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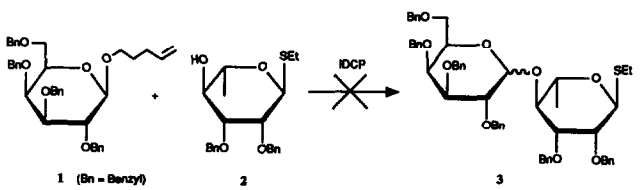
Abstract: *Chemospecific glycosidation of partially-benzoylated thioglycosides ("disarmed" acceptors) with perbenzylated thioglycosides ("armed" donors) can be realized in the presence of the promotor iodonium dicollidine perchlorate. The reaction results predominantly in the formation of α-linked saccharides and is compatible with the use of various protecting groups.*

Recently, Fraser-Reid *et al.* reported[1] that pent-4-enyl glycosides (*e.g.*, **1**) could be readily hydrolyzed under neutral conditions with halonium ions. The usefulness of the latter finding was later on nicely illustrated in the chemospecific liberation of the anomeric centre[2] and *in-situ* coupling of *n*-pentenyl glycosides to give oligosaccharides[3-5]. As part of a programme[6] to synthesize L-rhamnose containing fragments from a *Streptococcus pneumoniae* type-specific capsular polysaccharide, we attempted, according to Fraser-Reid *et al*[3]., to condense the *n*-pentenyl galactosyl donor **1** (*Scheme 1*) with the ethyl 1-thio-L-rhamnopyranoside acceptor **2** in the presence of the activator iodonium dicollidine perchlorate[7] (IDCP). However, analysis of the glycosidation reaction revealed no formation of the expected disaccharide **3**, but merely products arising from self-condensation of **2**.

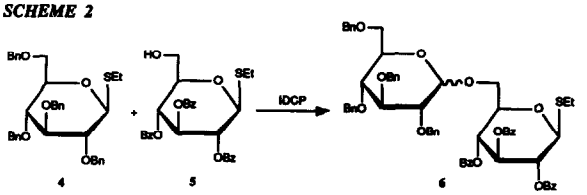
SCHEME 1



We now report that the unexpected outcome of the reaction in *Scheme 1* led to the development of a versatile glycosidation procedure in which a so-called[8] "armed" thioglycoside (donor) can be *in-situ* coupled, in the presence of IDCP, with a "disarmed" thioglycoside (acceptor).

The failure of preparing disaccharide **3** in *Scheme 1* may be explained by assuming that the electrophilic promotor activates the thioethyl on C1 in **2** more readily and effectively than the similarly located "armed" *n*-pentenyl function in **1**. We therefore anticipated, in analogy with the observed rapid IDCP promoted hydrolysis of *n*-pentenyl glycosides having at C2 an ether instead of an ester substituent, that a similar difference in rate would also prevail

SCHEME 2



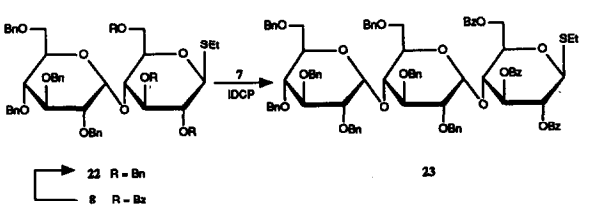
in the case of thioglycosides. To test this hypothesis (*Scheme 2*), we treated a mixture of the fully-benzylated and partially benzoylated (Bz) thioglycosides **4** (ref. 9) (1.15 mmol) and **5** (1 mmol) with IDCP (2 eq.) in 1,2-dichloro-

ethane/ether (1:5, 5 ml). TLC-analysis, after 60 min at 20°C, showed the reaction to be complete[10]. Work-up, followed by purification on silica gel, afforded disaccharide **6** in a yield of 84% (based on **5**) as a mixture of anomers (α:β = 7:1). The above result indicates that the IDCP-mediated coupling proceeds in such a way that the C2-benzylated thioglycoside ("armed" donor) reacts highly chemospecifically[11] with the hydroxyl group of a C2-benzoylated thioglycoside ("disarmed" acceptor).

The "armed-disarmed" principle was further illustrated by the results of the two coupling reactions (entry *1* and *2*) summarized in *Table 1*. It can be seen that the *in-situ* iodonium-ion-promoted glycosidations of the glucose and galactose donors **4** and **9** with the acceptors **7** and **10**, afforded the expected disaccharides **8** and **11**, respectively. It is also of interest to note that these two coupling reactions proceed, in comparison with the reaction in *Scheme 2*, with a high degree of stereospecificity. The latter may be rationalized by assuming that the relatively less reactive hydroxyl groups in **7** and **10** react preferentially with the more reactive β-orientated iodosulfenium intermediates of **4** and **9**, respectively. The pronounced tendency of the glycosidation reaction to yield α-linked disaccharides is also illustrated in entries *3* and *4*. Thus the presence of a less reactive C3-OH in **14** (ref. 12) is reflected in a twofold increase in the α-linked product **15**. In the light of the above results, it is not surprising that the L-rhamnose donors **16** and **18** in entries *5* and *6* yield exclusively the α-linked disaccharides **17** and **19**, respectively. It is also worthwile mentioning that the chloroacetyl (ClAc) and allyl (All) protective groups in donors **16** and **18** were compatible[13] with the IDCP promoted glycosidation conditions. Of particular interest is the result in entry *7* which shows that the stereospecific introduction of an α-linkage can be realized by condensation of the permethylated L-fucose donor **20** with the L-rhamnose acceptor **14**. The disaccharide **21** thus obtained promises to be a valuable synthon[14] for the assemblage of antigenic oligosaccharides from *Mycobacterium tuberculosis*[15].

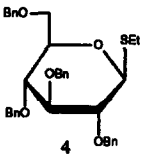
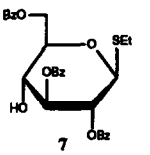
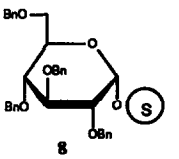
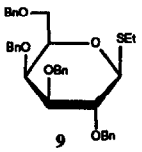
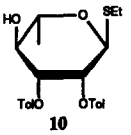
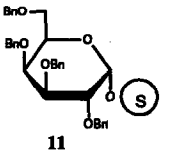
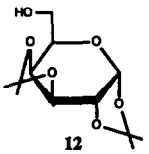
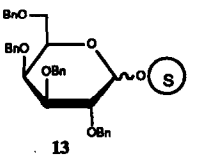
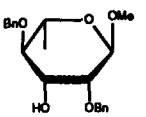
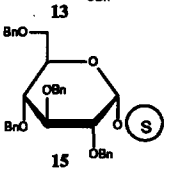
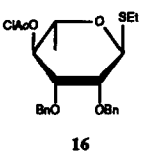
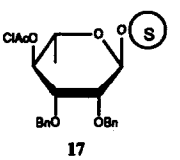
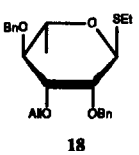
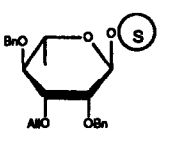
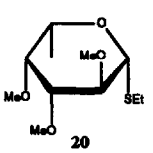
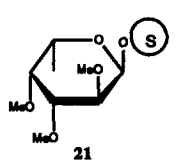
Another interesting and appealing aspect of the *in-situ* iodonium-ion-promoted thioglycoside approach is the feasibility to elongate the disaccharides **6**, **8** and **11** still containing a "disarmed" ethylthio function at the reducing

SCHEME 3



end. For example (*Scheme 3*), Zemplén debenzoylation (NaOMe/MeOH) of **8** and subsequent benzylation [$PhCH_2Br$, NaH, DMF, $(nBu)_4NI$] gave the "armed" disaccharide **22**. Glycosidation of **22** with **7** in the presence of IDCP led to the α-linked trisaccharide **23** (ref. 23) in 72% yield. On the other hand, it is well established that thioglycosides can be applied as hydroxylic acceptors and donors in oligosaccharide synthesis. The donors can either be converted into glycosyl halides[16] or used directly[17] for reaction, in the presence of a halophilic[18] or thiophilic[19] promotor, respectively, with a hydroxylic acceptor. Apart from this, it is also well-known that the presence of a participating 2-acyl substituent in the donor molecule results in the formation of 1,2-*trans* linked glycosides. On the basis of this knowledge together with the availability of effective thiophilic promotors[20,21], it is to be expected that the "disarmed" disaccharides **6**, **8** and **11** are also valuable synthons for the introduction of 1,2-*trans* linkages in a growing oligosaccharide chain.

TABLE 1 Results of IDCP promoted glycosidations.[a].

Entry	Donor[b]	Acceptor[b] (SOH)	Time (min)	Disaccharide[23]	%Yield (α:β)[c]
1	 **4**	 **7**	90	 **8**	91 (1:0)
2	 **9**	 **10**	90	 **11**	75 (1:0)
3	(9)	 **12**	30	 **13**	94 (2.5:1)
4	(4)	 **14**	60	 **15**	83 (5:1)
5	 **16**	(14)	30	 **17**	84 (1:0)
6	 **18**	(14)	30	 **19**	82 (1:0)
7	 **20**	(14)	30	 **21**	80 (1:0)

a) All reactions were carried out at 20°C using diethylether-1,2-dichloroethane 5:1 (v/v) as the solvent in the presence of IDCP (2 eq.) and powdered molecular sieves 5A.

b) The preparation of compounds **7, 9, 10, 16, 18** and **20** will be published elsewhere.

c) α/β ratio determined by NMR spectroscopy.

In conclusion, the high chemospecificity of the thiophilic promotor IDCP for "armed" thioglycosides enabled us for the first time to condense a "disarmed" thioglycoside directly with an "armed" thioglycoside resulting in oligosaccharides containing predominantly α-glycosidic bonds. We believe that the approach reported herein will be a valuable asset for the preparation of complex oligosaccharides *via* thioglycosides[22].

References and notes

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8. This terminology was originally introduced by Fraser-Reid *et al.* (ref. 4) to differentiate between the reactivity of a *n*-pentenyl glycoside having either an ester or ether substituent at C-2 towards halonium ions. Thus a *n*-pentenyl glycoside having an ether or ester substituent on the C-2 oxygen is called "armed" or "disarmed", respectively.
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10. When the glycosidations were performed at 0°C a dramatic decrease in rate, but no increase in stereoselectivity was observed. Further, no glycosidation products were found by executing the reaction in acetonitrile.
11. The high chemospecificity was also corroborated independently as follows. Prolonged (17 h at 20°C) treatment of the ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (ref. 9) with 1,2:3,4-di-*O*-isopropylidene-α-D-galactose did not reveal (TLC-analysis) any possible disaccharide formation.
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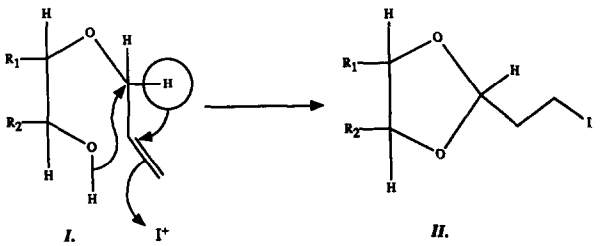
13. The presence of an allyl protective group adjacent to a suitable located hydroxyl fuction in an acceptor molecule (e.g. ***I***) may give rise to an IDCP-mediated side-reaction which inhibits glycosidation. Preliminary results indicated, based on NMR-spectroscopic evidence, the formation of 3-iodopropylidene acetals (e.g. ***II***). The cyclisation may be explained to proceed according to the following mechanism:



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20. Y. Ito and T. Ogawa, *Tetrahedron Lett.*, **29**, 1061 (1988).
21. F. Dasgupta and P.J. Garegg, *Carbohydr. Res.*, **177**, C13 (1988).
22. At present we are studying the effectiveness of the IDCP-mediated glycosidation procedure towards other alkyl and aryl thioglycosides.
23. Satisfactory elemental analyses were obtained for compounds **6**, **8**, **11**, **13**, **15**, **17**, **19**, **21** and **23**. Relevant ^{13}C-NMR-data (50.1 MHz): **6** (α-isomer): 99.7 (C-1^{1}), 83.5 (C-1); **8**: 99.7 (C-1^{1}), 83.5 (C-1); **11**: 99.7 (C-1^{1}), 81.9 (C-1); **13** (α-isomer): 97.5 (C-1), 96.3 (C-1^{1}); **15**: 99.0 (C-1), 94.8 (C-1^{1}); **17**: 99.9 (C-1^{1}), 98.2 (C-1); **19**: 99.8 (C-1^{1}), 98.6 (C-1); **21**: 99.2 (C-1), 97.7 (C-1^{1}); **23**: 99.7 (C-1^{11}), 96.9 (C-1^{1}), 83.5 (C-1).

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