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Az—a colourful azulene-derived protecting group

Mattie S. M. Timmer [a,b,*], Bridget L. Stocker [b], Peter T. Northcote [a], Brendan A. Burkett [a,*]

[a] School of Chemical and Physical Sciences, Victoria University of Wellington, PO Box 600, Wellington, New Zealand
[b] Malaghan Institute of Medical Research, PO Box 7060, Wellington, New Zealand

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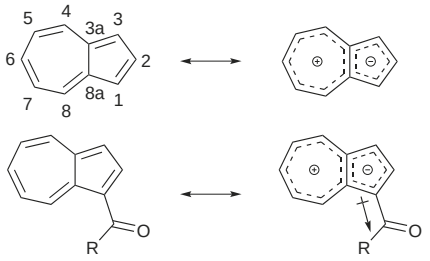
ABSTRACT

Azulen-1-yl-dicarbonyl (Az) is a novel, coloured, protecting group used to mask primary and secondary alcohols. In particular, the use of Az in the construction of carbohydrates, where a number of orthogonal protecting groups are typically required, is of merit. Introduction and removal of the Az-group is performed easily and in near quantitative yields in the presence of other commonly used protecting groups, and the Az-group is compatible with glycosylation reactions using trichloroacetimidate donors. The deep-red colour of the Az-group greatly facilitates the purification of carbohydrate building blocks and the monitoring of coupling reactions. Of particular note is that the Az-group can be selectively introduced on diol systems and removed in the presence of esters, such as acetates.

The use of protecting groups in organic synthesis remains of paramount importance.[1] As molecular targets become more complex, the demand for novel protection and cleavage techniques has increased.[2] This is particularly the case during the construction of oligosaccharides where recent synthetic developments have enabled highly branched structures to be synthesized which, in turn, increases the number of saccharide-coupling steps and the number and type of orthogonal protecting groups required.[3] The steric and electronic nature of protecting groups can also influence the reactivity and outcome of glycosylation reactions,[4] and the advent of solid-phase oligosaccharide synthesis has also placed greater demands on the choice of protecting group.[5]

Of particular interest to us was the development of a coloured hydroxy-protecting group. UV–vis detectable protecting groups have the advantage in that they aid in the monitoring of reaction progress and the purification of synthetic intermediates. They may also be used to monitor colorimetrically the progress of a reaction, an application that is highly desirable for solid-phase synthesis.[6] The most commonly used coloured-protecting groups are the UV-active 9-fluorenylmethoxycarbonyl (Fmoc) group, which has been extensively used in solid-phase peptide synthesis,[6] and the (methoxy) trityl groups, originally developed as a 5′-OH protecting group for the synthesis of DNA and RNA fragments.[7] Although both Fmoc and trityl groups have been used in oligosaccharide synthesis, the lability of the Fmoc group to basic conditions,[1,8] and the steric bulk of the trityl group (limiting its use to the protection of primary hydroxy functions), hinders their wider application. More recent developments in coloured-protecting groups have mainly focused on the peptide or ribonucleoside synthesis,[9] although work by Pohl and co-workers[10] and Manabe and Ito[11] nicely demonstrates the potential of coloured hydroxy protecting groups to facilitate the real time monitoring of solid-phase oligosaccharide synthesis. In addition, Lindhorst and co-workers reported on the use of functionalised guaiazulene derivatives as coloured markers in Chromophore-Supported Purification.[12]

In search of a new hydroxy protecting group, our attention was drawn towards azulene (Scheme 1). Azulene has a remarkable non-alternant aromatic 10-π-electron system, with a polar resonance structure that consists of a fused tropylium cation and cyclopentadienyl anion. This electronic structure gives rise to some unique physical properties, such as the intense blue colour of azulene, and interesting chemical reactivities—azulene reacts readily with both nucleophiles (at the 6-position and, to a lesser extent, the 4- and 8-positions) and electrophiles (at the 1- and 3-positions).[13] To tailor the properties of azulene, we considered introducing an electron-withdrawing group at the 1-position (Scheme 1). The



Scheme 1. Resonance stabilization of azulene and azulene-1-carbonyl derivatives.

* Corresponding authors. Tel.: +64 4 463 6529; fax: +64 4 463 5241 (M.S.M.T.); tel.: +64 6873 4805; fax: +64 6796 3700 (B.A.B.).
E-mail addresses: Mattie.Timmer@vuw.ac.nz (M.S.M. Timmer), Brendan_Burkett@ices.a-star.edu.sg (B.A. Burkett).

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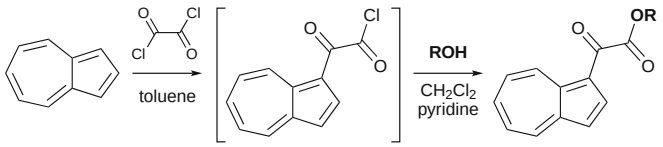
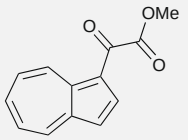
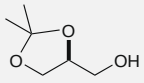
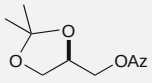
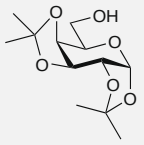
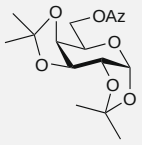
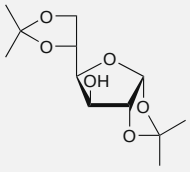
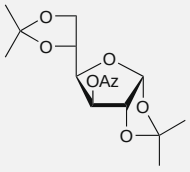
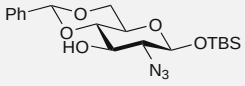
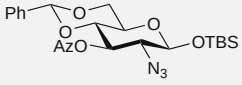
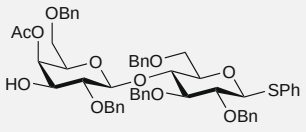
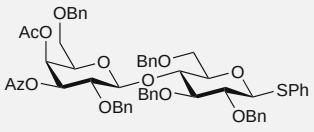
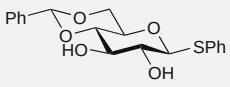
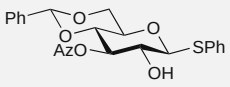
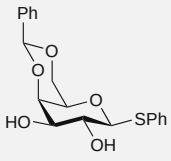
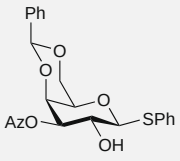
electron-withdrawing group would stabilise the negative charge on the cyclopentadienyl anion, thereby reducing the overall nucleophilic character of the azulene moiety and render it as a useful protecting group. Being coloured, the incorporation of an azulene protecting group onto a hydroxy moiety would aid in the monitoring of reaction progress by TLC and in the identification of products during column chromatography. It was also envisioned that, following deprotection, a modified-azulene derivative would result which could be used to monitor colorimetrically the progress of a reaction.

Herein, we present the use of azulen-1-yl-oxo-acetyl (Az) as a coloured protecting group. By taking advantage of the nucleophilicity of the azulene 1-position, we proposed that azulene could be readily reacted with oxalyl chloride[14] to give azulen-1-yl-oxo-

Table 1
Synthesis of azulene-protected carbohydrate building blocks



1 **2**

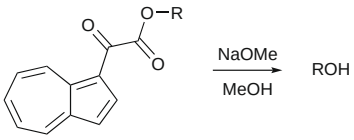
Entry	Alcohol	Ester	Yield (%)
1	MeOH	 **3**	99
2	 **4**	 **5**	99
3	 **6**	 **7**	96
4	 **8**	 **9**	95
5	 **10**	 **11**	95
6	 **12**	 **13**	99
7	 **14**	 **15**	89
8	 **16**	 **17**	96

acetyl chloride (AzCl), a convenient means by which to produce azulen-1-yl-oxo-acetic acid esters.

Azulene is commercially available or can be readily synthesized from pyridine and cyclopentadiene.[15] To examine its potential as a hydroxy-protecting group, azulene (**1**) was reacted with oxalyl chloride to produce the deep-red coloured AzCl (**2**) (Table 1). The colour change, from royal blue to blood red, was instantaneous. Concentration of the reaction mixture, to remove excess oxalyl chloride, and redissolution in dichloromethane allowed for the subsequent in situ reaction of the acyl chloride with methanol to produce methyl ester **3** (Table 1, entry 1). As anticipated, chromatographic purification (silica gel) was greatly facilitated by the bright red colour of ester **3**, for this could be visualised and tracked by eye on the column. Similarly, reaction of 1,2-*O*-isopropylideneglycerol (**4**)[16] with AzCl also proceeded smoothly to give the red azulene ester **5** in nearly quantitative yield (entry 2). In both instances, excess AzCl in the reaction mixture[17] was hydrolyzed following work-up to give the corresponding acid which, as a highly polar product, allowed for the easy purification of the azulen-1-yl-oxo-acetyl ester by SiO_2 column chromatography.

Encouraged by these results, we set out to react a series of orthogonally protected carbohydrates with AzCl (Table 1, entries 3–8). First, isopropylidene protected galactose **6**[18] was reacted with AzCl to give ester **7** in 96% yield (entry 3). More demanding substrates were then subjected to Az protection. The 3-position in diacetone glucose **8** was reacted with AzCl to yield, following purification through a short SiO_2 plug, the 3-*O*-Az protected glucose **9** in excellent yield (95%, entry 4). Glucosazide building block **10**[19] also reacted smoothly with AzCl to provide, after crystallization, the corresponding azulene ester **11** as deep-purple needles (95% yield, entry 5). Similarly, reaction of lactose building block **12**[20] with AzCl led to the formation of 3-*O*-Az protected thiolactoside **13** in excellent yield (entry 6). Of significant note is the ability of AzCl to be incorporated selectively onto the 3-OH of carbohydrate diols (entries 7 and 8). In the presence of 1.1 equivalents of AzCl, the more reactive 3-OH position of glucose **14**[21] was selectively protected to give 3-*O*-Az-glucoside **15** in 89% yield (entry 7). Only trace amounts (~5%) of the 2-OH regioisomer were observed. Similarly, selective protection of the 3-OH position of galactose **16**[13] occurred smoothly to give 3-*O*-Az-galactoside **17** in high yield (96%), with none of the 2-*O*-Az isomer observed (entry 8). Although the superior reactivity of the 3-OH position in 4,6-*O*-benzylidene-protected glucose and galactose derivatives has been noted,[22] the excellent selectivity of the azulene protection provides a convenient route for the construction of fully orthogo-

Table 3
Deprotection reactions



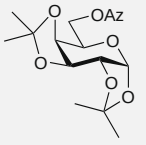
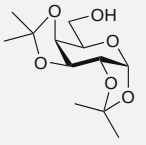
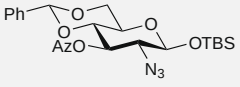
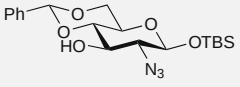
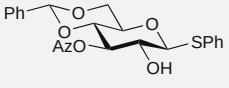
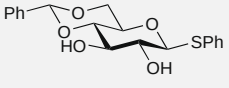
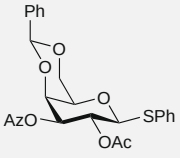
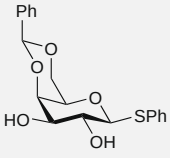
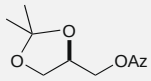
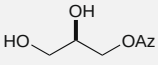
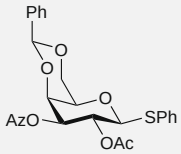
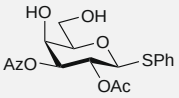
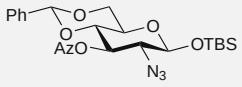
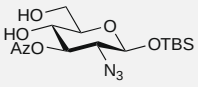
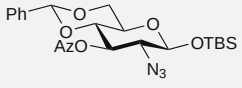
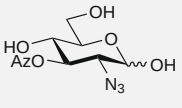
Entry	Alcohol	Ester	Yield (%)
1	 **7**	 **6**	94
2	 **11**	 **10**	94
3	 **15**	 **14**	98
4	 **19**	 **16**	95

Table 2
Acid stability of azulene-protected monosaccharides

Entry	Starting material	Deprotected sugar	Conditions	Yield (%)
1	 **5**	 **18**	80% AcOH/H_2O 50 °C, 2 h	92
2	 **19**	 **20**	80% AcOH/H_2O 50 °C, 2 h	89
3	 **11**	 **21**	80% AcOH/H_2O 50 °C, 2 h	78
4	 **11**	 **22**	80% AcOH/3 M HCl 50 °C, 1 h	69

nally protected glucose and orthogonally-protected galactose building blocks without the use of tin-ketals[23] or lengthy protecting group manipulations.

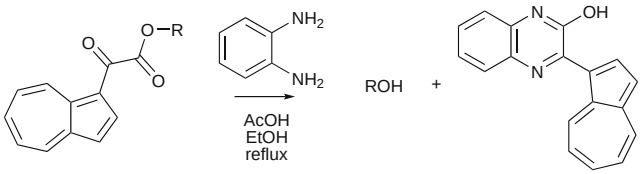
The stability of the Az-group under conditions used to cleave acid labile hydroxy-protecting groups was then explored (Table 2). Upon heating Az-protected glycol **5** in 80% aqueous acetic acid for 2 h, the isopropylidine group was cleaved to yield mono-Az-protected glycol **18** in excellent yield (entry 1). The benzylidine group in galactoside **19** (entry 2) was also removed smoothly under the same conditions to provide diol **20** in good yield. Subjection of azidoglucoside **11** to 80% acetic acid/water for 2 h led to the isolation of diol **21** in 78% yield (entry 3). To ascertain the stability of the Az group under more acidic conditions, azide **11** was then heated in 80% AcOH/3 M HCl for 1 h (entry 4). These conditions resulted in the acetolysis of the benzylidene acetal and cleavage of the *tert*-butyldimethylsilyl (TBS) protecting group to from triol **22** while the Az-protecting group remained (entry 4).

Paramount to the usefulness of Az as a protecting group is its ease of deprotection and the ability of Az to be selectively deprotected in the presence of other protecting groups. Not surprisingly, removal of the Az group is readily effected by treatment of the protected carbohydrates in methanol with catalytic sodium methoxide (Table 3). Here esters **7**, **11** and **15** were deprotected uneventfully to afford alcohols **6**, **10** and **14** in nearly quantitative yields (entries 1–3). Unsurprisingly, removal of the Az group under these conditions also led to the cleavage of other esters, as can be seen in the deprotection of Az/Ac-protected galactoside **19** (entry 4).

The identification of reaction conditions that would enable the Az group to be selectively removed in the presence of other esters were then explored. Herein, we envisioned exploiting the 'di-carbonyl' nature of the azulen-1-yl-oxo-acetyl group by the way of selective Az-deprotection using 1,2-diaminobenzene (Table 4). We also investigated whether the product of this reaction, 2-(azulen-1-yl)-3-hydroxy-benzopyrazine (**23**), could be used to monitor colorimetrically the progress of the reaction. Indeed, subjecting Az acetonide **7** to 1.5 equiv of 1,2-diaminobenzene and acetic acid in ethanol at reflux yielded alcohol **6** in excellent yield (entry 1, Table 4) and the orange 2-(azulen-1-yl)-3-hydroxybenzopyrazine (**23**). Though we were delighted with the selective deprotection of the Az-group, unfortunately the colour of benzopyrazine **23** (λ_{max} = 437 nm; log ε_0 = 4.4) was too similar to that of the azulen-1-yl-oxo-acetyl group (λ_{max} = 397; log ε_0 = 4.3) to enable effective colorimetric monitoring. The colour of benzopyrazine **23** nonetheless facilitated during its removal from the desired alcohol by flash chromatography. The orthogonality of the Az-group was further exemplified by subjecting the substrates containing both an acetyl and an Az group to treatment with 1,2-diaminobenzene (entries 2 and 3, Table 4). Again the Az group in both monosaccharide **19** and disaccharide **13** was removed selectively in the presence of an acetate to yield alcohols **24** and **12** in 92% and 87% yields, respectively. It is of interest to note that the deprotection using *o*-diaminobenzene required both the presence of equimolar acetic acid and elevated temperatures. Under neutral conditions, the addition of hydrazine, 1,2-diaminoethane, urea, carbazides, semicarbazides and thiosemicarbazides failed to remove the Az-group.

The compatibility of Az to reaction conditions used to functionalize carbohydrate building blocks was further explored (Table 5). First, 3-*O*-Az protected galactose building block **17** was subjected to Ac_2O in pyridine (entry 1). This led to the smooth formation of the corresponding acetate **19** in nearly quantitative yield. To prepare an azulene-protected carbohydrate donor, azidoglucose **11**

Table 4
Selective deprotection reactions



23

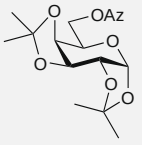
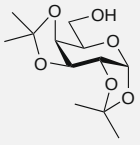
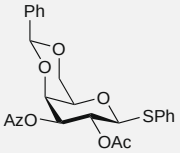
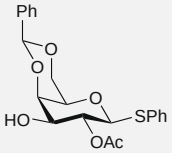
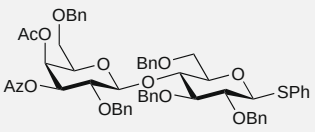
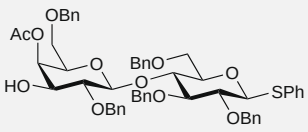
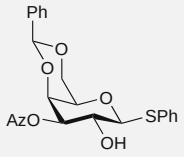
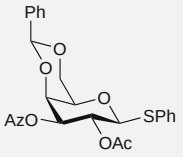
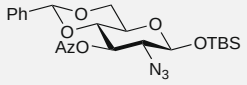
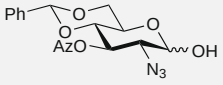
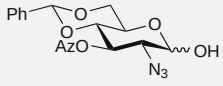
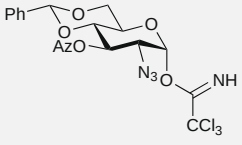
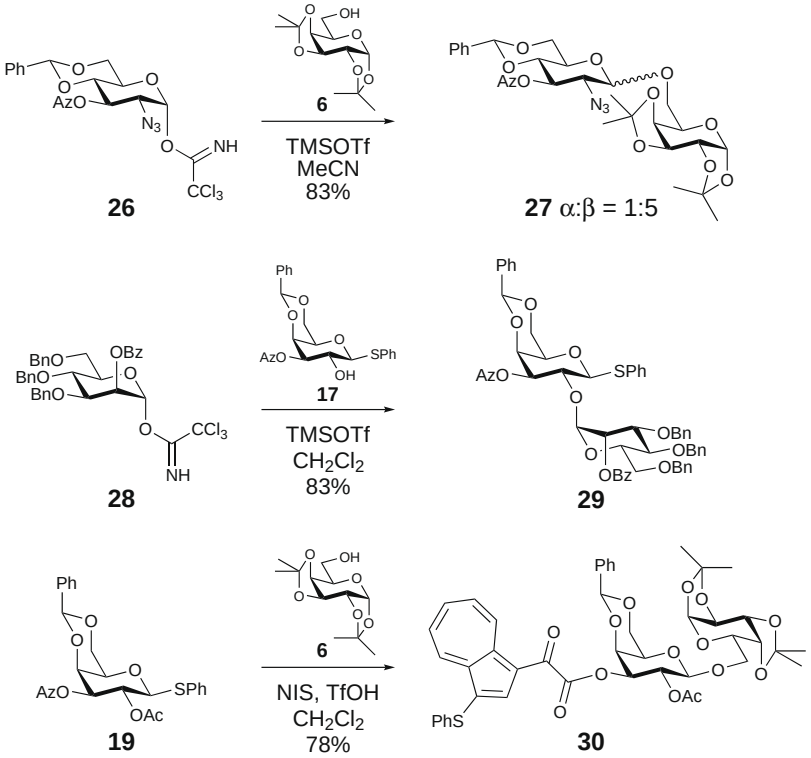
Entry	Ester	Alcohol	Yield (%)
1	 **7**	 **6**	88
2	 **19**	 **24**	92
3	 **13**	 **12**	87

Table 5
Compatibility of azulene protection towards building block manipulations

Entry	Starting material	Product	Conditions	Yield (%)
1	 **17**	 **19**	Ac_2O, pyridine rt, 12 h	95
2	 **11**	 **25**	HF·pyridine THF, rt, 2 h	89
3	 **25**	 **26**	Cl_3CCN, $CsCO_3$, CH_2Cl_2, rt, 2 h	78

was subjected to HF·pyridine in THF, to yield lactol **25** (entry 2). Subsequent reaction of the anomeric hydroxy group in **25** with trichloroacetonitrile,[24] in the presence of Cs_2CO_3 as base, provided imidate **26** in good yield (entry 3). Purification of each reaction product was readily performed by elution of the crude reaction products on a silica plug.

Finally, the compatibility of the Az-group to glycosylation conditions was investigated (Scheme 2). Trichloroacetimidate coupling reactions proved successful, and the coupling of the azulene-protected imidate **26** to di-isopropylidene-galactose acceptor **6** produced the desired disaccharide **27** in 83% yield. Glycosylation of Az-protected acceptor **17** with mannosyl-imidate **28**[3b] also gave the desired disaccharide **29** in good yield and with complete α-selectivity. In both instances, the bright red colour of the acceptor/donor and the dimeric product greatly facilitated in the monitoring of the reaction and in the isolation of the products via column chromatography. Unfortunately, the coupling of Az-protected thiol donor **19** with di-isopropylidene-galactose acceptor **6** using NIS and TfOH as the activating system[25] led to the formation of the phenylthio-substituted coupling product **30**. This result was disappointing, though not highly unexpected given the nucleophilicity of the 3-position of the azulen-1-yl-oxo-acetyl group. Herein, we postulate that phenylsulfenyl iodide, the by-product of the glycosylation reaction, reacts with azulene in an



Scheme 2. Coupling reactions.

electrophilic aromatic substitution reaction to give the 3-iodo azulenyl product.[26] Subsequent nulceophilic substitution of the iodide by thiophenol leads to the 3-phenylthioazulene derivative.[27] Given this result, the electrophilicy of the Az-group would also make it incompatible with pentenyl glycoside donors where NIS is commonly used as the activator. Removal of the 3-phenylthioazulene group can nonetheless be achieved as subjection of disaccharide **30** to NaOMe in MeOH resulted in the complete methanolysis of both the Az and acetyl protecting groups.

Azulen-1-yl-oxo-acetyl (Az) is a novel coloured hydroxy-protecting group for primary and secondary alcohols and is a useful addition to the arsenal of protecting groups currently available. The Az-group can be readily introduced and is stable to a variety of reaction conditions. Importantly, the Az group can be regioselectively incorporated onto the 3-OH position of benzylidene-protected glucosides and benzylidene-protected galactosides and its orthogonality has been illustrated by its selective removal in the presence of various silyl, ether and/or acetate protecting groups. The Az-group is also amenable to glycosylation reactions with the commonly used trichloroacetimidate donors. Unfortunately, removal of the Az-group cannot be used to colorimetrically monitor the reaction progress, however the colour of the Az-group itself aids in the monitoring of reactions by TLC and in the isolation of products via column chromatography. Investigation into the use of the Az-group during the construction of more complex oligosaccharides is currently underway.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.043.

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