Dipent-4-enyl Acetals as Acetalization Agents

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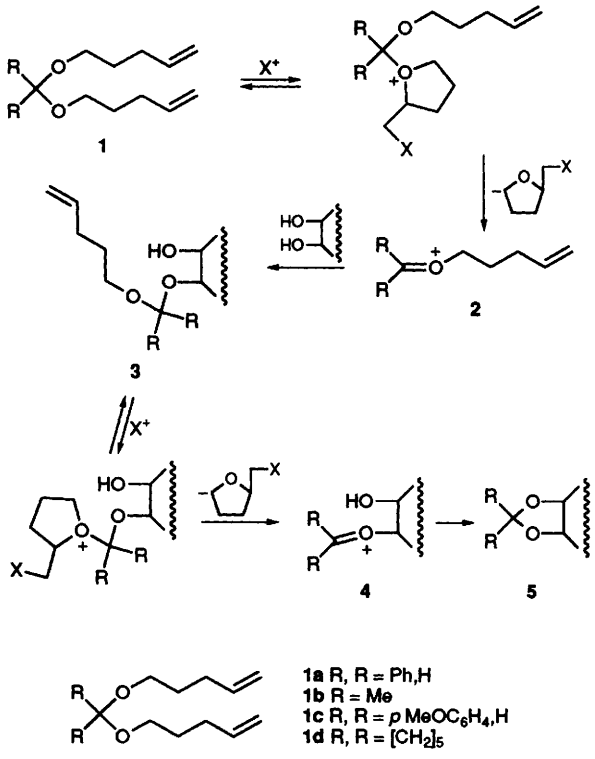
Dipent-4-enyl acetals, which are conveniently prepared by treating ketones or aldehydes with pent-4-enyl alcohol under standard conditions, readily acetalize diols in acetonitrile solvent, and although neutral promoters such as *N*-halogenosuccinimides and iodonium dicollidine perchlorate are effective, the rates and yields are greatly enhanced by the addition of catalytic amounts of an acid.

Cyclic acetals are of established value in synthetic organic chemistry[1] particularly with carbohydrate derivatives where they simultaneously protect two hydroxy groups, often with high regioselectivities,[2] and where they influence conformational choices[3] and, through torsional effects, modulate the rates at which glycosyl oxocarbenium ions are generated.[4] Traditionally these protecting groups are installed under acid,[1a,5] or less frequently base-catalysed[6] conditions, although strategies involving neutral conditions have been described.[7] In the last category, the recent development of phenyl halogenodiazirines for effecting benzylidination of *cis*- or *trans*-vicinal diols by Li and Vasella[8] is noteworthy. In this manuscript we describe a new acetalization strategy that employs readily prepared reagents and occurs under mild conditions such that acid- and base-sensitive groups are not affected.

The strategy grows out of *n*-pentenyl glycoside chemistry which has been explored in our group during the last five years.[9] We reasoned that a dipent-4-enyl acetal of type **1**, Scheme 1, would react with an halonium ion to give oxocarbenium ion **2** which could be trapped by a diol to give a mixed acetal **3**, and then react further *via* **4** to give the cyclic acetal **5**. The test reagents **1a–d** were readily prepared under standard conditions[10] and diol **6** was chosen as a test substrate for reaction with **1a** and **1b** to give **7a** and **7b** respectively (Table 1). Acetonitrile proved to be the solvent of choice, more polar solvents such as dimethylformamide and dimethyl sulfoxide giving poor results.



1a R, R = Ph,H
1b R = Me
1c R, R = *p* MeOC$_6$H$_4$,H
1d R, R = [CH$_2$]$_5$

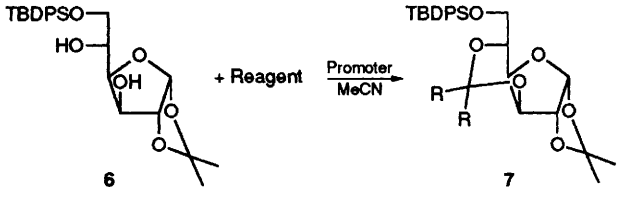
Scheme 1

The entries in Table 1 show that although *N*-halogenosuccinimides can be utilized by themselves (entries i, ii, vii, viii), acid catalysis[11] enhances their effectiveness with respect to both reaction times and product yields. With Lewis acids the reactions are faster than with protic acids for benzylidinations (entries iv and v *vs.* vi). For isopropylidinations Lewis acids are necessary for useful rates (entries x and xi *vs.* xii).

In the light of these results, *N*-bromosuccinimide and an acid were adopted for general use, and substrates **8a–13a** were converted into the corresponding acetals **8b–13b** respectively with the appropriate reagents **1a–1d** using the general conditions in Table 1, footnote *a*. Examples **8**, **9** and **10** show that robust acid-labile groups such as benzylidene acetals, trityl and silyl ethers are tolerated, and application for nucleoside protection is shown by **11**.

The example **12a–12b** is in keeping with previous reports from this laboratory showing that allyl groups are unaffected under conditions required for oxidative activation of pentenyl groups.[9,12]

Table 1 Exploratory acetalization of diol **6**[a]



6 **7**

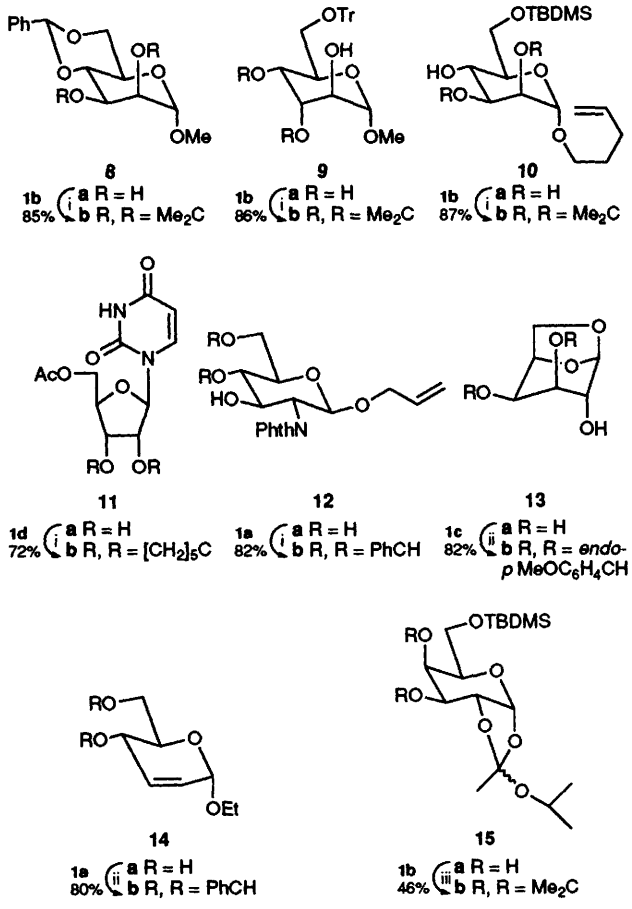
a R, R = Ph,H
b R = Me

Entry	Reagent	Promoter[c]	Reaction time	Product[b]	Yield (%)
i	**1a**	NBS	24 h	**7a**	61
ii	**1a**	NIS	18 h	**7a**	77
iii	**1a**	IDCP	5 min	**7a**	73
iv	**1a**	NBS–Et_3SiOTf	5 min	**7a**	91
v	**1a**	NBS–$BF_3{\cdot}OEt_2$	5 min	**7a**	90
vi	**1a**	NBS–CSA	15 min	**7a**	91
vii	**1b**	NBS	30 h	**7b**	46
viii	**1b**	NIS	20 h	**7b**	49
ix	**1b**	IDCP	30 h	**7b**	2
x	**1b**	NBS–Et_3SiOTf	5 min	**7b**	93
xi	**1b**	NBS–$BF_3{\cdot}OEt_2$	5 min	**7b**	94
xii	**1b**	NBS–CSA	7 h	**7b**	44

[a] Compound **6** (1 mmol) was rotoevaporated with toluene and dried for 30 min under high vacuum and then dissolved in MeCN (5 ml). The dipent-4-enyl acetal (1.2 mmol), the halogenosuccinimide or IDCP (2.7 mmol), and the acid (0.1 mmol) were added. The mixture was stirred at room temperature with protection from light for the time given and then cooled to 0 °C and quenched with Et_3N (25 μl). The solution was diluted with CH_2Cl_2 (15 ml) and washed successively with 10% aq. $Na_2S_2O_3$ (10 ml) and saturated aq. $NaHCO_3$ (10 ml). The organic solution was dried, concentrated, and xylene was evaporated five times to remove 2-halogenomethyloxolane. The residue was chromatographed on silica gel to give the corresponding acetal **7a** or **7b**. [b] The composition of the mixture of diastereoisomers at the newly introduced stereogenic centre in **7a** varied, ranging from 1 : 1 to 6 : 1. [c] NBS, NIS = *N*-bromo-, *N*-iodo-succinimide; IDCP = iodonium dicollidine perchlorate; Tf = CF_3SO_2; CSA = camphorsulfonic acid; TBDPS = Bu^tPh_2Si.

However the result with compound **10a** was surprising. The reaction to produce **10b** was extremely 'clean' thereby indicating no evidence for attack upon the glycosidic *n*-pentenyl group during the acetalization. The basis for this chemoselectivity is current under investigation.

The examples of the hex-2-enopyranoside **14a** and orthoester **15a** are of special interest since these compounds cannot withstand conditions for usual acid-catalysed acetalizations. The formation of **14b** under the protic or Lewis acid-catalysed reactions with NBS attests to the mildness of these conditions. Nevertheless with **15a** buffered conditions[13] were necessary to obtain modest yields of **15b**.



6 1b (i) 85%: a R = H; b R, R = Me_2C

9 1b (i) 86%: a R = H; b R, R = Me_2C

10 1b (i) 87%: a R = H; b R, R = Me_2C

11 1d (i) 72%: a R = H; b R, R = $[CH_2]_5C$

12 1a (i) 82%: a R = H; b R, R = PhCH

13 1c (ii) 82%: a R = H; b R, R = *endo*-*p* $MeOC_6H_4CH$

14 1a (ii) 80%: a R = H; b R, R = PhCH

15 1b (iii) 46%: a R = H; b R, R = Me_2C

Conditions: i, NBS, Et_3SiOTf, MeCN, 5 min; ii, NBS, CSA, MeCN, 15 min; iii, NIS, 2,6-di-*tert*-butyl-4-methylpyridine, MeCN, 24 h; Phth = phthaloyl; TBDMS = Bu^tMe_2Si

R. M. thanks the Danish Technical Research Council for a postdoctoral Fellowship. This work was supported by grants from NIH (GM 41071) and NSF (CHE 9311356).

Received, 29th November 1993; Com. 3/07059J

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