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New Method for Chloroamidation of Olefins. Application in the Synthesis of *N*-Glycopeptides and Anticancer Agents

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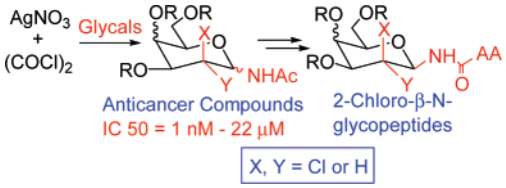
ABSTRACT



Chloroamidation of olefins using a new reagent system $(COCl)_2$-$AgNO_3$-CH_3CN was observed. Various glycals with this reagent system produce 2-chloro-1-acetamido sugars in good yields which, in turn, were converted to free amino derivatives and various glycopeptides. The acetamido sugar derivatives and free amines were found to be promising anticancer agents against the U-87 malignant glyoma (a brain tumor) cell line with IC-50 = 1 nm–22 μM, and they were found to be far less cytotoxic against a normal human embryonic kidney cell line.

Vicinal haloamines are important building blocks[1−5] in organic and medicinal chemistry which can be obtained from olefins either by aminohalogenation[6−7] via an aziridinium type intermediate followed by attack of a halogen or by haloamination[8] via a halonium type intermediate followed by attack of a nitrogen nucleophile. Although various methods of aminohalogenation of olefins have been reported they are limited to specific substrates[6] like α,β-unsaturated esters, ketones, and nitriles. Several nitrogen/halogen sources such as 4-$TsNCl_2$,[6a,b] 2-NsNNsCl (Ns = 4-nitrobenzenesulfonyl), a combination of 2-$NsNCl_2$ and 2-NsNHNa,[6c,d] and a combination of NBS and $TsNH_2$[6e] in the presence of different Lewis acids have been used for this purpose. The stereo- and regioselectivity of products during aminohalogenation suggests that the process occurs via an aziridinium ion intermediate. Haloamination reactions, on the other hand, have been reported[8] on a variety of olefins including glycals[9] which involve a source of a halonium ion (Cl^+, Br^+, or I^+) along with nitrogen nucleophiles. Very recently, Corey et al.[10] have reported bromoamidation of olefins using *N*-

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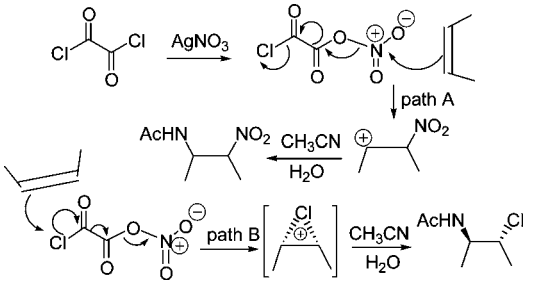
bromosuccinimide and acetonitrile in the presence of a Lewis acid catalyst. They have also reported conversion of cyclohexene to the corresponding chloroacetamide using *N*-chlorosuccinimide (NCS) acetonitrile in the presence of a Lewis acid; however, it requires longer reaction time (20 h). For fluoroamination reactions, selectfluor has been used[11] extensively as a source of fluorine. 2-Deoxy or 2-substituted 1-amino sugar derivatives are precursors for the synthesis of pharmaceutically and biologically important 2-deoxy-*N*-glycopeptides.[12] It has also been reported that sugar modified nucleosides are promising candidates for treatment of cancer and AIDS.[13] Although 2-iodo or 2-bromo glycosyl amino derivatives are readily obtained from glycals,[9] there is not much biological significance associated with these products. On the other hand, 2-fluoro and 2-chloro glycosyl amino derivatives are biologically more important.[14] For example, 2-deoxy-2-chloro-ribonucleotide was one of the first inhibitors of enzyme ribonucleotide reductase,[15] an important target for treating viral diseases, AIDS, and cancer.

As part of an ongoing research program[12c,16] in functionalizing glycals toward the synthesis of biologically important molecules, we proposed to introduce a new method to procure 2-nitro-1-amino sugars with the hope that the 2-nitro group could be converted into a variety of other functionalities.[17] Further, the nitro group could be reductively removed under radical conditions to form 2-deoxy sugar derivatives. A few years ago, we introduced[18] a new reagent system, namely $ClSiMe_3$-$AgNO_3$-CrO_3 for one-pot conversion of olefins into α-nitro ketones. This reagent system is believed to be a source of nitronium ion. We therefore anticipated that a new and somewhat similar reagent system, oxalyl chloride-$AgNO_3$-CH_3CN, could introduce a nitro group and acetamido group onto olefins as shown in Scheme 1 (path A). However, what we observed was formation of

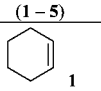
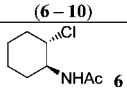
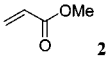
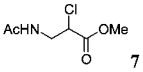
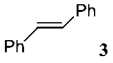
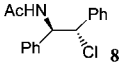
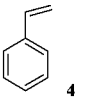
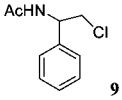
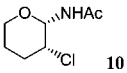
Scheme 1. Tentative Mechanism for Chloroamidation of Olefins



the corresponding 2-deoxy-2-chloro-1-acetamido sugars from glycals (path B) indicating that path A, involving a nitronium ion, was not operational. In view of the importance of sugar-derived chlorinated molecules (vide supra) we explored this chemistry in synthesizing a variety of sugar-derived vicinal chloro amines and chloro *N*-peptides and studied the cytotoxicity of some of them.

In initial experiments, the cyclohexene **6** was treated with the reagent system oxalyl chloride-silver nitrate in acetonitrile, and after optimization it was found that 1.5 equiv of oxalyl chloride and 1.5 equiv of silver nitrate in acetonitrile when mixed at −20 °C followed by the addition of cyclohexene gave 1-chloro-2-acetamido cyclohexane in 80% yield. The stereochemistry of the product was found to be

Table 1. Chloroamidation of Olefins

entry	substrates (1 – 5)	products (6 – 10)	time/temp/yield (min/°C/%)
1	 1	 6	60/-20/80
2	 2	 7	180/+20/65
3	 3	 8	90/-20/69
4	 4	 9	60/-20/78
5	 5	 10	45/-30/62

trans[19] which indicated that this reagent system is a source of chloronium ion (Cl^+). The scope of this chloroamidation process was explored by using different olefins like dihydropyran, *trans*-stilbene, styrene, and methyl acrylate (Table 1)

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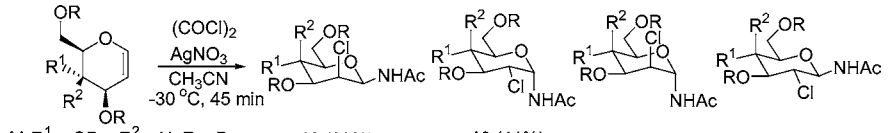
(19) Trans stereochemistry of the cyclohexene derivative **6** was confirmed by comparison of its spectral data as well as its M.P.

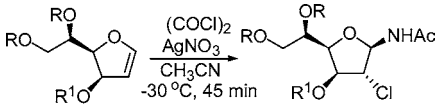
Scheme 2. Preparation of 2-Chloro-1-*N*-acetyl Sugar Derivatives from Pyrano Glycals



11 R^1 = OBn, R^2 = H, R = Bn	**12** (39%)	**13** (41%)	-	-
14 R^1 = OAc, R^2 = H, R = Ac	-	-	**15** (41%)	**16** (43%)
17 R^1 = H, R^2 = OBn, R = Bn	-	**18** (75%)	-	**19** (5%)
20 R^1 = H, R^2 = OAc, R = Ac	-	**21** (80%)	-	**22** (5%)

as well as by treating various pyran and furan glycals. Among the products derived from nonsugar based olefins, the X-ray crystal structure of the major chloroacetamide obtained from dihydropyran showed[20] that chloro and acetamido groups are cis to each other with chlorine at C-2 and the acetamido group at C-1. This indicates that an oxonium ion is formed after the initial reaction of dihydropyran with Cl^+ before acetonitrile attacks at the anomeric carbon thus leading mainly to a cis product due to the anomeric effect. Likewise, the crystal structure of styrene derived chloroacetamide[20] showed that the acetamido group is at the benzylic position and chlorine is at the terminal carbon. Thus, the regioselectivity in both of these compounds also indicates that the present reagent system is a source of Cl^+ ion. A tentative mechanism is shown in Scheme 1. Treatment of glycals, as expected, gave products with exclusive regioselectivity where chlorine was found to be at C-2 and acetamido group at C-1 (Schemes 2 and 3). It is worth mentioning that attempts to

Scheme 3. Preparation of 2-Chloro-1-*N*-acetyl Sugar Derivatives from Furano Glycals



23 (a-c) **24 (a-c)**

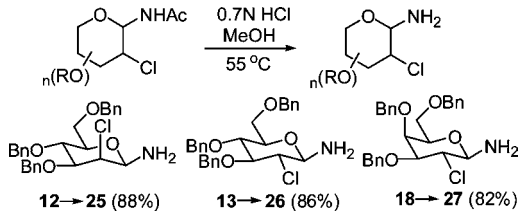
a R = R^1 = Bn (88%)
b R = R^1 = Bz (92%)
c R = Bz, R^1 = Bn (90%)

convert glycals using simple source of Cl^+ (NCS) along with NaN_3 in CH_3CN did not lead to any 2-chloro-1-amino sugar derivative. Further, reaction of 3,4,6-tri-*O*-benzyl glucal with NCS in presence of $BF_3{\cdot}Et_2O$[10] in CH_3CN at 0−10 °C was not clean and gave a number of products as revealed by thin layer chromatography, and none of these products matched with the expected 2-chloro-1-acetamide. Hence it appears that the present reagent system is a mild and good source of Cl^+ which could be used in carbohydrate chemistry.

Although glucal derivatives **11** and **14** gave a mixture of two diastereomers in equal ratio, better stereoselectivity was observed for galactal derivatives **17** and **20**. Further, a single diastereomer was obtained from furan glycals[21] **23a**−**c** via a chloronium ion intermediate from α-side followed by the attack of acetonitrile from *β*-side. The structures of sugar-derived chloroacetamides (Schemes 2 and 3) were confirmed by 1D, 2D NMR and mass spectral data, NOE experiments, and in some cases with the single-crystal X-ray data.[20]

Chloroacetamides **12**, **13**, and **18** were efficiently deprotected under optimized conditions[22] using 0.7 N HCl in MeOH at 55 °C to obtain the corresponding 2-chloro-glycosyl amines **25**, **26**, and **27**, respectively (Scheme 4). It

Scheme 4. Deprotection of Chloroacetamides to Chloroamines



12→**25** (88%) **13**→**26** (86%) **18**→**27** (82%)

is important to note that compounds **13** and **18** were epimerized under these conditions to the corresponding *β* anomers **26** and **27**, respectively. The free amines **25**−**27** were then coupled with suitably protected amino acids under the standard coupling conditions[23] using DCC and HOBt in THF to obtain the corresponding 2-chloro-*β*-*N*-glycopeptides **28**−**33** with gluco-, glacto-, and manno-configuration (Scheme 5). Dechlorination of these glyco-peptides under radical conditions using tributyltin hydride and AIBN in refluxing *tert*-butanol led to the 2-deoxy-*β*-*N*-glycopeptides **34**−**37** (Scheme 5).

Colinas et al.[24] have recently reported a few glycal-derived 2-deoxy-sulfonamides to be potent inhibitors for the growth of hepatacellular carcinoma cell lines. In view of this, we have carried out a preliminary study and investigated the

(20) CCDC 651000 (**9**), 651048 (**10**), 651049 (**15**), 651050 (**21**), 651051 (**22**), 651052 (**25**) contains the supplementary crystallographic data available free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(21) Stereochemistry was confirmed by comparing the *J* values of related structures from the following references. (We are thankful to one of the referees for suggesting to establish the stereochemistry of furano sugar derivatives by this comparison.) (a) Liautard, V.; Desvergnes, V.; Martin, O. R. *Org. Lett.* **2006**, *8*, 1299. (b) Blanco, J. L. J.; Sylla, B.; Mellet, C. O.; Fernandez, J. M. G. *J. Org. Chem.* **2007**, *72*, 4547.

(22) The *N*-glycosyl amides are chemically very stable. We here report for the first time that 1-*N* acetyl sugar derivatives can be successfully deprotected to free amines.

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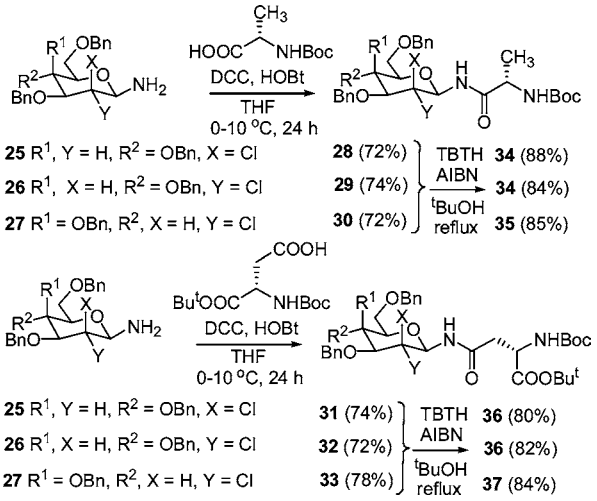
Scheme 5. Synthesis of 2-Chloro and 2-Deoxy-*N*-glycopeptides



cytotoxicity of some of these 2-chloro-glycosylacetamides and glycosyl amines against the U-87 malignant glyoma (brain cancer) and normal human embryonic kidney cell lines. Our results are summarized in Table 2. The IC-50 values clearly show that these compounds are highly cytotoxic against the U-87 cancer cell line (22 μM−1 nM), whereas these are much less toxic against the normal human embryonic kidney cell line. It is therefore expected that some of these compounds could be useful lead molecules for the development of novel anticancer agents. Detailed biological study with other cancer cell lines is in progress and will be published in due course.

In summary, we have developed a new reagent system for preparing vicinal chloroamides from olefins. Sugar-derived vicinal chloro amines so obtained are converted into 2-deoxy and 2-chloro glycopeptides. Further, vicinal chloroamides and chloroamines derived from sugars have been found to be potently cytotoxic against two cancer cell lines.

Table 2. IC-50 Values against U-87 Malignant Glyoma (Brain Tumor) and Human Embryonic Kidney (Normal) Cell Lines

entry	compound number	IC-50 (μM) for U-87 malignant glyoma cell line	IC-50 (μM) for normal Hek cell line
1	**12**	6	>100
2	**13**	22	>100
3	**18**	5	75
4	**19**	16.5	74
5	**24b**	37	>100
6	**25**	0.001	100
7	**26**	0.1	37
8	**27**	0.04	>100

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Supporting Information Available: Experimental procedures, physical data, and NMR spectra of all compounds as well as CIF data for **9**, **10**, **15**, **21**, **22**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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