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Application of silver N-heterocyclic carbene complexes in O-glycosidation reactions

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Abstract

We report the efficient O-glycosidation of glycosyl bromides with therapeutically relevant acceptors facilitated by silver N-heterocyclic carbene (Ag-NHC) complexes. A set of four Ag-NHC complexes was synthesized and evaluated as promoters for glycosidation reactions. Two new bis-Ag-NHC complexes derived from ionic liquids 1-benzyl-3-methyl-1H-imidazolium chloride and 1-(2-methoxyethyl)-3-methyl-1H-imidazolium chloride were found to efficiently promote glycosidation, whereas known mono-Ag complexes of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and 1,3-bis(2,6-di-isopropylphenyl)imidazolium chloride failed to facilitate the reaction. The structures of the promoters were established by X-ray crystallography, and these complexes were employed in the glycosidation of different glycosyl bromide donors with biologically valuable acceptors, such as estrone, estradiol, and various flavones. The products were obtained in yields considered good to excellent, and all reactions were highly selective for the β isomer regardless of neighboring group effects.

Keywords

O-glycosidation; Silver N-heterocyclic carbene complex; Carbohydrates

1. Introduction

Glycotherapeutic agents such as glycomimetics,¹ small-molecule therapeutically active carbohydrates and prodrugs,^{2–6} and carbohydrate-based vaccines^{7,8} are promising medicinal targets. The recent understanding of glycoprotein/proteoglycan structure and function,⁹ the ligand probing of human glycosyltransferases,¹⁰ and the synthesis of complex oligosaccharide constructs are examples of advancements that help to deconvolute the biological role of carbohydrates in a variety of disease states.¹¹ These advancements in

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Supporting Information: The supporting information contains additional data (¹H, ¹³C, GCOSY, GHSQC NMRs and HRMS) relating to compounds **1**, **2**, **3a–p**, **4a–d**, **5a–e**; CIFs for **1** and **2**; optimization data and X-ray crystal data for compounds **1** and **2**.

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understanding, in turn, have generated an increased demand for the synthesis of carbohydrate-containing targets, which requires efficient and selective methodology for the construction of glycosidic bonds. Frequently employed glycosidation donors include high-yielding trichloroacetimidate donors developed by Schmidt and coworkers,¹² thioglycosides, and glycosyl halides, while challenges in O-glycosidic bond construction often include issues with regioselectivity, stereoselectivity, low coupling yields, and product purification.¹³ The isolation of stable carbenes and subsequently silver N-heterocyclic carbene (Ag-NHC) complexes by Arduengo and coworkers^{14, 15} drew the attention of both organic and organometallic chemists to this area of research. As a result, Ag-NHC complexes¹⁶⁻¹⁸ have been used in the nucleophilic catalysis of a variety of reactions,^{19,20} and imidazolylidene groups have been used as transition-metal-coordinated electron-rich ligands.²¹ Although NHC's have been reported to form complexes with most transition metals, silver imidazolylidene complexes are particularly attractive because they are simple to access and stable under ambient conditions. However, despite increased interest in Ag-NHC complexes, limited attention has been given to their application in organic synthesis.

In our effort to develop therapeutic carbohydrates for the treatment of cancer, we recently reported on the efficient glycosidation of glycosyl bromides in imidazolium ionic liquids utilizing a heavy-metal base such as silver carbonate.^{22,23} NMR experiments suggested the transient formation of Ag-NHC complexes derived from the imidazolium halide ionic liquids (IL) and silver carbonate during the course of the glycosidation. Thus, we became interested in evaluating the ability of isolated carbene complexes to act as promoters in reactions of glycosyl halides with various biologically relevant acceptors.

2. Results and Discussion

We synthesized a small group of Ag-NHC complexes to use in a series of O-glycosidation reactions. In particular, our attention was focused on complexes that were room-temperature solids that could be easily manipulated for reactions and characterized unambiguously by X-ray crystallography. We found that the silver complexes of 1-benzyl-3-methylimidazol-2-ylidene silver(I) chloride (**1**) and 1-(2-methoxyethyl)-3-methylimidaz-2-ylidene silver(I) chloride (**2**) met these criteria (Figure 1). The NHC complexes were derived from 1-benzyl-3-methylimidazolium chloride (BnMIm-Cl) and 1-(2-methoxyethyl)-3-methylimidazolium chloride (MoeMIm-Cl) via reaction with silver oxide in dichloromethane. Similarly, we synthesized the known mono-Ag complexes of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride; these mono-Ag structures were previously established with X-ray crystallography by Nolan and coworkers,¹⁷ and we confirmed our products via comparison of the ¹H NMR spectra to the literature values. However, to unambiguously assign the structures of **1** and **2**, it was necessary to obtain X-ray crystal data, since it can be difficult to distinguish mono- and bis-Ag-NHC complexes using ¹H/¹³C NMR spectroscopy and mass spectrometry.¹⁸ It is worth noting that a mono-ligated analog of **1** was reported previously,²⁰ although the material was not characterized by X-ray crystallography. To the best of our knowledge, neither of the bis-NHC-Ag complexes **1** and **2** has been reported to date.

The X-ray crystal structures of **1** and **2** are depicted in Figure 1. In both cases, the bonding motif involves the coordination of two imidazolylidene ligands to a bridging silver atom. The coordinating anion is a halogeno counterion of type [AgX₂]⁻, and the interplanar angle between the imidazole ring plane and the plane formed by Ag1-Ag2-C1 is 83.08° for compound **1** and 88.00° for **2**. Interestingly, the two NHC ligands lie in the same plane for compound **1** but are twisted for compound **2** such that the dihedral angle between the imidazole ring planes is 20.89°. The Ag1-C1 bond lengths for **1** and **2** are 2.096(4) Å and

2.082(4) Å, respectively, and both complexes are linear around silver with a C1-Ag-C1' bond angle of 180.0° for **1** and 179.2(2)° for **2**. Other salient features of **1** and **2** include, respectively: an Ag1-Ag2 distance of 3.2279(4) Å and 3.1150(9) Å; Ag2-Cl bond lengths of 2.3406(14) Å and 2.3290(14) Å; Cl1-Ag-Cl2 bond angles of 180.0° and 176.37(8)° for the linear [AgCl2]⁻ counterion; and N1-C1-N2 angles of 104.7(3)° and 107.2(3)° for the imidazole rings.

Following their synthesis and characterization, the Ag-imidazolylidene complexes were evaluated as promoters for the model glycosidation reaction of tetra-*O*-acetyl- α -D-galactopyranosyl bromide (**3**) with 4-nitrophenol (Scheme 1). Initial attempts at glycosidation with the mono-Ag-NHC complexes at room temperature under ambient conditions failed to convert the starting materials after 24 h. In contrast, both **1** and **2** efficiently promoted the glycosidation reaction in high yields under the same conditions after 3 h. The reaction occurred faster in acetonitrile than in dichloromethane, though both solvents produced significant conversion to product. Optimization by screening reaction temperature and stoichiometry of promoter revealed that the reaction proceeded expediently and with high conversion at room temperature with one equivalent of promoter (see Table S1 in SI).

We subsequently examined a set of donors and acceptors to further probe the utility and scope of Ag-imidazolylidene complexes in O-glycosidation reactions (Table 1). High yields in the range of 78–95% were obtained for reactions of **3** with phenolic acceptors (Table 1, entries 1–5). A wide variety of acceptors including electron-rich and electron-deficient phenols were easily glycosidated. In the case of tetra-*O*-acetyl- α -D-glucopyranosyl bromide (**4**), yields were low as expected (Table 1, compare entries 1–4 and 7–10) due to C2 elimination of glycosyl halide.²⁴ For example, reaction with 4-nitrophenol, 4-methoxyphenol, and 2-naphthol yielded, after isolation by column chromatography, 67%, 45%, and 32%, respectively, of the C2 elimination product. In contrast, the rate of reaction and conversion to product with tetra-*O*-benzyl- α -D-glucopyranosyl bromide (**5**) was significantly higher than with acetylated analog **4**, presumably due to the higher reactivity and reduced tendency of **5** to undergo elimination (Table 2, entries 1–5).²⁵ Regardless of neighboring group effect, the β product was predominantly formed; we speculate that this may be due to coordination of the acceptor to the Ag-NHC (*vide infra*) and/or solvent intervention. Interestingly, Ag-NHC complex **2** proved to be a more effective promoter for reactions with benzyloxy donor **5** and often resulted in a 10% increase in yield over promoter **1** (Table 2, compare entries 1–4 with 6–9). These data suggest that promoters might be designed and tailored for individual substrates; we are in the process of screening additional Ag-NHC complexes for O-glycosidation reactions towards this end and will report the results when they become available.

With the methodology established, we turned our attention to exploring the application of these novel Ag-imidazolylidene complexes in the synthesis of biologically relevant glycosides. For example, glycosidation of flavone and isoflavone derivatives with noviose carbonate produced a series of Hsp90 inhibitors that exhibited anti-proliferative activity.⁶ Glycosidation of coumarin derivatives to increase coumarin solubility has been recently used in a prodrug strategy in antifungal therapy,²⁶ and 4-methylumbelliferyl glycosides²⁷ have been used in fluorimetric assays of glycoside hydrolase activity and have been studied as inhibitors of the concanavalin A.²⁸ There has been recent interest in the use of estradiol- β -3-glucoside in hormone replacement therapy as it is water soluble, readily absorbed in the gastrointestinal tract, and may bypass hepatic first pass metabolism associated with the deleterious side effects of portal absorption of estradiol.⁵

To evaluate these types of substrates, estrone (**6**), estradiol (**7**), coumarins (**8** and **9**), flavones (**10** and **11**), isoflavone (**12**), chromanone (**13**) and flavanone (**14**) were screened as acceptors for glycosidation reaction of **3** utilizing promoter **1** (Scheme 2). The reactions that occurred with steroids **6** and **7** and coumarin **8** were slower (24, 12 and 24 h, respectively) than those that occurred with other compounds (3 h). In general, most of the reactions with promoter **1** produced corresponding glycosides in good to excellent yields. In contrast, the reaction of 7-hydroxyflavone with compound **3** using silver triflate, silver perchlorate, or cadmium carbonate resulted only in decomposition of the starting materials as observed by TLC. When silver carbonate was used as promoter, the product was isolated with a 49% yield by column chromatography. Thus, Ag-NHC complexes may be superior to traditional promoters for O-glycosidations of flavonoid and coumarin acceptors. Estradiol, containing both a phenolic and aliphatic hydroxyl group, was exclusively glycosidated on the phenolic hydroxyl group to produce the mono-glycoside **3h** in one step without needing hydroxyl group protection. Interestingly, compound **3j** was obtained in high yield (86%) whereas closely related compound **3i** lacking the acetyl group was obtained in lower yield (17%). The results suggest that the absence of the acetyl group in **3i** impacts the yields, perhaps via decreased acidity of the hydroxyl group proton. Dihydroxyflavone **10** was primarily glycosidated on the vinylic hydroxyl group to produce a 65% yield of **3k**, although diglycosidated flavone **3l** was also isolated as the minor product with a 22% yield. To the best of our knowledge, compounds **3k**, **3n**, and **3p** have not been reported to date. All cases produced exclusively the β product with the exception of estrone **6**, which gave a separable 2:1 mixture of the α and β glycosides. Although cis glycosidation products are typically difficult to access, it is possible that the longer reaction time for this substrate facilitated equilibration to the more stable α isomer.

We speculated that the mechanism for Ag-NHC-promoted glycosidation may involve a dual role for the Ag-NHC complex: (i) as a heavy-metal ion source to assist with oxocarbenium ion formation, and (ii) as a base to deprotonate the phenol acceptor. The ability of heavy-metal salts to assist in oxocarbenium ion formation is well known.²⁹⁻³¹ Reports in the literature described the interaction between free NHCs with phenols as determined by X-ray analysis of the isolated imidazolium aryloxide.^{32, 33} In particular, Clyburne and coworkers³² observed phenol protonation of carbene complexes, which remained tightly associated to the phenoxide ion via a short CH-O interaction. Thus, we treated compound **2** with one equivalent of 4-nitrophenol in CD₃CN and examined the reaction via ¹H NMR. After the treated compound was stirred overnight at room temperature, ¹H NMR revealed a mixture of the starting Ag-NHC complex plus the formation of a second imidazolium species consistent with an imidazolium aryloxide complex (see Figure S1 and S2 in the SI). The new imidazolium species exhibited a downfield resonance in the ¹H NMR typical for H2 of imidazolium salts. Furthermore, we observed an upfield chemical shift of the ortho and meta aromatic protons from 6.93 ppm to 6.43 ppm and from 8.12 ppm to 7.92 ppm, respectively, which was consistent with increased ionic character of the phenolic oxygen.³⁴ These results suggest that the mechanism for the glycosidation involves, in part, deprotonation of the phenol by the imidazolium carbene.

3. Conclusions

In summary, we have demonstrated the utility of novel Ag-NHC complexes for coupling of glycosyl bromides to a set of simple phenolic acceptors. We have also synthesized a series of novel glycosides using steroid, flavone, and coumarin scaffolds. The reaction proceeds expediently under ambient conditions at room temperature, using one equivalent of promoter in acetonitrile. Commercially available, inexpensive donors can be easily used without further purification. Tetra-*O*-benzyl- α -D-glucopyranosyl bromide reacted faster and produced higher yields than the corresponding tetra-*O*-acetyl- α -D-glucopyranosyl bromide,

which underwent significant elimination. In general, all reactions were highly selective and yielded the β product regardless of neighboring group effects. Preliminary results suggest a dual role for these complexes as bases and as heavy-metal ion sources that may promote oxocarbenium ion formation. Furthermore, the difference in activity of **1** and **2** and the ability to adjust the structure of the promoter hold promise for developing substrate-specific Ag-NHC complexes for O-glycosidation reactions.

4. Experimental

4.1. General methods

TLCs were run on pre-coated Merck silica gel 60F₂₅₄ plates and observed by charring with 3.5% H₂SO₄–1% AcOH–2.5% *p*-anisaldehyde–EtOH and with UV light. The products were isolated and purified using a Teledyne ISCO Rf flash chromatography system with hexanes and ethyl acetate as eluents. For verification of the product and purity analysis, the LC-MS was taken on an Agilent 1200 series system with an Agilent 6210 Time-Of-Flight (TOF) mass detector. The ¹H (400 MHz), ¹³C (101 MHz), gCOSY and gHSQC NMR spectra were taken on a Varian 400MR spectrometer. Chemical shifts (δ) are expressed in ppm, coupling constants (*J*) are expressed in Hz, and splitting patterns are described as follows: s = singlet; d = doublet; t = triplet; q = quartet; q_{AB} = AB quartet; quintet; sextet; septet; br = broad; m = multiplet; dd = doublet of doublets; dt = doublet of triplets; td = triplet of doublets; ddd = doublet of doublet of doublets. Trace metal (ICP-OES) and elemental analyses were performed by Robertson Microlit Laboratories, Ledgewood, NJ, USA. All the imidazolium ionic liquids used in this study were purchased from Merck KgaA (EMD Chemicals), Darmstadt, Germany. 1-Butyl-3-methyl imidazolium chloride (BMIm-Cl) and all other chemicals were purchased from Sigma-Aldrich Co. and used without any further purification.

4.2. General procedure for the preparation of Ag-NHCs **1** and **2**

The imidazolium chloride salt (2 equiv.) and silver oxide (1 equiv.) were combined with 100 mL of dichloromethane in a 250 mL round-bottom flask under ambient atmosphere; the mixture was stirred at 25 °C for 24 h in the absence of light. After 24 h, consumption of Ag₂O was observed; the mixture was filtered through Celite, and the Celite was washed with 3 × 30 mL dichloromethane. The organic layers were concentrated in vacuo to produce the crude solid, which was recrystallized with dichloromethane and hexanes to produce white crystals. Yields for **1** and **2** are given in Scheme S1 (supplementary information).

4.2.1. Bis(1-benzyl-3-methyl-1H-imidazol-2(3H)-ylidene)silver (1**)**—¹H NMR (400 MHz, CD₃CN) δ 7.39–7.28 (m, 10H), 7.18 (d, *J* = 1.8 Hz, 2H), 7.15 (d, *J* = 1.8 Hz, 2H), 5.28 (s, 4H), 3.77 (s, 6H). ¹³C NMR (101 MHz, CD₃CN) δ 181.0, 138.0, 129.8, 129.1, 128.6, 123.9, 122.6, 55.7, 39.3. LC-MS (ESI-TOF): *m/z* [M]⁺ calcd for C₂₂H₂₄AgN₄: 451.1046; found 451.1056.

4.3. General glycosidation procedure

The promoter **1** or **2** (1 equiv.), acceptor (2 equiv.), and donor (1 equiv.) were combined with 2 mL of acetonitrile in a 14 mL borosilicate glass vial; the mixture was stirred at 25 °C for 30 min–24 h in the absence of light. To check the progress of the reaction, a small aliquot of reaction mixture was removed and diluted with dichloromethane, and this solution was used for TLC spotting. The TLC was performed using an ethyl acetate/hexanes (40/60) solvent system as the mobile phase. After completion of the reaction, the reaction mixture was loaded onto a silica gel cartridge for product isolation by flash chromatography using a gradient of ethyl acetate/hexanes (0–40% ethyl acetate). The product desired, which was a

white foam, was obtained; the yields with corresponding times are given in Tables 2 and 3 in the main text.

4.3.1. 7'-Oxo-(8'-acetyl-4'-methyl-2'H-chromen-2'-one) 2,3,4,6-tetra-O-acetyl- β -D-galactopyranoside (3j)—¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, J = 8.9 Hz, 1H), 7.11 (d, J = 8.9 Hz, 1H), 6.23–6.21 (m, 1H), 5.53–5.47 (m, 2H), 5.10 (dd, J = 10.6, 3.4 Hz, 1H), 5.05 (d, J = 8.0 Hz, 1H), 4.28 (dd, J = 11.2, 6.8 Hz, 1H), 4.21–4.04 (m, 2H), 2.57 (s, 3H), 2.42 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 198.5, 170.3, 170.1, 170.0, 169.4, 159.4, 155.2, 151.6, 150.3, 126.09, 121.5, 116.1, 113.9, 111.9, 100.2, 71.4, 70.4, 67.7, 66.6, 61.3, 32.4, 20.7, 20.6, 20.5, 18.8. LC-MS (ESI-TOF): m/z [M + Na]⁺ calcd for C₂₆H₂₈O₁₃ + Na: 571.1422; found 571.1429.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
ORTEP projections of **1** and **2** showing 50% probability ellipsoids.

Scheme 1.

O-glycosidation of different sugar donors and phenolic acceptors using Ag-NHC complexes.

Scheme 2.

Ag-NHC-promoted glycosidation of **1** with different phenolic compounds in ACN at r.t.

Table 1

Ag-NHC-promoted O-glycosidation of **3** and **4** with phenolic acceptors using **1**.^[a]

Entry	Donor	Acceptor (ArOH)	Product	Yield (%)	α : β ratio
1	3	4-nitrophenol	3a	88	β only
2	3	4-cyanophenol	3b	80	β only
3	3	4-methoxyphenol	3c	78/65 ^b	β only
4	3	2-naphthol	3d	95	β only
5	3	phenol	3e	92	β only
6	3	5-hydroxyindole	3f	61	13:87
7	4	4-nitrophenol	4a	27/25 ^{b,c}	β only
8	4	4-cyanophenol	4b	16 ^c	β only
9	4	4-methoxyphenol	4c	27/25 ^{b,c}	β only
10	4	2-naphthol	4d	24 ^c	β only

^[a] Reactions were performed in CH₃CN (2 mL) in the presence of promoter (1 equiv.), acceptor (3 equiv.), and donor (1 equiv.) for 3 h.

^[b] % yield using **2**.

^[c] 3,4,6-Tri-O-acetyl-D-glucal was also obtained as elimination byproduct.

Table 2

Ag-NHC-promoted O-glycosidation of **5** with phenolic acceptors using **1** or **2**.

Entry	AgNHC	Acceptor (ArOH)	Time (h)	Product	Yield (%)	α : β ratio
1	1	4-nitrophenol	0.5	5a	65	8:92
2	1	4-cyanophenol	0.5	5b	66	12:88
3	1	4-methoxyphenol	0.5	5c	51	5:95
4	1	2-naphthol	0.5	5d	63	6:94
5	1	5-hydroxyindole	24	5e	48	6:94
6	2	4-nitrophenol	0.5	5a	75	9:91
7	2	4-cyanophenol	0.5	5b	67	17:83
8	2	4-methoxyphenol	0.5	5c	62	10:90
9	2	2-naphthol	0.5	5d	72	17:83

[a] Reactions were performed in CH₃CN (2 mL) in the presence of promoter (1 equiv.), acceptor (3 equiv.), and donor (1 equiv.).