Pergamon

Tetrahedron Letters 43 (2002) 7225–7228

TETRAHEDRON LETTERS

Iron(II)-promoted amidoglycosylation and amidochlorination of an allal C3–azidoformate

David G. Churchill[a,†] and Christian M. Rojas[b,*]

[a]*Department of Chemistry, Columbia University, New York, NY 10027, USA*
[b]*Department of Chemistry, Barnard College, 3009 Broadway, New York, NY 10027, USA*

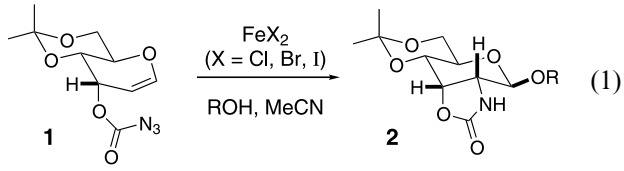
Received 25 June 2002; revised 6 August 2002; accepted 7 August 2002

Abstract—Iron(II) halides promoted intramolecular alkene amidation in a C3–allal azidoformate. In the presence of alcohols, one-pot β-glycosylation followed. Without added alcohol, amidochlorination occurred using $FeCl_2$, providing an anomeric mixture of glycosyl chlorides which could be used in subsequent silver ion-mediated couplings. A 2-amido glycosyl chloride with a nitrogen-bound iron center is proposed as the glycosylating agent for the in situ amidoglycosylations with $FeCl_2$.

Intramolecular reactions of glycal enol ether π-systems with hydroxyl-tethered groups can lead to stereoselective bond formation at C2 and subsequent glycosylation. In pursuing this route for the synthesis of 2-amido-2-deoxy allopyranosides, we have investigated photochemically generated acyl nitrenes[1] and metal-complexed nitrenoids[2] as the reactive nitrogen atom source.[3,4] Nitrogen-centered radicals[5] represent another option, as underscored in recent studies by Nicolaou involving single-electron oxidation of glycal *N*-aryl carbamates.[6]

Recently, Bach described *N*-centered radicals as intermediates in the iron(II)-mediated amidochlorination of allylic and propargylic azidoformates (2-alkenyloxy- and 2-alkynyloxy carbonyl azides).[7,8] These reactions were rendered catalytic in $FeCl_2$ by addition of trimethylsilyl chloride as the stoichiometric halide source.

In the case of our allal azidoformate **1**[1,9] (**CAUTION!** possible explosion hazard[10]), we anticipated that halide would be regenerated upon glycosylation, resulting in a one-pot approach to 2-amido-2-deoxy allopyranosides (Eq. (1)). We now report the feasibility of this tandem process, using a variety of Fe(II) sources and describe a direct NMR method for distinguishing anomeric stereochemistry in the oxazolidinone-protected 2-amino allopyranoside products **2**. Our approach proceeds directly to the N–H amino sugar oxazolidinones **2**,[11] making the route complementary to the Nicolaou process, which employs an oxidizable *N*-aryl auxiliary for radical generation.[6]



(1)

Table 1. Iron(II)-promoted amidoglycosylations of azidoformate **1**[a]

Entry	ROH (equiv.)	FeX_2 (equiv.)	**2** (% yield[b])	β:α[c]
1	EtOH (5.2)	$FeCl_2$ (0.4)	**2a** (34)	>10:1
2	EtOH (22)	$FeCl_2$ (0.3)	**2a** (55)	>10:1
3	MeOH (26)	$FeCl_2$ (0.3)	**2b** (52)	20:1
4	*i*-PrOH (25)	$FeCl_2$ (0.4)	**2c** (48)	>20:1
5	**4** (3.0)	$FeCl_2$ (0.4)	**2d** (24)	β only
6	**4** (3.0)	$FeBr_2$ (0.4)	**2d** (30)	4.6:1
7	**4** (3.0)	FeI_2 (0.4)	**2d** (38)	4.4:1
8	**4** (5.0)	FeI_2 (0.3)	**2d** (52)	4.8:1
9	*i*-PrOH (5.0)	FeI_2 (0.3)	**2c** (40)	7.0:1

[a] See Eq. (1). For a representative procedure, see Ref. 13.
[b] Combined yield of anomers after silica gel chromatography.
[c] Ratio based on isolated yields of separated anomers and/or ^1H NMR (300 MHz) analysis of the crude reaction mixture.

Keywords: amino sugars; glycosidation; iron and compounds; radicals and radical reactions.

* Corresponding author. Tel.: +1 212 854 5480; fax: +1 212 854 2310; e-mail: crojas@barnard.edu

† X-Ray structure determination.

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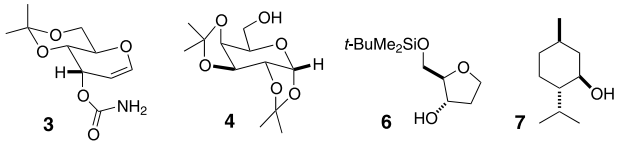
PII: S0040-4039(02)01658-1

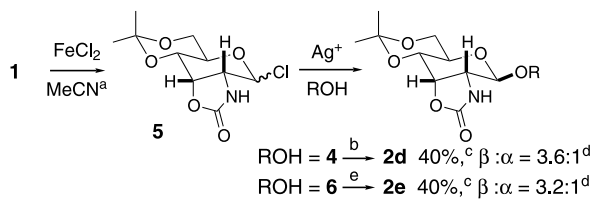
Treatment of an acetonitrile solution of azidoformate **1** with iron(II) chloride in the presence of ethanol (5 equiv.) produced immediate gas evolution and led to isolation of β-ethyl-2-amido allopyranoside **2a** in limited yield, but with high β-selectivity (Table 1, entry 1).[12] The optimal quantity of $FeCl_2$ was 0.3–0.4 equiv.; less iron(II) led to low conversion (less than 15% of **2a** after 90 h with 0.1 equiv. $FeCl_2$), while higher $FeCl_2$ levels increased the amount of urethane byproduct **3**.[7c] Including a larger excess of glycosyl acceptor increased yields, while maintaining excellent levels of anomeric stereocontrol (Table 1, entries 2–4).

With galactopyranose diacetonide **4** as the acceptor, we investigated alternative iron(II) sources (Table 1, entries 5–8). Amidoglycosylation was achieved using 0.4 equiv. of $FeCl_2$, $FeBr_2$, or FeI_2 and 3 equiv. of the saccharide acceptor. Yields increased in the series, but with erosion in β-selectivity. Increasing the amount of acceptor **4** (5 equiv.) and using FeI_2 provided the disaccharide product **2d** with useful yield and anomeric selectivity (Table 1, entry 8).

To reduce the quantity of glycosyl acceptor required, we investigated a two-stage amidohalogenation–glycosylation protocol (Scheme 1). Reaction of allal azidoformate **1** with $FeCl_2$ in the absence of alcohol provided crude glycosyl chlorides **5**,[12] having an anomeric composition dependent upon the reaction time (vide infra).



The crude anomeric chlorides **5** were used as donors in silver ion-promoted glycosylations[14] of sugar-derived acceptors **4** and **6**. The corresponding disaccharides were isolated in moderate overall yield for the two-step process. The advantage of proceeding via the isolated glycosyl chlorides was that smaller amounts of glycosyl acceptor (1.5–2.0 equiv.) could be employed. An attempt to extend this scheme, using alcohol-free reaction of **1** with $FeBr_2$, led only to decomposition upon attempted isolation of the crude bromides.



Scheme 1. *Reagents and conditions*: (a) $FeCl_2$ (0.6–0.9 equiv.), 0→23°C, 3 h. (b) AgOTf (1.5 equiv.), **4** (1.5 equiv.), 2,4,6-collidine (3 equiv.), 4 Å molecular sieves, −78→23°C, 17 h. (c) Isolated yield for two steps after silica gel chromatography. (d) Ratio based on isolated yields of separated anomers. (e) $AgClO_4$ (2.6 equiv.), **6** (2.0 equiv.), 2,4,6-collidine (2.5 equiv.), 4 Å molecular sieves, −78→23°C, 16 h.

Notably, β-selectivity in the Ag-mediated reactions was considerably lower than for the in situ $FeCl_2$ amidoglycosylations. Treatment with silver ion likely provided ionization of the glycosyl chlorides, so that the 3–4:1 β-selectivity in the subsequent anomeric bond formation was a measure of facial bias in the oxocarbenium intermediate. In accord with recent studies by Kerns on oxazolidinone-protected 2-amino-2-deoxy glucopyranose systems[15] the carbamate nitrogen does not provide significant neighboring group participation.

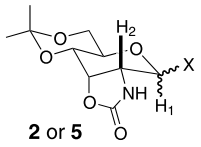
In products **2**, the oxazolidinone distorts the pyranose ring from the chair conformation, leading to intermediate values for the three-bond ^1H NMR coupling constant J_{12}, with no clear distinction between the anomers (Table 2). Chemical conversion to oxazolidinone-opened derivatives allowed assignment of anomeric stereochemistry in several instances,[1] and recent work led to accumulation of additional examples of α/β pairs **2e**, **2f**, and **9**.[2] Furthermore, we assigned the α- and β-isomers of glycosyl acetates **2g** on the basis of NOE measurements.[2] In the current study, we isolated and characterized the previously unavailable α-diastereomers of **2a**, **2b**, and **2c**.

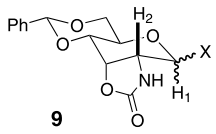
In all cases, the β-isomers had the H1 doublet well upfield of the corresponding resonance for the α-anomers in the ^1H NMR spectra obtained in $CDCl_3$ solution (Table 2). In the case of α-isopropyl-2-amido allopyranoside **2c**-α, unambiguous stereoassignment was obtained upon single-crystal X-ray analysis.[9] On the basis of δ H1 comparison, we assigned the anomeric stereochemistries in glycosyl chlorides **5**. Some further distortion of the β-form was evident from the low J_{12} value for **5**-β (similar to the β-acetoxy case **2g**-β), but the distinguishing $\Delta\delta$ H1 remained clear.[16]

Bach has provided compelling evidence that intramolecular amidochlorination of allylic and propargylic azidoformates with $FeCl_2$ proceeds via a radical process and without aziridine intermediates.[7c] By analogy to Bach's results, a reasonable mechanism for amidoglycosylation of azidoformate **1** begins with $FeCl_2$-promoted extrusion of N_2, leading to the Fe-complexed, nitrogen-centered radical **10** which undergoes 5-*exo* cyclization to **11** (Scheme 2). Very rapid[7c] internal chlorine atom transfer would provide **12**, an intermediate that may serve as a β-specific glycosylating species (**12**→**2**), with the *N*-bound iron center acting as a Lewis-acidic neighboring group. Conversion to the *O*-chelated tautomer **13** would deactivate the complex for glycosylation, while capture of **12** by external chloride would provide the β-glycosyl chloride **5**-β (not shown).

A variety of control experiments were consistent with the glycosylation part of this mechanistic scheme. In the absence of alcohol glycosyl acceptor, reaction of **1** with $FeCl_2$ at ice-bath temperature for 60 min then at 23°C for 40 min provided predominantly the α-chloride **5**-α (α:β = 2.6:1.0), as determined by ^1H NMR (300 MHz) analysis of the crude reaction mixture. When the reaction time was extended (0°C for 60 min then 23°C for 100 min), the β-chloride **5**-β became the major product

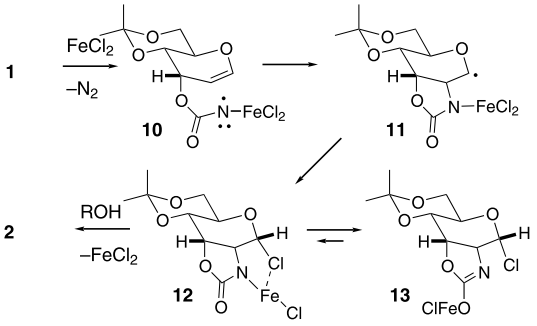
Table 2. ^{1}H NMR data (300 MHz, $CDCl_3$, 23°C) for stereoassignments





Compd	X	δ H1	$\Delta\delta$ H1	J_{12} (Hz)	Assignment basis[a]
2a-α	α-OEt	4.84		5.0	
2a-β	β-OEt	4.55	0.29	4.9	A
2b-α	α-OMe	4.72		5.0	
2b-β	β-OMe	4.45	0.27	5.1	A
2c-α	α-O*i*-Pr	4.93		5.0	
2c-β	β-O*i*-Pr	4.60	0.33	5.1	A, B
2d-α	α-OR_1[b]	4.85		5.2	
2d-β	β-OR_1[b]	4.71	0.14	6.3	A, C
2e-α	α-OR_2[b]	4.93		4.9	
2e-β	β-OR_2[b]	4.61	0.32	5.4	A
2f-α	α-OR_3[b]	4.90		4.9	
2f-β	β-OR_3[b]	4.61	0.29	5.8	D
2g-α	α-OAc	6.14		5.0	
2g-β	β-OAc	5.86	0.28	3.4	E
5-α	α-Cl	6.25		5.0	
5-β	β-Cl	5.85	0.40	1.9	D
9-α	α-OR_3[b]	4.94		4.9	
9-β	β-OR_3[b]	4.70	0.24	5.5	D

[a] A: Chemical conversion of the β-anomer (see Ref. 1). B: X-ray structure. C: Chemical conversion of the α-anomer (see Ref. 1). D: Assigned by analogy. E: NOE studies on both anomers (see Ref. 2).
[b] R_1OH = **4**, R_2OH = **6**, R_3OH = **7**.



Scheme 2. Mechanistic proposal for $FeCl_2$-induced amidoglycosylation of C3–allal azidoformate **1**.

(α:β = 1.0:1.8). The α- and β-chlorides were separated by chromatography on silica gel. Resubmission of the α-chloride to the reaction conditions led to <5% conversion to the β-chloride and some hydrolysis (10%) after aqueous workup. Separate experiments showed that neither the α- nor β-chloride provided any glycosylation of 2-propanol in the presence of $FeCl_2$ in acetonitrile.

In accord with Scheme 2, these results supported (1) initial α-face chlorine delivery and (2) that a transient reactive intermediate other than a discreet glycosyl chloride was responsible for β-selective glycosylation (or β-chloride formation in the absence of glycosyl acceptor). In Scheme 2 this reactive intermediate is the *N*-bound iron species **12**.[17] Our control experiments indicate that **12** is not regenerated from glycosyl chlorides **5** upon treatment with $FeCl_2$, possibly because of a preference for *O*- versus *N*-chelation of the oxazolidinone to iron.[7c] In situ glycosylations using $FeBr_2$ and FeI_2 would proceed via the corresponding glycosyl bromide[18] or iodide,[19] and the greater anomeric lability of these intermediates would explain the lowered anomeric selectivity in those cases (Table 1, entries 6–9).

In summary, iron(II) halides promote amidoglycosylation reactions of allal azidoformate **1**, providing 2-amido-2-deoxy allopyranosides with excellent β-anomeric stereoselectivity in the $FeCl_2$ cases. The reaction can be carried out as an in situ process or, with $FeCl_2$, via isolation of intermediate 2-amido glycosyl chlorides. Anomeric stereochemistry in the allopyranoside products is readily distinguished by comparison of δ H1 values. The glycosylating agent for the in situ, $FeCl_2$-promoted reactions may be a 2-amido glycosyl chloride with a nitrogen-bound iron (**12**), which loses its glycosylating ability upon N→O migration of the iron center.

Acknowledgements

We are grateful to the National Institutes of Health, Research Corporation, and the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research. We thank Dr. Brian M. Bridgewater for determination of the X-ray crystal structure of azidoformate **1**, Professor Gerard

Parkin (Columbia University) for use of the X-ray facility, and Professor Linda Doerrer (Barnard College) and her group for use of their glove box. The Barnard College NMR facility was funded in part by the National Science Foundation.

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9. Crystallographic data (excluding structure factors) for azidoformate **1** and α-isopropyl-2-amido-2-deoxy allopyranoside **2c**-α have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 185294 (**1**) and 185295 (**2c**-α). These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).
10. **CAUTION!** Azidoformates are potentially explosive. We have encountered no difficulties with the preparation and use of azidoformate **1**, but appropriate safety precautions are strongly recommended. For instance, since metal salts catalyze their decomposition, it may be wise to avoid using metal spatulas to handle larger quantities of azidoformates. Detonation of a low molecular weight azidoformate during distillation has been reported: Feyen, P. *Angew. Chem., Int. Ed.* **1977**, *16*, 115.
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12. Amidoglycosylation products were characterized by ^1H and ^{13}C NMR (including DEPT), IR, and HRMS; glycosyl chlorides were characterized by ^1H NMR, IR, and HRMS.
13. Representative procedure for iron(II)-promoted amidoglycosylation of **1**: A 0°C solution of azidoformate **1** (20.3 mg, 0.080 mmol, 1.0 equiv.) and EtOH (100 μL, 1.78 mmol, 22 equiv.) in MeCN (2.0 mL) was degassed with a gentle argon stream during 10 min, then added to $FeCl_2$ (3.2 mg, 0.025 mmol, 0.3 equiv.) at 0°C. The mixture was stirred at 0°C during 1 h (gas evolution) then at 23°C for 17 h. The reaction mixture was poured into satd aq. $NaHCO_3$ (12 mL) and extracted twice with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. ^1H NMR (300 MHz) analysis of the crude material indicated a >10:1 β:α ratio of amidoglycosylation products **2a**. Chromatography (60% EtOAc/hexanes→100% EtOAc gradient, 10 mL SiO_2) provided β-ethyl-2-amido allopyranoside **2a**-β (12.0 mg, 55%) as a glassy solid.
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16. $^1J_{C1-H}$ values were not promising for assigning anomeric configuration. For example, we measured essentially indistinguishable $^1J_{C1-H}$ values, 174 and 175 Hz, for **2g**-β and **2g**-α, respectively.
17. A C1 oxocarbenium intermediate might form via oxidation of the anomeric radical **11**, but glycosylation β-selectivities of the carbocation intermediate would likely be closer to those in the silver-mediated reactions (3–4:1) rather than the higher levels (>10:1) observed in the $FeCl_2$-promoted cases.
18. For examples of 2-azido- and 2-amido-glycosyl bromides as donors, see: (a) Marcaurelle, L. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 1587–1595; (b) Yeung, B. K. S.; Adamski-Werner, S. L.; Bernard, J. B.; Poulenat, G.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 3135–3138.
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