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Stereoselective synthesis of 2-amino-2-deoxysugars: *N*-alkyl-D-allosamines †

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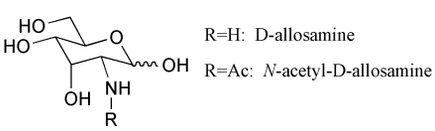
Stereoselective synthesis of *N*-alkyl-D-allosamines, designed for the preparation of *N*-alkyl derivatives of allosamidin (a chitinase inhibitor), is achieved by a 'carbonyl group transfer' reaction followed by stereoselective reduction and this method represents the first example of *N*-alkyl-D-allosamines synthesized from a 2-oxosugar.

Although 2-amino-2-deoxysugars are key constituents of a variety of naturally occurring polysaccharides,[1] available methods for their preparation are few in number. Carbohydrate glycals were used as efficient starting materials by the pioneers[2–5] for preparation of the corresponding 2-amino-2-deoxysugars, which have found widespread use in the construction of complex amine-containing polysaccharides. Among these 2-amino-2-deoxysugars, *N*-acetylallosamine is the repeat unit in the sugar portion of allosamidin,[4,6] which is an interesting chitinase inhibitor. Preparation of *N*-alkyl-D-allosamines, in order to synthesize *N*-alkyl derivatives of allosamidin, accordingly attracted our intense interest. In previous work, neither method involved nucleophilic addition of an amine to a 2-oxosugar for synthesis of the corresponding D-allosamine, because oxosugars are difficult to synthesize selectively and are unstable, especially in basic solution as we reported before.[7–10] Herein, we report a new, convenient method for synthesis of *N*-alkyl-D-allosamines as shown in Scheme 1. This methodology offers two attractive and important features: (1) the easily available 2-oxoglucopyranoside **1** is used for the first time as a reagent for synthesis of *N*-alkyl-D-allosamines and (2) both steps for this reaction bear very high stereoselectivity suitable for alkylamines. In addition, it first employs a 'carbonyl group transfer' reaction caused by nucleophilic addition of alkylamines to 2-oxoglucopyranoside.



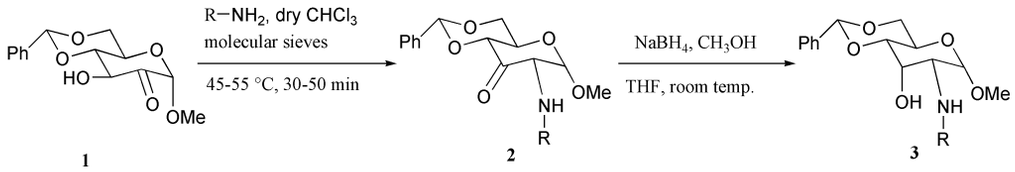
† Electronic supplementary information (ESI) available: spectroscopic data for **2a**–**2h** and **3a**–**3h**. See http://www.rsc.org/suppdata/ob/b3/b302587j/

Our synthesis began with **1**[9] reacting with 1 equiv. cyclopropylamine. Interestingly, carbonyl group transferred product *N*-cyclopropyl-3-keto-D-allosamine **2a** was formed, the possible pathway for which was nucleophilic addition of cyclopropylamine to **1** followed by dehydration and then enolic intermediate rearrangement. Reduction of **2a** with $NaBH_4$ was performed at room temperature to give *exo* attack product **3a** in good yield, whereas the *endo* attack product was not observed due to the unfavourable hindrance. Both **2a** and **3a** were isolated with solely *syn* 1,2 and *syn* 2,3 stereochemistry, respectively, as measured by ^{1}H NMR spectroscopy.‡ On the basis of 2D NMR spectra, the two protons of **2a** which appeared at δ 5.10 and 3.75 as two doublets with a coupling constant of 3.6 Hz were assigned to H-1 and H-2. In **3a**, the proton at δ 4.76 as a doublet and another one at 2.94 as a triplet were ascribed to H-1 and H-2, respectively, indicating that the coupling constant between H-2 and H-1 is equal to that between H-2 and H-3 (J = 3.2 Hz). The stereochemistries were definitely confirmed by spectroscopic data as shown in Scheme 1.

Our previous studies indicated that the carbonyl group in 2-oxoglucopyranoside **1** is extremely active compared with 3-, 4-, and 5-oxoglucoside, accordingly existing fully in the hydrate form.[8–13] The operation without water was therefore very necessary for nucleophilic addition of cyclopropylamine to **1**. We examined this reaction in detail. With the increase of alkalinity in solution, the yield decreased. Dry $CHCl_3$ as a solvent is superior to the others and the optimum temperature is 50 °C (Table 1, Entry 1). Under these conditions, the reaction was readily accomplished.

To explore the generality of this method, the experiments were performed with other alkylamines. The reactions were identical with that for cyclopropylamine and the optimum results are depicted in Table 1 (Entries 2–8, respectively). All the new compounds were characterized by ^{1}H NMR, ^{13}C NMR, 2D NMR, MS, and IR spectra.†

In conclusion, protected forms of various *N*-alkyl derivatives of naturally occurring 2-amino-2-deoxysugars, D-allosamines, have been readily synthesized from 2-oxoglucopyranoside. These derivatives are ideal building blocks for synthesis of various *N*-alkyl derivatives of allosamidin with further elaboration. This work represents the first example of a 2-oxosugar reacting



2a, 3a R= 
2b, 3b R= —$CH_2CH_2CH_3$
2c, 3c R= —$CH_2CH{=}CH_2$
2d, 3d R= —$CH_2CH_2CH_2CH_3$
2e, 3e R= —$CH_2CH(CH_3)_2$
2f, 3f R= —$CH_2CH_2CH_2CH_2CH_3$
2g, 3g R= —$CH_2CH_2CH(CH_3)_2$
2h, 3h R= —$CH_2CH_2CH_2CH_2CH_2CH_3$

Scheme 1 Stereoselective synthesis of *N*-alkyl-3-keto-D-allosamines **2** and *N*-alkyl-D-allosamines **3**.

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Table 1 Synthesis of *N*-alkyl-3-keto-D-allosamines **2** and *N*-alkyl-D-allosamines **3** from 2-oxoglucopyranoside[a]

	Synthesis of **2** by the reaction of alkylamines with **1**			Stereoselective reduction of **2** with $NaBH_4$ at room temperature (25–30 °C)	
Entry	Temp./°C	Time/min	Yield (%)	Time/h	Yield (%)
1	50	40	**2a** (65)	1.5	**3a** (95)
2	50	30	**2b** (63)	1.5	**3b** (93)
3	50	50	**2c** (60)	2.0	**3c** (90)
4	60	30	**2d** (60)	2.0	**3d** (90)
5	60	40	**2e** (55)	2.5	**3e** (87)
6	55	80	**2f** (57)	2.5	**3f** (90)
7	55	80	**2g** (50)	3.0	**3g** (88)
8	60	90	**2h** (52)	2.5	**3h** (92)

[a] General procedure: A mixture of **1** (0.40 g, 1.43 mmol), 4 Å molecular sieves (4.0 g), dry NH_4Cl (catalytic amount) and dry $CHCl_3$ (16 cm^3) was heated to 50–60 °C with stirring, to which alkylamine (1 equiv.) in 2 cm^3 of dry $CHCl_3$ was added dropwise. The reaction was monitored by TLC. Then the molecular sieve was removed and the solution was washed with saturated NaCl, dried over Na_2SO_4 and evaporated. The residue was crystallized from ethanol to afford **2** as colourless needles (50–65% yields). **2** (0.2 g) was dissolved in anhydrous THF (10 cm^3), then anhydrous CH_3OH (10 cm^3) and $NaBH_4$ (1 equiv.) were added. The mixture was stirred at rt (25–30 °C). When **2** disappeared, the reaction mixture was made neutral with acetic acid, then evaporated. The residue was dissolved in water, extracted with EtOAc, dried over Na_2SO_4 and evaporated. The residue was crystallized from ethanol to afford **3** as colourless needles (87–95% yields).

with amines for preparation of D-allosamine derivatives. The reaction sequence involving 'carbonyl group transfer' and reduction gives extremely high stereoselectivity. This method is a simple, convenient and direct pathway to *N*-alkyl-D-allosamines although the yield for the first step is somewhat low.

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Notes and references

‡ **2a:** mp 161 °C (dec) (Found: C, 63.96; H, 6.65; N, 4.41. $C_{17}H_{21}NO_5$ requires C, 63.94; H, 6.63; N, 4.39%); ν_{max} (KBr)/cm^{-1} 3336 (NH), 1738 (C=O); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.30–0.55 (4 H, m, cyclopropyl), 2.35–2.40 (1 H, m, cyclopropyl), 3.40 (3 H, s, OCH_3), 3.75 (1 H, d, *J* 3.6, 2-H), 3.95 (1 H, t, *J* 10.0, 6-H), 4.06 (1 H, dt, *J* 4.8 and 10.0, 5-H), 4.32 (1 H, d, *J* 10.0, 4-H), 4.41 (1 H, dd, *J* 4.8 and 10.0, 6′-H), 5.10 (1 H, d, *J* 3.6, 1-H), 5.59 (1 H, s, PhC*H*O_2), 7.37–7.39 (3 H, m, Ar*H*), 7.51–7.54 (2 H, m, Ar*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 6.4, 6.9, 28.8 (cyclopropyl), 55.4 (OCH_3), 66.1 (C-5), 67.9 (C-2), 69.6 (C-6), 82.9 (C-4), 101.9 (Ph*C*HO_2), 104.1 (C-1), 126.4, 128.3, 129.3, 136.5 (Ar), 199.3 (C=O); *m*/*z* (FAB) 320.1491 (M + 1. $C_{17}H_{22}NO_5$ requires 320.1498). **3a:** mp 159–161 °C (Found: C, 63.52; H, 7.18; N, 4.34. $C_{17}H_{23}NO_5$ requires C, 63.54; H, 7.21; N, 4.36%); ν_{max} (KBr)/cm^{-1} 3312 (NH), 3194 (OH); δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.34–0.37, 0.45–0.50, 2.26–2.31 (5 H, 3 × m, cyclopropyl), 2.94 (1 H, t, *J* 3.2, 2-H), 3.40 (3 H, s, OCH_3), 3.57 (1 H, dd, *J* 2.8 and 10.0, 4-H), 3.77 (1 H, t, *J* 10.0, 6-H), 4.12 (1 H, dt, *J* 5.2 and 10.0, 5-H), 4.37 (1 H, dd, *J* 5.2 and 10.0, 6′-H), 4.39 (1 H, br s, 3-H), 4.76 (1 H, d, *J* 3.2, 1-H), 5.60 (1 H, s, PhC*H*O_2), 7.34–7.37 (3 H, m, Ar*H*), 7.50–7.52 (2 H, m, Ar*H*); δ_C (100 MHz; $CDCl_3$; Me_4Si) 6.0, 6.7, 27.0 (cyclopropyl), 56.0 (C-2), 57.9 (OCH_3), 58.2 (C-5), 67.0 (C-3), 69.4 (C-6), 79.4 (C-4), 100.8 (C-1), 102.0 (Ph*C*HO_2), 126.3, 128.3, 129.2, 137.2 (Ar); *m*/*z* (FAB) 322.1654 (M + 1. $C_{17}H_{24}NO_5$ requires 322.1665).

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