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Amberlite IR-120 catalysed efficient synthesis of glycosyl enamines and their application

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Abstract—β-Keto esters and acetyl acetone on condensation with glycosylated amino esters in the presence of IR-120 resin resulted in high yields of glycosyl enamino esters or ketones. The latter on cyclisation with NaH in toluene at reflux gave 6-glycosyl-5,6-dihydro-1*H*-pyridin-4-ones in fair to good yields.

Enamines are interesting building blocks for the synthesis of a large number of heterocyclic compounds of biological significance.[1,2] Enamines may be regarded as the nitrogen equivalents of enols and can be used both in nucleophilic addition and electrophilic substitution reactions.[3,4] The synthesis of enamines generally involves the reactions of amines[5–7] and carbonyl compounds in the presence of an acid catalyst with simultaneous removal of water.[8] Glycosyl enamines have recently been used as intermediates in the synthesis of *C*-nucleosides[9] and glycosyl pyrazoles.[10] Encouraged by this work and also our current interest in the synthesis of biologically active *C*-nucleosides from amino sugars,[11,12] we sought an efficient method to synthesize dihydropyridone *C*-nucleosides. Earlier methods of synthesis involve the use of acetic acid or hydrochloric acid for enamine synthesis necessitating the neutralisation and workup of the reaction mixture. Our method involves the use of Amberlite IR-120 resin as an acidic reagent with the water formed during reaction being removed azeotropically. This method is very simple compared to earlier reported methods as none of the ions pass into the solution and thus no neutralisation is required; the desired compounds were obtained in quantitative yield. Moreover, this method is compatible with isopropylidene protecting groups.

To the best of our knowledge this is the first report of glycosyl enamine formation where the reaction is catalysed by Amberlite IR-120 resin. The method is very simple as the resin can be filtered from the reaction mixture and simple evaporation of the solvent gives the desired enamine. The latter could be transformed into dihydropyridones by treatment with NaH.

Thus, condensation of glycosyl β-amino ester **1a**, prepared by us earlier,[13,14] with ethyl acetoacetate in the presence of IR-120 resin in toluene at reflux with simultaneous removal of water azeotropically gave the enamino ester **2a** (Table 1, entry 1) in good yield.[15a] Formation of the enamino ester was confirmed by its ^{1}H NMR spectrum where a singlet at δ 4.43 for N–C=C*H* and a signal at δ 84.4 in the ^{13}C NMR for N–*C*=CH confirmed its formation. That compound **2a** is of the *Z* configuration was evident from the chemical shift (δ >8.0) of N*H* and the strong NOE observed between the C=C*H* and C=CC*H*$_3$ protons. Similarly, reaction of **1a** and **1b**, with ethyl acetoacetate, ethyl butyryl acetate and acetyl acetone separately resulted in the formation of the corresponding enamino ester or enamino ketones (**2b**, **2c**, **2d**, **2e** and **2f**) in good to quantitative yields (Table 1, entries 2–6). Reaction of galactopyranosyl amino ester **1c** with ethyl acetoacetate, ethyl butyryl acetate and acetyl acetone separately, was also carried out successfully to give compounds **2g**, **2h** and **2i** in very good yields (entries 7–9).

To demonstrate the synthetic utility of the enamino esters, glycosyl dihydropyridones **3a**–**f** (entries 10–15) were prepared by cyclisation of enamino esters **2a**, **2b**, **2d**, **2e**, **2g**, **2h** (see entries 1, 2, 4, 5, 7 and 8) in toluene

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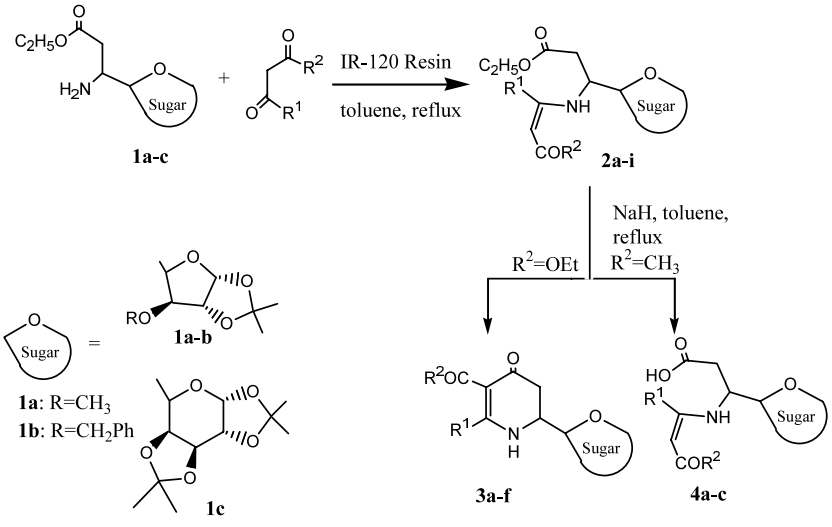
Table 1. Synthesis of glycosyl enamines **2a–i** and glycosyl dihydropyridones **3a–f** and the acids **4a–c**[15,16]

Entry	Compd. no	R	R^1	R^2	Yield (%)
1	**2a**	CH_3	CH_3	OC_2H_5	92
2	**2b**	CH_3	$CH_2CH_2CH_3$	OC_2H_5	65
3	**2c**	CH_3	CH_3	CH_3	95
4	**2d**	CH_2Ph	CH_3	OC_2H_5	95
5	**2e**	CH_2Ph	$CH_2CH_2CH_3$	OC_2H_5	67
6	**2f**	CH_2Ph	CH_3	CH_3	96
7	**2g**	–	CH_3	OC_2H_5	92
8	**2h**	–	$CH_2CH_2CH_3$	OC_2H_5	62
9	**2i**	–	CH_3	CH_3	93
10	**3a**	CH_3	CH_3	OC_2H_5	65
11	**3b**	CH_3	$CH_2CH_2CH_3$	OC_2H_5	62
12	**3c**	CH_2Ph	CH_3	OC_2H_5	65
13	**3d**	CH_2Ph	$CH_2CH_2CH_3$	OC_2H_5	67
14	**3e**	–	CH_3	OC_2H_5	65
15	**3f**	–	$CH_2CH_2CH_3$	OC_2H_5	66
16	**4a**	CH_3	CH_3	CH_3	90
17	**4b**	CH_2Ph	CH_3	CH_3	85
18	**4c**	–	CH_3	CH_3	88

at reflux in the presence of sodium hydride.[15b] However, the enaminones **2c**, **2f** and **2i** (entries 3, 6 and 9) with *N*-butenoyl substituents on reaction with sodium hydride in refluxing toluene did not afford the expected cyclised products, but instead resulted in the formation of the corresponding glycosylated β-amino acids (**4a–c**) on prolonged heating (entries 16–18) (Scheme 1).

The mechanism proposed for the above reaction involves protonation of the β-keto oxygen then nucleophilic attack by the amine to the same β-keto carbonyl carbon resulting in a tetrahedral intermediate. The latter would undergo dehydration and yield the enamine (Fig. 1). Further, intramolecular nucleophilic attack by the anion, generated with sodium hydride, to the carbonyl carbon of the glycosyl ester and subsequent removal of ethanol would result in formation of the dihydropyridone.

In conclusion we have developed a new, simple and efficient method for the synthesis of glycosyl enamines, which can be easily converted into dihydropyridones. These compounds with a chiral handle may serve as scaffolds for the stereoselective synthesis of diverse compounds of biological significance.



Scheme 1.

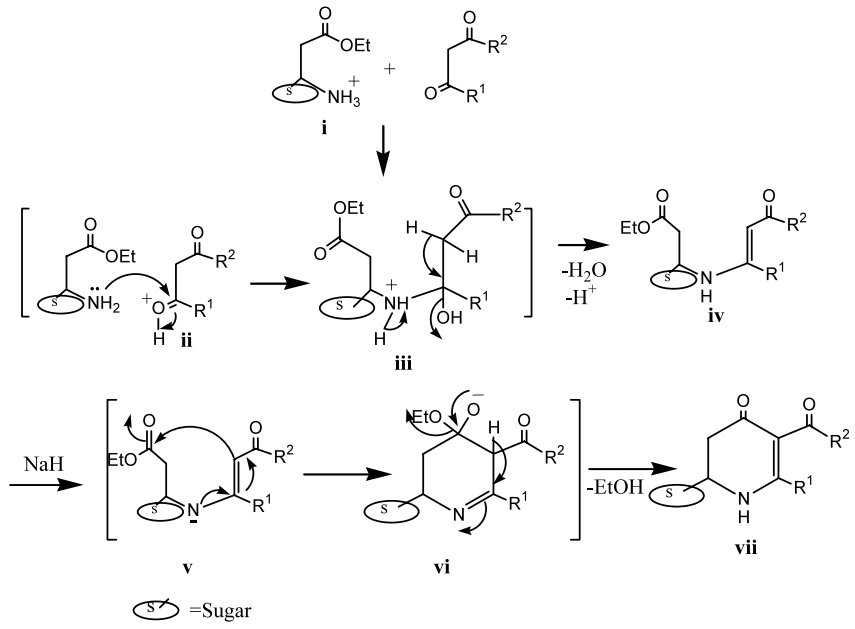


Figure 1. Proposed reaction mechanism.

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15. (a) General procedure for the synthesis of compounds (**2a**–**i**): A mixture of compound **1a** (1.4 g, 4.84 mmol), ethyl acetoacetate (0.61 ml, 4.84 mmol) and Amberlite IR-120 resin (1.4 g) was refluxed in anhydrous toluene (30 ml) for 3 h. The water formed in the reaction was removed using a Dean Stark apparatus. The resin was filtered off and the solvent was evaporated and the residue obtained was chromatographed on SiO_2 gel to give compound **2a**. Compounds **2b**–**i** were prepared in a similar manner; (b) General procedure for the synthesis of compounds **3a**–**f** and **4a**–**c**: A suspension of NaH (0.15 g, 6.27 mmol) in anhydrous toluene (10 ml) was stirred at 30°C for 10 min. A solution of compound **2e** (0.5 g, 2.09 mmol) in toluene (2 ml) was added dropwise over a period of 5 min and stirring was continued for 4 h at reflux. The reaction mixture was filtered and the solvent was evaporated under reduced pressure to give a crude mass, which was extracted with ethyl acetate and the extract washed with water. The organic layer was dried, evaporated and the residue chromatographed on SiO_2 gel to give compound **3d**. Compounds **3a**, **3b**, **3c**, **3e**, **3f** and **4a**–**c** were prepared analogously.
16. Physical data of selected compounds: **2a**: Colourless oil, yield 92%; $[\alpha_D]^{20} = -43.5$ (*c* 0.14, $CHCl_3$), FAB MS $m/z =$ 424 $[M+Na]^+$, IR ν_{max} cm^{-1} 1608 (NC=C). ^1H NMR (200 MHz, $CDCl_3$) δ 8.71 (bs, 1H, NH); 5.80 and 5.82 (each d, $J = 3.9$ Hz, each 1H, diastereomeric H-1), 4.67 and 4.65 (each d, $J = 3.9$ Hz, each 1H, diastereoisomeric H-2), 4.43 (s, 1H, –N–C=C*H*), 4.30 (m, 1H, H-4), 4.12 (two q merged with each other, $J = 7.2$ Hz, 4H, $2\times OCH_2CH_3$), 3.69 (d, $J = 3.0$ Hz, 1H, H-3), 3.43 and 3.36 (each s, each

3H, diastereoisomeric OCH_3), 2.69 and 2.64 (each m, each 1H, diastereoisomeric H-5), 2.57 and 2.50 (each m, each 2H, diastereoisomeric H-6), 1.91 and 1.88 (each s, 3H, $CH_3C{=}C$), 1.48, 1.31 (each s, 6H, $C(CH_3)_2$), 1.23 (two *t* merged with each other, $J=7.2$ Hz, 6H, 2× OCH_2CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ 171.1, 170.4 (*C*OOEt), 168.1 (N–*C*=C), 111.9 ($C(CH_3)_2$), 105 (C-1), 84.4 (N–C=*CH*), 83.6, 83.2, 81.7, 81.1 (C-2, C-3, C-4), 60.8, 58.4 (OCH_2CH_3), 57.5 (OCH_3), 49.3 (C-5), 37.3 ($COCH_2$), 26.8, 26.3 ($C(CH_3)_2$), 19.8 ($CH_3C{=}C$), 14.7, 14.2 (2×OCH_2CH_3). **2g**: Colourless oil, Yield 92%; $[\alpha_D]=-8.0$ (*c*, 0.10, $CHCl_3$); FAB MS $m/z=458$ $[M+H]^+$, IR ν_{max} cm^{-1} 1606 (N–C=C); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.71 (bs, 1H, NH); 5.51 and 5.48 (each d, $J=4.8$ Hz, each 1H, diastereomeric *H*-1), 4.58 (dd, $J=7.8$ and 1.8 Hz, 1H, diastereomeric *H*-3), 4.43 and 4.41 (each s, 1H, NC=C*H*), 4.29 (m, 2H, H-2 and H-4), 4.20–4.01 (m, 5H, 2×OCH_2CH_3 and H-6), 3.74 (d, $J=8.4$ Hz, 1H, H-5), 2.79 and 2.60 (each m, each 2H, H-7), 2.03 and 1.96 (each s, each 3H, $C{=}CCH_3$), 1.50, 1.49, 1.43 and 1.42 (each s, 6H, diastereomeric $C(CH_3)_2$), 1.31 and 1.29 (each s, 6H, diastereomeric $C(CH_3)_2$), 1.21 (two t, merged with each other, 6H, 2×OCH_2CH_3). ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.71 and 170.59 (*C*OOEt), 162.0 (N*C*=C), 110.03 and 109.15 (2×*C* $(CH_3)_2$), 96.86 (C-1), 83.72 (NC=*C*H), 71.65 (C-3), 71.41 (C-2), 70.92 (C-4), 69.79 (C-5), 61.13 and 58.58 (OCH_2), 50.79 (C-6), 37.46 (C-7), 26.43, 26.26, 25.35 and 24.90 (2×$(CH_3)_2C$), 20.10 ($CH_3C{=}C$), 15.04 and 14.53 (CH_3). **3d**: Colourless oil, Yield 67%; FAB MS $m/z=482$ $[M+Na]^+$, IR ν_{max} cm^{-1} 1547 (N–C=C), ^1H NMR (200 MHz, $CDCl_3$) δ 7.31 (m, 5H, Ar-*H*), 5.96 (d, $J=3.6$ Hz, 1H, *H*-1), 5.90 (bs, 1H, NH), 4.69 and 4.48 (each d, 2H, $J=11.7$ Hz, OCH_2Ph), 4.68 (d, $J=3.6$ Hz, 1H, H-2), 4.25 (q, $J=7.2$ Hz, 2H, OCH_2CH_3), 4.19 (dd, $J=6.0$ Hz and 9.6 Hz, 1H, H-4), 3.99 (m, 1H, H-5), 3.93 (d, $J=3.3$ Hz, 1H, H-3), 2.40 (m, 6H, H-6, and $CH_2CH_2CH_3$), 1.57 and 1.31 (each s, 6H, $C(CH_3)_2$), 1.28 (t, $J=7.8$ Hz, 3H, OCH_2CH_3), 0.88 (t, $J=7.5$ Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (200 MHz, $CDCl_3$) δ 186.6 ($COCH_2$), 173.0 (*C*OOEt), 168.1 (N*C*=C), 136.8 and 135.7 (Ar-C), 128.1, 127.8, 127.3 (Ar-*C*H), 111.6, 110.6 ($C(CH_3)_2$), 104.7, 104.3 (C-1), 81.5 (NC=*C*H), 81.2, 80.2, 77.2 (C-2, C-3, C-4), 71.5 (OCH_2Ph), 59.4 (OCH_2CH_3), 53.3 ($C{=}CH_2CH_2$), 50.8 (C-5), 38.9, 37.3 ($C{=}CCH_2CH_2CH_3$), 32.3 (C-6), 26.5, 25.9 (($CH_3)_2C$), 14.1, 13.7 (CH_3×2). **3e**: Colourless oil, Yield 65%; FAB MS $m/z=412$ $[M+H]^+$, IR ν_{max} cm^{-1} 1548 (N–C=C), ^1H NMR (200 MHz, $CDCl_3$) δ: 5.55 (d, $J=4.9$ Hz, 1H, diastereomeric H-1), 4.64 and 4.60 (dd, $J=7.9$ and 2.4 Hz, 1H, H-3), 4.37 and 4.35 (dd, $J=4.9$ and 2.4 Hz, 1H, H-2), 4.29–4.19 (m, 3H, H-4 and OCH_2CH_3), 3.89 (m, 1H, H-6), 3.75 (d, $J=7.6$ Hz, 1H, H-5), 2.69 and 2.52 (each m, each 1H, H-7a and H-7b), 2.29 (s, 3H, $C{=}CCH_3$), 1.50 and 1.43 (each s, 6H, $C(CH_3)_2$), 1.32 (s, 6H, $C(CH_3)$), 1.23 (t, 3H, $J=7.0$ Hz, diastereomeric OCH_2CH_3). ^{13}C NMR (200 MHz, $CDCl_3$) δ 187.63 (C=O), 167.03 ($COOC_2H_5$), 166.03 (N*C*=C), 110.21 and 109.56 (2×$C(CH_3)_2$), 104.32 ($C{=}CCOOC_2H_5$), 96.66 (C-1), 71.21 (C-3), 70.90 (C-2), 68.72 (C-4), 65.87 (C-5), 60.47 (OCH_2CH_3), 52.67 and 51.70 (C-6), 37.99 and 37.44 (C-7), 26.38, 26.19, 25.26 and 24.49 (2×$C(CH_3)_2$), 22.19 and 22.10 ($C{=}CCH_3$), 14.75 (OCH_2CH_3).