Pergamon

Tetrahedron Letters, Vol. 36, No. 52, pp. 9457-9460, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)02034-9

Direct Anomeric O-Arylation and O-Hetarylation of Glucose - Electron Deficient Aromatic and Hetaromatic Compounds in Aryl and Hetaryl Glycoside Synthesis[1]

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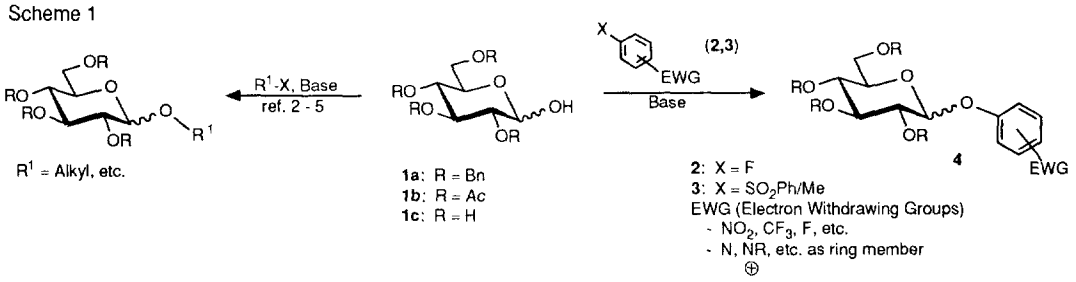
Abstract: Anomeric O-arylation and O-hetarylation of tetra-O-benzyl-, tetra-O-acetyl-, and O-unprotected glucose (**1a-c**) can be directly performed with electron deficient aromatic and heteroaromatic systems having fluoro- (**2A-2F**) or phenylsulfonyl (**3B**, **3G-3K**), respectively, as leaving groups. The reactions were carried out in DMF as solvent at room temperature with NaH as the base; they led in the products **4** to an exchange of the leaving group by the glucopyranosyloxy moiety; mainly β-products were obtained.

Direct anomeric O-alkylation of O-protected sugars has been recently extensively investigated yielding O-glycosides in a most convenient and effective manner[2-4]. Application of this method to O-unprotected sugars seemed to be rather difficult because not only α- and β-pyranosides but also α- and β-furanosides can be obtained; additionally, all the other hydroxy groups could be readily accessible to O-alkylation. However, studies with various alkylating agents exhibited highly regioselective and stereoselective O-glycoside bond formation[4]. Obviously, the anomeric hydroxy group is the most acidic and the generated 1-oxide sufficiently nucleophilic to overcome competing reactions at other hydroxy groups (Scheme 1)[2,4,5].

Scheme 1



R^1 = Alkyl, etc.

1a: R = Bn
1b: R = Ac
1c: R = H

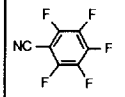
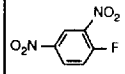
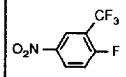
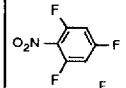
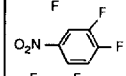
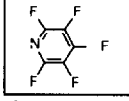
2: X = F
3: X = SO_2Ph/Me
EWG (Electron Withdrawing Groups)
- NO_2, CF_3, F, etc.
- N, NR, etc. as ring member
⊕

These findings were reason to investigate direct anomeric O-arylation and O-hetarylation of sugars because sugar attachment to such systems may create interesting new physical and/or biological properties required for transport or for specific receptor binding, respectively, of active compounds in living systems[6]. Additionally, hetaryl O-glycosides could be interesting glycosyl donors, because leaving group character could be generated with the help of acid catalysts, thus, similar to the trichloroacetimidate method, experiencing energy gain by the imidate to amide transformation[2,7].

Nucleophilic substitution at aromatic and heteroaromatic compounds via an addition-elimination mechanism (S_N-Ar/AE) generally requires activation by electron-withdrawing groups (EWG) (Scheme 1).

Therefore, we investigated some typical aromatic and heteroaromatic substrate types and the required leaving groups. Because glucose exhibits typical sugar reactivity, tetra-O-benzyl-(**1a**), tetra-O-acetyl-(**1b**), and unprotected glucose (**1c**) were employed; thus, also typical protective group patterns were studied which greatly influence anomeric reactivity. Recent work on 2,4-dinitrophenyl glycoside formation[8] and syntheses of some O-protected hetaryl glycosides employed in glycoside synthesis[9,10] are reason to report on our results[6,7,11].

Table 1. FLUORIDE EXCHANGE AT AROMATIC AND HETEROAROMATIC SYSTEMS **2A - 2F**

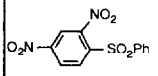
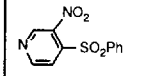
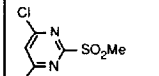
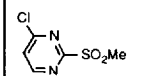
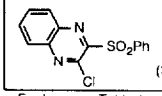
2 \ 1		**1a** PRODUCT (YIELD, α, β)	**1b** PRODUCT (YIELD, α, β)	**1c** PRODUCT (YIELD, α, β)
	(2A)	**4Aa** (90 %, β)	a	a
	(2B)	**4Ba** (75 %, β)	**4Bb** (51 %, 1/3)	**4Bc** (53 %, β) $\xrightarrow{b}$ **4Bb**
	(2C)	**4Ca** (26 %, 1/4)	**4Cb** (19 %, β)	**4Cc** (20 %, β) $\xrightarrow{b}$ **4Cb**
	(2D)	**4Da** (52 %, α:β ~ 3:7)	**4Db** (36 %, β)	**4Dc** (34 %, β) $\xrightarrow{b}$ **4Db**
	(2E)	**4Ea** (22 %, β)	c	c
	(2F)	**4Fa** (92 %, β)	**4Fb** (80 %, β)	**4Fc** (48 %, β) $\xrightarrow{b}$ **4Fb**

[a] Not investigated; [b] Per-O-acetylation with Ac_2O/Pyr.; [c] No reaction.

Fluoride has become a common leaving group in S_NAr/AE reactions because it exhibits generally excellent leaving group character. The monocyclic systems **2A-2F** which were investigated are summarized in Table 1[12]. All reactions with **1a** and **1b** were carried out in CH_2Cl_2 and with **1c** in DMF as solvent at room temperature; sodium hydride and 15-crown-5 were employed as base system. Pentafluorobenzonitrile (**2A**) reacts readily with **1a** to give **4Aa** in high yield; only the β-product could be isolated, thus revealing high anomeric diastereocontrol. With 2,4-dinitro-fluorobenzene (**2B**) all sugars (**1a-c**) reacted cleanly to give **4Ba-4Bc**, hence even unprotected glucose furnished directly known O-unprotected β-glucopyranoside **4Bc**[8] in good yield. For the structural assignment all products derived from **1c** were O-acetylated by treatment with acetic anhydride in pyridine. Replacement of the 2-nitro group in **2B** by a trifluoromethyl group (→ **2C**) led to a decrease in reactivity; however, still all products (**4Ca-4Cc**) were directly obtained; **4Ca** consisted of a 1:4 α/β-mixture. 2,4,6-Trifluoronitrobenzene (**2D**) exhibited similar reactivity and afforded **4Da-4Dc** in good yields; expectedly, the 4-fluorine atom was exchanged by the β-D-glucopyranosyloxy residue. Lower reactivity was observed for less activated 3,4-difluoronitrobenzene (**2E**); only with **1a** product **4Ea** was obtained; no reaction was found for **1b** under the standard conditions. Replacement of nitro- or cyano substituents by nitrogen as a ring member generally leads to related reactivity in S_NAr/AE reactions. This is also confirmed for pentafluoropyridine (**2F**) which gives high product yields with **1a-c**, affording exclusively the β-isomers **4Fa-4Fc**.

The alkyl- and arylsulfonyl group have also become useful leaving groups in S_N-Ar/AE reactions; they can be readily generated from the corresponding thio substituents via oxidation[13]; generally, they exhibit higher leaving group character than fluorine[14]. This is shown in Table 2[12] for 2,4-dinitro-1-phenylsulfonyl benzene (**3B**) which gives even higher product yields of **4Ba-4Bc** than **2B**; with unprotected glucose (**1c**) **4Bc** is directly obtained in 60% yield as pure β-product. Replacement of the 4-nitro group by a ring nitrogen (→ **3G**) led expectedly to a slight decrease in reactivity (→ **4Ga-4Gc**); however, most surprisingly, in the reaction with **1a** only the α-product was isolated. 4,6-Dichloro-2-methylsulfonylpyrimidine (**3H**) exhibited similar results (→ **4Ha-4Hc**). Pyrimidine derivative **3J** showed much lower reactivity; it gave only with **1a** the corresponding glucoside **4Ja** (only β-product). Similarly, with quinazoline derivative **3K** only **4Ka** could be obtained. The structures of all new products could be readily assigned by their ^1H NMR data[15].

Table 2. METHYLSULFONYL AND PHENYLSULFONYL GROUP EXCHANGE AT AROMATIC AND HETEROAROMATIC SYSTEMS **3B, 3G - 3K**

3 \ 1	1a	1b	1c
	PRODUCT (YIELD, α, β)	PRODUCT (YIELD, α, β)	PRODUCT (YIELD, α, β)
 (3B)	**4Ba** (89 %, β)	**4Bb** (65 %, β)	**4Bc** (60 %, β) [b] → **4Ba**
 (3G)	**4Ga** (69 %, α)	**4Gb** (50 %, β)	**4Gc** (29 %, β) [b] → **4Gb**
 (3H)	**4Ha** (83 %, α)	**4Hb** (61 %, β)	**4Hc** (57 %, β) [b] → **4Hb**
 (3J)	**4Ja** (10 %, β)	c	c
 (3K)	**4Ka** (19 %, β)	c	c

For b, c, see Table 1

Preliminary investigation of some hetaryl glycosides as glycosyl donors (**4Fa**, etc.[7,11]) exhibited for all cases studied lower reactivities than those observed for the corresponding trichloroacetimidates[2]. Additionally, stereocontrolled formation of the hetaryl α- or β-glycoside was not possible because the anomeric O-hetarylation is irreversible under the reaction conditions. Yet, for this endeavour more appropriate systems can be envisaged.

In conclusion, direct anomeric O-arylation and O-hetarylation can be employed successfully not only for the synthesis of O-protected glucopyranosyloxy derivatives but also for the direct generation of O-unprotected representatives. O-Benzyl protected **1a** exhibits generally higher reactivity than O-acetyl (**1b**) or unprotected glucose (**1c**). Because the O-benzyl group has an inductive effect comparable to that of hydrogen the lower reactivity of **1c** must be due to other effects (solvent, hydrogen bonding, etc.). For monocyclic aromatic systems activation by at least two EWG's is required when fluorine or phenylsulfonyl are the leaving groups. Because still better leaving groups and also catalysts for S_N-Ar/AE reactions are available and condensed systems exhibit higher reactivity, this reaction should have a wide scope. As found for anomeric O-alkylation, generally high β-selectivity is observed. Two examples exhibiting high α-selectivity cannot be fully rationalized yet.

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15. Selected physical data ($[\alpha] = [\alpha]_{589}^{22}$): **4Aa**: Colorless oil; TLC (PE/EE, 7:3): $R_f = 0.67$, $[\alpha] = +19$ (c = 1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 5.35$ (d, $J_{1,2} = 8.1$ Hz, 1 H, 1-Hβ). **4Ba**: Colorless crystals, m.p. 108°C; TLC (PE/EE, 7:3): $R_f = 0.53$; ^{1}H-NMR (250 MHz, $CDCl_3$), $\delta = 5.20$ (d, $J_{1,2} = 7.1$ Hz, 1 H, 1-Hβ). **4Bb**(α): Colorless crystals, m.p. 184°C, $[\alpha] = +16.8$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.41$; ^{1}H-NMR (250 MHz, $CDCl_3$), $\delta = 6.03$ (d, $J_{1,2} = 3.6$ Hz, 1 H, 1-Hα). **4Bb**(β): Colorless crystals, m.p. 176°C, $[\alpha] = +35.2$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.54$; ^{1}H-NMR (600 MHz, $CDCl_3$), $\delta = 5.27$ (d, $J_{1,2} = 7.19$ Hz, 1 H, 1-Hβ). **4Bc**: TLC (Aminophase, CH_3CN/H_2O, 8:1): $R_f = 0.46$. **4Ca**: Colorles crystals, m.p. 91°C, $[\alpha] = -28.1$ (c = 0.5, $CHCl_3$); TLC (PE/EE, 7:3): $R_f = 0.66$ - 0.72; ^{1}H-NMR (250 MHz, $CDCl_3$), $\delta = 5.21$ (d, $J_{1,2} = 7.1$ Hz, 0.8 H, 1-Hβ), 5.50 (d, $J_{1,2} = 3.6$ Hz, 0.2 H, 1-Hα). **4Cb:** Colorless crystals, m.p. 142°C, $[\alpha] = -38.2$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.50$; ^{1}H-NMR (600 MHz, $CDCl_3$), $\delta = 5.24$ (d, $J_{1,2} = 7.67$ Hz, 1 H, 1-Hβ). **4Cc**: TLC (Aminophase, CH_3CN/H_2O, 8:1), $R_f = 0.48$. **4Da**: Colorless crystals, m.p. 104°C, $[\alpha] = -2.2$ (c = 1, $CHCl_3$); TLC (PE/EE, 7:3): $R_f = 0.78$; ^{1}H-NMR (600 MHz, $CDCl_3$), $\delta = 5.04$ (d, $J_{1,2} = 7.36$ Hz, 0.7 H, 1-Hβ, 5.28 (d, $J_{1,2} = 3.64$ Hz, 0.3 H, 1-Hα). **4Db:** Colorless crystals, m.p. 139°C, $[\alpha] = +28.2$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.46$; ^{1}H-NMR (600 MHz, $CDCl_3$) $\delta = 5.07$ (d, $J_{1,2} = 7.46$ Hz, 1 H, 1-Hβ). **4DC:** TLC (Aminophase, CH_3CN/H_2O, 8:1): $R_f = 0.48$. **4Ea**: Colorless crystals, m.p. 107°C, $[\alpha] = -36.4$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.81$; ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 5.05$ (d, $J_{1,2} = 7.63$ Hz, 1 H, 1-Hβ). **4Fa:** Colorless oil; TLC (PE/EE, 7:3): $R_f = 0.61$, $[\alpha] = +8.1$ (c = 1.0, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 5.19$ (d, $J_{1,2} = 7.3$ Hz, 1 H, 1-Hβ). **4Fb:** Colorless crystals, m.p. 135°C; TLC (PE/EE, 6:4): $R_f = 0.81$, $[\alpha] = +25.2$ (c = 1, $CHCl_3$); ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 5.44$ (d, $J_{1,2} = 7.8$ Hz, $J_{H,F} = 3.6$ Hz, 1 H, 1-Hβ). **4Ga:** Colorless crystals, m.p. 76°C, $[\alpha] = +99.3$ (c = 1, $CHCl_3$); TLC (PE/EE): $R_f = 0.74$; ^{1}H-NMR (250 MHz,$CDCl_3$): $\delta = 6.73$ (d, $J_{1,2} = 3.4$ Hz, 1 H, 1-Hα). **4Gb:** Colorless crystals, m.p. 141°C, $[\alpha] = +15.4$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.61$; ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 6.23$ (d, $J_{1,2} = 8.0$ Hz, 1 H, 1-Hβ). **4Gc:** TLC (Aminophase, CH_3CN/H_2O, 8:1): $R_f = 0.52$. **4Ha:** Colorless crystals, m.p. 141°C, $[\alpha] = +14.1$ (c = 0.5, $CHCl_3$); TLC (PE/EE, 7:3): $R_f = 0.81$; ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 5.22$ (d, $J_{1,2} = 3.4$ Hz, 1 H, 1-Hα). **4Hb:** Colorless crystals, m.p. 135°C, $[\alpha] = -12.6$ (c = 1, $CHCl_3$); TLC (PE/EE, 1:1): $R_f = 0.57$; ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 6.03$ (d, $J_{1,2} = 8.0$ Hz, 1 H, 1-Hβ). **4Hc:** TLC (Aminophase, CH_3CN/H_2O, 8:1): $R_f = 0.41$. **4Ja:** Colorless crystals, m.p. 132°C, $[\alpha] = +12.3$ (c = 0.5, $CHCl_3$); TLC (PE/EE, 7:3): $R_f = 0.57$; ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 5.93$ (d, $J_{1,2} = 7.9$ Hz, 1 H, 1-Hβ). **4Ka**: Pale yellow oil, $[\alpha] = +8.7$ (c = 1, $CHCl_3$); TLC (PE/EE, 7:3): $R_f = 0.72$; ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 6.17$ (d, $J_{1,2} = 7.7$ Hz, 1 H, 1-Hβ).

(*Received in Germany* 11 *October* 1995; *accepted* 25 *October* 1995)